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CASE REPORT
Heart failure

Severe functional tricuspid regurgitation due to wild-type transthyretin amyloid cardiomyopathy without left ventricular hypertrophy: a case report

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Background Transthyretin amyloid cardiomyopathy (ATTR-CM) is usually characterized by left ventricular (LV) hypertrophy or LV systolic dysfunction. However, right atrial (RA) amyloidosis without LV hypertrophy, leading to severe functional tricuspid regurgitation (FTR), is extremely rare.

Case summary We present 75-year-old female with exertional dyspnoea and pre-syncope. Transthoracic echocardiography showed a normal LV function and no LV hypertrophy. A sick sinus syndrome and severe FTR due to right ventricular (RV) and RA dilatation were observed. A leadless cardiac pacemaker implantation was performed for sick sinus syndrome and the symptoms improved, but she complained of leg oedema and fatigue on effort again. A repeated transthoracic echocardiogram showed no notable changes in LV function, but progression of RV and RA dilatation was observed, with worsening FTR. Despite treatment of loop diuretics with 30 mg daily of azosemide, symptoms did not improve, and the patient underwent tricuspid valve annuloplasty. Pathological findings from right atrium led to a diagnosis of ATTR-CM, and deoxyribonucleic acid sequence analysis did not indicate any typical mutation, which supported a diagnosis of wild type of ATTR-CM (ATTRwt-CM). She has been asymptomatic after the surgical operation. She has also been treated with 80 mg daily of tafamidis meglumine to prevent further accumulation of transthyretin in the myocardium and potentially improve long-term outcomes.

Discussion Isolated atrial amyloidosis, especially occurring predominantly in the right atrium and caused by ATTRwt-CM without LV hypertrophy, is extremely rare. However, differential diagnosis should be considered for patients with unexplained dilatation of the right-sided heart or bradyarrhythmia.

Keywords Transthyretin amyloid cardiomyopathy • No left ventricular hypertrophy functional tricuspid regurgitation • Right atrial dilatation • Right ventricular dilatation • Case report

ESC Curriculum 2.2 Echocardiography • 4.5 Tricuspid regurgitation • 5.7 Bradycardia • 5.9 Pacemakers • 6.5 Cardiomyopathy

Learning points

- Transthyretin amyloid cardiomyopathy is usually characterized by left ventricular hypertrophy and/or systolic dysfunction.
- Right atrial amyloidosis without left ventricular hypertrophy is extremely rare.
- Amyloidosis should be considered in the differential diagnoses of patients with isolated dilatation of the right chambers of the heart.

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Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) usually presents as left ventricular (LV) hypertrophy, and left atrial dilatation and dysfunction are usually late manifestations of ATTR-CM. The degree of atrial dysfunction was also found to correlate with LV dysfunction, suggesting a natural history of amyloid deposition in atrial and ventricular myocardium.[1] However, isolated atrial amyloidosis, especially when occurring predominantly in the right atrium without LV hypertrophy, leading to severe functional tricuspid regurgitation (FTR) is extremely rare.

Timeline

Date	Events
June 2020	Admitted to our hospital because of exertional dyspnoea and pre-syncope. The 12-lead electrocardiogram showed bradycardia with an ectopic atrial rhythm. Transthoracic echocardiography showed a normal left ventricular (LV) function and no LV hypertrophy. Right ventricular (RV) and right atrial (RA) dilatation were detected, leading to severe functional tricuspid regurgitation (FTR).
July 2020	Implantation of a leadless cardiac pacemaker due to bradycardia.
January 2021	Presented leg oedema and fatigue on effort.
February 2021	Re-admitted to our hospital. Transthoracic echocardiography showed no notable changes in LV function, but progression of RV and RA dilatation. The entire tricuspid valvular coaptation had separated, and severe FTR was worsening.
August 2021	Performed a tricuspid valve annuloplasty using a prosthetic ring.
September 2021	Pathological findings from right atrium led to a diagnosis of transthyretin amyloid cardiomyopathy.
October 2021	DNA sequence analysis did not indicate any typical mutation, which supported a diagnosis of wild type of ATTR-CM.
December 2021	Started to treat with 80 mg daily of tafamidis meglumine.

Case presentation

A 75-year-old female was admitted to our hospital because of exertional dyspnoea and pre-syncope with bradycardia. The patient had a previous history of endoscopic operation for carpal tunnel syndrome 5 years ago and had been used β-blocker eye drops for normal-tension glaucoma for 20 years. On physical examination, blood pressure was 122/76 mmHg, and an irregular pulse was 42 beats/min. Jugular venous dilatation and bilateral leg oedema were observed. A Levine II systolic heart murmur was detected at the right sternal border in the fourth intercostal space, but lung sounds were clear. Chest X-ray showed an increase in the cardiothoracic ratio of 61.8%. The 12-lead electrocardiogram performed at admission showed bradycardia with an ectopic atrial rhythm. Laboratory data revealed elevated brain natriuretic peptide of 306.6 pg/mL (reference interval ≤18.4 pg/mL) and normal high-sensitive troponin I of 9.3 pg/mL (reference interval ≤ 26.2 pg/mL). Transthoracic echocardiography showed a normal LV ejection fraction of 68.9% and LV end-diastolic volume of 39 mL. No LV hypertrophy was observed since the interventricular septum thickness was 8.8 mm, the posterior wall thickness 9.3 mm, and the LV mass index 65.5 g/m^2 (*Figure 1*). Right ventricular (RV) and right atrial (RA) dilatation were detected with an RV basal diameter of 47 mm and RV longitudinal diameter of 66 mm, and an RA transverse dimension of 56 mm and RA longitudinal dimension of 61 mm. RV systolic function was preserved with a tricuspid annular plane systolic excursion (TAPSE) of 21.3 mm, tricuspid lateral annular systolic velocity by tissue Doppler imaging (TDI) of 11.0 m/s, and RV fractional area change (RVFAC) of 32% (*Figure 1*; see Supplementary material online, *Videos S1–S2*). In addition, there was no organic lesion of the tricuspid valve, and severe FTR with maximum TR jet velocity of 2.04 m/s due to RV and RA dilatation was observed (*Figure 1*; see Supplementary material online, *Video S3*). The right heart catheterization showed pulmonary capillary wedge pressure of 6 mmHg, cardiac index of 3.47 L/min/m^2, pulmonary blood pressure of 24/8 mmHg with the mean pulmonary artery blood pressure of 14 mmHg, and pulmonary vascular resistance of 138.2 dyn·s/cm^5. The differential diagnosis of the severe FTR with RV and RA dilation based on the patient's presentation included chronic obstructive pulmonary disease, primary pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, carcinoid syndrome, and arrhythmogenic RV cardiomyopathy. A diagnosis of chronic obstructive pulmonary disease was discarded, because of normal findings on chest computed tomography and spirometry. The pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension were ruled out because of the findings of right heart catheterization and lung perfusion scintigraphy. Carcinoid syndrome was eliminated because of the absence of typical physical findings such as lower abdominal pain, diarrhoea, flushed skin, bronchial asthma, and ovarian findings on computed tomography. Arrhythmogenic RV cardiomyopathy was also eliminated due to her age, no specific signs on the electrocardiogram, and absence of ventricular tachycardia. We provisionally diagnosed the patient's presentation as chronic right heart failure with severe FTR secondary to dilated tricuspid annulus and as an atrial standstill or sick sinus syndrome. She was haemodynamically stable, and the symptoms were mainly due to bradycardia. It was therefore decided to implant a leadless cardiac pacemaker into the RV septum via the right femoral vein approach instead of a conventional pacemaker to avoid further deterioration of TR.

After the implantation, the symptoms improved, and the patient was discharged. However, she complained of leg oedema and fatigue on effort 6 months after discharge. A repeated transthoracic echocardiogram did not show any deterioration in LV systolic function. However, progression of RV and RA dilatation was observed, with an RV basal diameter of 58 mm and RV longitudinal diameter of 75 mm, and an RA transverse dimension of 69 mm and RA longitudinal dimension of 71 mm. Compared with the previous study, TAPSE, tricuspid lateral annular systolic velocity by TDI, and RVFAC worsened to 18.7 mm, 8.5 m/s, and 28.1%, respectively (*Figure 2*; see Supplementary material online, *Video S4*). Furthermore, due to absent tricuspid leaflets coaptation, FTR worsened severe, with a maximum TR jet velocity of 1.90 m/s (*Figure 2*; see Supplementary material online, *Video S5*). The cause of her symptoms was considered to be the severe FTR, and she was treated with loop diuretics of azosemide (30 mg daily). However, her symptoms did not improve over time, and her renal function continued worsening, so that we decided that surgical repair of the tricuspid valve was essential for improving the symptoms as was the performance of an

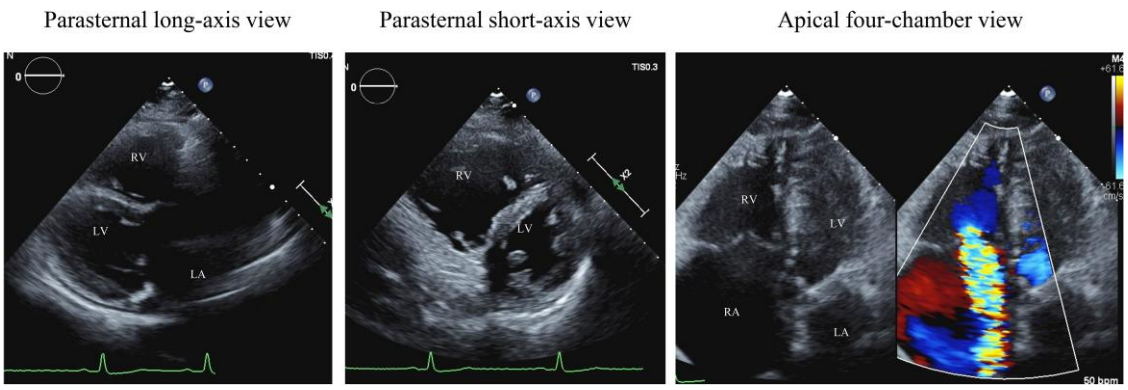


Figure 1 Transthoracic echocardiography at first admission, showing right ventricular and right atrial dilatation, and severe functional tricuspid regurgitation without left ventricular hypertrophy.

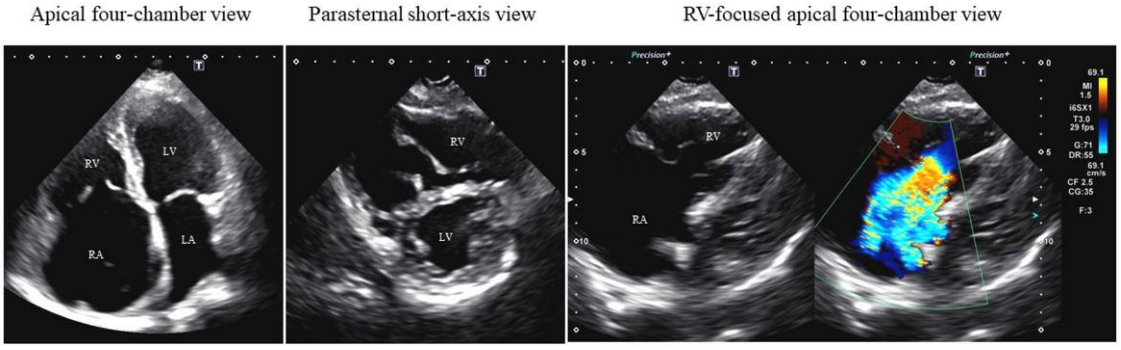


Figure 2 Transthoracic echocardiography at second admission, showing progression of right ventricular and right atrial dilatation, and functional tricuspid regurgitation.

intraoperative tissue biopsy for a correct diagnosis. Totally endoscopic, minimally invasive beating-heart cardiac surgery with right thoracotomy was performed for the tricuspid valvuloplasty. Surgical operative findings showed an enlarged tricuspid valve annulus and some sclerotic shortening at the anterior leaflet. We performed a tricuspid valve annuloplasty using a prosthetic ring as well as a left atrial appendectomy. We also performed a biopsy of a portion of the RV septum and the right atrium for microscopic examination. The operation was successfully performed without any complications, and the post-operative course was uneventful.

Pathological examination of right atrium using haematoxylin-eosin staining did not find any hypertrophy of cardiomyocytes, fibrosis of the myocardial interstitium, inflammatory cell infiltration, or granulomas. However, some vitreous-like eosinophilic tissue deposits were found. These deposits were evident in the endocardium and vessel walls of the right atrium. In addition, direct fast scarlet staining revealed an orange-coloured area with apple green polarization, which was determined to be amyloid deposition. Finally, immunostaining was negative for amyloid A and positive for transthyretin (*Figure 3*). These findings led to a diagnosis of ATTR-CM. However, the ventricular morphology showed that our patient was far from a typical case of ATTR-CM. Cardiac magnetic resonance imaging and ^{99m}Tc-pyrophosphate scintigraphy were also performed to obtain other clinical information. Cardiac magnetic resonance imaging showed an LV ejection fraction of 54% and LV mass index of 55 g/m^2, while gadolinium enhancement delayed imaging showed no delayed contrast in the right atrium and RV or in the LV (*Figure 4*). ^{99m}Tc-pyrophosphate scintigraphy showed grade 1 uptake in the RV and atrium (*Figure 5*), while DNA sequence analysis did not indicate any typical mutation, which supported a diagnosis of wild type of ATTR-CM (ATTRwt-CM). Our patient has been asymptomatic during the follow-up period after the surgical operation. She has also been treated with 80 mg daily of tafamidis meglumine to prevent further accumulation of transthyretin in the myocardium. Careful echocardiographic follow-up will therefore be needed.

Discussion

The survival of patients with ATTRwt amyloidosis was poor that the median survival after diagnosis was only 43–47 months.[2] Although there is no proven therapy for patients with ATTR-CM, a study in 2018 of patients with ATTR-CM found that tafamidis meglumine, a TTR stabilizer, was associated with reductions in all-cause mortality

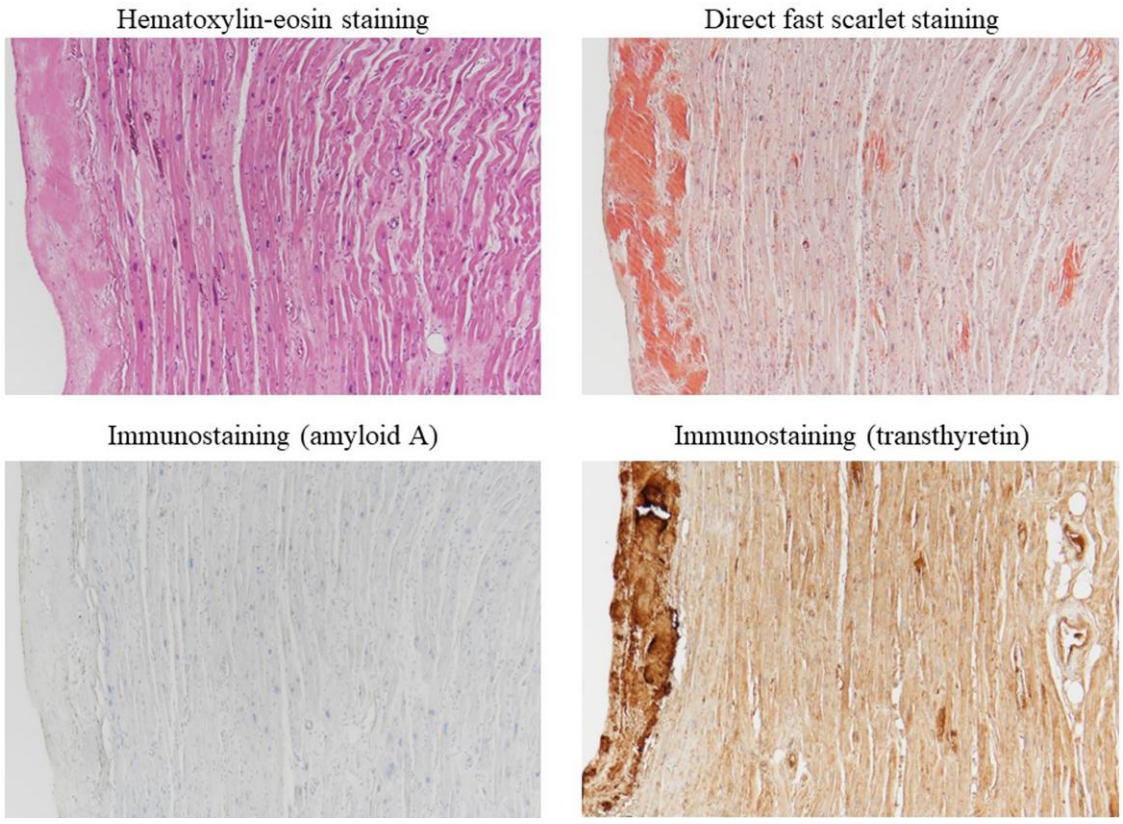


Figure 3 Pathological findings for right atrium led to a diagnosis of transthyretin amyloid cardiomyopathy.

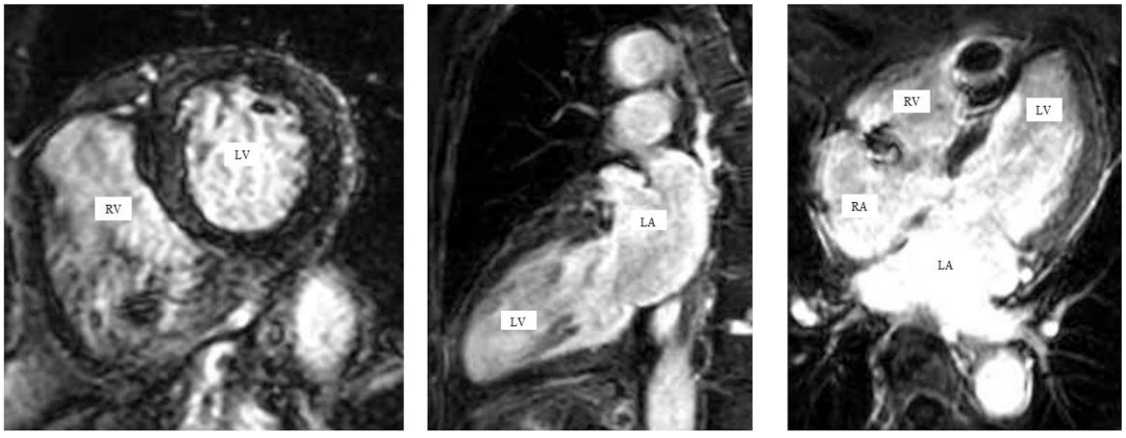


Figure 4 Cardiac magnetic resonance imaging showed normal left ventricular ejection fraction and mass, while gadolinium enhancement delayed imaging showed no delayed contrast.

and cardiovascular-related hospitalizations, as well as with a reduction in the decline in functional capacity and quality of life compared with the effects of a placebo.[3] As a result of these findings, tafamidis meglumine is currently the only drug approved for patients with both ATTRwt-CM and variant ATTR-CM and should be considered for patients whose survival can be reasonably expected.[4] Atrial anomalies by amyloid infiltration are more commonly linked to LV diastolic dysfunction rather than hypertrophy and systolic dysfunction at later stages.[1] The degree of left atrial dysfunction was also found to correlate with LV dysfunction.[1] Moreover, atrial involvement has been

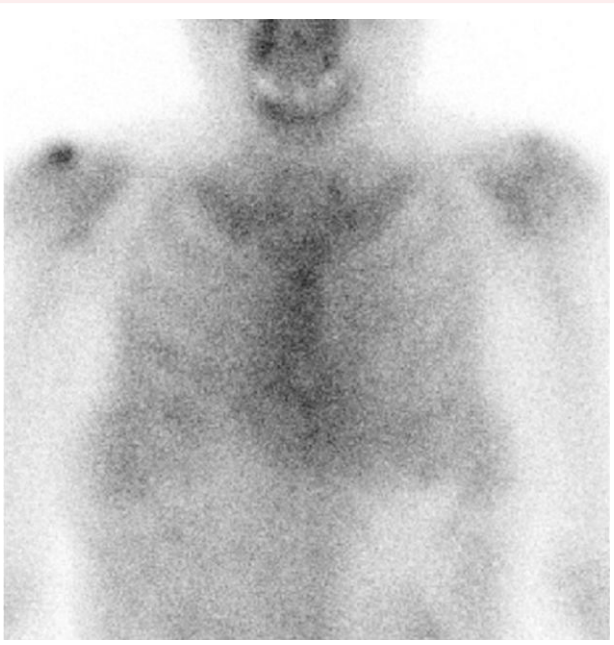


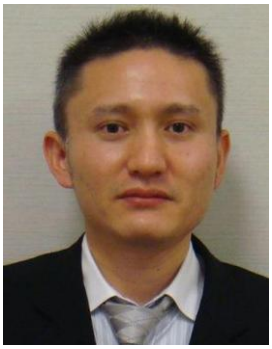
Figure 5 ^{99m}Tc-pyrophosphate scintigraphy showed Grade 1 uptake was detected in the right ventricle and right atrium.

identified as a high risk for the development of atrial fibrillation and the formation of atrial thrombi regardless of sinus rhythm in patients with ATTR-CM.[5] Isolated atrial amyloidosis, especially when occurring predominantly in the right atrium without LV hypertrophy, is extremely rare. In our case, the cause of severe FTR was RV and RA amyloid infiltration, while LV hypertrophy was not observed even in ATTRwt-CM. ^{99m}Tc-pyrophosphate scintigraphy and cardiac magnetic resonance imaging can provide specific images of ATTR-CM. Especially, late gadolinium enhancement is highly prevalent and more common in ATTR-CM. Furthermore, in the disease process, a new quantitative method of T1 mapping and extended extracellular volume imaging may detect amyloid infiltrates earlier than late gadolinium enhancement imaging.[6] Utsunomiya *et al.*[7] reported that atrial fibrillation was an independent exacerbating factor of FTR severity. Comparing these reports with our case, it is reasonable to assume that the RA damage caused by long-standing RA amyloid infiltration had contributed to RA enlargement and FTR as well. The patient was started on tafamidis before amyloid deposition occurred in the LV. Although this may be an earlier-than-usual therapeutic intervention, the administration was initiated to prevent the future development of LV hypertrophy because amyloid deposition was already present in the right-sided heart in this case. To the best of our knowledge, this is the first reported case of severe FTR caused by ATTRwt-CM without LV hypertrophy, with PubMed not listing any cases such as ours up to January 2022.

Conclusions

Isolated atrial amyloidosis, especially occurring predominantly in the right atrium and severe FTR caused by ATTRwt-CM without LV hypertrophy, is extremely rare. However, differential diagnosis should be considered for patients with unexplained dilatation of the right-sided heart or bradyarrhythmia.

Lead author biography



Hiroki Matsuzoe, MD, PhD, is a cardiologist in Yodogawa Christian Hospital, Osaka, Japan. He trained in an echocardiography laboratory at Kobe University Graduate School of Medicine from 2014 to 2018 and earned his doctor of philosophy in medicine (PhD) in 2018. He is an expert in echocardiography, valvular heart disease, cardiomyopathy, and heart failure. He is also currently engaged in the interventional cardiology such as coronary artery disease and vascular disease, and device therapy for cardiac arrhythmias in Yodogawa Christian Hospital.

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 has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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