Correct Diagnosis of Wild-Type Transthyretin-Related Amyloidosis Followed by the Introduction of a Novel Therapy in a Patient With Cardiac Wall Thickening of Unknown Cause

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Summary

We report here the case of a 67-year-old man who was initially diagnosed with myocardial hypertrophy with progressive hypertensive heart disease. After 6 years a cardiac biopsy was conducted because of changes in the electrocardiogram and transthoracic echocardiogram results, revealing amyloid deposition. Additional genetic studies revealed no TTR gene mutations, leading to a definitive diagnosis of wild-type transthyretin-related amyloidosis (ATTR). The patient started taking diflunisal as a stabilizer which is one of the advanced therapies for ATTR, and then the heart failure symptoms and brain natriuretic peptide (BNP) level improved in short-term follow-up. We present an elderly patient with ATTR, which is believed to be rare. We also discuss the apparent efficacy of novel therapeutic agents that increase the incentive to diagnose ATTR at an early stage. Therefore, we should always consider the existence of cardiac amyloidosis when we initiate the management of an elderly patient with cardiac wall thickening. (Int Heart J 2017; 58: 147-150)

Key words: Amyloid deposition, Biopsy, Transthoracic echocardiogram, Cardiac amyloid, Senile systemic amyloidosis

Cardiac wall thickening in elderly patients with or without heart failure is not a rare condition. The morbidity of left ventricular hypertrophy in adults who are free of cardiovascular disease is 19%. Because the most common causes of cardiac wall thickening are systemic hypertension and valvular diseases including aortic stenosis, wall thickening in elderly patients has a high probability of hypertrophy secondary to cardiovascular disorders. Otherwise, the prevalence of cardiac amyloidosis which is often incorrectly described as hypertrophy is rare. Here we present a case of ATTR diagnosed in the course of left ventricular hypertrophy treatment and in which we were able to safely induce diflunisal intake, a type of advanced therapy.

Case Report

A 67-year-old man with type 2 diabetes and hypertension was initially diagnosed with asymptomatic cardiac hypertrophy in our hospital. The patient was a non-smoker with occasional alcohol consumption. He had no family history of cardiovascular disease but had an allergy to aspirin. An electrocardiogram (ECG) revealed a complete right bundle branch block (Figure 1A). A transthoracic echocardiogram (TTE) showed increased wall thickness (diastolic septal thickness, 14–16 mm) with unclear high echogenicity, normal diastolic function with a ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (‘e’, E/e’ ratio) of 11.1, and preserved left ventricular ejection fraction (EF; 70%) (Figure 1B). Three years later, the patient was hospitalized because of an exacerbation of congestive heart failure with new onset atrial fibrillation. TTE revealed wall thickening (diastolic septal thickness, 19 mm) with diffuse hypokinesis (EF; 47%). Coronary computed tomography (CT) showed moderate stenosis in the left anterior descending coronary artery, and drug therapy was initiated. Because of the history of hypertension as well as no remarkable appearance of high echogenicity in the cardiac wall by TTE, the patient was diagnosed with myocardial hypertrophy with progressive hypertensive heart disease. The patient was discharged and instructed to undergo an echocardiogram on a regular basis; he received conservative treatment that consisted of diuretic, β-blocker, and angiotensin-converting-enzyme inhibitor drugs. When the patient was 72 years old, he underwent percutaneous coronary intervention (PCI) because of findings suggestive of cardiac ischemia in stress myocardial scintigraphy. The patient’s course thereafter was clinically stable without any change in cardiac wall thickening or motion; however, lowering of the QRS voltage gradually progressed as observed by ECG.

A year after PCI, the patient was admitted for progressive dyspnea worsening over the prior two weeks, and his functional status was estimated to be New York Heart Association Class IV. In a physical examination, blood pressure was 130/70 mmHg, heart rate was 30 beats/minute, and oxygen saturation...
was 95% in room air. Otherwise, the physical examination was unremarkable. There were no co-existing symptoms including carpal tunnel syndrome. The ECG revealed low voltage and junctional rhythm with a ventricular rate of 30 beats/minute (Figure 1C). Chest X-rays showed cardiac dilatation and bilateral pleural effusion. Serum values of blood urea nitrogen and creatinine were 39.7 mg/dL and 1.7 mg/dL, respectively, and the plasma concentration of BNP was 500.5 pg/mL. The patient was diagnosed with congestive heart failure induced by bradycardia and underwent temporary pacemaker implantation. TTE showed bi-ventricular wall thickening with an interventricular septal thickness of 19 mm with granular sparkling

**Figure 1.** Changes in ECG and TTE. A: Electrocardiogram (ECG) 6 years before the second admission. B: Transthoracic echocardiogram (TTE) 6 years before the second admission. C: ECG at the second admission. D: TTE at the second admission. The low QRS voltage observed on ECG and high echogenicity in the cardiac wall as evidenced by TTE were noteworthy emerging clinical findings in the second admission at our hospital.

**Figure 2.** Myocardial biopsy analysis. A: Hematoxylin and eosin staining. B: Congo red staining. C: Direct fast scarlet staining (high-power field). D: Immunohistochemical staining for transthyretin.
Correct Diagnosis of Elderly with Amyloidosis

(Figure 1D), lowered left ventricular EF of 27%, and elevated E/e’ ratio of 52.4. A coronary angiogram showed neither in-stent restenosis nor native coronary lesions. The changes in ECG and TTE parameters prompted us to perform a right ventricular biopsy, and biopsied sections with hematoxylin and eosin staining, Congo red staining, and direct fast scarlet staining clearly revealed amyloid deposition (Figure 2A, B and C). Immunohistochemical analysis revealed that the amyloids were derived from transthyretin (TTR) accumulation (Figure 2D). At this point, the patient was diagnosed with TTR type amyloidosis. Considering that the additional genetic test on the TTR gene revealed no mutations, a definitive diagnosis of wild-type ATTR was established. After the regular medication for heart failure, the patient successfully recovered and was discharged on the 22nd day after the admission; however, his BNP level gradually increased after leaving the hospital. He was scheduled to receive the administration of diflunisal, a known TTR-tetramer stabilizer. According to rules of the Ethics Committee at the University of Tokyo, informed consent for the diflunisal treatment for ATTR was obtained. Two months after taking diflunisal 500 mg daily, the exertional shortness of breath had improved and the BNP level decreased from 396.0 pg/dL to 310.4 pg/mL (Figure 3). Echocardiography also showed the improvements of systolic function (EF, 46%) and diastolic function (E/e’ ratio, 33.3). The patient was kept on a low dose of diflunisal (250 mg daily) with an average BNP level of 400 pg/dL because the creatinine level became slightly elevated after taking high doses diflunisal. We lowered the dosage level of diflunisal and no adverse events were observed for 6 months after starting the diflunisal treatment.

Discussion

Amyloidosis is a rare systemic disease caused by the deposition of abnormal fibrils in the extracellular matrix. Cardiac amyloidosis leads to cardiac wall thickening, heart failure, and various arrhythmias. Because of its low prevalence, amyloidosis is often overlooked. The diagnosis is made by confirming amyloid deposition in myocardial biopsy specimens. Wild-type ATTR is a systemic amyloidosis caused by deposition of wild-type TTR in affected organs. According to recent reports, TTR deposition can be observed in 25% of autopsied elderly aged > 80 years and 37% of autopsied elderly aged > 95 years. Patients with the disease are usually present with cardiovascular symptoms and carpal tunnel syndrome. The first appearance of cardiac manifestations is atrial fibrillation, followed by heart failure. Correct diagnosis of amyloidosis in the elderly, however, poses complex problems. Usually, the clinical course in the elderly is suggestive of cardiovascular diseases due to atherosclerosis and/or hypertension, which may unlikely urge physicians to speculate that increased cardiac wall thickening was caused by amyloid deposition. Sometimes the typical characteristics of amyloidosis cannot be observed at its early stage. Moreover, most physicians hesitate to perform an endomyocardial biopsy, which is currently the only approach for a definite diagnosis of cardiac amyloidosis, because an endomyocardial biopsy is associated with a non-negligible risk of complications. The late gadolinium enhancement by cardiac magnetic resonance is one of the tools used to reach the diagnosis of cardiomyopathy, but it could not be used in this case because of an existing pacemaker implantation. Cardiac amyloidosis remains to be rarely diagnosed and recognized because of the diversity in its clinical course, the diagnostic work-up involving invasive procedures, and that
vastly no therapy established is effective for amyloidosis; hence, wild-type ATTR is mostly a post mortem diagnosis.

Recently, research on drugs for amyloid fiber formation has been conducted.\textsuperscript{7,8} The TTR usually forms a tetramer, functioning as a carrier protein for thyroxine and retinol binding. However, it is speculated that mutated TTR is relatively unstable and easily forms misfolded monomers, leading to fiber formation. Diflunisal and tafamidis have been shown to be effective as TTR-tetramer stabilizers. These drugs are expected to prevent TTR amyloid production and are well-tolerated.\textsuperscript{8} We speculated these drugs may also be effective against wild-type ATTR, which is caused by the accumulation of wild-type TTR. There are only a few reports about oral diflunisal treatment for wild-type ATTR, but we plan to use diflunisal in the present case because of its safety and potential for efficacy.\textsuperscript{2} The heart failure of this case improved after oral intake of diflunisal. However, diflunisal appeared to induce an elevation in serum creatinine so we reduced the daily diflunisal dose. Diflunisal is traditionally classed as a non-steroidal anti-inflammatory drug; therefore, deterioration of renal function is one of the major side effects of diflunisal treatment. Continuous careful monitoring is needed to assess the effect of diflunisal treatment and further study in a randomized placebo-controlled trial is required. Considering the application of emerging effective treatments, it goes without saying that early diagnosis is essential in the management of cardiac amyloidosis such as wild-type ATTR. In this context, the existence of cardiac amyloidosis should be considered when we initiate the management of an elderly patient with cardiac wall thickening.

**Disclosure**

**Declaration of interest:** The authors report no conflicts of interest.

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