Diverse phenotypic expression associated with the same genetic variant in female heterozygote patients of Anderson–Fabry disease: a case series

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Background	Anderson–Fabry disease (AFD) is an X-linked lysosomal storage disorder resulting from a mutation of alpha-galactosidase A gene (*GLA*), causing deficiency in alpha-galactosidase activity. The enzyme deficit can lead to storage of globotriaosylceramide in various organs including heart. Studies suggest that vasospastic angina (VSA) is associated with AFD.
Case summary	This clinical case series aimed to present two female patients with AFD, including progressive cardiac involvement: a 50-year-old woman (patient number 1) and a 39-year-old woman (patient number 2) who are siblings with a male AFD patient harbouring p. Arg342Glu missense variant in alpha-galactosidase A gene (*GLA*), who suffered VSA and subsequent ventricular fibrillation. Enzymatic tests and genetic analysis confirmed AFD in both female patients and histological tests revealed globotriaosylceramide deposits in their hearts. In patient number 1, a 12-lead electrocardiography and transthoracic echocardiography revealed cardiac hypertrophy. Coronary angiography revealed no organic coronary artery stenosis and vasospasms was induced by spasm provocation test. In patient number 2, no signs of cardiac hypertrophy were found, and coronary arteries had no organic stenosis with negative spasm provocation test. Both patients received enalapril therapy and enzyme replacement therapy (ERT).
Discussion	Different phenotype of AFD was occurred even with the same genetic variant in female heterozygote patients. The duration of exposing accumulation of Gb3 might affect cardiac hypertrophy and vasospasms. Coronary angiography with acetylcholine provocation test should be considered in female AFD patient, especially in case with cardiac hypertrophy.
Keywords	Anderson–Fabry disease • Cardiac hypertrophy • Vasospasms • Case series

Learning points

- Vasospasms in female heterozygote AFD patients with cardiac hypertrophy should be considered as cardiac involvement.
- Cardiac imaging plays an important role in identifying cardiac involvement with AFD especially in case with a family history of VSA or ventricular arrhythmia.

Introduction

Anderson–Fabry disease (AFD) is an X-linked lysosomal (Xq22.1) storage disorder resulting from a hereditary deficiency in alpha-galactosidase A activity, which causes intracellular accumulation of substrates, such as globotriaosylceramide (Gb3).[1] The intracellular deposits lead to multiple organ dysfunction, including the kidneys, nervous system, and the heart.[2] Cardiac involvement is common in AFD and manifests as cardiomyopathy and arrhythmia.[3–5] Meanwhile, some patients with AFD were reported to have vasospastic angina pectoris (VSA).[6] Male AFD patients typically experience severe symptoms, females can range from being asymptomatic to having severe symptoms.[7] Previously, we reported a case of male AFD patient harbouring p. Arg342Glu missense variant in alpha-galactosidase A gene (*GLA*), who suffered VSA and subsequent ventricular fibrillation.[8] In this case series, we present two female AFD patients who are siblings of that AFD male patient. These two female patients affected by the same *GLA* variant in a heterozygous fashion. However, clinical manifestation of cardiac hypertrophy and response to the spasm provocation test of VSA were different between two. Through this case series, the cause of variability in their clinical expression in female AFD will be discussed.

Timeline

Timeline	Events
Patient 1	
Age 42	A 12-lead electrocardiography (ECG) and transthoracic echocardiography (TTE) revealed repolarization abnormalities as well as mild cardiac concentric hypertrophy.
Age 48	She presented exertional dyspnoea and was diagnosed with Anderson–Fabry disease (AFD).
	No organic stenosis was observed on coronary angiography, and acetylcholine provocation test induced vasospasms.
	Enzyme replacement therapy (ERT) and enalapril were administered.
Age 50	She continued ERT without symptoms during follow-up.
Patient 2	
Age 38	She was referred to the cardiology department without any abnormal findings in her heart and was diagnosed with AFD.
	No organic stenosis was observed on coronary angiography, and acetylcholine provocation test did not induce vasospasms.
	ERT and enalapril were administered.
Age 39	She continued ERT without symptoms during follow-up.

Case presentation

Patient 1

The first case is of a 50-year-old woman. She was referred to our cardiology department for diagnosis of hypertension at 42 years of age. The 12-lead electrocardiography (ECG) and transthoracic echocardiography (TTE) revealed repolarization abnormalities and mild concentric hypertrophy in the left ventricular lateral wall. Thereafter, she underwent an annual medical examination to evaluate hypertensive heart disease.

She had exertional dyspnoea at 48 years of age, at the same timing, her brother was diagnosed with AFD. He developed ventricular fibrillation caused by VSA and subsequently received an implanted cardiac defibrillator, as our previous report. She complained of dyspnoea on exertion.

On admission, her blood pressure was 119/81 mmHg and pulse rate was regular at 60 beats per minute (b.p.m.). On physical examination, jugular venous pressure was not elevated; however, lower leg pitting oedema was present. Her heart sounds were regular, and pulmonary auscultation revealed no pulmonary rales. Her 12-lead ECG showed high voltage with repolarisation abnormalities in the inferior leads, I, aVL, and precordial leads (*Figure 1A*). Transthoracic echocardiography showed concentric hypertrophy with a maximal thickness of 11 mm at the left ventricle (*Figure 1B*). Laboratory examination showed proteinuria, while her estimated glomerular filtration rate (eGFR) was maintained as 84.6 mL/min/1.73 m^2. We performed enzymatic tests for AFD. The alpha-galactosidase A activity level was low (15.2 μmol/L/h; $N > 20$ μmol/L/h), and lyso-globotriaosylceramide (lyso-Gb3) level was high (5.83 ng/mL; $N < 2$ ng/mL). Genetic analysis revealed a missense variant p. Arg342Glu in exon 7 of *GLA*, the same *GLA* variant of her brother. She was diagnosed as having AFD with cardiac hypertrophy.

The patient underwent coronary angiography because her brother developed ventricular fibrillation associated with VSA. She had no organic stenosis in the coronary artery. However, intracoronary acetylcholine injection (50–100 μg) induced multiple spasms and ST depression in the inferior leads on ECG (*Figure 2*). Endomyocardial biopsy of the right ventricular wall with light microscopy revealed vacuolated myocytes in cardiomyocytes (*Figure 3A*). Late gadolinium enhancement was exhibited at the basal of left inferolateral ventricular wall (*Figure 3B*).

Enzyme replacement therapy (ERT) with aglasidase-β was started and continued. Enalapril, an angiotensin-converting enzyme inhibitor, at an oral dose of 2.5 mg o.d. and diltiazem, a calcium channel blocker, at an oral dose of 100 mg o.d. were administered. Beta-blocker was not used. After 12 months of ERT and other medication therapy, proteinuria disappeared, while lyso-Gb3 level did not decrease (6.89 ng/mL) and TTE findings of cardiac hypertrophy remained unchanged.

Patient 2

The second case is of a 39-year-old woman who was referred to our cardiology department for the diagnosis of AFD due to the confirmed
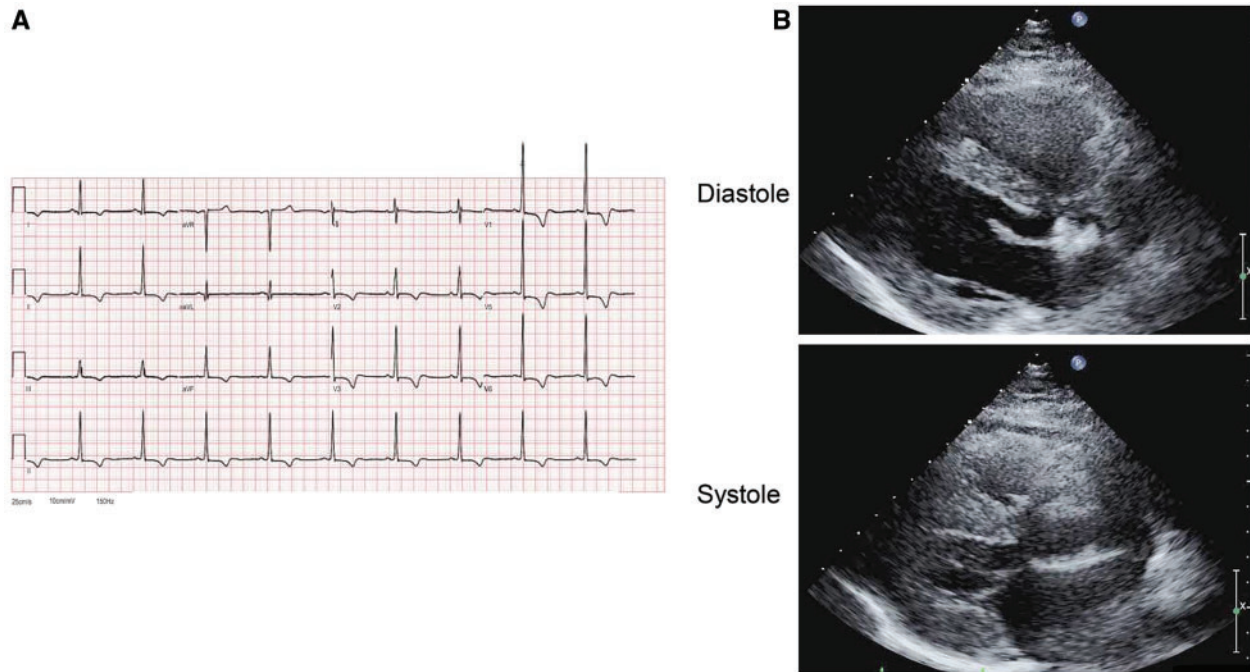
Figure 1 Electrocardiography at the time of diagnosis: (A) electrocardiography showed sinus rhythm and left ventricular hypertrophy with repolarization disorder. Transthoracic echocardiography at the time of diagnosis: (B) The top shows end diastole, and the bottom shows end systole in the long-axis view. At the time of diagnosis, transthoracic echocardiography showed that the left ventricular motion was normal, and left ventricular hypertrophy in lateral wall was observed.

AFD diagnosis of her siblings. She had been receiving an annual medical examination without any abnormal findings in her heart. She had bronchial asthma but denied having any cardiac symptoms, including dyspnoea on exertion.

Clinical examination revealed a blood pressure of 105/60 mmHg and pulse rate of 54 b.p.m. Physical examination revealed normal findings, and peripheral oedema was not observed. No signs of cardiac hypertrophy were observed on 12-ECG and TTE. Laboratory examination presented absence of proteinuria with normal renal function (eGFR 68.0 mL/min/1.73 m^2). Enzymatic tests revealed α-galactosidase A activity level was low (6.0 μmol/L/h) and lyso-GB3 level was high (27.2 ng/mL). Genetic test revealed that she had the same missense variant of her siblings. She was diagnosed as having AFD without cardiac hypertrophy. She also received coronary angiography with a spasm provocation test. She had no organic stenosis, and intracoronary acetylcholine injection (50–100 μg) did not induce spasm in any segment of the coronary artery (*Figure 4*). Endomyocardial biopsy of the right ventricular wall with electron microscopy revealed Gb3 deposits in the cardiomyocytes (*Figure 5*).

Enzyme replacement therapy with agalsidase-β was started and continued for 12 months to minimize the risk of cardiac events. Enalapril with an oral dose of 1.25 mg o.d. was administered. Beta-blocker was not used. During 12 months of ERT and other medication therapy, there was no significant change in her TTE findings and renal function.

Discussion

In this case series, we presented two cases of female AFD patients, including progressive cardiac involvement.

Cardiac hypertrophy can be observed in AFD as a result of deposits of Gb3 in cardiomyocytes. In addition to that, Gb3 storage in cardiovascular smooth cells and vascular endothelial cells can lead to coronary artery disease.[9] Clinically cardiovascular diseases are common in AFD patients of both genders, while sudden arrhythmic death remains unclear.[2] Kitani *et al.*[6] so far reported a series of AFD cases manifesting VSA including hemizygote male and heterozygote female patients. As we reported before, *GLA* p. Arg342Glu variant caused ventricular fibrillation associated with spontaneous coronary vasospasms in a male hemizygote AFD patient.[8] In present female cases also, the elder patient with cardiac hypertrophy manifested typical vasospasms induced by intracoronary acetylcholine infusion, suggesting the importance to identify coronary artery diseases in those who already presented with cardiac hypertrophy regardless of their form of inheritance. Coronary angiography with acetylcholine infusion test should be considered in such patients, especially in case with a family history of VSA or ventricular arrhythmia. Administrations of vasodilators should be recommended for those who were positive in the acetylcholine provocation test.

In patients with AFD, it is recognized that ERT cannot improve cardiac function and involvement after cardiac fibrosis reached the
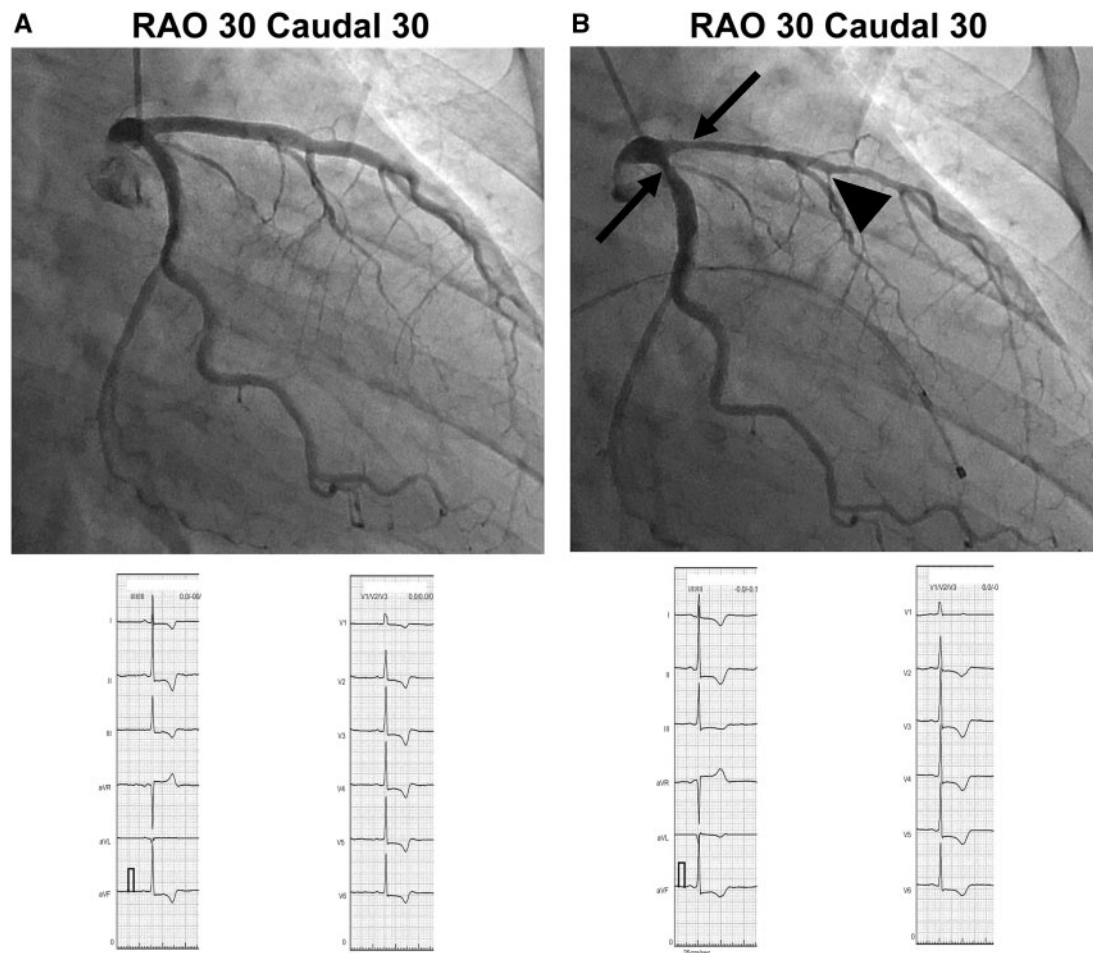
Figure 2 The top shows coronary angiography in left coronary arteries from the right anterior oblique (RAO) view (RAO 30, Caudal 30). The bottom shows ECG at the examination. (*A*) No significant coronary stenosis was found. ST depression and repolarization abnormalities found on ECG before intracoronary acetylcholine infusion. (*B*) Coronary artery spasms were induced following intracoronary acetylcholine injection (100 μg) in the left coronary artery (black broad arrow) and proximal segment of 6 and 11 (black arrows). Electrocardiography showed ST depression by 0.15 mm in the inferior leads compared to those of electrocardiography at rest.

advanced stage,[10] while earlier treatment of ERT could improve left ventricular mass and hypertrophy in this disease.[11,12] However, the indication of the ERT-initiation in female heterozygote patients without cardiac involvement has not been fully established.[13,14] In this series, both patients carried the same *GLA* p. Arg342Glu missense variant in a heterozygous fashion. The younger sister did not show vasospasms or cardiac hypertrophy, although histological and blood examinations revealed accumulation of Gb3. In contrast, older sister, in her forties, had already reached an advanced stage with cardiac hypertrophy and coronary artery disorder, such as positive spasm provocation test. The possible reason for this phenotype difference is that the elder sister had been exposed to the accumulation of Gb3 for a longer period of time compared to younger sister. This finding indicated that the early initiation of ERT may be beneficial in preventing cardiac involvement including cardiac vasospasms before the Gb3 storage leads to irreversible endothelial dysfunction. Moreover, a family history of cardiac involvement may be crucial in the early initiation of ERT.

This clinical presentation highlights the difference in cardiac phenotype at the time of their diagnosis between sisters and emphasizes the possible benefit of early initiation of ERT in female heterozygote patients to prevent cardiac hypertrophy and vasospasms.

This study has some limitations. Some examinations to detect early cardiac involvement, such as global longitudinal strain on TTE[15] and T1/T2 mapping on cardiac magnetic resonance imaging,[16] were not performed.

Conclusion

The different phenotype of AFD was occurred even with the same genetic variant in female heterozygote patients. The duration of Gb3-accumulation might affect cardiac hypertrophy and vasospasms. Coronary angiography with acetylcholine provocation test should be considered in female AFD patient, especially in the case of cardiac hypertrophy.
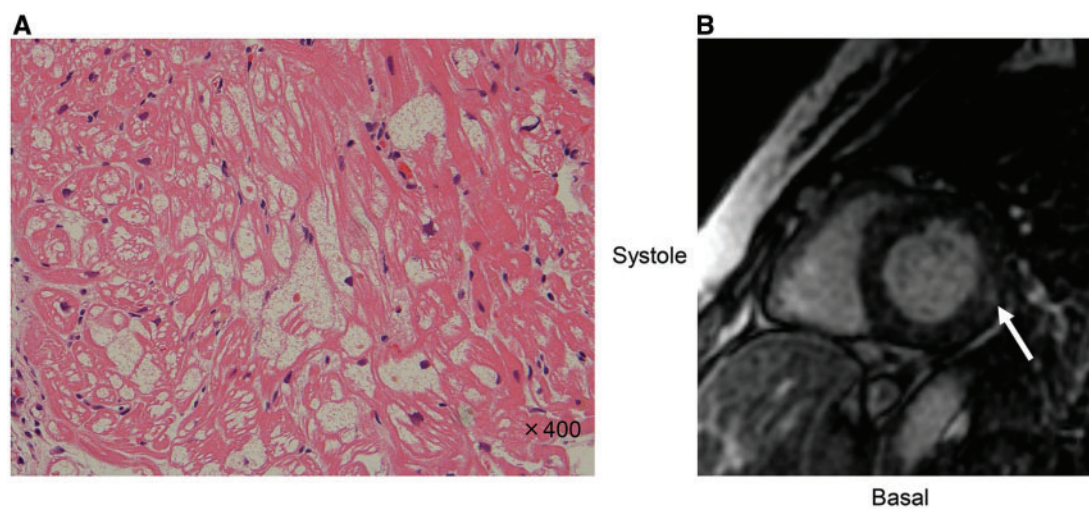
Figure 3 Biopsy of the right ventricular wall: (*A*) Vacuolated myocytes in cardiomyocytes (haematoxylin–eosin staining) Cardiac magnetic resonance imaging at the initiation of enzyme replacement therapy: (*B*) The slide shows end systole at the basal inferolateral wall in the short-axis view. Cardiac magnetic resonance imaging showed left ventricular apical hypertrophy and the late gadolinium enhancement is exhibited (white arrow).
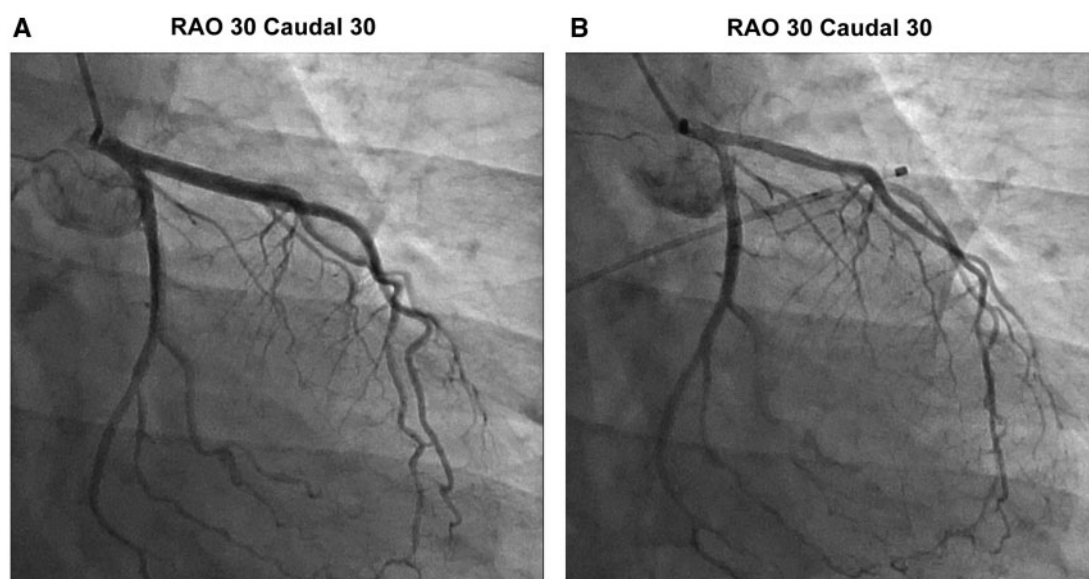

Figure 4 Coronary angiography in left coronary arteries from the RAO view (RAO 30, Caudal 30) (*A*) No significant coronary stenosis was found in the coronary arteries in control coronary angiography. (*B*) Coronary artery spasms were not induced following intracoronary acetylcholine injection (100 µg) in the coronary artery.
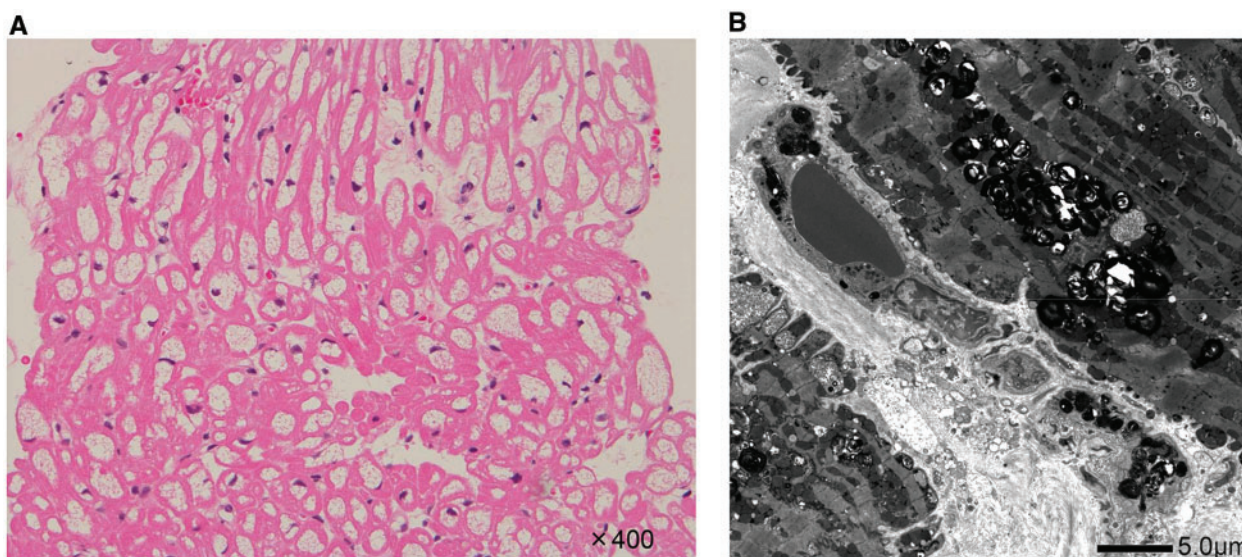
Figure 5 Endomyocardial biopsy of the right ventricular wall (*A*) Vacuolated myocytes in cardiomyocytes (haematoxylin–eosin stain). (*B*) The annual substrate accumulates in the endothelial cells (electron microscopy).

Lead author biography

Daisuke Tomioka, MD, is a physician of Cardiovascular Medicine at Nagahama Red Cross Hospital. He achieved a bachelor's degree in medicine from Shimane University of Medical Science. His research focuses on heart failure and cardiomyopathy.

Supplementary material

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

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

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