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**GRAND ROUND**
*Arrhythmias/electrophysiology*

# Sick sinus syndrome concomitant with myopathy associated with anti-mitochondrial antibodies: a case report

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**Background** Anti-mitochondrial antibody (AMA)-associated myopathy is known to be concomitant with primary biliary cirrhosis and to cause both skeletal muscle disorders and arrhythmias, myocardium disorders, and respiratory muscle disorders. We report a case of AMA-associated myopathy in which the bradycardia-related symptoms preceded the skeletal muscle symptoms.

**Case summary** A 59-year-old woman visited the emergency room in our hospital following a syncopal event. The patient was bradycardiac (45 b.p.m.) with a junctional rhythm resulting from sick sinus syndrome (SSS) and was suffering from heart failure. Blood tests revealed elevated creatine kinase (CK) and hepatic enzymes. She underwent permanent pacemaker implantation. However, it proved difficult to detect the electrical potential in the right atrium. Although successful atrial pacing was achieved at the lower right atrial septum, the atrial threshold was markedly high and she depended on ventricular pacing. One year later, neurological examination and muscle biopsy confirmed the diagnosis of AMA-associated myopathy. Following this diagnosis, steroid pulse therapy was initiated. Steroid administration relieved her symptoms and lowered the CK levels but the atrial standstill persisted. The patient takes low-dose prednisolone and has had an uneventful course for 3 years.

**Discussion** To the best of our knowledge, this is the first case of AMA-associated myopathy diagnosed by the first symptom related to bradycardia due to SSS. Patients with AMA-associated myopathy can experience a variety of cardiac symptoms, including arrhythmias, and initially complain of cardiac symptoms without symptoms of skeletal myopathy. This disease should be considered when diagnosing patients with arrhythmia and elevated CK.

**Keywords** Bradycardia • Cardiac pacemaker • Cardiomyopathy • Case report

**ESC Curriculum** 5.7 Bradycardia • 5.1 Palpitations • 5.9 Pacemakers • 6.5 Cardiomyopathy

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## Learning points

- To be able to make a differential diagnosis of myopathy associated with anti-mitochondrial antibodies in middle-aged individuals with significant arrhythmias and elevated creatine kinase.
- To understand the importance of the detection of anti-mitochondrial antibodies and muscle biopsy as useful tools in the diagnosis of myopathy associated with anti-mitochondrial antibodies.
- To recognize cardiac complications and preferential involvement of atria in anti-mitochondrial antibody-associated myopathy.

## Primary specialities involved other than cardiology

The neurologists and pathologists played the most important role in appropriate diagnosis of this case. The special staining of muscle biopsy specimen was essential in diagnosis. The decision of treatment strategies including steroid, immunosuppressive therapy, and IVIF were made by the neurologists.

## Introduction

Anti-mitochondrial antibody (AMA) is an autoantibody directed against several mitochondrial antigens. Anti-mitochondrial antibody-associated myopathy is a rare form of myopathy, known to be concomitant with primary biliary cirrhosis (PBC), and causes both skeletal muscle disorders and myocardial disorders, including arrhythmias. Compared with other forms of myopathy, arrhythmia is a specific feature of AMA-associated myopathy.[1–5] Herein, we report a case of AMA-associated myopathy that manifested with bradycardia due to sick sinus syndrome (SSS).

## Timeline

| | |
|---|---|
| 1993 (aged 35 years) | An elevated creatine kinase (CK) level was noted during a health check-up |
| March 2016 (aged 58 years) | Experienced chest pain and started to feel palpitations due to frequent premature ventricular contractions.<br>No significant abnormalities in left ventricular (LV) wall motion by transthoracic echocardiography or late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMRI). |
| January 2017 (aged 59 years) | Visited the emergency room and was admitted for a syncopal attack.<br>A permanent pacemaker was implanted.<br>CMRI showed mildly reduced LV systolic function (LVEF 45.9%), positive LGEs, and slight dilatation of the left and right atria. Endomyocardial biopsy revealed non-specific findings. |
| October 2017 (aged 59 years) | Reported fatigue and difficulty in grasping objects strongly.<br>The diagnosis of anti-mitochondrial antibody-associated myopathy was made based on the blood test and muscle biopsy from the left biceps brachii.<br>Steroid pulse therapy was initiated and followed by oral prednisolone administration. |
| 2021 (aged 63 years) | Low-dose prednisolone administration relieved her symptoms and lowered the CK levels.<br>Sinus node disease and atrial standstill remained. |

## Case presentation

A 59-year-old woman with a history of frequent premature ventricular contractions (PVCs) visited the emergency room for chest discomfort and dyspnoea following a syncopal event and was admitted to our hospital. At admission, the patient was bradycardic (45 b.p.m.) with a junctional rhythm resulting from SSS (*Figure 1A*). High blood pressure (151/52 mmHg), coarse crackle in her lower lung field, and mild leg oedema were noted. No significant heart murmur was detected. These findings suggested that she was suffering from heart failure. Chest X-ray revealed pulmonary congestion and bilateral pleural effusion (*Figure 1B*). Blood tests revealed mildly elevated creatine kinase [CK, 705 IU/L, (normal range: 45–163 IU/L)] and hepatic enzymes [alanine aminotransferase 79 IU/L, (normal range: 10–40 IU/L); aspartate aminotransferase 56 IU/L, (normal range: 5–40 IU/L); lactate dehydrogenase 304 IU/l, (normal range: 124–222 IU/L); alkaline phosphatase 434 IU/l, (normal range: 115–359 IU/L); γ-glutamyl transpeptidase 49 IU/L, (normal range: <30 IU/L)]. However, no findings suggesting hepatic cirrhosis were observed on computed tomography.

One year before admission, she experienced chest pain with an elevated CK level and underwent coronary angiography at another hospital. However, no coronary stenosis was detected. For suspected vasospastic angina, a calcium channel blocker was initiated but she started to experience palpitations due to frequent PVCs. After discharge, she was referred to our hospital for further investigation of her symptoms and evaluation of arrhythmias. Electrocardiography revealed polymorphic PVCs and non-sustained ventricular tachycardia (NSVT) (*Figure 2A and B*). Transthoracic echocardiography (TTE) showed no significant abnormalities in morphology or left ventricular (LV) wall motion. For further evaluation of suspected cardiomyopathy, she underwent cardiac magnetic resonance imaging (CMRI), which revealed normal LV morphology and systolic function and negative late gadolinium enhancement (LGE, *Figure 2C*). Thallium/$^{123}$I-β-methyl-P-iodophenyl-pentadecanoic acid scintigraphy showed a mismatch that did not correspond to coronary artery territories (*Figure 2D*), and this was non-specific and did not suggest myocardial ischaemia. Based on these findings, sarcoidosis and amyloidosis were also deemed unlikely. At 35 years of age, an elevated CK level was noted during a health check-up, but the patient was not advised to visit a hospital. Thereafter, she did not have any muscular symptoms or cardiac disease-related ones, such as chest pain, palpitation, dyspnoea on exertion, dizziness, or syncope. History and

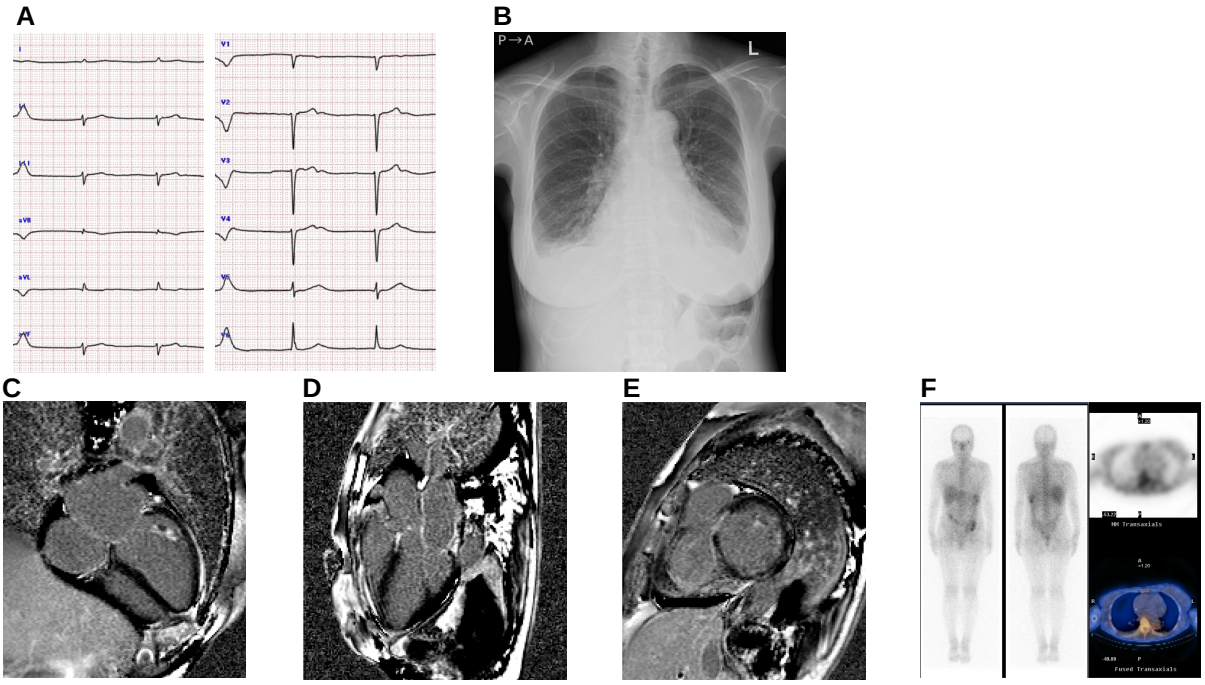



**Figure 1** Electrocardiogram (*A*), chest X-ray (*B*), cardiac magnetic resonance images (*C–E*), and gallium scintigraphy (*F*) at admission. At admission, electrocardiogram revealed bradycardia (47 b.p.m.) with junctional rhythm (*A*). Chest X-ray showed pulmonary congestion and bilateral pleural effusion (*B*). Late gadolinium enhancements were found in the basal mid-ventricular region, anterior papillary muscle, and interatrial septum (*C–E*). Gallium scintigraphy was negative (*F*). CMR, cardiac magnetic resonance; Ga, gallium; Tl, thallium; BMIPP, $^{123}$I-β-methyl-P-iodophenyl-pentadecanoic acid; LGE, late gadolinium enhancement.

symptoms related to substance abuse, genetic cardiomyopathy, or ischaemic heart disease were negative. Her family did not have the same symptoms or any heart or muscle disease. Thus, she had been treated as suspected idiopathic PVCs and NSVT, and β-blocker (bisoprolol 2.5 mg) was prescribed. She had been well before she came to the emergency room this time.

At the time of this hospitalization, TTE revealed normal LV wall motion and chamber size. Cardiac magnetic resonance imaging showed almost normal LV morphology and mildly reduced LV systolic function (LVEF 45.9%, LVEDV 140 mL, LVESV 76 mL, LV mass 66.8 g), and positive LGEs in the mid-wall of the interventricular septum, anterior papillary muscle, and even in the interatrial septum (*Figure 1C–E*), which was not found 1 year prior (*Figure 2C*). Slight dilatation of the left and right atria was also noted (*Figure 1C*). The LGE site in this case indicated non-ischaemic myocardial injury, but it was not specific to certain forms of cardiomyopathy. The differential diagnoses at this time point included sarcoidosis, amyloidosis, myopathy-related cardiac disease, myocarditis, and dilated cardiomyopathy (DCM). Since arrhythmias were prominently observed, sarcoidosis was particularly suspected. However, the levels of lysozyme- and angiotensin-converting enzyme were within the normal range in the blood test. Further, gallium (Ga) scintigraphy demonstrated a negative finding (*Figure 1F*). The ophthalmologic and dermatologic examination also revealed no findings indicating sarcoidosis. Thus, sarcoidosis was excluded. Endomyocardial biopsy was conducted and revealed non-specific findings, such as slight hypertrophy and derangement of cardiomyocytes and interstitial fibrosis (*Figure 3A and B*). Based on these findings, myocarditis and other forms of secondary cardiomyopathy were unlikely.

The patient underwent permanent pacemaker implantation because of heart failure due to SSS. However, it proved difficult to detect the electrical potential and obtain electrical excitation in response to pacing in the right atrium. Successful atrial pacing was achieved solely at the lower right atrial septum, where the pacing lead was placed. Postoperative recovery was uneventful, and the hepatic enzyme levels reduced to a normal level, suggesting ameliorated hepatic congestion. However, the atrial threshold was markedly high (5 V/2 ms), and the P-wave height could not be measured even though the lead was not dislodged; thus, she depended on ventricular pacing. One month later, the atrial threshold had been non-captured (*Table 1*). These findings suggested that sinus node dysfunction further progressed to an atrial standstill. Her symptoms such as dizziness, chest discomfort, and dyspnoea disappeared, and she had not had any muscle weakness or disability in activities of daily living. One year later, the patient reported fatigue and difficulty in grasping objects strongly. She underwent a neurological examination. Blood tests were positive for anti-mitochondrial M2 antibody. Muscle biopsy from the left biceps brachii showed some necrotic and scattered regenerating muscle fibres, in addition to mild type 2 fibre atrophy. Mild mononuclear cell infiltration was seen in the perimysium. No granulomas were observed. Mild endomysial fibrosis was observed. On immunohistochemistry, human leucocyte antigen (HLA)-ABC was mildly

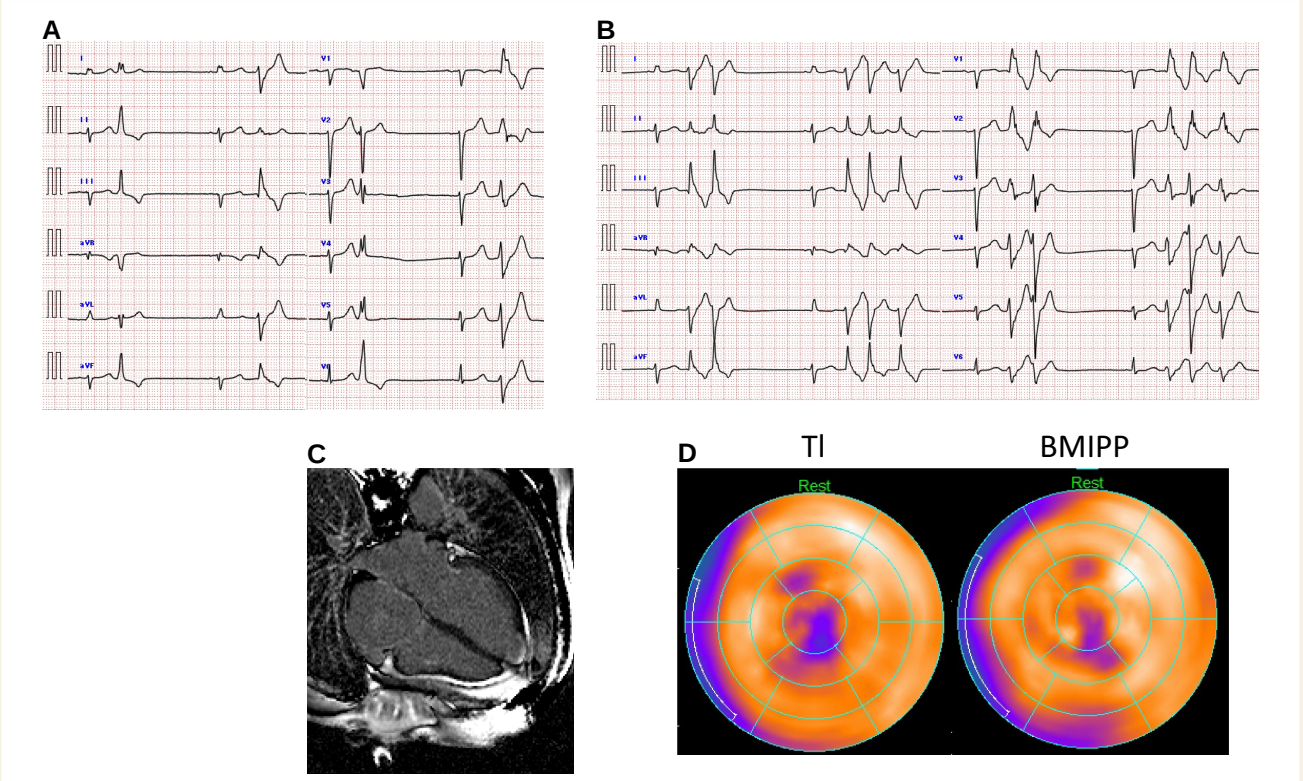



**Figure 2** Electrocardiogram (*A* and *B*), cardiac magnetic resonance image (*C*), and Thallium/123I-β-methyl-P-iodophenyl-pentadecanoic acid scintigraphy (*D*) at 1 year before admission. Electrocardiogram showed sinus rhythm but polymorphic premature ventricular contraction and non-sustained ventricular tachycardia were detected. There was no late gadolinium enhancement in cardiac magnetic resonance image (*C*). Thallium/123I-β-methyl-P-iodophenyl-pentadecanoic acid scintigraphy showed a mismatch that did not correspond to coronary artery territories (*D*). CMR, cardiac magnetic resonance; Tl, thallium; BMIPP, 123I-β-methyl-P-iodophenyl-pentadecanoic acid; PVC, premature ventricular contraction; NSVT, non-sustained ventricular tachycardia; b.p.m., beats per minute; LGE, late gadolinium enhancement.

expressed in scattered fibres. The membrane attack complex was deposited in the sarcolemma in some fibres (*Figure 3D–F*). These findings suggest the presence of a longstanding active myofibre necrotic and regenerating process, which is compatible with myopathy associated with anti-mitochondrial M2 antibodies. Serum hepatic enzymes remained within the normal range and abdominal ultrasound and computed tomography revealed no findings indicating PBC. A hepatologist was consulted and a liver biopsy was deemed unnecessary. Following the diagnosis of AMA-associated myopathy, steroid pulse therapy was initiated and was followed by oral prednisolone (PSL) administration. Steroid administration relieved her symptoms and lowered the CK levels (*Figure 4*). The patient has taken low-dose PSL and has had an uneventful course for 3 years. However, sinus node disease and atrial standstill remained. Annual echocardiography showed preserved LV systolic function and chamber size but the left atrial (LA) volume has increased gradually, indicating slowly progressive LA structural remodelling (*Table 2*).

## Discussion

We reported a case of SSS concomitant with AMA-associated myopathy. To the best of our knowledge, this is the first case of AMA-associated myopathy diagnosed by the patient's first symptom related to bradycardia due to SSS. It appears that her cardiac symptoms preceded her skeletal muscle symptoms. However, since her elevated CK level had been noted at 35 years of age, the patient may have had signs of subclinical myopathy before the development of cardiac manifestations. Furthermore, the causality between AMA myopathy and sinus node disease is not firm but remains a possibility.

An AMA-associated myopathy is a rare form of myopathy that was first described in 1974.[6] It is common in middle-aged individuals, and the prevalence of AMA among patients with myopathy ranges from 0.6% to 19.5%.[7–11] Anti-mitochondrial antibody-associated myopathy is sometimes concomitant with PBC and causes a variety of cardiac and skeletal muscle symptoms, including arrhythmias.[1–4] Cardiac involvement is not rare (33%,[7] or 2/7, 29%[11]) and is almost comparable with concomitant PBC.[11] Arrhythmia (23–71%[5,8,10]) and LV systolic dysfunction (16–71%[8,10,12]) were common, and their prevalence was reported to be higher compared with AMA-negative myopathy,[7,8] although the prevalence of AMA in DCM patients is not high (3/270, 1.1%).[13] Thus, patients with AMA-associated myopathy may initially complain of cardiac symptoms without symptoms of skeletal myopathy,[10] as in the present case.

Anti-mitochondrial antibody-associated myopathy might affect the atria more frequently than the ventricles. In a previous case

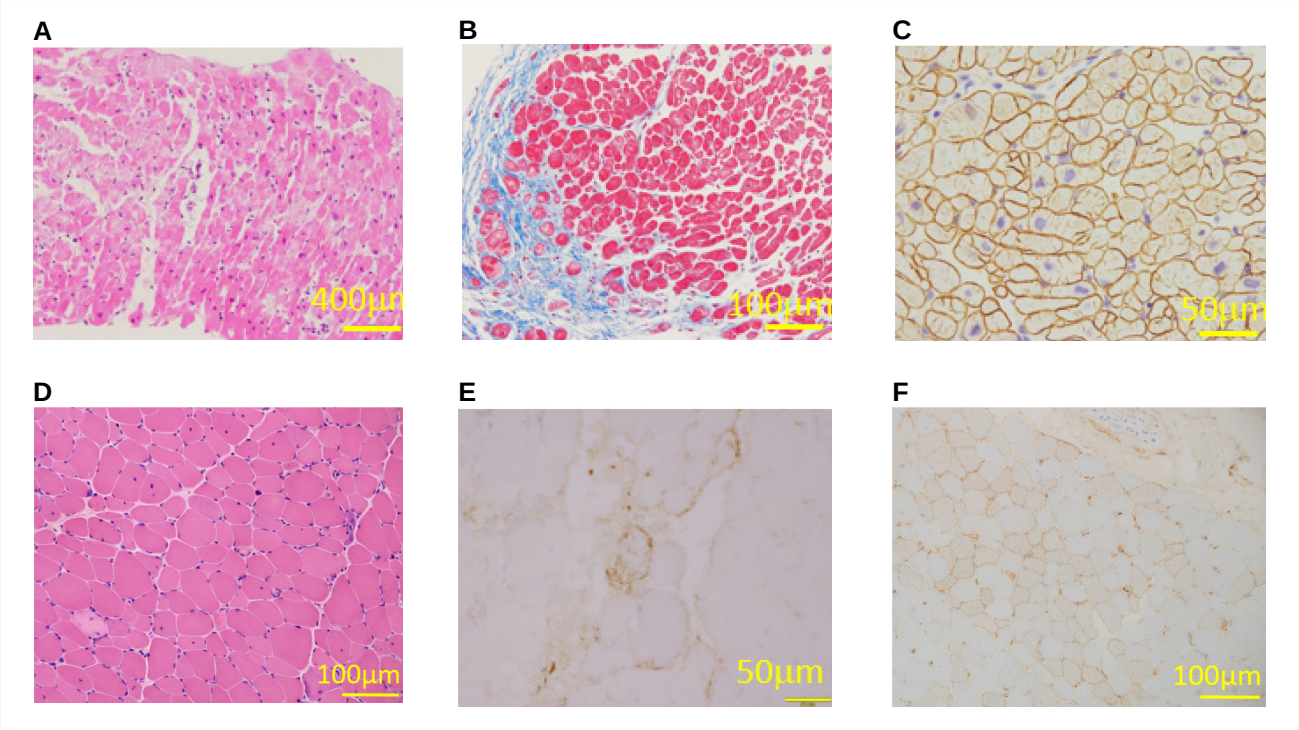



**Figure 3** Pathological findings of (*A–C*) heart and (*D–F*) skeletal muscle biopsy samples. Slight hypertrophy and derangement of cardiomyocytes was detected by haematoxylin and eosin staining (*A*). Interstitial fibrosis was detected by Masson's trichrome staining (*B*). Immunohistochemical staining for dystrophin was positive in heart tissue (*C*). Regenerating muscle fibres were found in the biceps brachii muscle by haematoxylin and eosin staining (*D*). On immunohistochemical staining, the C5b-9 membrane attack complex was deposited in the muscle fibre membrane in some fibres (*E*). No myofibre expression of human leucocyte antigen-ABC was detected (*F*).

**Table 1 The trajectory of the pacemaker setting**

| Date | After operation | 1 POD | 7 POD | 1 month | 1.5 year | 3 year |
|---|---|---|---|---|---|---|
| Mode | VVI | VVIR | VVIR | VVIR | VVIR | VVIR |
| Rate | 70– | 70–130 | 60–130 | 60–130 | 60–130 | 60–130 |
| RA lead impedance (Ω) | 615 | 636 | 657 | 760 | 787 | 762 |
| Threshold | 5 V/2 ms | 5 V/2 ms | 5 V/2 ms | Non-capture | Non-capture | Non-capture |
| Sense (mV) | – | – | – | – | – | – |
| RV lead impedance (Ω) | 743 | 739 | 728 | 752 | 710 | 651 |
| Threshold | 0.6 V/0.4 ms | 0.6 V/0.4 ms | 0.8 V/0.4 ms | 0.8 V/0.4 ms | 1.2 V/0.4 ms | 1.4 V/0.4 ms |
| Sense (mV) | 8.9 | 13.0 | 12.3 | 11.4 | 11.1 | 9.4 |
| Pacing rate | | 95% | 91% | 68% | 34% | 77% |

POD, post-operative day; RA, right atrium; RV right ventricle.

report, an electrophysiological study (EPS) revealed broad low-voltage and scar areas in the right atrium.[14] Patients with AMA were much more likely to experience atrial arrhythmia compared with patients without AMA, whereas the frequency of ventricular arrhythmia was similar.[15] Sick sinus syndrome and atrial standstill were also noted. Positive AMA was an independent risk factor for supraventricular arrhythmias.[15] In the present case, we were unable to obtain the right atrial electrical potential during pacemaker implantation, and the atrial standstill persisted after the operation. This might suggest that the electrical remodelling of the atrial muscle was already severe at the time of pacemaker implantation and it might lead to an atrial standstill.

Mid-wall LGEs in CMRI are common findings in cardiomyopathy concomitant with AMA-associated myopathy.[4,14,16,17] A previous study reported that diffuse LGE was found in the majority of cases (10/12, 83%), and was more common than cardiomyopathy concomitant with AMA-negative myopathy (7/19, 37%).[18] Subendocardial and epicardial LGEs were also observed but their

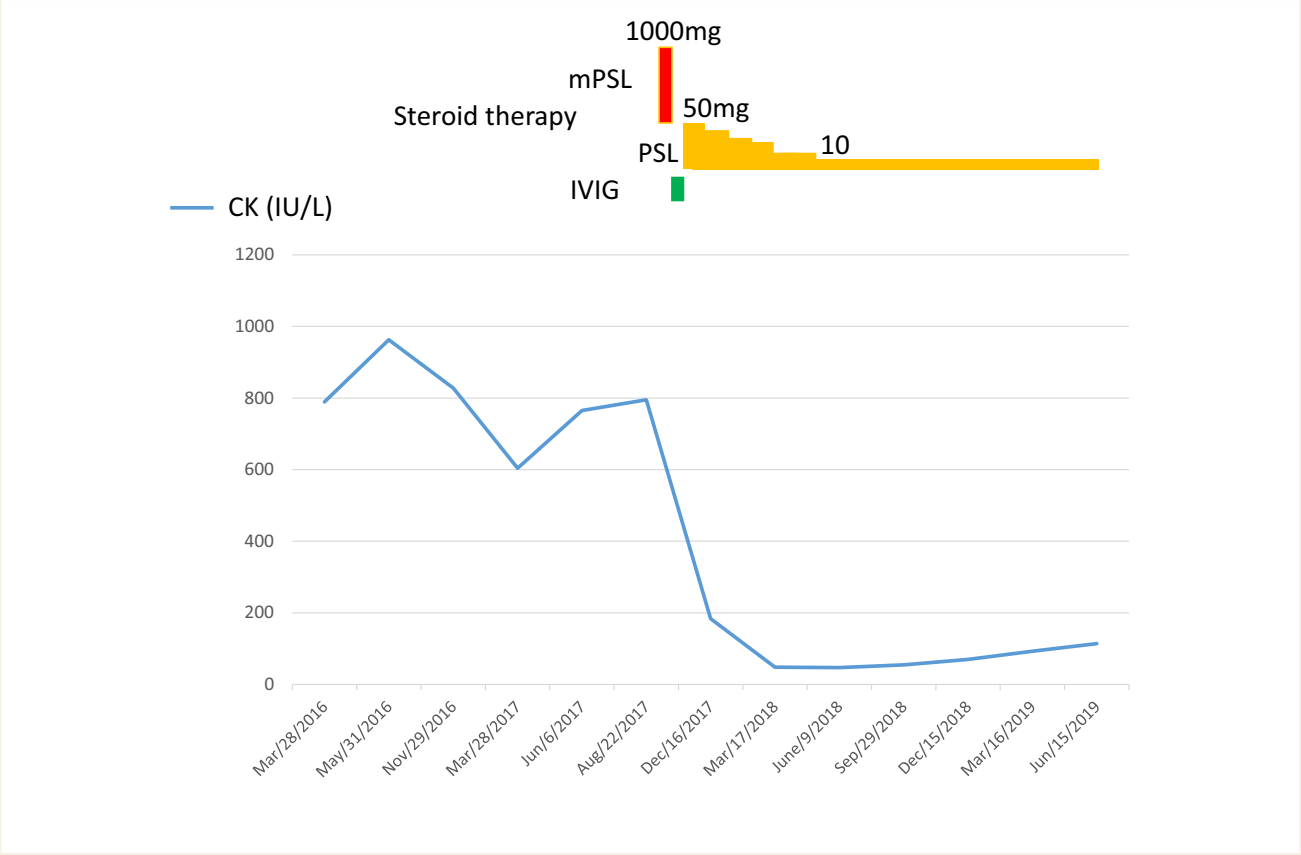



**Figure 4** The clinical course and changes in creatine kinase. After steroid administration, the patient's creatine kinase level decreased and remained low thereafter. CK, creatine kinase; mPSL, methylprednisolone; PSL, prednisolone; IVIG, intravenous immunoglobulin.

**Table 2 The trajectory of TTE findings**

| Year | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|---|
| LVEF (m-Simpson) | 58.8 | 57.3 | 57.1 | 56.5 | 55.5 | 55.3 |
| LVDd | 47 | 48 | 50 | 51 | 52 | 52 |
| LVDs | 31 | 32 | 38 | 37 | 38 | 37 |
| LVEDV | 99.9 | 106.8 | 102.1 | 104.1 | 101.8 | 116.2 |
| LVESV | 41.2 | 45.6 | 43.8 | 45.2 | 45.3 | 51.9 |
| LAD | 32 | 40 | 37 | 37 | 40 | 41 |
| LAVI | 51 | 38.2 | 45.7 | 47.7 | 51.4 | 60.4 |
| MR | 1 | 1 | 1 | 1 | 1 | 1 |
| TR | 2 | 2–3 | 2–3 | 2 | 2–3 | 3 |
| TRPG | 23 | 21 | 18 | 21 | 24 | 28 |

TTE, transthoracic echocardiography; LVEF, left ventricular ejection fraction; m-Simpson, modified Simpson method; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LAD, left atrial dimension; LAVI, left atrial volume index, MR, mitral regurgitation; TR, tricuspid regurgitation; TRPG, tricuspid regurgitation pressure gradient.

proportion was reported to be comparable with cardiomyopathy concomitant with AMA-negative myopathy.[18] The LGEs observed in the present case were compatible with these findings.

The pathology in cardiomyopathy concomitant with AMA-associated myopathy showed almost non-specific findings, such as mild hypertrophy of cardiomyocytes,[3,16,17] interstitial fibrosis, and mild inflammatory cell invasion.[14] The histological findings in the present case were compatible with these findings.

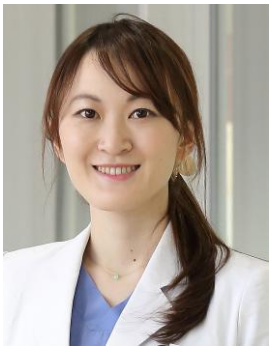
In response to immunotherapy including steroids and intravenous immunoglobulin (IVIG), a swift decrease in the CK level and recovery of muscle weakness were reported[10,11,14,17] Cardiac complications related to AMA-associated myopathy also appeared to exhibit a certain response to immunotherapy, such as improvement of LVEF,[10,16] suppression of arrhythmias, and improvement of hemodynamics.[19] However, even during steroid administration, some cases showed no improvement of cardiac diseases,[10] no marked changes in LGE,[4] or even slowly progressing cardiac injury evidenced by LGEs and thinning of the LV wall in echocardiography.[17] Arrhythmias might be especially refractory to medical treatment. In some cases, relapse of arrhythmias [4,7,10,17] and progressively diminished voltage in the right atrium evidenced by EPS during steroid administration [14] were reported. A high percentage (2/3, 66%) of worsening arrhythmia was reported in cases that did not receive immunotherapy.[7] The present case showed a swift response to steroid pulse therapy and IVIG in terms of the amelioration of muscle symptoms and CK elevation but the bradyarrhythmia persisted and atrial electrical remodelling appeared progressively worsened.

Reports on the long-term prognosis of AMA-associated myopathy have been sparse. Cardiovascular death has rarely been reported, even though some cases showed deterioration of cardiac disease, as stated above. Cardiac death was not reported in three cases of cardiomyopathy concomitant with AMA-associated myopathy over an ~5-year follow-up.[13] Only one case showed progressive deterioration of haemodynamics and died from cardiogenic shock.[20] Since this case was not treated with immunotherapy, the prognosis of this disease might be poor unless adequately treated by immunotherapy.[20] In the present case, muscle weakness and CK elevation favourably responded to the steroid and IVIG. Although her cardiac function remained stable over the 3-year follow-up, this patient needs to be followed carefully to monitor for the deterioration of cardiac conditions.

# Conclusion

We treated a case of SSS concomitant with AMA-associated myopathy. Anti-mitochondrial antibody-associated myopathy should be considered as a differential diagnosis when middle-aged patients present with significant arrhythmias and elevated CK.

# Lead author biography



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# Supplementary material

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

## Acknowledgements

None.

**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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