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Case Report

Transthyretin amyloidosis of the myocardium in a patient with monoclonal gammopathy of undetermined significance

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A 73-year-old Japanese man was admitted with heart failure due to AL amyloidosis caused by left ventricular hypertrophy and IgA-kappa monoclonal gammopathy. However, endomyocardial biopsy revealed eosinophilic amorphous material in the myocardium, which was positive for Congo red staining and transthyretin (TTR), but negative for the kappa chain. The patient was diagnosed with wild-type amyloid TTR (ATTR) amyloidosis and monoclonal gammopathy of uncertain significance. Among the different types of amyloidosis including AL amyloidosis (primary amyloidosis from an abnormality of plasma cells), AA amyloidosis (secondary amyloidosis in association with chronic inflammatory disease), and dialysis-related amyloidosis (deposition of beta-2 microglobulin), ATTRwt amyloidosis is a slowly progressive disease that affects most commonly the hearts of elderly in elderly patients who sometimes have other diseases. Thus, pathological examination is important for the diagnosis of amyloidosis.

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Key words: amyloid, pathology, diagnosis

Introduction

Amyloidosis is a rare disease that results from the deposition of misfolded proteins into organs for which more than 30 related amyloid precursor proteins have been identified to date. Among them, amyloid fibrils formed by immunoglobulin light chains, transthyretin, or amyloid A (AA) proteins accumulate in the heart and cause cardiac dysfunction. AA amyloidosis is associated with chronic inflammatory diseases. Light-chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis are the most common types of cardiac amyloidosis. ATTR amyloidosis includes the variant type ATTR (ATTRv) amyloidosis caused by a pathogenic mutation in the *TTR* gene, and the wild-type ATTR (ATTRwt). AL amyloidosis is a multisystem disorder caused by clonal proliferation of plasma cells. Multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS), which usually causes monoclonal proteins, are at risk of developing AL amyloidosis. Differential diagnoses to determine subtypes of amyloid are critical to managing patients because the therapies, clinical course, and prognosis between these types of amyloidosis differ. Herein, we present a case of wild-type ATTR cardiac amyloidosis with MGUS.

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Case Presentation

A 73-year-old Japanese man with heart failure was admitted to our hospital.

Present illness

He had undergone aortic valve replacement (AVR) for aortic stenosis five years prior. After AVR, the patient had no symptoms of heart failure with furosemide (20 mg); however, he began to experience shortness of breath when going up the stairs and slope one year prior. His symptoms gradually deteriorated, and he could not walk more than 300m without rest because of shortness of breath three months prior. The patient visited his home doctor, where chest radiography revealed pleural effusion, for which he was admitted to our department.

Past medical history

The patient had a history of appendectomy, tonsillectomy, cholecystectomy, and surgery for lumbar herniated discs.

Family history

Family history included ischemic heart disease and cerebral hemorrhage. However, he had no other family history of amyloidosis or hematological diseases.

Laboratory data

On admission, transthoracic echocardiography revealed a left ventricular (LV) hypertrophy (Fig. 1A; interventricular septum, 20 mm; LV posterior wall, 15 mm) with normal LV ejection fraction (60%) (Fig. 1B) and global longitudinal strain, -6.0% with apical sparing (Fig. 1C).

Laboratory data showed high levels of NT-pro-B-type natriuretic peptide (4808 pg/mL), high-sensitivity troponin T (0.085 ng/mL), and serum IgA (968 mg/dL), low levels of IgG and IgE, and a high free light chain (FLC) ratio (10.22; kappa, 95 mg/dL; lambda, 9.3 mg/dL) (Table 1), and IgA-Kappa monoclonal gammopathy by serum immunofixation electrophoresis. As myeloid disease, including malignant myeloma, was suspected, a bone marrow aspiration was performed, revealing 6.7% monoclonal plasma cells by flow cytometry. The was subsequently diagnosed with MGUS.

Scintigraphy

To diagnose ATTR cardiac amyloidosis noninvasively, ^{99m}technetium-pyrophosphate (^{99m}TC-PYP) scintigraphy was performed, revealing grade 3 myocardial uptake (visual

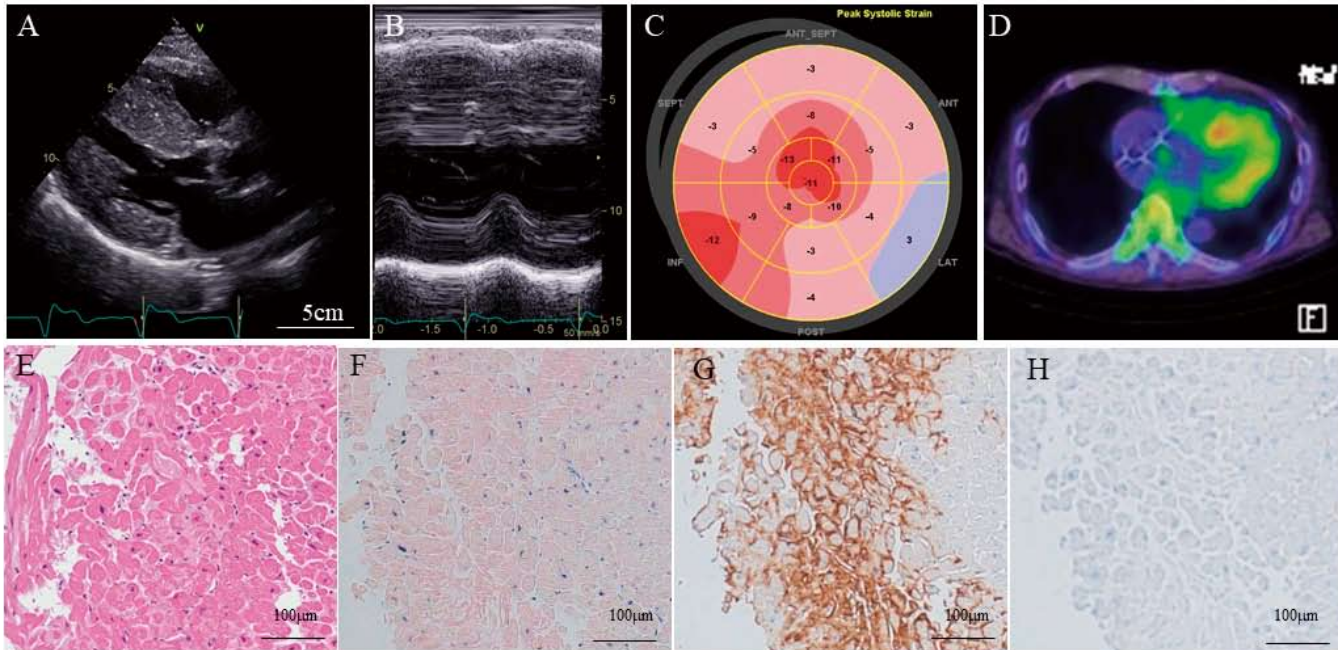

Figure 1. Radiological and histological findings
Transthoracic echocardiography on admission: parasternal long-axis view (A), B-mode of parasternal long-axis (B), and global longitudinal strain (C). Results of ^{99m}technetium-pyrophosphate pyrophosphate scintigraphy (D). Microphotographs of the myocardium with hematoxylin-eosin staining (E), Congo red staining (F), transthyretin (G), and kappa chain (H).

Table 1. Laboratory data upon admission.

WBC	6,900 x 10^3/μl	TP	7.2 g/dL	Comp.	47.9 CH50/mL
RBC	4.73 x 10^6/μl	Alb	4.1 g/dL	ANA	<80
Hb	9.8 g/dl	T. bil	0.9 mg/dL	sIL-2R	308 U/L
Hct	44.4%	AST	28 U/L	IgG	610 mg/dL
Plt	17.6 x 10^4/μl	ALT	21 U/L	IgA	968 mg/dL
PT (INR)	1.71	ALP	69 U/L	IgM	801 mg/dL
D-dimer	<0.5 μg/mL	γ-GTP	98 mg/dL	IgE	5.9%
CRP	0.04 mg/dL	LDH	284 U/L	FLC κ	95 mg/mL
Na	139 mEq/L	CK	92 U/L	FLC λ	9.3 ng/mL
K	4.4 mEq/L	TG	98 mg/dL	κ/λ	10.22
Cl	101 mEq/L	HDL-C	69 mg/dL	SAA	7.8 μg/mL
Ca	9.2 mg/dL	LDL-C	118 mg/dL	ACE	9.6 U/L
BUN	31 mg/dL	FPG	112 mg/dL	FT3	2.59 pg/mL
Cre	1.11 mg/dL	HbA1c	5.9%	FT4	1.30 ng/mL
UA	6.0 mg/dL	NTproBNP	4808 pg/mL	TSH	4.06 μIU/mL
TP	7.2 g/dL	Troponin T	0.085 ng/mL		
Alb	4.1 g/dL	RF	<5.0 IU/mL		

WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; Hct, hematocrit
Plt, platelet count; PT (INR), prothrombin time (international normalized ratio); CRP, c-reactive protein; BUN, blood urea nitrogen; Cre, creatinine; UA, uric acid; TP, total protein; Alb, albumin; T. bil, total bilirubin;; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase LDH, lactate dehydrogenase; CK, creatine kinase; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; NT-pro BNP, N terminal-pro brain natriuretic peptide, RF, rheumatoid factor; Comp., complement level; ANA, antinuclear antibody; sIL-2R, soluble interleukin-2 receptor; FLC, free light chain; SAA, serum amyloid A protein; ACE, angiotensin-converting enzyme; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone

assessment, grade 2 and 3 classified as positive) and a heart/contralateral lung (H/CL) ratio of 3.659 (quantitative assessment, H/CL ratio >1.5 as positive) that suggested ATTR amyloidosis (Fig. 1D).

Cardiac catheterization and endomyocardial biopsy

Cardiac catheterization and endomyocardial biopsy were performed to confirm ATTR cardiac amyloidosis and to exclude other myocardial diseases, including hypertrophic cardiomyopathy. Coronary angiography revealed no significant stenosis.

The biopsied samples were fixed in 10% neutral buffered formalin (pH 7.4), embedded in paraffin, cut into 3 μm thick slices, and mounted on glass slides. Endomyocardial biopsy showed amorphous material in the myocardium (Fig. 1E, hematoxylin, and eosin staining), which was positive for Congo red staining (Fig. 1F). Immunohistochemical analysis was performed on pericardial tissue sections (3 μm). Sections were incubated with antibodies for amyloid A, amyloid P, TTR (preincubation with formic acid; rabbit polyclonal antibody, antigen recognition site, TTR115-124), beta2-microglobulin, immunoglobulin light-chain kappa, immunoglobulin light-chain lambda, and immunoglobulin lambda-like poly-peptide 5. Primary antibodies were visualized using horseradish peroxidase-conjugated secondary antibodies and an ultraView Universal DAB Detection Kit (cat. no. 760-500; Ventana Medical Systems, Inc.), and the sections were counterstained for 1 min with Carrazzi's hematoxylin solution. Amyloidosis was positive for transthyretin (TTR) (Fig. 1G), but negative for the kappa chain (Fig. 1H). The patient had no ATTR variants. Finally, the patient was diagnosed with wild-type ATTR amyloidosis and MGUS, and tafamidis (80 mg/day) was initiated. The patient's condition was stable and the patient's condition was stable without any side effects.

Discussion

The previous studies have demonstrated a high prevalence (23-39%) of MGUS in wild-type ATTR amyloidosis[1,2]. The finding of monoclonal gammopathy or an abnormal FLC ratio in an elderly man may confuse the diagnosis of the type of amyloidosis[1]. Treatment generally consists of anti-plasma cell chemotherapy for AL amyloidosis, and tafamidis to prevent the destabilization of the TTR tetramer for wild-

type ATTR amyloidosis[3]. Moreover, all MGUS patients should be routinely screened for AL amyloidosis, and the diagnosis of AL amyloidosis can be confirmed by tissue biopsy. AL amyloidosis can cause deposition in any organ except for the central nervous system; therefore, endomyocardial biopsy is not necessarily required because gastrointestinal biopsy, skin biopsy, and abdominal fat pad aspiration will demonstrate AL amyloid deposits in 64 to 100% of patients, which has reasonable diagnostic sensitivity in cardiac AL amyloidosis, particularly in patients with a large whole-body amyloid burden[3-6]. Conversely, endomyocardial biopsy is regarded as the gold standard to confirm the diagnosis of ATTR amyloidosis because the heart is most commonly involved, and the amyloid protein detection rates of abdominal fat pad aspiration (14-15%) and biopsy of the intestinal tract (38%) are relatively low in patients with wild-type ATTR[3,7].

^{99m}Tc-PYP cardiac imaging can differentiate ATTR from AL cardiac amyloidosis[8,9]. Moreover, grades 2 and 3 ^{99m}Tc-PYP have only a sensitivity of 94% and specificity of 89% for ATTR cardiac amyloidosis, with 100% specificity for grade 3 scans[8].

Recently, guidelines for diagnosis and treatment of cardiac amyloidosis have indicated that cardiac ATTR amyloidosis can be diagnosed in the absence of histology in the setting of typical echocardiographic/CMR findings when ^{99m}Tc- PYP scintigraphy shows grade 2 or 3 myocardial uptake of radiotracer and clonal dyscrasia is excluded by all the following tests: serum free light chain assay, serum, and urine protein electrophoresis with immunofixation in Europe and the United States[10,11]. According to the diagnostic criteria for the guideline of cardiac amyloidosis in the Japanese Circulation Society[7], histological confirmation of amyloid deposition in cardiac or extracardiac tissue is required to definitively diagnose ATTR cardiac amyloidosis.

Taken together, this suggests that tissue biopsy is necessary to establish a diagnosis of amyloidosis in amyloidosis patients with coexisting ATTR scintigraphy, and data indicating MGUS and immunohistochemical staining (or mass spectrometric analysis) is used for amyloid typing. In some patients with variant ATTR amyloidosis caused by *ATTR* gene mutations, tissue biopsy can be replaced with genetic testing.

However, recent reports have described cases of cardiac amyloidosis with concurrent ATTR and AL cardiac amyloidosis[12,13]. This finding suggests that endomyocardial biopsy may be more important for the diagnosis of cardiac amyloidosis than initially believed.

In our patient, wild-type ATTR amyloidosis was diagnosed using endomyocardial biopsy and immunostaining, in addition to *ATTR* gene testing. Subsequently, tafamidis (80 mg/day) was started, and the patient's condition was stable. In conclusion, a biopsy of the affected organ should be performed to confirm the diagnosis of ATTR amyloidosis in patients with MGUS.

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Conflicts of Interest

The authors declare no conflict of interest associated with this report

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