Unusual Case of Cardiac Amyloidosis Preceded by a Twenty-year History of Dilated Cardiomyopathy and Heart Failure

Seijiro Shimada¹, Shunji Maekura², Hikaru Ino¹, Masayosi Matsuura¹, Nobutaka Masunaga¹, Takahiro Matsumoto¹ and Junkichi Hama¹

Abstract

Amyloidosis is a well-known but uncommon disease, and the physician must maintain a high index of suspicion in order to make a timely diagnosis. The expected survival of patients with cardiac amyloidosis is generally poor. In particular, survival has been reported to be 4-12 months for patients with amyloid light-chain amyloidosis with congestive heart failure. We herein report a rare case of cardiac amyloidosis in which the patient presented with cardiac hypertrophy after a 20-year history of dilated cardiomyopathy and heart failure.

Key words: amyloidosis, cardiomyopathy, heart failure, prognosis

(Intern Med 55: 1109-1115, 2016) (DOI: 10.2169/internalmedicine.55.5835)

Introduction

The clinical classification of amyloidosis is based on the type of protein constituting the amyloid fibril (1). In many cases of amyloidosis, there are no characteristic laboratory findings or symptoms, and unless one considers amyloidosis in the differential diagnosis, the condition may go undiagnosed. In cardiac amyloidosis (CA), echocardiography typically demonstrates a sparkling granular echo pattern with restrictive cardiomyopathy and a marked decrease in the diastolic function (2, 3). Electrocardiography shows an anteroseptal myocardial infarction-like pattern in the chest leads and low QRS voltages with poor R-wave progression, even when CA is accompanied by cardiac hypertrophy (4). In the presence of these findings, one should suspect amyloidosis. We report an unusual case of CA that was eventually diagnosed at autopsy. The patient had a 20-year history of dilated cardiomyopathy (DCM) and chronic heart failure that transitioned to cardiac hypertrophy just before death.

Case Report

A 68-year-old Japanese man was admitted to our hospital with heart failure. The patient had been noted to have cardiac enlargement and atrial fibrillation on a physical examination performed 29 years earlier at 40 years of age. He was hospitalized nine years later, at 49 years of age, for an evaluation of exertional dyspnea. At that time, he was diagnosed with congestive heart failure due to DCM with mitral regurgitation and atrial fibrillation. Ischemia and other causes of DCM were ruled out based on cardiac catheterization and serological testing, and treatment for heart failure secondary to idiopathic DCM was begun at that time. At 60 years of age, he was treated with carvedilol for heart failure at our hospital; he required hospitalization for one month before he was stable enough to be discharged. He was hospitalized again seven years later, at 67 years of age, for one month for exacerbation of heart failure. On admission to our hospital, as described in this report, he presented with exacerbation of heart failure at 68 years of age.

The patient’s medical history included dyslipidemia and...
terolemia (total cholesterol, 272 mg/dL; low-density lipoprotein cholesterol, 149 mg/dL), diabetes (hemoglobin A1C, 6.6%), a slightly increased brain natriuretic peptide level (31.0 pg/mL) and normal serum protein electrophoresis. Test results for antinuclear antibodies and urine protein were negative, and the thyroid function was normal. There were no findings suspicious for amyloidosis. The laboratory data obtained on a previous admission showed evidence of mild malnutrition (total protein, 6.2 g/dL; albumin, 3.3 g/dL), a reduced renal function (blood urea nitrogen, 44 mg/dL; serum creatinine, 1.7 mg/dL), hyperuricemia due to diuretic use (uric acid, 10.3 mg/dL), normocytic anemia (hemoglobin, 10.3 g/dL) and an elevated brain natriuretic peptide level (212 pg/dL).

An electrocardiogram confirmed the presence of atrial fibrillation, first diagnosed 29 years earlier. The poor R-wave progression and low voltage in the precordial leads characteristic of amyloidosis were not observed when the patient was admitted to our hospital the first time. However, these findings subsequently appeared gradually (Fig. 1).

Chest radiography showed cardiomegaly (cardiothoracic ratio, 65%), hazy hilar enlargement and bilateral pleural effusion (Fig. 2A).

Cardiac ultrasound performed eight years previously showed changes consistent with DCM: left ventricular end-diastolic diameter, 55 mm (normal value: 36-56 mm); left ventricular end-systolic diameter, 42 mm (normal value: 20-38 mm); interventricular septal thickness, 8 mm (normal value: 5-12 mm); left ventricular posterior wall thickness, 8 mm (normal value: 5-12 mm); %fractional shortening, 25 (normal value: 30-50); ejection fraction, 48% (normal value: 60-80%); and deceleration time (DCT), 175 ms (normal value: 150-250 ms). However, on the current admission, cardiac ultrasound revealed the following findings: left ventricular end-diastolic diameter, 51 mm; left ventricular end-systolic diameter, 31 mm; interventricular septal thickness, 13 mm; left ventricular posterior wall thickness, 11 mm; %fractional shortening, 39; and ejection fraction, 69%. These findings were consistent with cardiac hypertrophy accompanied by a decrease in the diastolic function (DCT, 90 ms). In addition, the left atrial diameter, including the annulus, was markedly increased (67 mm), severe mitral valve regurgitation due to prolapse was recognized and severe tricuspid regurgitation was observed. The patient’s heart failure did not improve. Therefore, we opted for surgical repair for the tricuspid and mitral valve regurgitation (Fig. 2B, C).

Preoperative coronary angiography showed three-vessel disease: segment 2, 75% stenosis; segment 5, 75% stenosis; segment 6, 75% stenosis; and segment 13, 75% stenosis (Fig. 3). Mitral valvuloplasty, tricuspid annuloplasty, coronary artery bypass grafting and the maze procedure were performed.

Although the amount of mitral and tricuspid valve regurgitation was mild, postoperative cardiac ultrasound showed an improvement in the cardiac hypertrophy, with the following data: left ventricular diastolic function (left ventricular end-diastolic diameter, 46 mm; left ventricular end-systolic diameter, 35 mm; interventricular septal thickness, 11 mm; left ventricular posterior wall thickness, 9 mm; %fractional shortening, 24; and DCT, 161 ms).

The patient began rehabilitation for postoperative disuse.
syndrome. Three months after the surgery, he recovered and was discharged from the hospital. However, around that time, he complained of appetite loss. Laboratory data showed normocytic anemia (hemoglobin: 9.5 g/dL) and a positive stool occult blood test. Therefore, upper and lower gastrointestinal endoscopy were performed to evaluate this condition. Both endoscopic procedures showed hemorrhagic mucosa and an inflammatory surface layer. Subsequently, the patient developed diarrhea several times daily and severe hypoproteinemia despite the administration of intravenous albumin, most likely due to protein-losing gastroenteropathy. Concomitantly, the patient’s renal dysfunction worsened. Six months postoperatively, he had a syncopal episode resulting from bradycardic atrial fibrillation, and his renal function declined rapidly once again. He underwent permanent pacemaker implantation and began hemodialysis. The protein-

![Figure 2](image1.png)

**Figure 2.** (A) Chest radiography on admission showed cardiomegaly, hazy hilar enlargement and bilateral pleural effusion. (B) Transthoracic echocardiography performed at 60 years of age showed changes consistent with DCM: dilated left ventricular cavity and a normal thickness of the walls and septum. (C) Transthoracic echocardiography performed on admission showed concentric left ventricular hypertrophy and left atrial enlargement.

![Figure 3](image2.png)

**Figure 3.** Coronary angiography showed three-vessel disease, as shown by the arrows: segment 2: 75% stenosis, segment 5: 75% stenosis, segment 6: 75% stenosis, and segment 13: 75% stenosis.
losing gastroenteropathy and malnutrition persisted, and he became hypotensive, making performing hemodialysis difficult. The patient died seven months after surgery at 69 years of age, 20 years after the initial diagnosis of DCM, and an autopsy was performed.

The cardiac ultrasound data from 20 years prior clearly showed findings consistent with DCM (maximum left ventricular end-diastolic diameter, 60 mm); however, more recent studies showed a reduction in left ventricular dilation and ultimately the development of cardiac hypertrophy. The bottom section represents the albumin level and renal function. Both values gradually declined until the more precipitous deterioration just prior to the patient’s death.

The gross autopsy findings revealed an increased heart weight (602 g) and waxy luster of the cut surfaces of the heart, which are well described in cases of amyloidosis (Fig. 5). The results of a microscopic examination of the heart were as follows. Hematoxylin and eosin staining revealed significant multifocal interstitial fibrosis and eosinophilic deposits. A Congo red staining revealed amyloid deposition; amyloid deposition was not seen in the myocardial interstitium, but was predominantly noted in the vessel walls, causing microvascular stenosis and occlusion. Immunohistochemical staining for the amyloid P component was positive. Additionally, immunohistochemical staining with antibodies against kappa light chain, lambda light chain and amyloid A was negative, and immunohistochemical staining for transthyretin was positive. As a result of these findings, we diagnosed transthyretin-related amyloidosis (Fig. 6). Additionally, amyloid was deposited in the lungs, liver, kidney and intestinal tissues and was mainly identified in the microvessel walls.
Discussion

We herein presented an unusual case of CA in which the diagnosis was made based on the autopsy findings. There have been no previous reports of CA in patients who presented with a long duration of heart failure resulting from DCM whose disease evolved from DCM into hypertrophic cardiomyopathy (HCM) and who underwent surgery for severe valvular and coronary artery disease. Therefore, we will discuss these three points individually.

Our patient had transthyretin-related amyloidosis (ATTR). This type of amyloidosis is systemic and classified as familial or senile. Familial ATTR is inherited in an autosomal-dominant fashion and typically has an onset at a relatively young age. It is accompanied by a variety of autonomic nervous system symptoms and cardiac disorders, such as sensory dissociation, constipation, diarrhea, dysuria, orthostatic hypotension, sinus dysfunction, atrioventricular block and heart failure. However, some familial cases have been reported with onset at an age of >50 years. These were sporadic cases in which no family history was recognized or the patient had inconspicuous autonomic nervous system manifestations (5). Therefore, genetic screening is necessary in cases where the differential diagnosis includes familial or senile amyloidosis. We were unable to establish this diagnosis in our patient. After the diagnosis of amyloidosis was made at autopsy, one of the patient’s two sons underwent genetic screening, although the results were negative.

The prognosis of CA is generally poor. The median period from diagnosis to death or orthotopic heart transplant is 36 months in patients with familial ATTR and 67 months in those with senile ATTR (6). In patients with congestive heart failure, survival has been reported to be 4-12 months (3, 7-9). According to one report, only 30 out of 810 amyloidosis patients survived >10 years and only 7% of survivors had heart failure (10). Our patient’s 20-year history of heart failure was unusual. Additionally, DCT with Doppler echocardiography is a useful prognostic factor for CA with a very poor prognosis when the DCT value is < 150 ms (11). In patients with atrial fibrillation, previous reports have documented that a DCT of ≤130 ms predicts a poor prognosis of restrictive diastolic dysfunction (12) and that a DCT of ≤100 ms indicates an increased pulmonary capillary wedge pressure (13). In our case, the DCT was 90 ms on the patient’s last admission, whereas it had been > 150 ms on earlier admissions. This may be one reason why our patient was able to survive for a long duration despite the presence of heart failure.

It has previously been reported that 41 of 1,278 patients (3.2%) with DCM have underlying amyloidosis (14). Nevertheless, case reports of DCM secondary to amyloidosis are rare (9, 15-17). The predominant deposition of amyloid in vessel walls causes microvascular stenosis or occlusion and is considered to be one of the primary mechanisms for the development of DCM in amyloidosis patients (18, 19). In our patient, amyloid was predominantly deposited in the vessel walls, causing microvascular stenosis, occlusion and DCM, as in the cases reported above. However, it has been reported that not all such cases present with DCM (17). Ad-
ditionally, the fact that our patient eventually presented with cardiac hypertrophy before his death suggests that DCM may be absent even in the presence of amyloid deposition in the vessel walls of the myocardium. Incidentally, we suspect that our patient’s coronary artery disease was based on his underlying age, dyslipidemia and impaired glucose tolerance and was not related to his underlying amyloidosis. The reason for this is that the epicardial coronary stenosis in our patient was a classical atherosclerotic lesion. Ultimately, the mechanisms of cardiac dilation and hypertrophy in CA are not known.

Only one previous report has documented a transition from DCM to HCM in a case of familial ATTR (20). This case was similar to ours in that it described a patient diagnosed with DCM in the early stages of illness, who, 13 years later, was diagnosed with familial ATTR at 63 years of age. Two prior myocardial biopsies had been performed over the previous 13 years, although staining for amyloid was not performed. A third myocardial biopsy was performed when the patient developed gastrointestinal and neurological symptoms and progressed to New York Heart Association class III heart failure with cardiac hypertrophy. Amyloid staining established the diagnosis in association with this biopsy. Interestingly, this case was similar to our case in that the patient’s cardiac function markedly declined and the left atrial diameter significantly increased with the transition from DCM to HCM. The authors felt that idiopathic DCM had occurred coincidentally and was not secondary to amyloidosis in their patient; however, there are reports of CA presenting with DCM, as described above.

Therefore, cardiac hypertrophy may not be present in the early stages of CA, and only mild cardiac dysfunction or dilation may occur. We believe that many patients with CA go undiagnosed in the early stages before heart failure worsens, while other systemic symptoms of amyloidosis become more apparent. By the time some patients undergo a more extensive evaluation, they may have already developed cardiac hypertrophy.

There are several case reports of CA patients who underwent cardiac surgery. These reports include one in which the diagnosis of CA was made at autopsy in the perioperative period (21), a case requiring surgery for severe mitral regurgitation due to sudden papillary muscle dysfunction (22) and the case of a patient with CA arising from multiple myeloma who underwent aortic and mitral valve replacement (23). However, these reports provide little information regarding the postoperative course. Our patient underwent mitral valvuloplasty, tricuspid annuloplasty, coronary artery bypass grafting and the maze procedure and showed an improvement in cardiac hypertrophy and left ventricular diastolic dysfunction in the months prior to his death. Considering the prognosis of severe congestive heart failure in patients with CA, we believe that this surgery was beneficial for our patient.

Retrospectively, several typical complications of amyloidosis were ultimately present in our patient. However, the diagnosis of amyloidosis was not apparent for several reasons. First, due to the cardiac hypertrophy, the decrease in the left ventricular diameter and cardiac dilatation with the progression of cardiac hypertrophy, there was little change in the cardiac mass and the degree of hypertrophy was not apparent. Second, the patient’s renal dysfunction was attributable to diabetic nephropathy and a decrease in the renal blood flow due to heart failure. Third, the appetite loss and protein-losing gastroenteropathy were thought to be related to gastrointestinal congestion resulting from heart failure. In patients with systemic amyloidosis, amyloid deposition in the gastrointestinal tract is found in nearly 90% of cases (3), and an endoscopic biopsy may have allowed us to establish a pre-mortem diagnosis of amyloidosis.

In conclusion, we experienced a very unusual and instructive case. A high index of suspicion for amyloidosis should be maintained in patients with unexplained cardiomyopathy.

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

References

1. Sipe JD, Benson MD, Buxbaum JN, et al. Nomenclature 2014: Amyloid fibril proteins and clinical classification of the amyloidosis. Amyloid 21: 221-224, 2014.
2. Siqueira-Filho AG, Cunha CL, Tajik AJ, Seward JB, Schattenberg TT, Giuliani ER. M-mode and two-dimensional echocardiographic features in cardiac amyloidosis. Circulation 63: 188-196, 1981.
3. Loizos S, Shiakalli Chrysa T, Christos GS. Amyloidosis: review and imaging findings. Semin Ultrasound CT MR 35: 225-239, 2014.
4. Buja LM, Khoi NB, Roberts WC. Clinically significant cardiac amyloidosis. Clinicopathologic findings in 15 patients. Am J Cardiol 26: 394-405, 1970.
5. Koike H, Misu K, Ikeda S, et al. Type I (transthyretin Met30) familial amyloid polyneuropathy in Japan: early- vs late-onset form. Arch Neurol 59: 1771-1776, 2002.
6. Givens RC, Russo C, Green P, Maurer MS. Comparison of cardiac amyloidosis due to wild-type and V122I transthyretin in older adults referred to an academic medical center. Aging Health 9: 229-235, 2013.
7. Shah KB, Inoue Y, Mehra MR. Amyloidosis and the heart: a comprehensive review. Arch Intern Med 166: 1805-1813, 2006.
8. Falk RH, Dubrey SW. Amyloid heart disease. Prog Cardiovasc Dis 52: 347-361, 2010.
9. Ikeda S. Cardiac amyloidosis: heterogeneous pathogenic backgrounds. Intern Med 43: 1107-1114, 2004.
10. Kyle RA, Gertz MA, Greipp PR, et al. Long-term survival (10 years or more) in 30 patients with primary amyloidosis. Blood 93: 1062-1066, 1999.
11. Klein AL, Hatle LK, Taliercio CP, et al. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis. A Doppler echocardiography study. Circulation 83: 808-816, 1991.
12. Hurrell DG, Oh JK, Mahoney DW, Miller FA Jr, Seward JB. Short deceleration time of mitral inflow E velocity: prognostic implication with atrial fibrillation versus sinus rhythm. J Am Soc Echocardiogr 11: 450-457, 1998.
13. Matsukida K, Kisanuki A, Toyonaga K, et al. Comparison of transthoracic Doppler echocardiography and natriuretic peptides in predicting mean pulmonary capillary wedge pressure in patients with chronic atrial fibrillation. J Am Soc Echocardiogr 14: 1080-1087, 2001.
14. Felker GM, Hu W, Hare JM, Hruban RH, Baughman KL, Kasper EK. The spectrum of dilated cardiomyopathy. The Johns Hopkins experience with 1,278 patients. Medicine (Baltimore) 78: 270-283, 1999.

15. Yoshita M, Ishida C, Yanase D, Yamada M. Immunoglobulin light-chain (AL) amyloidosis with myasthenic symptoms and echocardiographic features of dilated cardiomyopathy. Intern Med 45: 159-162, 2006.

16. Suresh R, Grogan M, Maleszewski JJ, et al. Advanced cardiac amyloidosis associated with normal interventricular septal thickness: an uncommon presentation of infiltrative cardiomyopathy. J Am Soc Echocardiogr 27: 440-447, 2014.

17. Mueller PS, Edwards WD, Gertz MA. Symptomatic ischemic heart disease resulting from obstructive intramyocardial coronary amyloidosis. Am J Med 109: 181-188, 2000.

18. Smith RR, Hutchins GM. Ischemic heart disease secondary to amyloidosis of intramyocardial arteries. Am J Cardiol 44: 413-417, 1979.

19. Cueto-Garcia L, Tajik AJ, Kyle RA, Edwards WD, Wood DL, Seward JB. Echocardiographic features of amyloid ischemic heart disease. Am J Cardiol 55: 606-607, 1985.

20. Kristen AV, Ehlermann P, Helmke B, et al. Transthyretin valine-94-alanine, a novel variant associated with late-onset systemic amyloidosis with cardiac involvement. Amyloid 14: 283-287, 2007.

21. Fitzmaurice GJ, Wishart V, Graham AN. An unexpected mortality following cardiac surgery: a post-mortem diagnosis of cardiac amyloidosis. Gen Thorac Cardiovasc Surg 61: 417-421, 2013.

22. Nishi H, Mitsuno M, Ryomoto M, Miyamoto Y. Severe mitral regurgitation due to cardiac amyloidosis—a rare reason for ruptured chordae. Interact Cardiovasc Thorac Surg 7: 1199-1200, 2008.

23. Namai A, Sakurai M, Sasaki O, Meguro K. Cardiac surgery in a patient with multiple myeloma combined with renal amyloidosis. Gen Thorac Cardiovasc Surg 58: 341-343, 2010.

© 2016 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html