INTERNAL MEDICINE

□ **CASE REPORT** □

An Isolated Case of Late-onset Amyloidogenic Transthyretin Type Familial Amyloid Polyneuropathy Associated with a Mutant Transthyretin Substituting Methionine for Valine at Position 30 Showing Latent Progressive Cardiac Involvement Confirmed by Serial Annual Electrocardiograms

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Abstract

Late-onset amyloidogenic transthyretin (ATTR) type familial amyloid polyneuropathy (FAP) shows features distinct from those of early-onset hereditary ATTR type FAP. We herein describe an asymptomatic 68-year-old man with late-onset ATTR type FAP whose serial annual electrocardiograms demonstrated progressive left bundle branch block. Latent but severe cardiac involvement seems to be one feature of late-onset ATTR type FAP, similar to senile systemic amyloidosis (SSA). Early differential diagnosis of late-onset ATTR type FAP from SSA is important because, currently, only the former has new therapeutic options available in Japan. The present case report, therefore, highlights the necessity of careful observation for periodic electrocardiograms.

Key words: amyloidogenic transthyretin, cardiac amyloidosis, electrocardiogram, familial amyloid polyneuropathy, senile systemic amyloidosis, Val30Met

Introduction

Amyloidogenic transthyretin (ATTR) type familial amyloid polyneuropathy (FAP) associated with a mutant transthyretin substituting methionine for valine at position 30 (Val30Met) is the most common type of hereditary FAP, with special endemic foci in Arao City and Ogawa Village in Japan. In contrast, sporadic late-onset patients with ATTR type FAP associated with Val30Met, with no apparent family history or relationship with other families in the endemic focus, has been reported all over Japan (1). We herein describe a case of a 68-year-old man diagnosed with late-onset ATTR type FAP. Although he had no cardiac symptoms, his serial annual electrocardiograms (ECGs) showed the gradual progression of cardiac involvement during an asymptomatic stage over eight years.

Case Report

A 68-year-old man with diabetes mellitus was referred to our hospital for further examination of abnormal ECG and left ventricular hypertrophy with decreased left ventricular contractility. He had no family history of cardiac disease.
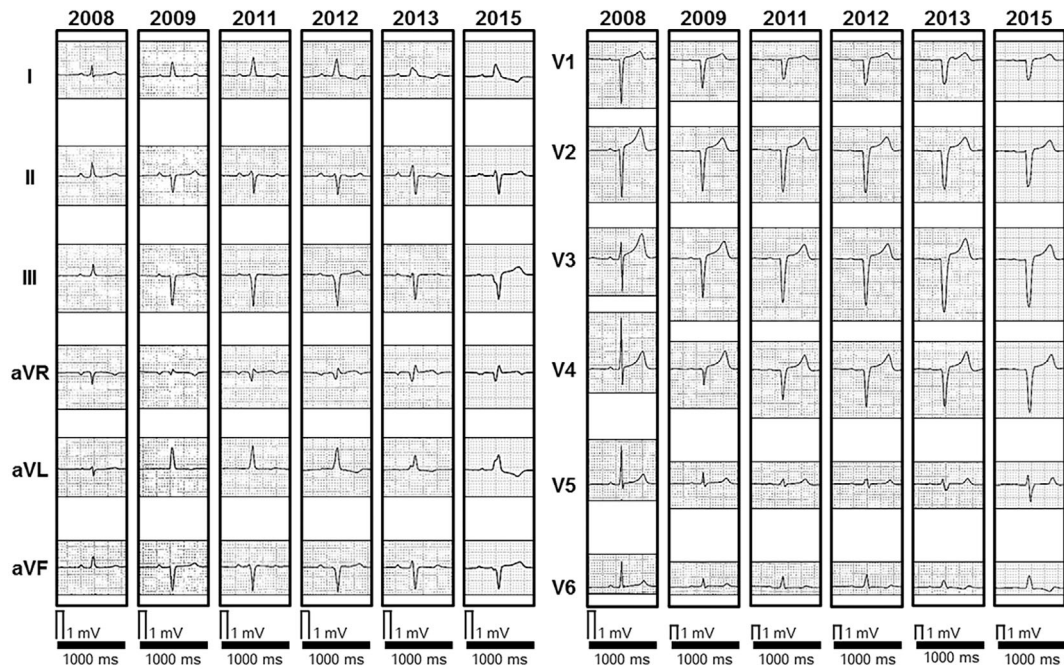
Figure 1. **12-Lead electrocardiogram for 8 years. Incomplete left bundle branch block appeared in 2009 and progressed to complete left bundle branch block in 2011. The QRS width further increased in 2015. The PR interval also widened over 8 years.**

On admission, he had no clinical symptoms of heart failure and was classified as New York Heart Association Class I. No cardiac murmur or respiratory crackles were audible. His blood pressure was 120/60 mmHg with a regular pulse rate of 72 beats/min. A neurological examination revealed impairment of pain and temperature sensation in the distal lower limbs. Chest radiography showed cardiomegaly (cardiothoracic ratio, 56.5%) without congestion or pleural effusion. He had undergone an annual routine ECGs for 8 years at the previous clinic, except in 2010 and 2014 (Fig. 1). In 2008, a QS-wave in V1 and rS-wave in V2 were observed without QRS axis deviation and prolongation in QRS width (93 ms). Incomplete left bundle branch block with left axis deviation and precordial QS-waves appeared in 2009 (QRS width, 116 ms) and progressed to complete left bundle branch block in 2011 (QRS width, 129 ms). A markedly notched QRS in aVL was observed from 2013. The QRS width further increased to 144 ms on admission in 2015. Furthermore, the PR interval widened from 169 ms to 207 ms over 8 years. The laboratory findings indicated mild renal dysfunction (estimated glomerular filtration rate, 51.1 mL/min/1.73 m^2). The serum brain natriuretic peptide level was elevated at 198.65 pg/mL. Primary light-chain (AL) amyloidosis and Fabry disease were unlikely based on the blood results and urinalysis (Table). Typical M-peak was not detected on serum protein electrophoresis. He had no proteinuria, including Bence-Jones protein. The serum κ-light chain and λ-light chain were all in the normal range, as revealed by immunoelectrophoresis. The α-galactosidase and pyruvic acid levels were within the reference range (102.2 nmol/mg/protein/h and 0.37 mg/dL, respectively). The level of serum transthyretin was 19.2 mg/dL, which was decreased. Echocardiography showed concentric left ventricular hypertrophy (septal wall end-diastolic thickness, 17 mm; inferolateral wall end-diastolic thickness, 19 mm). The ejection fraction had slightly decreased (51%) in 2013 and deteriorated to 41% in 2015. Right ventricular hypertrophy and a small amount of pericardial effusion anterior to the right ventricle were also noted (Fig. 2). Transmitral Doppler inflow patterns (E/A, 1.3) showed pseudo-normalization, and tissue Doppler velocity at the mitral annulus (e', 3.2 cm/s) suggested severely impaired left ventricular relaxation. Late gadolinium-enhanced cardiac magnetic resonance imaging (MRI) showed a characteristic global subendocardial and transmural pattern of myocardial late gadolinium enhancement in the thickened wall of both ventricles (Fig. 3A). ^{99m}Tc-pyrophosphate scintigraphy revealed diffuse accumulation in the entire myocardium (Fig. 3B). Coronary angiography showed an intact coronary artery. The patient was hemodynamically compensated, as revealed on right heart catheterization, which showed that the mean pulmonary capillary wedge pressure was 14 mmHg, the pulmonary artery pressure was 32/14 mmHg, and the mean right atrial pressure was 6 mmHg. The cardiac index, as measured with a standard thermodilution method, was also preserved at 2.6 L/min/m^2. Endomyocardial biopsy was avoided because of the left bundle branch block. Instead, colonal biopsy was performed, which showed amyloid deposits on the submucosal arterioles stained by direct fast scarlet (Fig. 4A), showing apple green birefringence (Fig. 4B). Immunohistochemical staining for ATTR was positive (Fig. 4C).

Contrary to our initial expectations that cardiac predomi-

Table.   Laboratory Data.

| Peripheral blood		Electrophoresis	
White blood cells	4,100 /μL	Albumin	61.9%
Red blood cells	412×10⁴/μL	α1-globulin	2.9%
Hemoglobin	12.7 g/dL	α2-globulin	8.2%
Hematocrit	38.9%	β-globulin	8.8%
Platelets	17×10⁴/μL	γ-globulin	18.2%
Biochemistry		**Serology**	
Sodium	137 mEq/L	Immunoglobulin G	1,145 mg/dL
Potassium	4.4 mEq/L	Immunoglobulin A	149 mg/dL
Chloride	102 mEq/L	Immunoglobulin M	90 mg/dL
Calcium	8.8 mg/dL		
Urea nitrogen	14.3 mg/dL	β2-microglobulin	2.1 mg/L
Serum creatinine	1.12 mg/dL		
Estimated glomerular filtration rate	51.1 mL/min/1.73m²	M protein (Immunofixation)	(-)
Uric acid	5.5 mg/dL	Free light chain (κ)	(-)
Total protein	5.9 g/dL	Free light chain (λ)	(-)
Serum albumin	3.5 g/dL		
Asparate aminotransferase	25 IU/L	Hepatitis B virus antigen	(-)
Alanine aminotransferase	32 IU/L	Hepatitis C virus antibody	(-)
Alkaline phosphate	183 IU/L		
Creatine kinase	269 IU/L	White blood cell α-galactosidase A activity	102.2 nmol/mg protein/h
Creatine kinase MB	4 IU/L		
Lactate dehydrogenase	184 IU/L	**Urinalysis**	
Pyruvic acid	0.37 mg/dL	Protein (qualitative)	(-)
Serum amyloid A	<5 μg/mL	Glucose	(-)
Transthyretin	19.2 mg/dL	Urinary red blood cells	(-)
Total cholesterol	189 mg/dL	Granular casts	(-)
Triglycerides	50 mg/dL	Fatty casts	(-)
Brain natriuretic peptide	198.7 pg/mL	Bence-Jones protein (Immunofixation)	(-)
Hemoglobin A1c	7.1%	Protein (quantitative)	<3 mg/dL
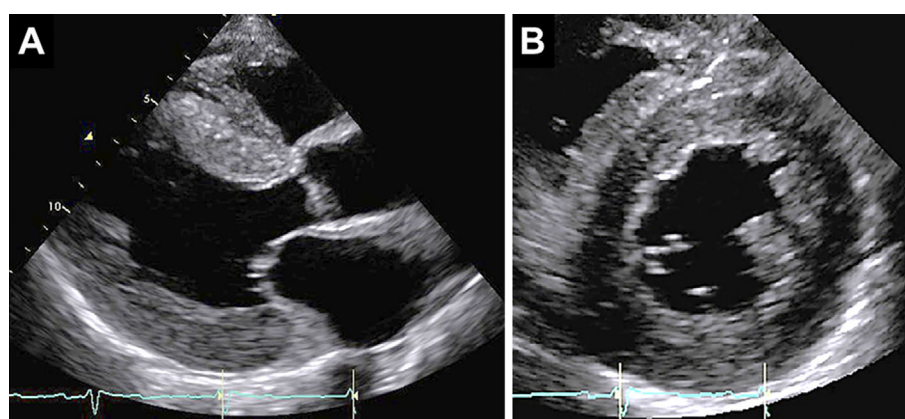
Figure 2.   Transthoracic echocardiography on admission. Transthoracic echocardiography showed concentric biventricular hypertrophy. A small amount of pericardial effusion was observed anterior to the right ventricle.

nant involvement in this aged man would indicate senile systemic amyloidosis (SSA), a transthyretin gene analysis by direct nucleotide sequencing confirmed a diagnosis of late-onset ATTR type FAP associated with Val30Met. Admini-stration of tafamidis, a novel drug for ATTR type FAP, was initiated for his neurological symptoms.
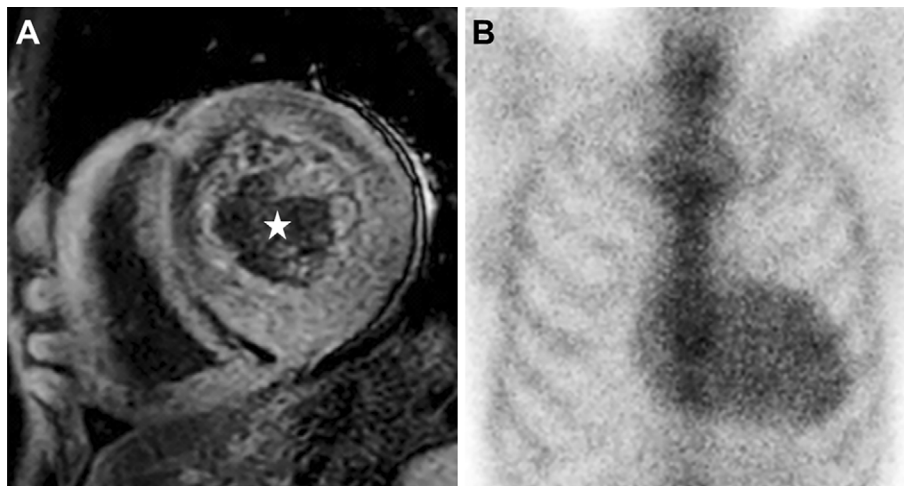
Figure 3.   A: Late gadolinium-enhanced cardiac magnetic resonance imaging. Characteristic global subendocardial and transmural pattern of myocardial late gadolinium enhancement is shown in the thickened wall of both ventricles, since the contrast agent distributed to the extracellular space expanded by amyloid infiltration. Note that, in cardiac amyloidosis, the blood pool is abnormally dark (white star), possibly reflecting fast blood pool washout of the contrast media. B: The ⁹⁹ᵐTc-pyrophosphate scintigraphic findings. Diffuse cardiac accumulation of ⁹⁹ᵐTc-pyrophosphate was observed.
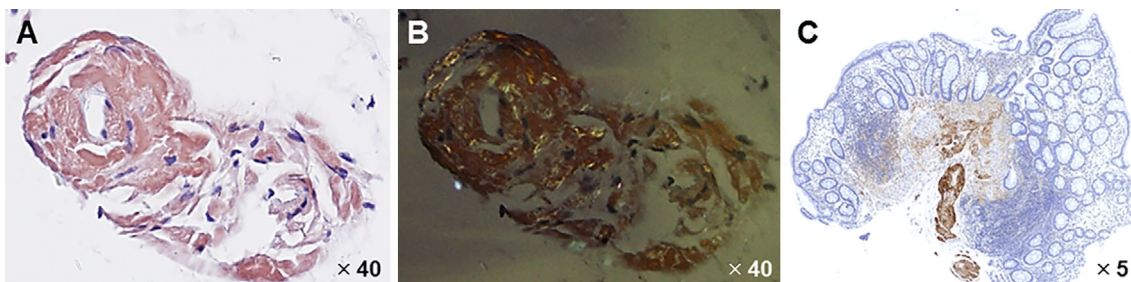

Figure 4.   The pathological findings of a colonal specimen. A colonal biopsy specimen by colon fiber shows amyloid deposits on the submucosal arterioles stained by direct fast scarlet (A), showing apple green birefringence (B). Immunohistochemical staining for amyloidogenic transthyretin was positive (C).

Discussion

In general, cardiac amyloidoses involve three main systemic types: AL amyloidosis, hereditary ATTR type FAP, and SSA (2). We herein report an isolated case of late-onset ATTR type FAP associated with Val30Met showing latent and progressive cardiac involvement proven by serial ECGs.

ATTR type FAP is a form of hereditary systemic amyloidosis characterized by infiltration of mutant transthyretin. Typical hereditary ATTR type FAP is usually early-onset (30-40 years), showing autosomal dominant inheritance with a high rate of penetrance, concentration in endemic foci (Arao City and Ogawa Village), and predominant loss of superficial sensation and severe autonomic dysfunction (1, 3, 4). The occurrence of ATTR type FAP is similar between men and women. In contrast, the clinical features of isolated cases of late-onset ATTR type FAP associated with Val30Met involve clinical onset at the age of 50 or later without family history or kinship associated with endemic foci, sensorimotor complaints in the legs as an initial symptom, parallel involvement of superficial and deep sensation, mild autonomic dysfunction, and marked male predominance (1, 3, 4).

SSA is characterized by infiltration of wild-type ATTR. Cardiac involvement is frequent, and carpal tunnel syndrome might precede the cardiac involvement (5, 6). The typical onset is after the age of 70, with strong male predominance (6).

Late-onset ATTR type FAP appears to have common clinical characteristics with SSA, in that both mainly occur in aged men and frequently show cardiac involvement (3, 4). It is critical to make the differential diagnosis of late-onset ATTR type FAP and SSA, because ATTR type FAP currently has therapeutic options, such as liver transplantation and some new medications. Since ECG, present imaging modalities, and tissue biopsy cannot differentiate mutant ATTR from wild-type ATTR, transthyretin gene analysis or

mass spectrometry is necessary for a definitive diagnosis (6).

Aging is a significant factor in amyloid deposition in the myocardium. Late-onset ATTR type FAP, therefore, would be more prone to develop cardiac amyloidosis than early-onset hereditary ATTR type FAP (4). Accordingly, latent progressive conduction disturbance seems to be a feature of late-onset ATTR type FAP associated with Val30Met, as first demonstrated in the case of a 52-year-old man by Takigawa et al. (3). They observed 5 years of gradually progressive left anterior fascicle block before the appearance of complete left bundle branch block (3). The present case showed good agreement with their case. In contrast, although neither patient had symptoms of heart failure, more progressive impairment of the cardiac conduction system was observed in the present case; incomplete left bundle branch block progressed to complete left bundle branch block within 2 years, with further widening of the QRS complex even after the occurrence of complete left bundle branch block. Furthermore, our case showed more advanced myocardial involvement, as revealed by a thicker left ventricular wall (14-15 mm vs. 17-19 mm), lower left ventricular ejection fraction (56% vs. 41%), and larger extent of late gadolinium enhancement (subendocardial vs. transmural).

As observed in the present case, Buxbaum et al. demonstrated lower serum transthyretin concentrations in carriers of ATTR type FAP associated with Val30Met (7), possibly reflecting the consumption of transthyretin into amyloid fibril (6).

We avoided endomyocardial tissue biopsy because of the complete left bundle branch block. Instead, gastrointestinal tissue biopsy successfully revealed the amyloid deposit. Considering the frequently observed conduction disturbances in patients with cardiac amyloidosis (2, 3), gastrointestinal tissue biopsy or subcutaneous abdominal fat tissue aspiration are safer and preferable to endomyocardial tissue biopsy (4, 8).

There are feasible methods for distinguishing ATTR amyloidosis from AL amyloidosis. Left ventricular wall thickness has been reported to be greater in ATTR amyloidosis, typically 15-18 mm, compared with 13-15 mm in AL amyloidosis (2, 6). In cardiac MRI, ATTR amyloidosis shows a more transmural enhancement pattern with frequent biventricular involvement than AL amyloidosis, which shows a subendocardial enhancement pattern (6). Intensely diffuse myocardial retention of ^{99m}Tc-pyrophosphate has been observed in patients with ATTR amyloidosis compared to those with AL amyloidosis (6, 9). The findings in the current case are consistent with these characteristics of ATTR amyloidosis. Recently, Minamisawa et al. demonstrated that patients with wild-type ATTR were characterized by a lower left ventricular ejection fraction and left ventricular radial strains than patients with mutant ATTR, indicating the utility of echocardiography for distinguishing between wild-type ATTR and mutant ATTR (10).

Treatment for ATTR type FAP includes liver transplantation and stabilizers of transthyretin tetramers. However, liver transplantation failed to prevent progression of cardiac amyloidosis in ATTR type FAP patients (11) due to the continued formation of wild-type ATTR derived from the transplanted normal liver graft (12). Furthermore, patients with late-onset ATTR type FAP are generally contra-indicated for liver transplantation due to their age. Tetrameric transthyretin itself is nonamyloidogenic, but the dissociation of tetramers into compact non-native monomers with low conformational stability can lead to amyloid fibril formation (13). Tafamidis, which stabilizes transthyretin tetramers, has been approved in Europe and Japan for treatment of adult FAP patients with early symptomatic polyneuropathy to delay neurological impairment (14). The therapeutic effect of tafamidis on cardiac ATTR amyloidosis remains to be elucidated (15).

In conclusion, we observed latent progressive conduction disturbance which appeared to be a feature of late-onset ATTR type FAP associated with Val30Met. At this point, there are therapeutic options for ATTR type FAP which should be initiated earlier. Therefore, careful observation for any subtle changes in the periodic ECGs and consultation with a cardiologist to identify any early changes are important for making a timely differential diagnosis.

The authors state that they have no Conflict of Interest (COI).

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