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CASE REPORT
Cardiac Imaging

Marked recovery of cardiac function by chemotherapy and autologous stem cell transplantation of a patient with heart failure with preserved ejection fraction due to primary amyloid light-chain amyloidosis: a case report

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Background Cardiac involvement of amyloid light-chain (AL) amyloidosis is strongly associated with poor outcome, but the early detection of cardiac involvement of AL amyloidosis can be challenging.

Case summary We present a case of 49-year-old-female with heart failure with preserved ejection fraction. Echocardiography revealed normal left ventricular (LV) ejection fraction of 63% and an enlarged left atrium with a left atrial volume index (LAVI) of 54 mL/m^2. Mild LV hypertrophy with an interventricular septum of 12.3 mm and posterior wall thickness of 11.0 mm was observed, and Doppler-derived LV diastolic filling showed a restrictive filling pattern. The conventional echocardiographic findings did not unequivocally indicate typical cardiac amyloidosis, but global longitudinal strain (GLS) was as low as 14.2%, and an apical sparing pattern was observed with relative apical longitudinal strain of 1.11. Finally, the patient was diagnosed as primary AL amyloidosis including histological examination of the endomyocardial specimen. After treatment with a regime of bortezomib and dexamethasone followed by high-dose melphalan followed by autologous peripheral blood stem cell transplantation (auto-PBSCT), Doppler-derived LV diastolic filling improved to normal filling pattern, and left atrial size had also decreased with an LAVI of 31 mL/m^2. Moreover, GLS improved to 19.8%, and the apical sparing pattern had disappeared with relative apical longitudinal strain of 0.62. The patient has been asymptomatic during 18-month follow-up after auto-PBSCT, and recovered LV function has been maintained.

Discussion An earlier diagnosis of cardiac amyloidosis by using apical sparing may therefore allow for earlier treatment intervention for AL amyloidosis.

ESC Curriculum 2.2 Echocardiography • 6.3 Heart failure with preserved ejection fraction

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Learning points

- Cardiac involvement of amyloid light-chain (AL) amyloidosis is strongly associated with poor outcome, but the early detection of cardiac involvement of AL amyloidosis can be challenging.
- An earlier diagnosis of cardiac amyloidosis by using apical sparing may therefore allow for earlier treatment intervention for AL amyloidosis.
- Early detection and treatment of AL amyloidosis can reverse cardiac involvement.

Introduction

Diagnosis of cardiac involvement is a critical finding for patients with amyloid light-chain (AL) amyloidosis because it is associated with a median survival of 6 months if left untreated,[1] while heart failure (HF) detected at presentation carries a worse prognosis than any other manifestations, even though HF symptom assessment is underrepresented in current analyses of treatment effects. Thus, the early detection of cardiac involvement of AL amyloidosis followed by specific treatment is essential for a favourable prognosis, but such early detection can be challenging.

Timeline

Date	Events
April 2018	Presented to local hospital with symptoms of acute heart failure and treated with diuretics.
July 2019	Referred to our institution from a local hospital.
	Echocardiogram performed which left ventricular (LV) diastolic function, global longitudinal strain (GLS) and apical sparing pattern in keeping with.
	Heart failure with preserved ejection fraction (HFpEF).
	Bloods demonstrated increase serum free kappa free light chains with and an increased kappa-lambda ratio. Serum protein electrophoresis detected IgA kappa-type M-protein, and kappa-type Bence-Jones protein was detected with urine immunofixation electrophoresis.
August 2019	Cardiac magnetic resonance imaging revealed mild LV hypertrophy without right ventricular hypertrophy. Focal late gadolinium enhancement was observed in the LV subendocardial of the LV basal anterior, antero-lateral, inferior and inferior-lateral walls, leading to a suspicion of cardiac amyloidosis.
	^{99m}technetium pyrophosphate scintigraphy did not show cardiac uptake, so that transthyretin cardiac amyloidosis was not suspected.
September 2019	Histologic findings obtained with polarization microscopy of the endomyocardial biopsy specimens from the right ventricle showed amyloid deposition stained by Congo red with apple-green birefringence.
	No evidence of multiple myeloma from the smear obtained from bone marrow.
	Diagnosed as HFpEF due to primary amyloid light-chain amyloidosis.
October 2019	Treated with a regime of bortezomib and dexamethasone with subsequent high-dose melphalan.
December 2019	Underwent autologous peripheral blood stem cell transplantation
October 2020	Marked recovery of LV diastolic function and GLS, and apical sparing pattern had also disappeared by means of echocardiography. The patient has become asymptomatic.
April 2021	Repeat echocardiography showed continued recovery of LV diastolic function, and the patient has been asymptomatic.

Case presentation

A 49-year-old-female without a history of any cardiovascular disease, presented with complaints of progressive breathlessness of New York Heart Association functional class II and oedema at a local clinic, where she was diagnosed with acute HF and treated with diuretics,

after which she was referred to our institution for further examination of the cause of acute HF. Physical examination showed blood pressure of 104/70 mmHg and a regular pulse of 68 beats/min. No cardiac murmur and abnormal lung sound were observed. Slight pitting oedema was observed in both legs. Laboratory findings demonstrated an increase in brain natriuretic peptide level to 368 pg/mL (reference interval ≤18.4 pg/dL). The determination of serum-free light chains (FLCs) found an increased level of kappa at 137.0 mg/L (reference interval 2.42–18.92 mg/dL), a normal level of lambda at 6.9 mg/L (reference interval 4.44–26.18 mg/dL), and an increased kappa-lambda ratio of 19.9. Serum protein electrophoresis detected IgA kappa-type M-protein, and kappa-type Bence-Jones protein was detected with urine immunofixation electrophoresis. An electrocardiogram showed a normal sinus rhythm and poor R progression in the precordial leads (*Figure 1*), and echocardiographic examination revealed normal left ventricular (LV) ejection fraction (LVEF) of 63% and normal LV size of LV end-diastolic volume of 66 mL and LV end-systolic volume of 18 mL (*Figure 2*). Enlargement of the left atrium was observed with a left atrial volume index (LAVI) of 54 mL/m^2, and mild LV hypertrophy (LVH) with an interventricular septum of 12.3 mm and posterior wall thickness of 11.0 mm (*Figure 2*). Doppler-derived LV diastolic filling showed a restrictive filling pattern with a trans-mitral early filling wave deceleration time of 165 ms and an elevated peak ratio of early to late diastolic mitral flow velocity (*E*/*A*) of 2.2. The ratio of *E* to tissue Doppler-derived early diastolic velocity from the septal mitral annulus (*E*/*e*′) was 15.6, indicating elevated LV filling pressure (*Figure 2*). In addition, global longitudinal strain (GLS) by means of two-dimensional speckle-tracking strain was as low as 14.2%, while an apical sparing pattern was also observed with relative apical longitudinal strain of 1.11 (*Figure 3A*). On the basis of these findings, the patient was diagnosed with HF with preserved ejection fraction (HFpEF). Although echocardiographic features of cardiac amyloidosis, such as thickened papillary muscles, thickened valves, better appreciation of the thickened right ventricular (RV) wall, and a characteristic granular sparkling appearance of the thickened cardiac walls, were not observed, cardiac amyloidosis was suspected in this patient because of the speckle-tracking findings. Cardiac magnetic resonance imaging revealed mild hypertrophy of the interventricular septum with an LV mass of 88 g without RV hypertrophy. Focal late gadolinium enhancement was observed in the LV subendocardial of the LV basal anterior, antero-lateral, inferior and inferior-lateral walls, leading to a suspicion of cardiac amyloidosis (*Figure 4*). ^{99m}technetium pyrophosphate scintigraphy did not show cardiac uptake, so that transthyretin cardiac amyloidosis was not suspected. Histologic findings obtained with polarization microscopy of the endomyocardial biopsy specimens from the right ventricle showed amyloid deposition stained by Congo red with apple-green birefringence. Furthermore, histological examination of the endomyocardial specimen showed no signs suggesting the presence of other cardiomyopathies or transthyretin deposition. There was no evidence of multiple myeloma from the smear obtained from bone marrow. Therefore, the patient was diagnosed with HFpEF because of the presence of primary AL amyloidosis.

The patient received BD treatment with bortezomib of 1.3 mg/m^2 and dexamethasone of 20 mg/day on Days 1, 2, 4, 5, 8, 9, 11, and 12 for 2 cycles subsequent high-dose melphalan of 200 mg/m^2 for 2 days followed by autologous peripheral blood stem cell transplantation (auto-PBSCT) for primary AL amyloidosis. *Figure 5* shows the follow-up echocardiogram obtained 8 months after auto-PBSCT. Left ventricular ejection fraction and LV size had remained unchanged with LV ejection fraction (LVEF) of 64%, LV end-diastolic volume (LVEDV) of 68 mL, and LVESV of 24 mL. The severity of LVH was also unchanged with an interventricular septum of 12.1 mm and posterior wall thickness of 12.1 mm. Moreover, Doppler-derived LV diastolic filling had markedly improved to attain a normal diastolic filling pattern with a trans-mitral early filling wave deceleration time of 205 ms, an *E*/*A* ratio of 1.1, and an *E*/*e*′ ratio of 10.6. Left atrial size had also decreased with an LAVI of 31 mL/m^2. Moreover, GLS improved to 19.8%, and the apical sparing pattern had disappeared

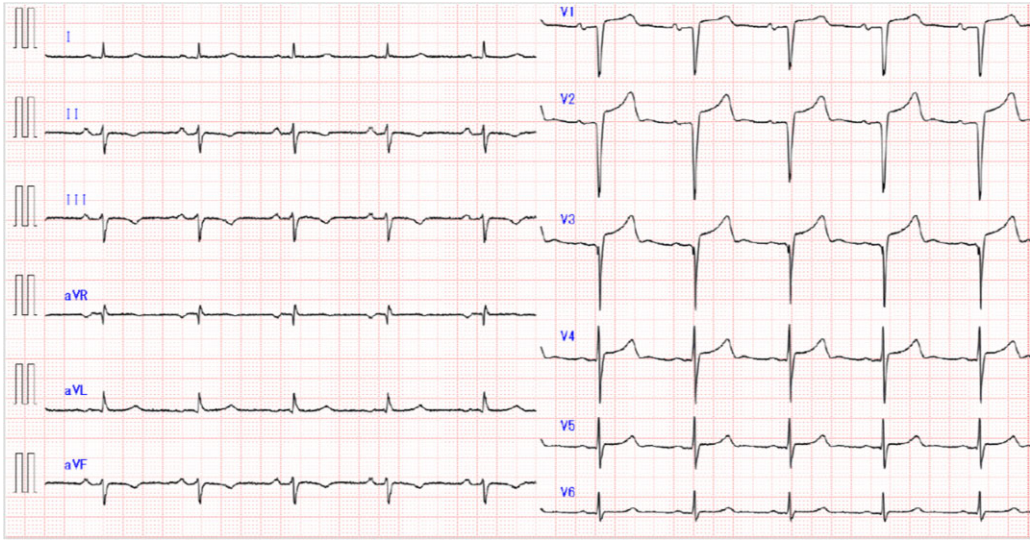

Figure 1 An electrocardiogram, showing a normal sinus rhythm and poor R progression in the precordial leads.

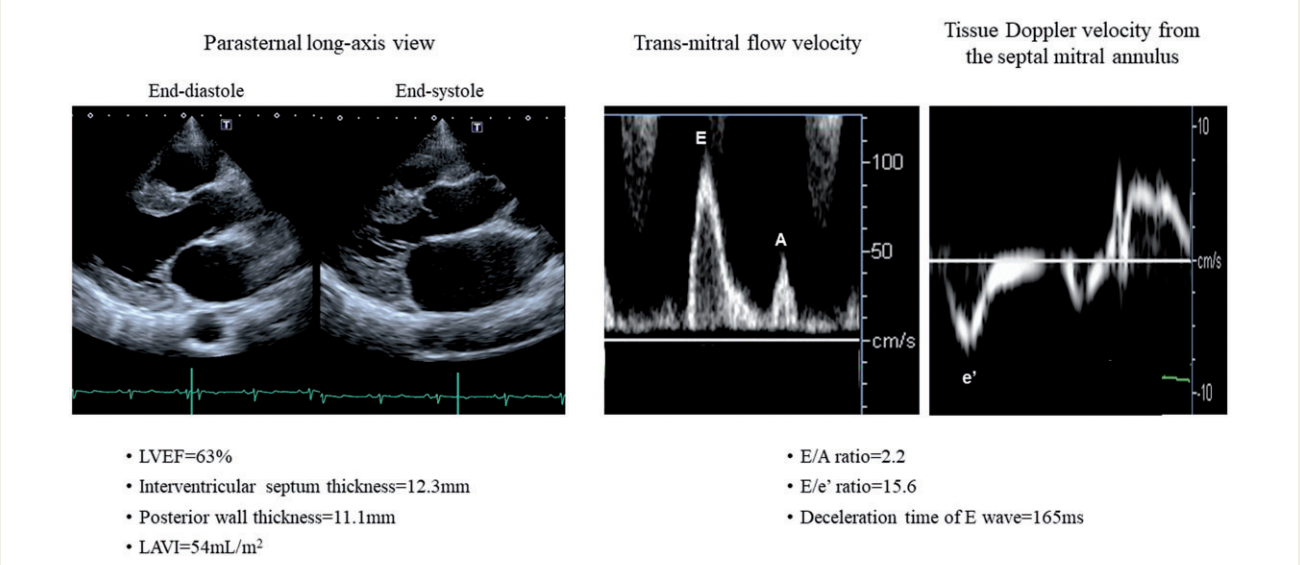

Figure 2 Transthoracic echocardiography performed during the patient's first visit to our institution, showing that normal left ventricular ejection fraction of 63% and normal left ventricular size. Enlargement of the left atrium was observed with a left atrial volume index of 54 mL/m^2, and mild left ventricular hypertrophy with an interventricular septum of 12.3 mm and posterior wall thickness of 11.0 mm. Doppler-derived left ventricular diastolic filling showed a restrictive filling pattern with a trans-mitral early filling wave deceleration time of 165 ms, an elevated peak ratio of early to late diastolic mitral flow velocity (*E*/*A*) of 2.2, and the ratio of *E* to tissue Doppler-derived early diastolic velocity from the septal mitral annulus (*E*/*e*′) was 15.6.

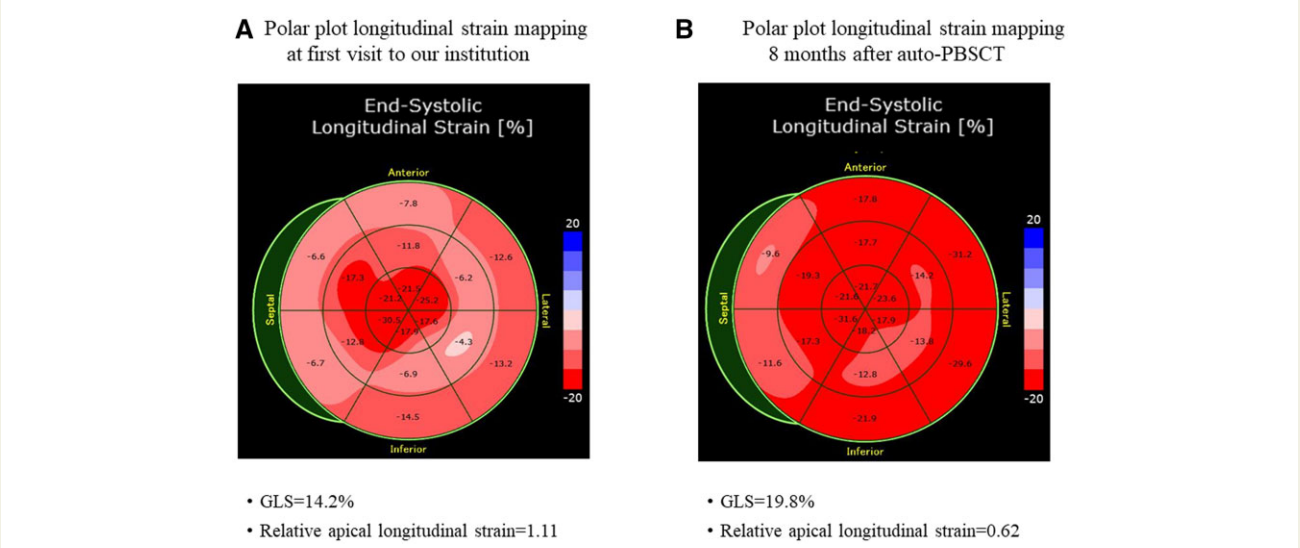

Figure 3 (*A*) Transthoracic echocardiography performed during the patient's first visit to our institution, showing that global longitudinal strain was as low as 14.2%, while an apical sparing pattern was also observed with relative apical longitudinal strain of 1.11. (*B*) Follow-up echocardiography 8 months after BD treatment (bortezomib + dexamethasone) subsequent high-dose melphalan followed by autologous peripheral blood stem cell transplantation, showing that global longitudinal strain improved to 19.8%, and the apical sparing pattern had disappeared with relative apical longitudinal strain of 0.62.

with relative apical longitudinal strain of 0.62 (*Figure 3B*). Brain natriuretic peptide had decreased to 66 pg/mL, and FLCs had also reached normal levels with kappa at 9.7 mg/L, lambda at 9.1 mg/L, and a kappa-lambda ratio of 1.07. The patient has been asymptomatic during a follow-up period of 18 months after auto-PBSCT, and recovered LV diastolic function has been maintained.

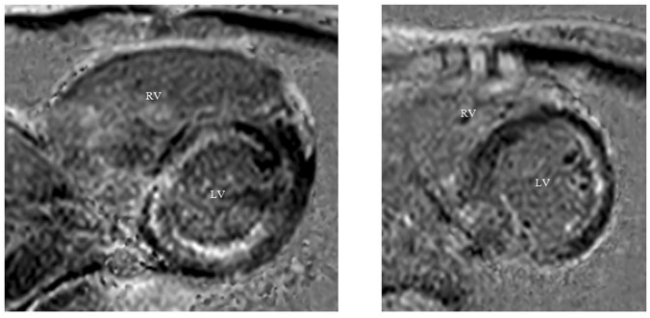

Figure 4 Cardiac magnetic resonance imaging, showing that focal late gadolinium enhancement was observed in the left ventricular subendocardial of the left ventricular basal anterior, antero-lateral, inferior and inferior-lateral walls, leading to a suspicion of cardiac amyloidosis.

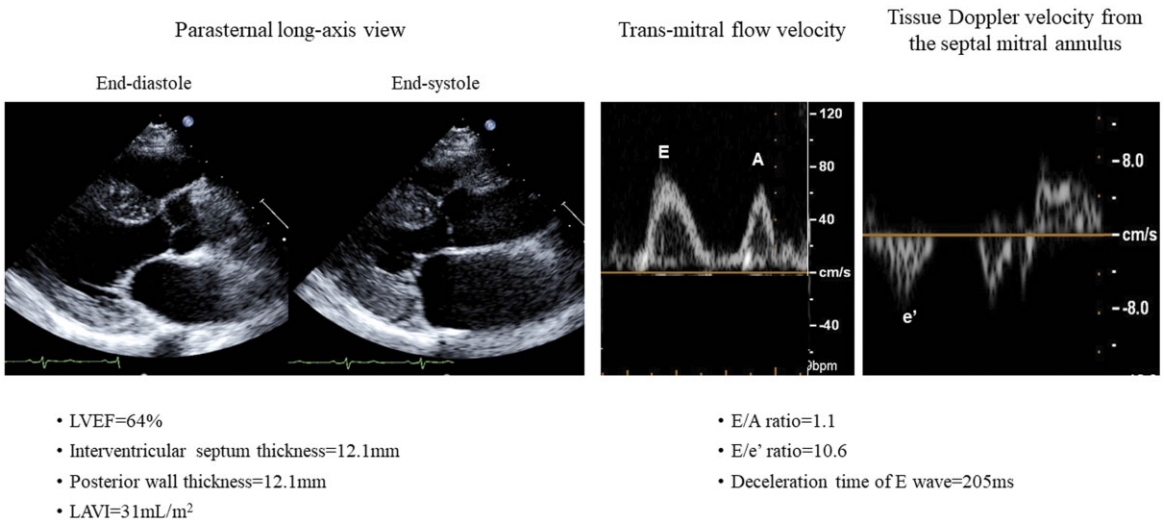

Figure 5 Follow-up echocardiography 8 months after BD treatment (bortezomib + dexamethasone) subsequent high-dose melphalan followed by autologous peripheral blood stem cell transplantation, showing that left ventricular ejection fraction and size had remained unchanged. The severity of left ventricular hypertrophy was also unchanged with an interventricular septum of 12.1 mm and posterior wall thickness of 12.1 mm, but left atrial size had decreased with an left atrial volume index of 31 mL/m^2. Doppler-derived left ventricular diastolic filling had markedly improved to attain a normal diastolic filling pattern with a trans-mitral early filling wave deceleration time of 205 ms, the peak ratio of early to late diastolic mitral flow velocity (*E*/*A*) ratio of 1.1, and the ratio of *E* to tissue Doppler-derived early diastolic velocity from the septal mitral annulus (*E*/*e*′) was 10.6.

Discussion

Amyloid light-chain amyloidosis is a plasma cell dyscrasia characterized by the pathologic production of amyloid fibrils formed by misfolded monoclonal light chains that are deposited in tissues and cause organ dysfunction.[2] The prognosis of patients with AL amyloidosis is highly dependent on the involved organs and the severity of organ damage. Diagnosis of cardiac involvement is a critical finding for patients with AL amyloidosis because it is associated with a median survival of 6 months if left untreated,[1] while HF detected at presentation carries a worse prognosis than any other manifestations, even though HF symptom assessment is underrepresented in current analyses of treatment effects. In addition, recent study showed that prognosis in patients with kappa type AL cardiac amyloidosis was better than that in patients with lambda type AL cardiac amyloidosis.[3] In spite of the poor prognosis for patients with AL amyloidosis, HF presenting with symptomatic HF, chemotherapy and/or auto-PBSCT is associated with improved outcomes for eligible patients.[1,4–7] Therefore, the early detection of cardiac involvement of AL amyloidosis followed by specific treatment is essential for a favourable prognosis, but such early detection can be challenging. Specifically, cardiac involvement of AL amyloidosis can be suspected in HF patients associated with carpal tunnel syndrome, peripheral or autonomic neuropathy, periorbital ecchymosis, or nephrotic syndrome, along with LVH LV diastolic dysfunction by means of conventional echocardiogram and low-voltage QRS complexes on electrocardiogram.[8]

Reduced LV longitudinal myocardial function in patients with cardiac amyloidosis can be detected earlier by means of two-dimensional speckle-tracking strain than by conventional echocardiographic findings.[9–11] Furthermore, speckle-tracking strain parameters can discriminate cardiac amyloidosis from other causes of cardiac hypertrophy.[9,11,12] Cardiac amyloidosis is characterized by regional variations in longitudinal strain from base to apex. In addition, a longitudinal strain gradient with preserved systolic strain at apical segments and significantly reduced systolic strain at mid and basal segments are consistently observed. Previous studies have demonstrated that this pattern, known as 'apical sparing', is specific, thus suited to differentiate patients with cardiac amyloidosis from patients with other causes of LVH.[12,13] This specific relative apical sparing can be easily visualized by polar plot longitudinal strain mapping for patients with cardiac amyloidosis, while apical sparing is observed both in patients with transthyretin cardiac amyloidosis and in those with AL amyloidosis. Moreover, Barros-Gomes *et al.*[14] showed that LV longitudinal myocardial function as assessed by GLS could predict all-cause mortality for 150 consecutive patients with AL amyloidosis and preserved LVEF as well as provide additional prognostic information for all-cause mortality better than established clinical, echocardiographic, and serological markers. They also used multivariate Cox regression analysis to show that GLS was an independent predictor of all-cause mortality.

Conclusions

Ours was a case with AL amyloidosis manifesting as HFpEF, but conventional echocardiographic findings did not unequivocally indicate typical cardiac amyloidosis. However, the presence of apical sparing can lead to an early diagnosis of AL amyloidosis to be followed by an early intervention. It was noteworthy that cardiac function including LV diastolic function and speckle-tracking parameters improved after BD treatment subsequent high-dose melphalan and auto-PBSCT without cardioprotective drugs such as such as renin–angiotensin–aldosterone system blockers, β-blockers, or mineralocorticoid receptor blockers. An earlier diagnosis of cardiac amyloidosis by using apical sparing may therefore allow for earlier treatment intervention for AL amyloidosis.

Lead author biography

Hidekazu Tanaka, MD, PhD, FACC, FASE, FAHA, FESC, is currently working as a chief of heart failure unit in the Division of Cardiovascular Medicine, Kobe University Hospital, Kobe, Japan. His main academic interests include heart failure, valvular heart disease, cardiomyopathy, and echocardiography.

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 patients in line with COPE guidance.

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