Multimodality Assessments of Wild-Type Transthyretin Amyloid Cardiomyopathy Presenting With Eccentric Hypertrophy and Aortic Regurgitation

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INTRODUCTION

While patients with transthyretin (TTR) cardiac amyloidosis (CA) typically present with concentric or asymmetric hypertrophy, a small percentage of patients with TTR-CA are known to present with atypical cardiac morphologies such as eccentric hypertrophy or even no hypertrophy. However, detailed reports of multimodality assessment of TTR-CA with atypical morphology are lacking. Herein, we report a case of a 70-year-old man who was initially referred to our institution for aortic regurgitation (AR) with left ventricular (LV) dilatation and dysfunction; detailed multimodality assessments led to a diagnosis of wild-type TTR-CA with eccentric hypertrophy and moderate AR.

CASE PRESENTATION

A 70-year-old man with a history of spinal canal stenosis and no cardiac history was referred to our institution for dyspnea on exertion, with an initial diagnosis of AR and LV dysfunction. The patient was in New York Heart Association functional class II. On physical examination, blood pressure was 104/56 mm Hg, heart rate was 78 bpm, respiratory rate was 16/min, and oxygen saturation (room air) was 98%. Cardiac auscultation revealed a Levine grade 2 diastolic murmur at the third intercostal space of the left sternal border. Electrocardiogram (Figure 1A) showed normal sinus rhythm with LV hypertrophy. Chest x-ray (Figure 1B) showed cardiomegaly. Laboratory findings revealed a B-type natriuretic peptide of 416 pg/mL (reference range, <18.4 pg/mL) and troponin T of 0.041 ng/mL (reference range, <0.014 ng/mL).

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Transthoracic echocardiography showed an LV end-diastolic/end-systolic diameter of 73/62 mm, interventricular septum/LV posterior wall thickness of 10/10 mm compatible with eccentric hypertrophy (LV mass index, 164 g/m²; relative wall thickness, 0.25), and LV ejection fraction of 39% by modified Simpson’s method (Figure 2A and B). Global longitudinal peak systolic strain was –7.2%, and its distribution showed an apical sparing pattern (Figure 2C). Right ventricular (RV) hypertrophy was observed (RV free wall thickness, 6 mm) with a normal RV fractional area change of 48% (Figure 2D and E, Videos 3 and 4). Left atrial volume index (LAVI), atrial septal hypertrophy, and reduced LV systolic function.

Video 1: Transthoracic echocardiography parasternal long-axis view demonstrates dilated left ventricle (LV) with eccentric hypertrophy and reduced systolic function.

Video 2: Transthoracic echocardiography apical 4-chamber view demonstrates biventricular hypertrophy, dilated left atrial volume index (LAVI), atrial septal hypertrophy, and reduced LV systolic function.

Video 3: Transthoracic echocardiography subcostal view confirms the RV hypertrophy.

Video 4: Transthoracic echocardiography RV focused apical 4-chamber view showed RV hypertrophy and normal RV fractional area change of 48%.

Video 5: Transthoracic echocardiography apical 5-chamber view with color flow Doppler demonstrates moderate eccentric AR.

Video 6: Transthesophageal echocardiography X-plane display of the trileaflet aortic valve revealed malcoaptation and degeneration of the right coronary cusp.

Video 7: Transesophageal echocardiography zoomed 136° view with color Doppler showed an eccentric AR jet toward the anterior mitral leaflet.

Video 8: Contrast aortography from the right anterior oblique view showed Sellers grade 2 AR.

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Figure 1  (A) A 12-lead electrocardiogram demonstrated normal sinus rhythm with LV hypertrophy. (B) Chest x-ray revealed cardiomegaly without evidence for a pleural effusion.

Figure 2 Transthoracic echocardiography. Parasternal long-axis view (A) and apical 4-chamber view (B) showed eccentric hypertrophy. (C) Global longitudinal strain was –7.2%, and its distribution showed an apical sparing pattern. Subxiphoid view (D) and RV focused apical 4-chamber view (E) showed RV hypertrophy (arrows). (F) An eccentric AR jet graded as moderate was observed.
Regurgitant orifice area of approximately 0.23 cm² using the proximal isovelocity surface area method.

Transesophageal echocardiography revealed malcoaptation of the aortic valve due to degenerative change of the right coronary cusp, resulting in an eccentric AR jet on color flow Doppler (B) toward the anterior mitral leaflet. (C) Diastolic flow reversal with pulsed-wave Doppler was intermediate in the descending aorta. (D) Thickening of the interatrial septum (arrows) was observed in the bicaval view. Three-dimensional imaging with color flow (E) revealed a vena contracta area of 0.23 cm².

As Doppler methods may have underestimated the severity in eccentric AR jets, we performed aortography to confirm the AR severity, which showed Sellers grade 2 AR (Figure 4A, Video 8). Coronary angiography showed no significant coronary stenosis (Figure 4B).

Although the moderate AR may have affected the LV morphology, we assessed that the patient’s LV dilatation and dysfunction could not be explained solely by AR; thus, further analysis was performed with a suspicion of concomitant cardiomyopathy. Cardiovascular magnetic resonance (CMR) showed midseptal and inferoseptal hypertrophy.
diffuse late gadolinium enhancement of the left and right ventricles (Figure 5B), prolonged native T1 relaxation time of 1,487 ms (Figure 5C), and increased extracellular volume fraction of 58.1% (Figure 5D), which suggested the possibility of CA. Regurgitant fraction of AR using phase-contrast CMR was 37.8%, which was also in the moderate range (Figure 5E-G).

Technetium-pyrophosphate ($^{99m}$Tc-PYP) scintigraphy performed at 3 hours after injection revealed grade 3 uptake with a heart/contralateral ratio of 1.65 on planar image, and single photon emission computed tomography confirmed myocardial uptake (Figure 6A). Serum-free light chain assay results were within normal limits, and serum/urine protein electrophoresis with immunofixation showed no monoclonal proteins.

As the LV morphology was not typical for TTR-CA, we performed endomyocardial biopsy, which confirmed amyloid deposits by Congo red staining with apple-green birefringence under polarized light and positive immunohistochemical staining for TTR (Figure 6B). A TTR gene analysis showed no variant.

With a diagnosis of wild-type TTR-CA, the patient has been treated with tafamidis, angiotensin II receptor antagonist, diuretics, and low-dose β-blocker and has had no acute heart failure events for 24 months since diagnosis. Moderate AR has been followed up annually, and his cardiac function and AR have shown no significant worsening (LV end-diastolic/end-systolic diameter of 73/64 mm, LV ejection fraction of 34%, and moderate AR at 12 months; LV end-diastolic/end-systolic diameter of 72/60 mm, LV ejection fraction of 37%, and moderate AR at 24 months).

**DISCUSSION**

We report an elderly man who presented with an initial diagnosis of AR with LV dilatation and dysfunction who was eventually diagnosed as having wild-type TTR-CA with eccentric hypertrophy and moderate AR, using multimodality assessments.

Recent studies have shown that TTR-CA is underdiagnosed in elderly heart failure patients, including a prevalence around 8%-16% of aortic stenosis referred for transcatheter aortic valve replacement. Our case emphasizes that in patients with cardiac morphology that is not explained solely by the severity of the valvular
disease, the possibility of concomitant cardiomyopathy including TTR-CA should be considered. We evaluated that the severity of AR was moderate and that AR alone could not explain the LV dilatation and dysfunction; however, the patient had no previous cardiac history and the time course of AR could not be determined. We believe that previously existing AR could have contributed to the eccentric hypertrophy. Furthermore, it should be taken into account that Doppler methods may underestimate the severity of AR in eccentric jets. As performed in our case, evaluating severity using multimodality imaging including aortography, phase-contrast CMR, and vena contracta area using three-dimensional Doppler echocardiography may be useful to provide further information on AR severity.9,10

Use of multimodality imaging has changed the diagnosis of TTR-CA over the last decade. Echocardiography is not only essential for evaluating cardiac function and morphology but also may reveal a relative apical sparing pattern with speckle-tracking. This pattern, although not diagnostic, has been shown to be common in CA and may help to differentiate this from other cardiomyopathies with ventricular hypertrophic morphologies.11,12

Bone scintigraphy, together with the absence of monoclonal proteins, has high sensitivity and specificity in diagnosing TTR-CA and has become the key approach for establishing nonbiopsy diagnosis of TTR-CA.13-15 Cardiovascular magnetic resonance evaluation (with late gadolinium enhancement and extracellular volume estimation) has been accepted as one of the imaging criteria for CA diagnosis and has also been shown to be useful for prognostic stratification of CA.3,14,15

Detailed reports of multimodality assessments of TTR-CA with atypical morphology are lacking, and it is not easy to screen and diagnose

Figure 5 Cardiovascular magnetic resonance imaging. (A) Four-chamber (left) and short-axis (right) steady-state free precession cine images in end diastole showed a dilated left ventricle as well as mild midseptal and inferoseptal hypertrophy (arrows). (B) Diffuse late gadolinium enhancement was observed in both the LV and RV myocardium. (C) Native T1 relaxation time was prolonged at 1,487 ms. (D) Extracellular volume fraction was increased to 58%. (E-G) Phase-contrast flow measurement in the ascending aorta. Magnitude image (E), phase-encoded image (F), and flow-over-time graph (G) showed that the regurgitant fraction of the AR was 38% (moderate).
atypical TTR-CA. Our report suggests that CMR and bone scintigraphy including 99mTc-PYP scintigraphy may be useful for diagnosing TTR-CA even in patients with atypical cardiac morphologies.

CONCLUSION

In patients with cardiac morphology unexplained by the severity of the valvular disease, the possibility of concomitant cardiomyopathy including TTR-CA should be considered, especially in elderly patients with heart failure. A small percentage of TTR-CA cases present with atypical cardiac morphologies including eccentric hypertrophy or even no hypertrophy, and our report also suggests that CMR and bone scintigraphy including 99mTc-PYP scintigraphy may be useful for screening and diagnosing TTR-CA even in patients with atypical cardiac morphologies.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2022.04.003.

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