

Systemic sclerosis complicated by chronic thromboembolic pulmonary hypertension treated with balloon pulmonary angioplasty: a case report

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Background

Systemic sclerosis (SSc) is known to induce pulmonary hypertension (PH), resulting in poor prognosis. Pulmonary hypertension secondary to connective tissue disease is usually classified as Group 1. In patients with SSc, PH owing to left heart failure (Group 2) and interstitial pneumonia (Group 3) are also known; however, there have been limited reports on chronic thromboembolic PH (CTEPH), which corresponds to Group 4.

Case summary

A 39-year-old female with SSc was admitted with shortness of breath on exertion for the past 4 months. Right heart catheterization revealed severe PH. Group 1 PH secondary to collagen tissue disease was suspected; however, thoracic computed tomography and lung perfusion scan led to the diagnosis of CTEPH of Group 4. We treated the PH with several medications and balloon pulmonary angioplasty (BPA), which improved the PH and right heart failure. Consequently, her overall condition also improved.

Discussion

This is a rare case report of SSc complicated by CTEPH, which was treated with BPA. Patients with SSc are prone to complications of various type of PH. Thus, it is important to distinguish CTEPH in terms of treatment choice and prognosis.

Keywords

Pulmonary hypertension • Systemic sclerosis • Chronic thromboembolic pulmonary hypertension • Balloon pulmonary angioplasty • Case report

ESC Curriculum

9.5 Pulmonary thromboembolism • 9.6 Pulmonary hypertension

Learning points

- Pulmonary hypertension (PH) in systemic sclerosis (SSc) comprises a variety and overlap of phenotypes.
- It is important to properly investigate the different possible causes of PH associated with SSc, including chronic thromboembolic PH (CTEPH).
- Balloon pulmonary angioplasty may improve the exercise capacity and the prognosis in patients with CTEPH with SSc.

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Introduction

Systemic sclerosis (SSc), an immune-mediated rheumatic disease, is characterized by fibrosis of the skin and internal organs and vasculopathy. Therefore, SSc can lead to various complications, such as scleroderma, renal crisis, pulmonary arterial hypertension (PAH), and gastro-oesophageal reflux.¹ Pulmonary arterial hypertension in SSc is one of the complications known to have the worst survival rate, occurring in ~15% of patients.² Early detection of pulmonary hypertension (PH) by echocardiography and appropriate treatment may contribute to better outcomes.³ Right heart catheterization is recommended in cases of suspected PAH to confirm the diagnosis of PH. The mechanisms of PH in SSc are known to be varied. Pulmonary hypertension not only occurs in PAH, which is caused by impairment of pre-capillary arterioles (Group 1 of the updated PH classification⁴) but also in interstitial lung disease (Group 3 PH) and left heart disease (Group 2 PH).⁴ Moreover, reports on PH by chronic thromboembolic PH (CTEPH) (Group 4 PH) in patients with SSc is limited.^{5,6}

Chronic thromboembolic PH is a condition in which an organising thrombus physically reduces the pulmonary artery blood flow. Chronic thromboembolic PH differs from other forms of PH, in that surgical treatment is the standard of care.⁷ Balloon pulmonary angioplasty (BPA) may be considered when surgical pulmonary endarterectomy (PEA) is not indicated owing to surgically inaccessible peripheral lesions or comorbidities.⁸

We report a rare case of SSc complicated by CTEPH, which was treated with pulmonary vasodilators and BPA.

Timeline

Time	Events
11 years ago	Patient was diagnosed with systemic sclerosis.
4 months ago	Patient became awareness of shortness of breath and leg oedema.
Day 0	Right heart catheterization (RHC) revealed severe pulmonary hypertension (PH) evidenced by mean pulmonary artery pressure of 38 mmHg and pulmonary vascular resistance (PVR) of 18.7 wood unit (WU). Chronic thromboembolic PH (CTEPH) was suspected based on the computed tomography and lung perfusion scans. The patient was administered pulmonary vasodilators.
Day 63	Pulmonary angiography was performed, and the patient was diagnosed with CTEPH. Balloon pulmonary angioplasty (BPA) was subsequently performed.
Day 317	After several BPA procedures, follow-up RHC revealed decreased pulmonary arterial pressure and increased cardiac output, i.e. PVR was 8.7 WU, which was decreased.

Case presentation

A 39-year-old female with SSc was admitted at our hospital with a complaint of shortness of breath on exertion [World Health Organization-functional class (WHO-FC) was III]. The patient was diagnosed with SSc with positive anti-centromere protein antibodies when she was 28 years old. She developed pseudo intestinal obstruction for which a central venous (CV) catheter was employed for feeding at the age of 33. She was taking 5 mg of prednisolone and 240 µg of beraprost for Raynaud's symptoms and intestinal disturbance due to SSc. Since the past 4 months, she became aware of shortness of breath while riding a bicycle and walking. She was referred to our department due to worsening shortness of breath and cardiac enlargement on chest X-ray. The outpatient doctor decided to admit her for a thorough examination.

On admission, her blood pressure was 94/60 mmHg, pulse rate was 75 beat per minute, and oxygen saturation was 97% in room air. Physical examination revealed juglar veins dilation, systolic murmur (Levine III/VI), and Raynaud's phenomenon. Laboratory testing revealed brain natriuretic peptide (BNP) levels of 754.8 pg/mL (<20 pg/mL) and D-dimer levels of 2800 ng/mL (<1000 ng/mL). In terms of coagulation factors, protein C, protein S, and lupus anticoagulant were normal. Electrocardiogram revealed findings of right ventricular loading (*Figure 1A*). Chest X-ray revealed enlargement of the heart and a CV catheter inserted from the right subclavian vein (*Figure 1B*). Echocardiogram revealed normal left ventricular ejection fraction and severe tricuspid valve regurgitation (*Figure 2*). Peak velocity of tricuspid regurgitation was 3.6 m/s, the diameter of the inferior vena cava was 14/11 mm, and the right ventricular systolic pressure was 61.8 mmHg. Right heart catheterization revealed severe PH evidenced by mean pulmonary artery pressure (PAP) of 38 mmHg, pulmonary vascular resistance (PVR) of 18.7 wood unit (WU), normal range of mean pulmonary artery wedge pressure (9 mmHg), and low cardiac output (1.5 L/min). We performed enhanced thoracic computed tomography (CT) and lung perfusion scans for CTEPH screening while investigating the cause of PH. Computed tomography detected multiple thromboemboli in the peripheral pulmonary arteries, mosaic pattern of the lung field, and dilation of the right heart (*Figure 3A*). No thrombus was observed around the CV catheter that was inserted from the right subclavian vein. The spirogram of the pulmonary functional tests revealed a normal range. Perfusion scintigraphy of the lung revealed heterogeneous blood flow distribution in both the lungs and multiple segmental defects (*Figure 3B*). There was no deep vein thrombosis (DVT) on lower limb echography. We performed pulmonary angiography, which revealed multiple webs and narrowing of the pulmonary arteries (*Figure 4*). Considering these results, we diagnosed the patient with CTEPH complicated by SSc. She did not have a history of DVT or pulmonary embolism (PE). Moreover, she did not have any risk factors for DVT/PE, including the use of birth control, travel, cancer, etc.

Figure 5 shows the patient's clinical course of medication for severe PH; 10 mg of macitentan (endothelin receptor antagonist), 20 mg of tadalafil (phosphodiesterase-5 inhibitor), and an anticoagulant were administered. Since she was suffered from gastrointestinal symptoms

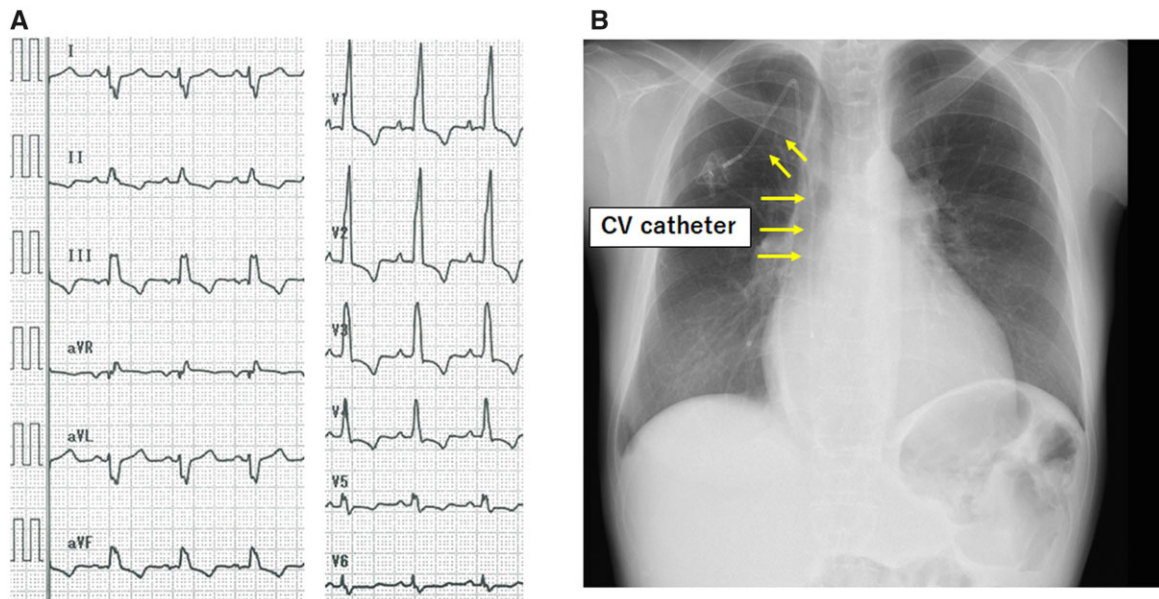


Figure 1 Electrocardiogram and chest X-ray on admission. (A) Electrocardiogram: electrocardiogram on admission shows normal sinus rhythm with right axis deviation, high R-wave in V1, and negative T-wave in II, III, aVF, V1, V2, V3, and V4. (B) Chest X-ray: chest X-ray on admission shows enlargement of the heart and central venous port (arrow) implanted in the right subclavian vein.

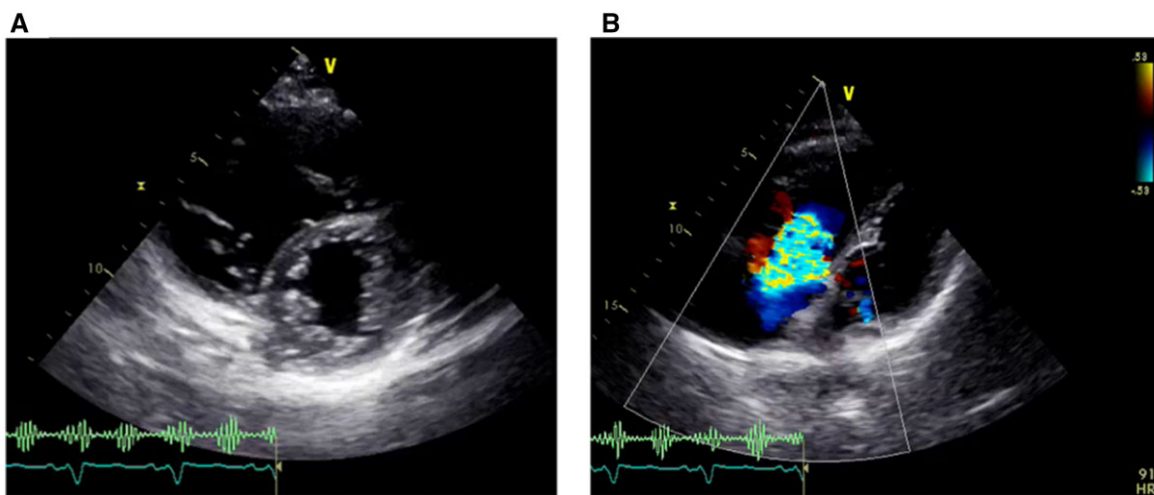


Figure 2 Transthoracic echocardiography. (A) Short-axis view shows a D-shape, which indicates intense right heart load. (B) Four-chamber view shows enlargement of the right ventricle and severe tricuspid valve regurgitation.

owing to pseudo intestinal obstruction, we did not use riociguat (stimulator of soluble guanylate cyclase).

Oxygen therapy was also initiated. Two months following the start of these medications, mean PAP was still high at 34 mmHg (PVR was 15 WU); hence, we decided to perform BPA for CTEPH. We decided that the treatment with BPA rather than PEA was more feasible considering the absence of an obvious thrombus in the central pulmonary artery. We judged that the comorbidities, such as pseudo

intestinal obstruction associated with SSc, rendered PEA a high-risk procedure. We mainly performed BPA to the regions at both sides of the peripheral pulmonary arteries, which gradually decreased her PVR. Perfusion scintigraphy of the lung following the 1st BPA session (targeted vessels: multiple peripheral right pulmonary arteries) revealed a reduced blood flow deficit in the right lung (Figure 3C). We performed four sessions of BPA guided with the deficit image on perfusion scintigraphy of the lung in ~1 year with the goal of improving

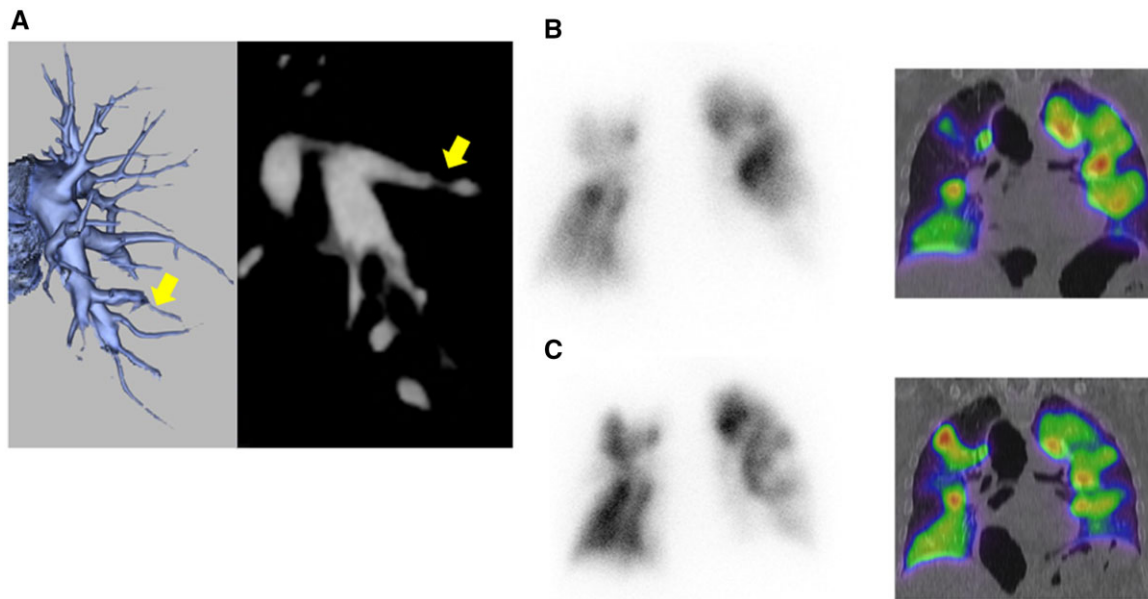


Figure 3 Chest computed tomography and perfusion scintigraphy of the lung. (A) Contrast chest computed tomography. Volume rendering image (left) and oblique view (right) of the left pulmonary artery. Computed tomography angiography shows steep narrowing of the segmental branches of the pulmonary arteries and contrast defects (arrow). (B) Perfusion scintigraphy of the lung. Planar anterior image (left) and single photon emission computed tomography image (right) of ^{99m}Tc -MAA pulmonary perfusion scintigraphy show multiple perfusion defects in the bilateral lung. (C) Perfusion scintigraphy of lung following the 1st balloon pulmonary angioplasty session (targeted vessels: multiple peripheral right pulmonary arteries). It shows a reduced blood flow deficit in the right lung.

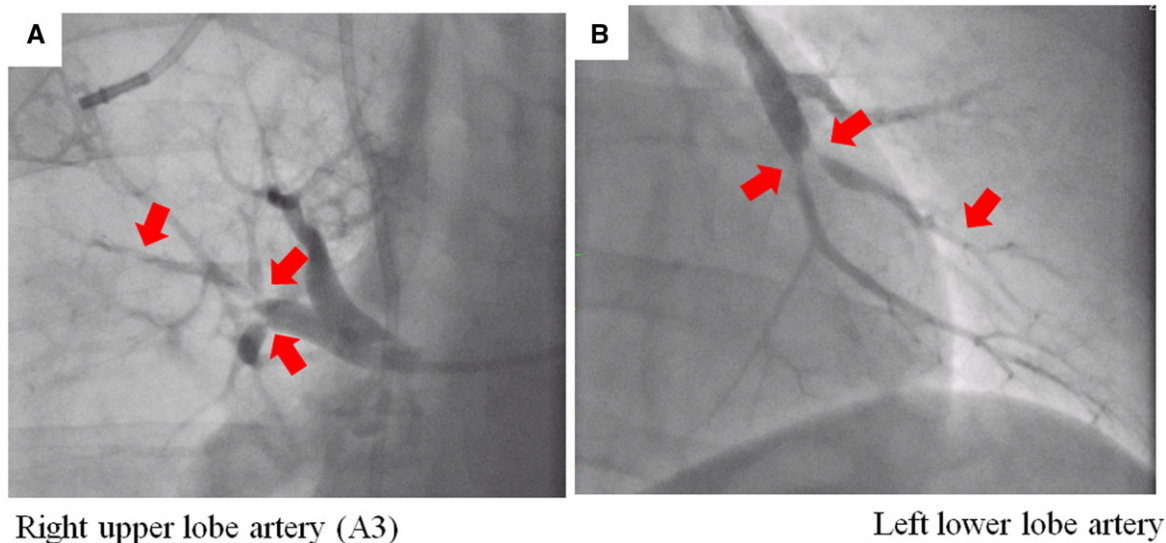


Figure 4 Pulmonary angiography. Pulmonary angiography shows multiple webs and narrowing in the bilateral pulmonary arteries (arrow). (A) Right upper lobe pulmonary artery (A3) [left anterior oblique (LAO) 50°]; (B) Left lower lobe pulmonary artery [right anterior oblique (RAO) 30°].

the haemodynamics. Complications, such as haemoptysis and pulmonary oedema were not observed throughout the BPA sessions. Compared with the time of diagnosis, at ~1 year after initiating treatment, PVR decreased from 18.7 WU to 8.7 WU, and BNP decreased

from 754.8 to 131.7 pg/mL. Her 6-min walking distance increased from 250 to 450 m, and her WHO-FC improved from class III to class II. Since her PVR is currently high, we plan to repeat BPA to treat the residual CTEPH at the next follow-up (in 3 months) (Figure 5).

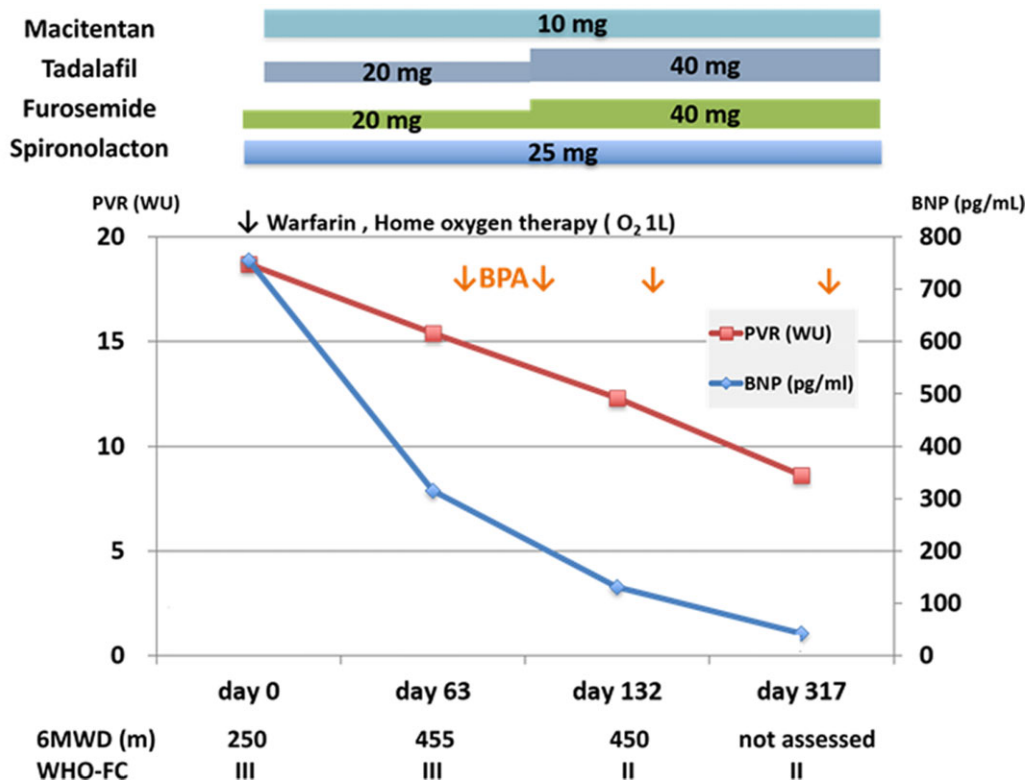


Figure 5 Clinical course of the case. The details of the treatment and trends of pulmonary vascular resistance, brain natriuretic peptide, 6-min walking distance, and World Health Organization-functional class are shown. Despite treatment with pulmonary artery dilators for severe pulmonary hypertension, pulmonary hypertension persisted. Following repeated balloon pulmonary angioplasty procedures for the treatment of chronic thromboembolic pulmonary hypertension, pulmonary hypertension and its symptoms improved. 6MWD, 6-min walking distance; BNP, brain natriuretic peptide; PVR, pulmonary vascular resistance; WHO-FC, World Health Organization-functional class.

Discussion

This is a rare case report of a patient with SSc complicated by CTEPH and treated with BPA. The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines provide the algorithms for the diagnosis of PH.⁴ According to these guidelines, it is important to identify and diagnose CTEPH earlier since its treatment options are highly specific and effective. Surgical PEA or BPA can be considered as a treatment for CTEPH. The choice of the treatment differs based on the aetiology of PH. It has been reported that lower PAP results in a better prognosis⁹; therefore, it is important to identify the correct classification of PH. It is known that patients with SSc are prone to complications of PH; however, most of them belong to Group 1, and sometimes Group 2 or 3 PH. Although the reports on patients with SSc with CTEPH (Group 4 PH) are limited, it is known that these patients have a risk of thrombosis. A previous study has reported that the risks of developing PE and DVT are higher in the SSc group than in the non-SSc group; several possible mechanisms for the same have also been described.¹⁰ Patients with SSc may also suffer increased damage to the blood vessel walls since vasculopathy and vascular injury are predominant in this disease.¹¹ Endothelial damage leads to the release of thrombin and subsequent initiation of the coagulation cascade.¹² Therefore,

SSc is a potential risk factor for developing CTEPH (Group 4). We should screen CTEPH using enhanced thoracic CT and lung perfusion scans even in patients without prior history of PE because ~25% of the patients diagnosed with CTEPH have no known history of PE.¹³

Long-term insertion of CV catheters is known to pose a risk of thrombus formation.¹⁴ In this case, we believe that both SSc and long-term insertion of the CV catheter contributed to the development of CTEPH. Appropriate diagnosis of CTEPH led to the initiation of treatment with BPA and other therapies, resulting in symptomatic improvement. Pulmonary endarterectomy is the first treatment choice for CTEPH provided there are no serious contraindications, such as comorbidities. Balloon pulmonary angioplasty is a percutaneous interventional treatment option for patients with inoperable CTEPH.⁵ We decided to perform BPA for two reasons: (i) the absence of an obvious thrombus in the central pulmonary artery and (ii) comorbidities, such as pseudo intestinal obstruction, caused by SSc.

Although we observed an improvement of PH following BPA, the insufficient drop in PVR results may have been influenced by PAH (Group 1), not only CTEPH. We plan to continue to monitor the patient's progress carefully and treat her with pulmonary vasodilators and BPA. Since SSc is a complex, systemic multi-organ connective

tissue disease, an overlap between more than one type of PH is experienced. Newly diagnosed PH in patients with SSc should be screened for CTEPH by enhanced thoracic CT and lung perfusion scans, and so on.

In conclusion, we report a rare case of a patient with SSc who developed CTEPH. We treated her with pulmonary vasodilators and BPA. Our case findings and outcome suggest that it is important to identify CTEPH among patients of SSc with PH to improve treatment decision and patient's prognosis.

Lead author biography



Tomoyo Matsui, MD, is a senior resident of cardiology at the Tokyo Women's Medical University. She graduated from the Aichi Medical University in 2017. She completed her junior residency programme in 2019 and started her career as a cardiologist in 2017. Membership: The Japanese Circulation Society and The Japanese Heart Failure Society.

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 patient in line with COPE guidance.

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