Persistent Left Ventricular Wall Thickening after Transcatheter Aortic Valve Replacement: A Hidden Cardiomyopathy

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INTRODUCTION

Amyloid heart disease is an underdiagnosed cause of heart failure. Wild-type transthyretin amyloidosis (ATTRwt), a subtype of amyloid heart disease, sometimes coexists with aortic stenosis (AS) because of their similar demographic characteristics, and the prevalence of both increases with age.[1,2] Although transcatheter aortic valve replacement (TAVR) is an established treatment for patients with AS, coexistent ATTRwt may be associated with a poor outcome after TAVR.[3] We report a complicated case of severe AS with ATTRwt, which was diagnosed after TAVR.

CASE PRESENTATION

A 90-year-old man with severe AS presented to our hospital with dyspnea of New York Heart Association functional class IV. Other medical history included paroxysmal atrial fibrillation and hypertension. Eight years prior, initial transthoracic echocardiography (TTE) revealed mild AS with a peak velocity of 2.3 m/sec and preserved left ventricular systolic function with an ejection fraction (EF) of 66% (Table 1). Initial electrocardiography showed normal sinus rhythm without any abnormalities. AS gradually progressed, and he had three subsequent admissions for heart failure.

Chest auscultation revealed a systolic ejection murmur (Levine grade 4/6) at the right upper sternal border radiating to the neck. Electrocardiography showed sinus rhythm with first-degree atrioventricular block and ST-segment depression in leads I, aVL, V_4, V_5, and V_6. TTE revealed severe AS due to a calcified aortic valve (peak velocity 4.3 m/sec, mean gradient 46 mm Hg, calculated aortic valve area 0.3 cm^2; Figure 1, Table 1). Global left ventricular systolic function was reduced, with an EF of 47% by the biplane method of disk summation and a stroke volume index of 23 mL/m^2. TTE also showed severe diastolic dysfunction, with a ratio of early diastolic mitral wave velocity to mitral annulus velocity (E/e′) of 30, increased left ventricular wall thickness, and a small pericardial effusion (Figure 2, Video 1, Table 1). The left atrium was moderately enlarged, with a left atrial volume index of 42 mL/m^2. Coronary angiography showed no significant coronary artery disease.

Although the patient had previously refused aortic valve replacement for progressive AS, he decided at this time to undergo surgery. The patient was deemed to be at high risk for a surgical aortic valve replacement, with a Society of Thoracic Surgeons score of 14%. Therefore, he was referred for TAVR and consented to the transcatheter treatment.

Transfemoral TAVR was achieved without any complications; however, the patient was readmitted for decompensated heart failure with dyspnea and peripheral edema after 2 weeks of TAVR. Electrocardiography showed sinus rhythm with complete left bundle branch block. TTE revealed recovered systolic function with an EF of 61%. AS was reduced, with a peak velocity of 1.5 m/sec, and the prosthetic valve worked correctly. In contrast, diastolic dysfunction and left ventricular wall thickening were comparable with preoperative records (Figure 3, Video 2, Table 1).

The patient was an older man with atrial fibrillation, pericardial effusion, significant cardiac diastolic dysfunction, and left ventricular wall thickening. Given these findings, we suspected ATTRwt. We reevaluated TTE with speckle-strain imaging and performed ^{99m}Tc pyrophosphate (PYP) cardiac scintigraphy soon after this post-TAVR admission. Speckle-strain imaging showed an "apical-sparing pattern" with global longitudinal strain of −17.3% and a relative regional strain ratio of 2.08 (Figure 4). ^{99m}Tc PYP cardiac scintigraphy showed intense myocardial uptake of the isotope on planar imaging; his heart-to-contralateral ratio was 1.93, and the semiquantitative visual score of cardiac retention was grade 2 (Figure 5). Given his sex, age, and the findings on TTE and ^{99m}Tc PYP cardiac scintigraphy, the patient was diagnosed with ATTRwt. Furthermore, we analyzed transthoracic echocardiographic examinations retrospectively. The apical-sparing pattern was, surprisingly, present 8 years before TAVR, with a relative regional strain ratio of 1.71 (Figure 6).

Although the patient's symptoms diminished with medication therapy, his ability to perform activities of daily living gradually worsened. The patient was transferred to a hospice care unit, where he died of sudden cardiac arrest 7 months after TAVR.

DISCUSSION

Amyloid heart disease is a devastating cause of heart failure. In particular, it is an underrecognized cause of heart failure with preserved EF. ATTRwt was recently discovered in 13% of patients with heart failure with preserved EF with left ventricular wall thickening.[4]

As the first manifestation, our patient showed mild low-flow (LF) AS with heart failure with preserved EF. TTE revealed normal diastolic function. Eight years later, he was treated using TAVR for progressive severe AS with LF/high-grade condition. Despite successful treatment, his condition rapidly deteriorated and he was admitted within

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VIDEO HIGHLIGHTS

Video 1: TTE on admission before TAVR. Parasternal long-axis view, showing reduced left ventricular systolic function, left ventricular wall thickening, and a small pericardial effusion behind the posterior wall.

Video 2: TTE on admission 2 weeks after TAVR. Parasternal long-axis view, showing recovered left ventricular systolic function with an EF of 61% and persistent left ventricular wall thickening.

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Table 1 Comparison of echocardiographic measurements before and after TAVR

	Initial TTE	Preoperative	Postoperative	Postoperative
	8 years before TAVR	2 weeks before TAVR	2 weeks after TAVR	4 months after TAVR
LAVI, mL/m^2	-	42	52	50
LVEF, %	66	47	61	47
IVS, mm	10	13	17	12
LVMI, g/m^2	72	140	160	120
E/e′	12	30	31	34
AV mean gradient, mm Hg	10	46	4	4
LVOT VTI, cm	14	11	17	15
SVI, mL/m^2	29	23	41	36

AV, Aortic valve; *IVS*, interventricular septum; *LAVI*, left atrial volume index; *LVEF*, left ventricular EF; *LVMI*, left ventricular mass index; LVOT, left ventricular outflow tract; *SVI*, stroke volume index; *VTI*, velocity-time integral.
Initial TTE showed mild AS with LVEF and normal diastolic function. Preoperative TTE (2 weeks before TAVR) showed LF/high-grade AS with severe diastolic dysfunction. Postoperative TTE (2 weeks after TAVR) showed recovered LVEF, but diastolic dysfunction was comparable with preoperative records. Following postoperative TTE (4 months after TAVR) showed reduced LVEF and retained diastolic dysfunction.

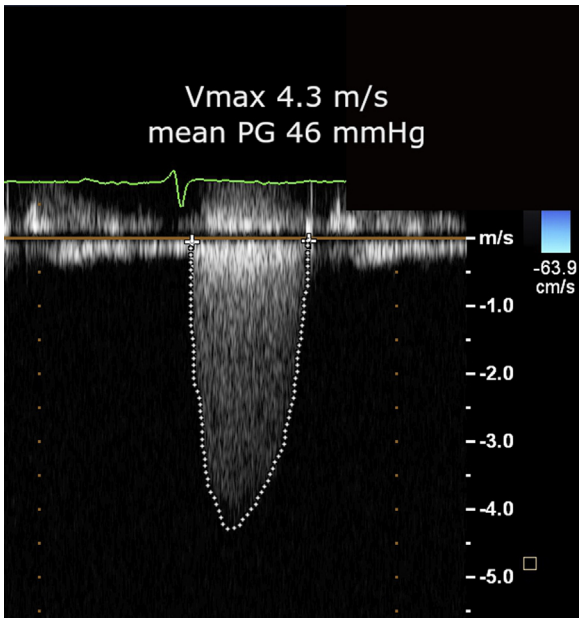

Figure 1 Continuous-wave Doppler showing an aortic valve peak velocity of 4.3 m/sec and a mean pressure gradient (PG) of 46 mm Hg.

1 month. ATTRwt was later diagnosed using ^{99m}Tc PYP cardiac scintigraphy postoperatively, and the patient died 7 months after TAVR.

Several reports describe the coexistence of AS and ATTRwt.[5,6] AS and ATTRwt share similar demographic and clinical profiles. Both increase with age, causing excessive left ventricular wall thickening and diastolic dysfunction leading to heart failure.[1,2] Although left ventricular wall thickening is observed in each disorder, the mechanisms are thought to be different. AS shows left ventricular hypertrophy (LVH) compensating for pressure overload, accompanied by interstitial myocardial fibrosis. ATTRwt shows interstitial expansion by extracellular amyloid deposition. As echocardiographic appearance is similar, ATTRwt can often be overlooked in patients with AS.

Recently, TAVR has become an important innovation that provides treatment for high-risk surgical patients with severe AS. Despite benefiting from TAVR, compared with medical therapy, there remains a sizable group of patients who die soon after TAVR because of a lack of improvement in the quality of life.[7] ATTRwt is thought to be associated with poor outcomes in patients undergoing TAVR.[3] In terms of prognosis and cost-effectiveness, the indication of patients with AS and ATTRwt for TAVR warrants further investigation to prevent futile TAVR.

The detection of cardiac amyloidosis is still challenging. The established criteria for a diagnosis of cardiac amyloidosis required an endomyocardial biopsy; however, a noninvasive multimodality imaging system, consisting of echocardiography, cardiac scintigraphy, and cardiac magnetic resonance, now plays an important role in diagnosis. Regarding echocardiography, the apical-sparing appearance of longitudinal strain using two-dimensional speckle-tracking echocardiography (STE) could be a sign of cardiac amyloidosis. Phelan *et al.*[8] reported that apical sparing could distinguish cardiac amyloidosis from other causes of LVH, AS, and hypertrophic cardiomyopathy with 93% sensitivity and 82% specificity. As well as two-dimensional STE, cardiac scintigraphy can be used to make the diagnosis, as it is highly sensitive and specific for the identification of ATTRwt. Gillmore *et al.*[9] reported that cardiac scintigraphy was a reliable modality with >99% sensitivity and 86% specificity for cardiac amyloidosis. These noninvasive modalities can predict prognosis and detect amyloid deposits before heart failure becomes obvious.

In our patient, there was an apical-sparing appearance 8 years before TAVR. Since then, the patient had been hospitalized three times for heart failure. If a two-dimensional STE (unavailable at our institution at that time) could have been performed at initial TTE, ATTRwt would have been suspected, and further examinations would have been done. Although TTE was repeatedly performed at every admission after initial TTE, we did not suspect coexistent ATTRwt and believed that progressive AS was the only cause of the recurrent heart failures.

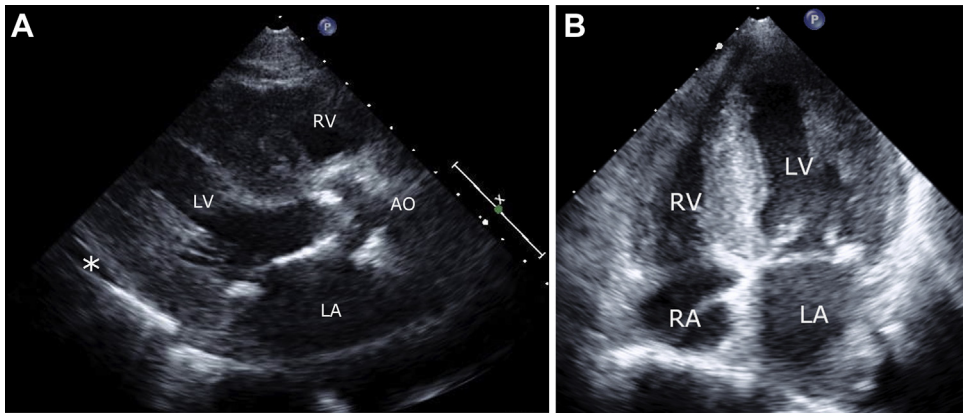

Figure 2 TTE on admission before TAVR. **(A)** Parasternal long-axis view, showing left ventricular wall thickening and a small pericardial effusion behind the posterior wall (*asterisk*). **(B)** Apical four-chamber view, showing left ventricular wall thickening and left atrial dilatation. *AO*, Aorta; *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

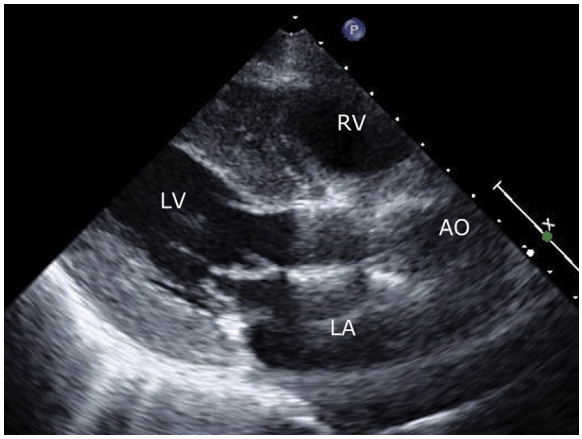

Figure 3 TTE on admission 2 weeks after TAVR. Parasternal long-axis view showing progressive left ventricular wall thickening. The prosthetic valve worked correctly. *AO*, Aorta; *LA*, left atrium; *LV*, left ventricle; *RV*, right ventricle.

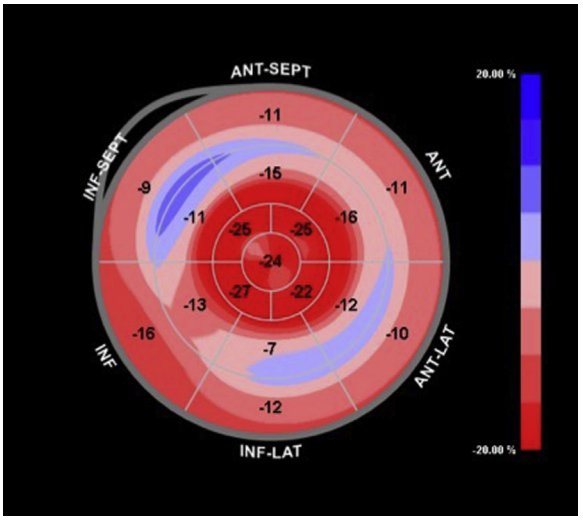

Figure 4 Longitudinal strain analysis of TTE after TAVR, showing reduced global longitudinal strain (−17.3%) with apical-sparing pattern. Relative regional strain ratio was 2.08. *ANT*, Anterior; *ANT-LAT*, anterolateral; *ANT-SEPT*, anteroseptal; *INF*, inferior; *INF-LAT*, inferolateral; *INF-SEPT*, inferoseptal.

Recognizing ATTRwt before TAVR is crucial. Coexistent ATTRwt can affect therapeutic decision-making. Sperry *et al.*[10] compared 27 patients with transthyretin cardiac amyloidosis (ATTR) with moderate to severe AS and 144 patients with ATTR without AS. They reported that there was no difference in mortality between the two groups, suggesting that ATTR is strongly associated with morbidity rather than coexistent AS and AS treatment. Aortic valve replacement may not improve mortality in patients with ATTR with AS. Another previous study showed that patients with AS with ATTRwt were more likely to have LF/low-gradient (LG) AS than patients without ATTRwt; additionally, LF/LG status carries a poor prognosis.[11] Furthermore, LF/LG and LF/high-grade AS were identified as strong independent determinants of poor prognosis in patients with severe AS.[12] Before TAVR, the coexistence of ATTR and the flow/grade status of AS should be considered.

In detecting ATTRwt, clinicians should be aware of the following signs. Patients with ATTRwt tend to be older and to present with peripheral manifestations, such as carpal tunnel syndrome or macroglossia. Electrocardiographic signs include arrhythmias, such as low voltage and atrial fibrillation. Echocardiographic signs include apical sparing, reduction in longitudinal strain, pericardial effusion, granular sparkling myocardium, left ventricular wall thickening, and severe diastolic dysfunction, which seems out of proportion to regular LVH. Clinicians should recognize these signs to detect coexisting ATTRwt in patients with AS.

In this case, electrocardiographic transitions with paroxysmal atrial fibrillation and atrioventricular block appeared during the 8-year period between initial TTE and TAVR. Pre-TAVR TTE showed all of the signs just mentioned, including an anatomic change in the left ventricle with granular sparkling myocardium and notable worsening of diastolic dysfunction from a normal to severe range.

In terms of the limitations of this case, ATTRwt was diagnosed not by biopsy but by cardiac scintigraphy. However, the utility of cardiac scintigraphy in diagnosing ATTRwt has been established.[9] Another limitation is that ATTRwt was undiagnosed at the time of the initial TTE and before TAVR, and the diagnosis was delayed until after TAVR.

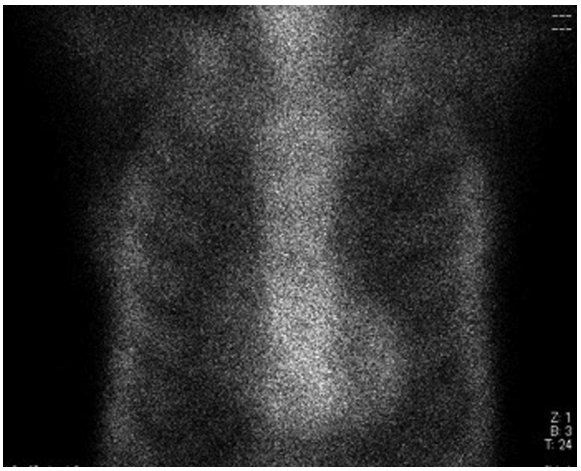

Figure 5 ^{99m}Tc PYP cardiac scintigraphy showing intense myocardial uptake of the isotope on planar imaging; the heart-to-contralateral ratio was 1.93, and the semiquantitative visual score of cardiac retention was grade 2.

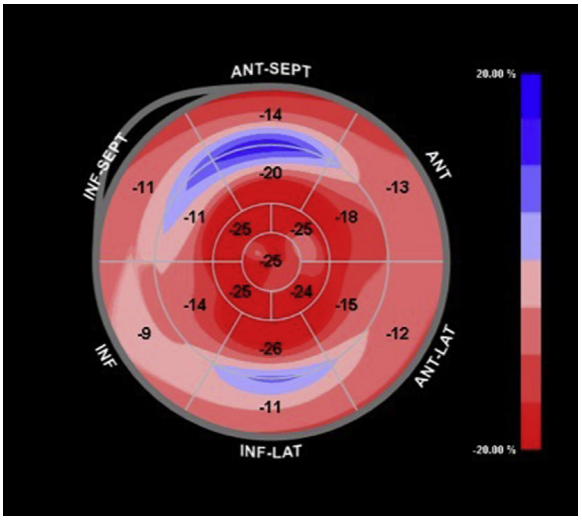

Figure 6 Longitudinal strain analysis of initial TTE 8 years before TAVR, showing reduced global longitudinal strain (−18.9%) with apical-sparing pattern. Relative regional strain ratio was 1.71. *ANT*, Anterior; *ANT-LAT*, anterolateral; *ANT-SEPT*, anteroseptal; *INF*, inferior; *INF-LAT*, inferolateral; *INF-SEPT*, inferoseptal.

This case highlights the potential coexistence of ATTR in patients with severe AS. Sufficient caution is required for the patients with AS who are candidates for TAVR, and noninvasive imaging modalities including echocardiography and cardiac scintigraphy are desirable for screening for coexistent ATTRwt. The advent of new agents makes the identification of ATTRwt imperative. Two-dimensional STE should be a standard part of the echocardiographic evaluation of LVH, especially if there is LF/LG AS. Still, quantitative evaluation of ATTRwt severity is difficult. It is unclear how coexistent ATTRwt influences the prognosis of AS patients. Further investigations are needed to reveal the prognosis of AS patients with ATTRwt.

CONCLUSION

We report a complicated case of severe AS with ATTRwt. Our case highlights the potential coexistence of ATTR in patients with severe AS. Noninvasive multimodality imaging systems with STE and cardiac scintigraphy should be performed to screen for ATTRwt in patients with AS who are TAVR candidates.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2020.03.005.

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