

Isolated cardiac sarcoidosis associated with coronary vasomotion abnormalities: a case report

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Background

Cardiac sarcoidosis is a chronic, inflammatory disease that can affect the heart and often results in heart failure and lethal arrhythmias. A multimodality imaging approach without endomyocardial biopsy allows for the diagnosis of isolated cardiac sarcoidosis. Coronary vasomotion abnormalities are highly prevalent in various cardiovascular and inflammatory diseases. It remains unknown whether active myocardial inflammation due to cardiac sarcoidosis is associated with coronary vasomotion abnormalities.

Case summary

A 68-year-old man without a past medical history experienced an out-of-hospital cardiac arrest due to ventricular fibrillation and was successfully resuscitated without neurologic sequelae. Coronary angiography showed normal coronary arteries; however, intracoronary acetylcholine provocation testing demonstrated both epicardial coronary and coronary microvascular spasm. He was diagnosed with isolated cardiac sarcoidosis by fulfilling the diagnostic criteria proposed by the Japanese Circulation Society 2016 diagnostic guidelines, including fatal ventricular arrhythmia, focal left ventricular wall asynergy, increased myocardial fluorodeoxyglucose uptake by positron emission tomography, and late gadolinium enhancement by cardiac magnetic resonance in the heart. He was treated with calcium-channel blocker for coronary artery spasm and prednisolone for cardiac sarcoidosis and underwent implantation of an implantable cardioverter-defibrillator for secondary prevention. Following the treatment, the severity of coronary artery spasm was reduced along with regression of the myocardial inflammation.

Discussion

Epicardial coronary artery and coronary microvascular spasm can be accompanied by active myocardial inflammation of isolated cardiac sarcoidosis, and the treatment with corticosteroid and calcium-channel blocker may be effective for relieving the severity of coronary artery spasm in association with regression of myocardial inflammation of the disease.

Keywords

Case report • Coronary artery spasm • Coronary microvascular spasm • Isolated cardiac sarcoidosis

ESC Curriculum

3.1 Coronary artery disease • 3.4 Coronary angiography • 2.5 Nuclear techniques

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Learning points

- Active cardiac sarcoidosis can be accompanied by coronary vasomotion abnormalities.
- Corticosteroid and calcium-channel blocker treatment may be effective for relieving the severity of coronary artery spasm in association with regression of the myocardial inflammation of isolated cardiac sarcoidosis.

Introduction

Sarcoidosis is a chronic, systemic inflammatory disease of unknown aetiology, characterized by the presence of non-caseating epithelioid cell granulomas in each affected organ.¹ Although the clinical course is often self-limiting with spontaneous remission, the prognosis may be unfavourable especially when the disease involves the heart resulting in heart failure, atrioventricular block, ventricular arrhythmias, and even sudden death.¹ Indeed, a large autopsy study from Japan showed that cardiac sarcoidosis accounted for approximately two-thirds of deaths from sarcoidosis.² Coronary vasomotion abnormalities, such as coronary artery spasm and coronary microvascular dysfunction, have gained growing attention in view of their significant prognostic impacts and high prevalence in various cardiovascular and inflammatory diseases.^{3,4} Vascular inflammation plays important roles in the underlying mechanisms behind coronary vasomotion abnormalities.^{3,5} We have previously demonstrated a high prevalence of acetylcholine-induced epicardial coronary artery spasm in patients without organic heart disease who survived out-of-hospital cardiac arrest.⁶ However, whether active myocardial inflammation due to cardiac sarcoidosis is associated with coronary vasomotion abnormalities remains unknown because only a single case report is available regarding this issue.⁷

We herein present the case of a patient with isolated cardiac sarcoidosis complicated by coronary vasomotion abnormalities manifested as coronary spasm at both epicardial and microvascular levels, which was successfully managed by corticosteroid and calcium-channel blocker (CCB) therapy.

Timeline

Day Events

1	Successful resuscitation from out-of-hospital cardiac arrest due to ventricular fibrillation
20	Coronary spasm revealed by acetylcholine provocation testing
31	Implantable cardioverter-defibrillator implantation
55	Angina at rest with ST-segment elevation
117	Active cardiac inflammation detected by ¹⁸ F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸ F-FDG-PET/CT) imaging
193	Initiation of prednisolone with a starting dose of 30 mg/day followed by gradual weaning

Continued

Continued

Day Events

319	Reduced cardiac inflammation revealed by repeat ¹⁸ F-FDG PET/CT imaging
405	Significant remission of inducible coronary spasm by repeat acetylcholine provocation testing
614	Prednisolone tapered to 5 mg/day and subsequent clinical course uneventful over 6 months

Case presentation

A 68-year-old man without past medical history complained of palpitations due to frequent ventricular premature beats (5767/day) and was prescribed mexiletine (300 mg/day). Two months later, he experienced out-of-hospital cardiac arrest due to ventricular fibrillation and was successfully resuscitated by bystander cardiopulmonary resuscitation and direct-current countershocks without neurologic sequelae. He was referred to our department for the evaluation and management of possible underlying heart disease. His clinical course is illustrated in *Figure 1*.

Physical examination and laboratory findings were unremarkable except for elevated serum levels of soluble interleukin-2 receptor (710 U/mL; reference range, 205–587 U/mL) and high-sensitivity cardiac troponin-T (0.289 ng/mL; reference range, 0.000–0.014 ng/mL), the latter of which soon decreased to normal levels in a monotonic manner (*Figure 1*). Electrocardiogram (ECG) showed sinus rhythm with first-degree atrioventricular block (PR interval 220 ms) (*Figure 2*). Echocardiography showed mild hypokinesis in the basal posteroinferior wall of the left ventricle with a left ventricular ejection fraction of 69% (*Video 1*). Cardiac magnetic resonance (CMR) imaging revealed a band-like, non-ischaemic pattern of late gadolinium enhancement (LGE) involving the middle of the basal inferoseptal wall of the left ventricle (*Figure 3* and [Supplementary material online, Video S1](#)). These preliminary findings, including ventricular arrhythmias, localized left ventricular wall motion abnormalities, and non-ischaemic pattern of LGE by CMR, led us to hold a high index of suspicion for cardiac sarcoidosis. ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT) imaging demonstrated a focal hot spot of FDG uptake in the same region but without abnormal FDG accumulation in any organs other than the heart (*Figure 3*). Coronary angiography showed normal coronary arteries (*Figure 4* and *Video 2*). Intracoronary acetylcholine provocation testing was subsequently performed to assess coronary reactivity, as described previously.^{6,8–10} Briefly, incremental doses of acetylcholine were injected into the left coronary artery at 20, 50,

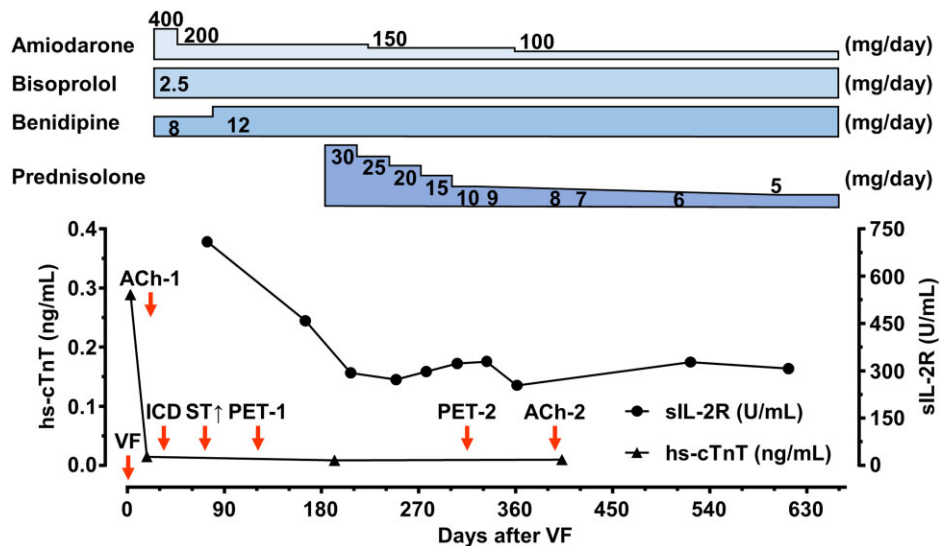


Figure 1 Clinical course. ACh, intracoronary acetylcholine provocation testing; hs-cTnT, high-sensitivity cardiac troponin-T; ICD, implantable cardioverter-defibrillator; PET, positron emission tomography; sIL-2R, soluble interleukin-2 receptor; VF, ventricular fibrillation.

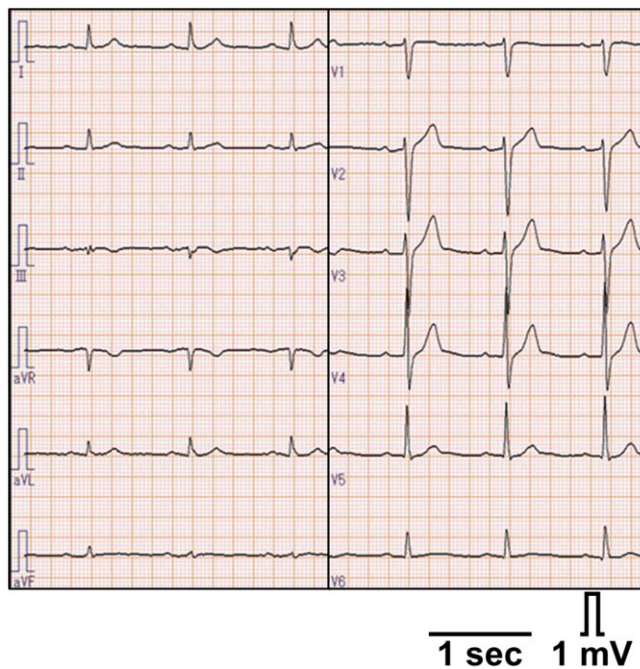
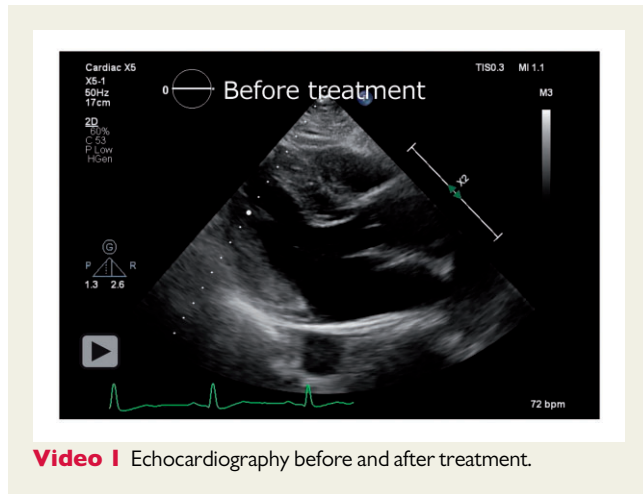


Figure 2 An initial electrocardiogram on his presentation to our department.

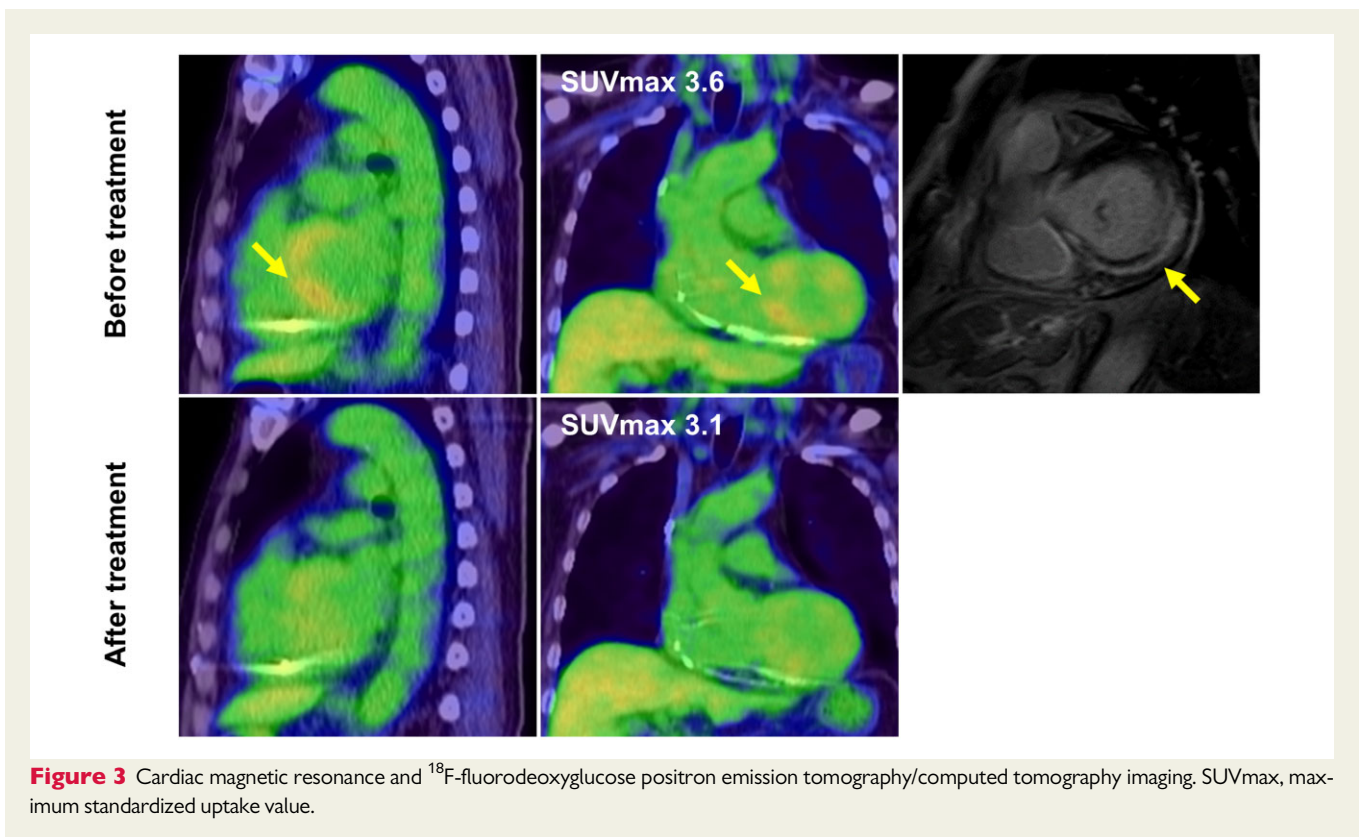
and 100 µg and the right coronary artery at 20 and 50 µg over 20 s with at least a 3-min interval between each injection.⁶ Coronary angiography was performed 1-min after each injection or when chest pain or ischaemic ECG changes were induced.⁶ To assess lactate

production in the coronary circulation as an objective marker of myocardial ischaemia, lactate concentrations were measured using paired blood samples simultaneously obtained from the left coronary artery and coronary sinus vein during acetylcholine testing.^{8,11,12} As

illustrated in *Figure 4* and *Video 2*, diffuse spasm accompanied by ST-segment elevation in leads II, III, aVF, and V4-6 was induced by the highest dose of acetylcholine (100 μg) in the proximal to distal segments of the left anterior descending and left circumflex coronary arteries. Epicardial coronary spasm was relieved after intracoronary isosorbide dinitrate administration (*Video 2*). Remarkably, myocardial lactate production was noted during acetylcholine administration even at 20 μg in the absence of angiographic, epicardial coronary artery spasm or ECG changes (*Figure 4*). This finding is attributable to coronary microvascular spasm.¹¹



He was treated with benidipine (8 mg/day) for coronary artery spasm and bisoprolol (2.5 mg/day) and amiodarone (200 mg/day) for ventricular arrhythmias based on LGE findings by CMR¹³ and underwent implantation of an implantable cardioverter-defibrillator (ICD) with a continuous ST-monitoring function (Neutrino™, Abbott, formerly St. Jude Medical) for secondary prevention of sudden cardiac death.¹³ Three weeks after implantation of the ICD, when he had been taking benidipine for 5 weeks, the intracardiac ECG monitoring revealed marked ST-segment elevation during an episode of transient chest discomfort at rest (*Figure 5*), suggestive of coronary artery spasm refractory to a standard dose of benidipine. Accordingly, the dose of benidipine was increased up to 12 mg/day, and thereafter significant ST changes were not detected by the ICD. The 'clinical' diagnosis of isolated cardiac sarcoidosis was made by satisfying all of the major criteria for cardiac involvement proposed by the Japanese Circulation Society 2016 diagnostic guidelines, including fatal ventricular arrhythmia, focal left ventricular wall asynergy, increased myocardial FDG uptake by PET, and LGE by CMR in the heart.¹³ He was initiated on oral prednisolone with the starting dose of 30 mg/day (~0.5 mg/kg/day), which was tapered by 5 mg/day every 4 weeks to a maintenance dose of 10 mg/day.¹³ He did not show any adverse events related to corticosteroid therapy with unchanged left ventricular function (*Video 1*). Repeat ¹⁸F-FDG PET/CT imaging 6 months after the initiation of treatment revealed a marked decrease in FDG uptake in the heart (*Figure 3*). Moreover, repeat intracoronary acetylcholine provocation testing showed significant remission of inducible coronary spasm (*Figure 4* and *Video 3*). Note that he had withheld all



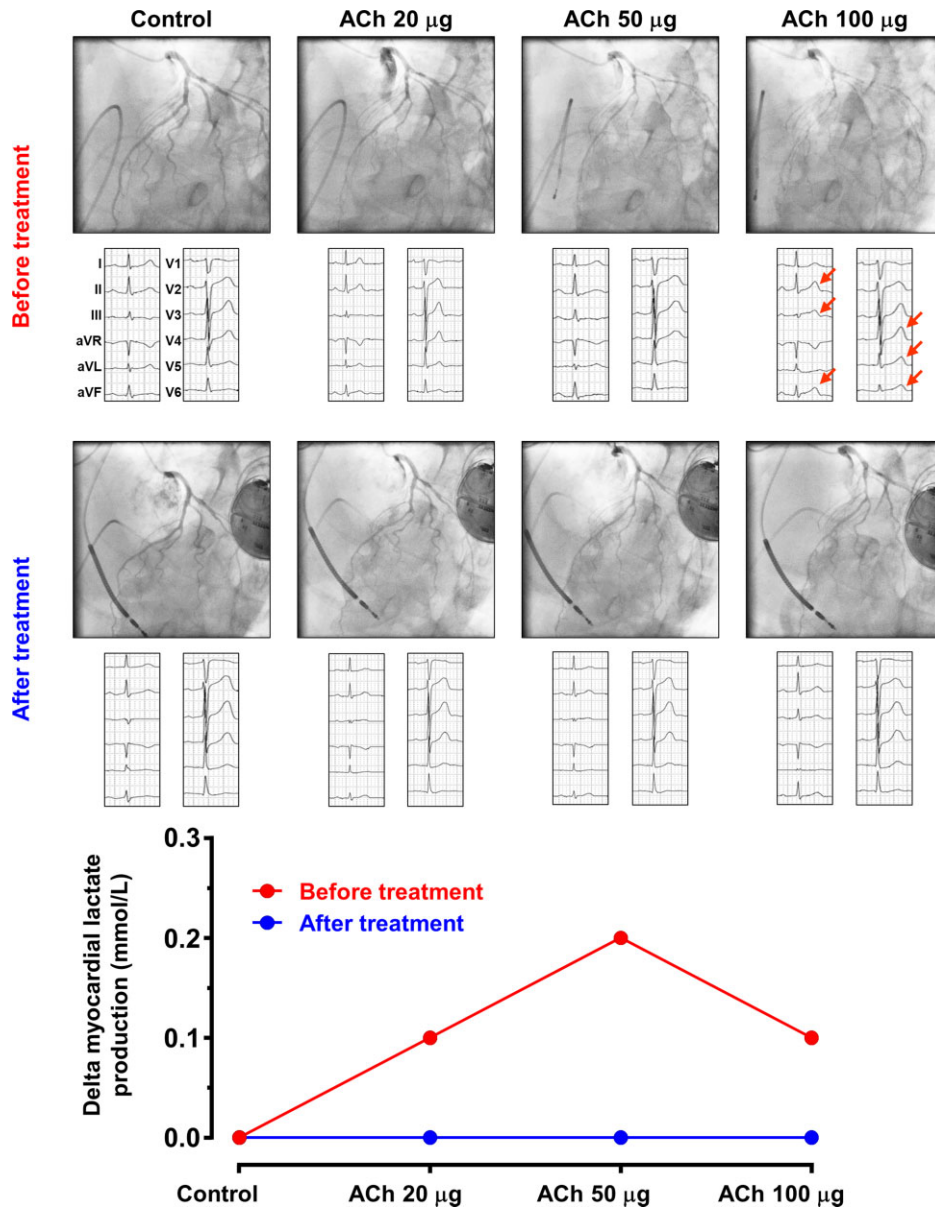


Figure 4 Intracoronary acetylcholine provocation testing and assessment of myocardial lactate production. See the left anterior descending coronary artery running around the apex of the heart. ACh, acetylcholine.

vasodilators, including benidipine for more than 48 h prior to the catheterization. Based on these results, the dose of prednisolone was tapered to a maintenance dose of 5 mg/day. His subsequent clinical course was uneventful over 6 months on the maintenance dose of prednisolone.

Discussion

The course of our patient highlighted two major clinical implications. First, active myocardial inflammation of isolated cardiac sarcoidosis was associated with coronary vasomotion abnormalities as evidenced

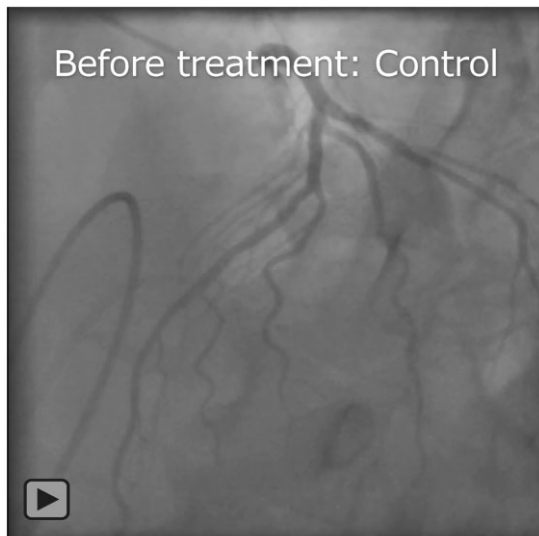
by acetylcholine-induced coronary spasm at both epicardial and microvascular levels. Second, the severity of coronary artery spasm was reduced along with regression of the myocardial inflammation following the treatment with corticosteroid and CCB. This is the first case with isolated cardiac sarcoidosis showing that corticosteroid and CCB therapy was effective for coronary artery spasm.

The most important lesson we can learn from this case is that acetylcholine-induced coronary spasm at both epicardial and microvascular levels was associated with active myocardial inflammation of isolated cardiac sarcoidosis as shown by an elevated serum level of soluble interleukin-2 receptor, a marker of disease activity in sarcoidosis, to the same extent as previous studies¹⁴ and increased

myocardial FDG uptake by PET. Given that coronary functional abnormalities, in particular coronary artery spasm, have significant prognostic impacts in patients with ischaemia and no obstructive coronary artery disease,¹⁵ the caution with regard to coronary vasomotion abnormalities including coronary artery spasm in patients with cardiac sarcoidosis provides important clinical implications. Although it is inconclusive, lethal ventricular arrhythmias in our patient may be associated with active myocardial inflammation due to isolated cardiac sarcoidosis, coronary artery spasm, or both.

Another lesson from this case is that coronary artery spasm was relieved in parallel with reduced cardiac inflammation in response to corticosteroid and CCB therapy. Chronic, low-grade vascular inflammation contributes to the development of coronary vasomotion abnormalities in various cardiovascular and inflammatory diseases.^{3,4} We have previously demonstrated that the extent of coronary perivascular inflammation was markedly attenuated in the spastic

coronary artery after treatment with CCB, a drug of choice for vasodilator therapy in patients with vasospastic angina.⁵ It may be speculated that inflammatory responses in active cardiac sarcoidosis are a possible mechanism underlying enhanced coronary vasoconstrictive reactivity (e.g. coronary spasm) at both epicardial and microvascular levels. This hypothesis may be supported by a previous randomized control trial; the SCAST study demonstrated that an addition of statin therapy to the conventional CCB therapy for 6 months significantly reduced coronary spasm induced by intracoronary injection of acetylcholine and C-reactive protein levels.¹⁶ In the present patient who survived out-of-hospital cardiac arrest due to ventricular fibrillation, LGE findings by CMR indicated a substrate of ventricular arrhythmias. β -blockers are listed as a Class IIa recommendation in the current guidelines for the treatment of tachyarrhythmia associated with cardiac sarcoidosis.¹³ In the guidelines for diagnosis and treatment of patients with vasospastic angina, concomitant use of β -



Video 2 Intracoronary acetylcholine provocation testing before treatment.



Video 3 Intracoronary acetylcholine provocation testing after treatment.



Figure 5 Transient ST-segment elevation recorded by intracardiac continuous electrocardiogram monitoring.

blockers for vasospastic angina without significant stenosis of coronary artery is listed as a Class IIb recommendation.⁸ Indeed, a recent prospective, randomized, double-blind trial demonstrated that concomitant use of β -blockers with CCB did not worsen vasomotor response to acetylcholine or symptoms assessed by the Seattle Angina Questionnaire.¹⁷

Conclusions

The present case might provide two important clinical implications: coronary vasomotion abnormalities, such as epicardial coronary artery spasm and coronary microvascular spasm, can be accompanied by active myocardial inflammation of isolated cardiac sarcoidosis, and the treatment with corticosteroid and CCB may be effective for relieving the severity of coronary artery spasm in association with regression of the myocardial inflammation of the disease. In conclusion, coronary vasomotion abnormalities should be suspected as a comorbidity, which is otherwise prone to be medical oversight, in the setting of active myocardial inflammation due to isolated cardiac sarcoidosis.

Lead author biography



Dr Shigeo Godo is a board-certified member of the Japanese Circulation Society, who obtained his MD and PhD degrees at the Tohoku University School of Medicine in Sendai, Japan. His research interests focus on endothelial function and coronary physiology. He completed research fellowship training in cardiovascular medicine in the Center for Coronary Physiology and Imaging at the Mayo Clinic, Rochester, MN, USA.

Supplementary material

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

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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 in line with COPE guidance.

Conflict of interest: None declared.

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