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Echocardiographic findings in nine patients with cardiac amyloidosis: Their correlation with necropsy findings

Hideo NISHIKAWA
Shinichiro NISHIYAMA
Shigeyuki NISHIMURA
Kunio KONDO
Susumu IMAI
Kenichi KATO
Shigemoto NAKANISHI
Akira SEKI
Tetsu YAMAKADO*
Naoki ISAKA*
Takeshi NAKANO*
Hideo TAKEZAWA*

Summary

The echocardiographic abnormalities of nine patients with cardiac amyloidosis were correlated with their postmortem findings. All had congestive heart failure and autopsy-proven amyloidosis. M-mode echocardiographic features included (1) small or normal left ventricular (LV) dimensions; (2) thickened interventricular septa and posterior LV walls (89%); (3) left atrial enlargement (89%); and (4) reduced LV distensibility (78%, 100%) and contractility (22%, 44%). Serial M-mode echocardiography revealed that cardiac amyloidosis was initially manifested as diastolic LV dysfunction rather than systolic dysfunction. The final stage of this disease was characterized by severe impairment of both systolic and diastolic LV functions. Two-dimensional echocardiography provided additional features: (1) a more accurate diagnosis of pericardial effusion (67%) and (2) a characteristic "granular sparkling" appearance of the ventricular wall (55%). In four of five cases, these hyperrefractile myocardial echoes corresponded to scattered amyloid deposits histopathologically. There was no correla-

Division of Cardiology, Cardiovascular Center, Toranomon Hospital, Toranomon 2–2–2, Minato-ku, Tokyo 105
*The First Department of Internal Medicine, School of Medicine, Mie University, Edobashi 2–174, Tsushi, Mie 514

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tion between the types of amyloid deposits and the hyperrefractile myocardial echoes. Thus, cardiac involvement in systemic amyloidosis could be non-invasively assessed by M-mode and two-dimensional echocardiography.

Key words
Cardiac amyloidosis Echocardiography Necropsy

Introduction

Amyloidosis is a rare but important cause of infiltrative cardiomyopathy in adults. Cardiac involvement is also the most common cause of death in patients with systemic amyloidosis.[1~6] Its early recognition, differentiation from other cardiomyopathies, and appropriate therapy are recurring clinical problems.[7] Echocardiography is a useful means of screening subjects suspected of having cardiac amyloid infiltration.[6,8~14] Markedly increased thickness of the ventricular free wall and septum combined with depressed left ventricular (LV) systolic function of varying degree are typical findings observed in advanced cases.[12,13]

Although previously reported studies have described a number of echocardiographic abnormalities, there are few reports of the correlation of echocardiographic and postmortem findings.[15] Such correlations between echocardiographic and pathological findings are described in the present study.

Materials and methods

Subjects

The study population consisted of nine patients, five men and four women, all of whom were examined at the Toranomon Hospital or Mie University Hospital. All had autopsy-proven amyloidosis. Their ages ranged from 48 to 82 years (mean: 62 years). Five patients had primary amyloidosis; two had secondary amyloidosis associated with multiple myeloma. They did not take cytotoxic drugs before or at the time of echocardiography which might affect LV contractility. Two cases had secondary amyloidosis related to rheumatoid arthritis and tuberculosis. M-mode and two-dimensional echocardiography were performed for all patients.

M-mode echocardiography

M-mode echocardiography was performed with a commercially-available ultrasonoscope (Hewlett-Packard 77020A or Toshiba SSH 11A or 40A) and was recorded with a multichannel strip-chart recorder (Hewlett-Packard 77500A) or a line scan recorder (Toshiba LSR 20B). Studies were peformed with a 2.4, 2.5 or 3.5 MHz transducer. Patients were examined in the supine or left lateral decubitus position, with the transducer placed at the left sternal border.

All measurements were made at the level of the chordae of the mitral apparatus. End-diastolic measurements for cavity size (LVDd) and wall thickness were made at the peak of the R wave of the ECG. Systolic measurements of the left ventricular internal dimension (LVDs) were made at the nadir of septal motion. Left atrial dimension (LAD) was measured in ventricular end-systole at the level of the aortic valve leaflets, and the measurements included posterior aortic wall thickness. Left ventricular ejection fraction (EF) was calculated by subtracting the end-systolic volume (ESV) from the end-diastolic volume (EDV), and expressing this difference as a percentage of the end-diastolic volume (EDV):

$$EF = \frac{EDV - ESV}{EDV} \times 100\%$$

Ventricular volumes (EDV and ESV) were calculated from ventricular dimensions (LVDd and LVDs) according to the formula of Teichholtz:[16]

$$Volume = \frac{7}{2.4 + D} \times D$$

The mean rate of circumferential shortening (mVcf) was calculated as the left ventricular diastolic minus systolic dimension divided by

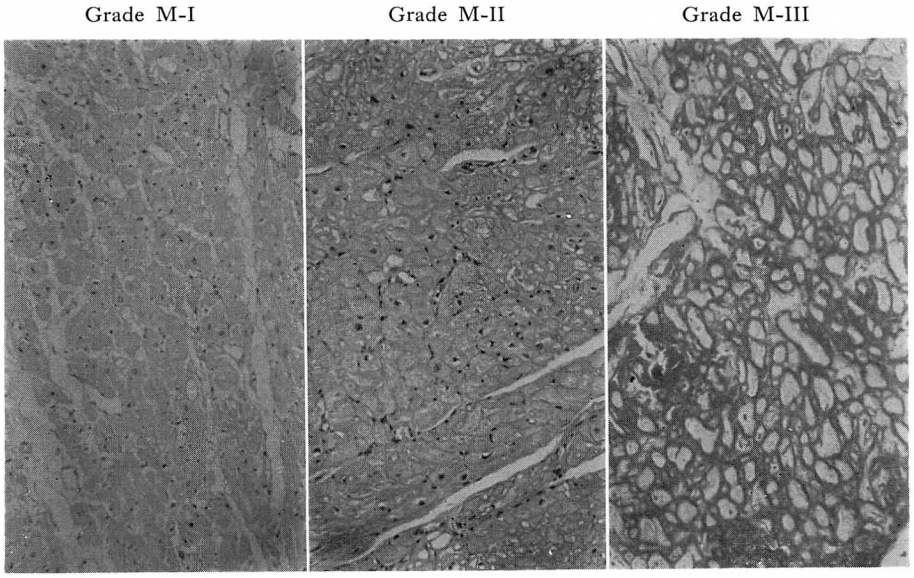

Fig. 1. Grading of amyloid deposition in the myocardium.

Grade M-I: a small amount of amyloid deposition. Grade M-II: a moderate amount of amyloid deposition, or approximately 10 to 40 percent amyloid deposition in the myocardium. Grade M-III: a massive amount of amyloid deposition greater than 40 percent of the myocardium.

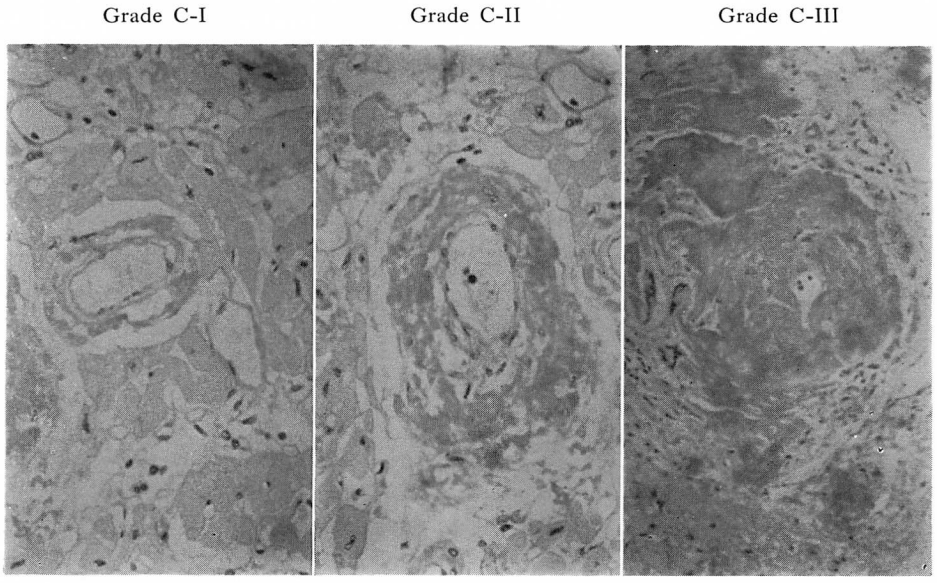

Fig. 2. Grading of amyloid deposition in the coronary arteries.

Grade C-I: a small amount of amyloid deposition. Grade C-II: a moderate amount of amyloid deposition greater than the inherent thickness of the vessel wall. Grade C-III: massive or nodular amyloid deposition with severe stenosis or occlusion of coronary arteries.

the left ventricular diastolic dimension and ejection time (ET):

$$mVcf = \frac{LVDd - LVDs}{LVDd \times ET} \text{ (circumferences/sec)}$$

The rate of early diastolic closure of the anterior leaflet of the mitral valve (DDR) was determined in the section of each echocardiogram in which the anterior and posterior mitral leaflets were simultaneously visualized, and the maximal excursion of the anterior mitral leaflet was noted.[17] The D/S ratio was calculated by the method shown in Fig. 4.[18]

The following ranges of normal values of our laboratory were used: interventricular septal thickness (IVST) and left ventricular posterior wall thickness (LV-PWT), 7.5 to 11.5 mm; left ventricular end-diastolic dimension (LVDd), 40 to 55 mm; left ventricular end-systolic dimension (LVDs), 30 to 44 mm; left atrial dimension (LAD), 19 to 28 mm; ejection fraction (EF), 56 to 75%; mean circumferential shortening rate (mVcf), 0.97 to 1.65 circumferences/sec; rate of early diastolic closure of the anterior leaflet of the mitral valve (DDR), 72 to 150 mm/sec; and D/S ratio, 0.35 to 0.60.

Two-dimensional echocardiography

Two-dimensional echocardiography was performed with a commercially-available sector scanner (Hewlett-Packard 77020A or Toshiba SSH 11A or 40A). Images were recorded directly on a 3/4-inch video cassette with a Sony SLO-325 or on a 1-inch reel to reel tape using a Sony VO 5800 video recorder. Patients were examined in the supine position or in a partial left lateral decubitus position. Cross-sectional views of the heart were obtained from the parasternal, apical and subxiphod positions. The long- and short-

Table 1. Clinical features in nine cases

Case no.	Age (yr) & Sex	Diagnosis	NYHA class	Causes of Death	Duration of Disease	Electrocardiogram	Chest radiography
1	62 F	PA	III	CHF	10 mo	Low voltage; RAD; small R V_1-V_4	Cardiomegaly; pleural effusion
2	48 M	PA	III	CHF	14 mo	Low voltage; LAD; I° AV block; small R V_1-V_3	Slight left ventricular enlargement
3	54 M	PA	II	CRF	12 mo	Low voltage; RBBB	Cardiomegaly
4	68 F	PA	III	CHF	10 mo	Low voltage; small R V_1-V_4; T-wave abnormality	Cardiomegaly
5	62 M	PA	II	CHF	15 mo	RAD; I° AV block; RBBB	Cardiomegaly
6	63 M	MM	II	Pneumonia	20 mo	Low voltage; RAD; small R V_1-V_3	Cardiomegaly
7	56 M	MM	II	CHF	4.4 yr	Low voltage; I° AV block; small R V_1-V_3	Cardiomegaly
8	82 F	SA	III	CHF	2 yr	Low voltage; I° AV block; small R V_1-V_3	Marked cardiomegaly; old inflammatory lesions
9	60 F	SA	II	CRF	19 mo	Low voltage; RAD; atrial fibrillation	Cardiomegaly; pulmonary congestion

Abbreviations: M=male; F=female; PA=primary amyloidosis; MM=amyloidosis associated with multiple myeloma; SA=secondary amyloidosis; CHF=congestive heart failure; CRF=chronic renal failure; mo=months; yr=years; RAD=right-axis deviation; LAD=left-axis deviation; RBBB=right bundle branch block.

axis and four-chamber views were visualized from each transducer position in most patients. Two-dimensional studies were interpreted independently by at least three investigators. During the analysis of measurements, those of pericardial effusion, mural thrombi, and the hyperrefractile "granular sparkling" appearance of the thickened ventricular myocardium were qualitatively evaluated and were designated as normal or abnormal. Abnormalities were graded as mild, moderate or severe.

Histopathology

All hearts were examined grossly, and histologic sections were made from both ventricles. The presence of amyloid was confirmed by Congo red staining and dichloic birefringence in histologic sections of the myocardium. At least 20 sections of the myocardium, including the left and right ventricles, were examined.

We evaluated the presence and degree of amyloid deposition both in the myocardium and the coronary arteries. Grading was based on estimates of the quantities of amyloid (Figs. 1 & 2). According to the amount of amyloid deposition in the myocardium, we defined "Grade M-I" as a small quantity without an increase in interstitial diameter, "Grade M-II" as approximately 10 to 40 percent amyloid deposition or moderate amount with an increase in the interstitium, but less than the cross-section of a myocardial fiber; and "Grade M-III" as a marked amount of amyloid deposition, greater than 40 percent of the myocardium and/or greater than the cross-section of a myocardial fiber. The "interstitial type" was defined as Grade M-II or more. According to the degree of amyloid deposition in the coronary arteries, "Grade C-I" was defined as a small amount of amyloid deposition less than the thickness of the vessel wall; "Grade C-II", as a moderate amount of amyloid deposition greater than the normal thickness of vessel wall without massive or nodular deposition; and "Grade C-III", as massive or nodular amyloid deposition with severe stenosis or occlusion of the coronary arteries. The "perivascular type" was defined

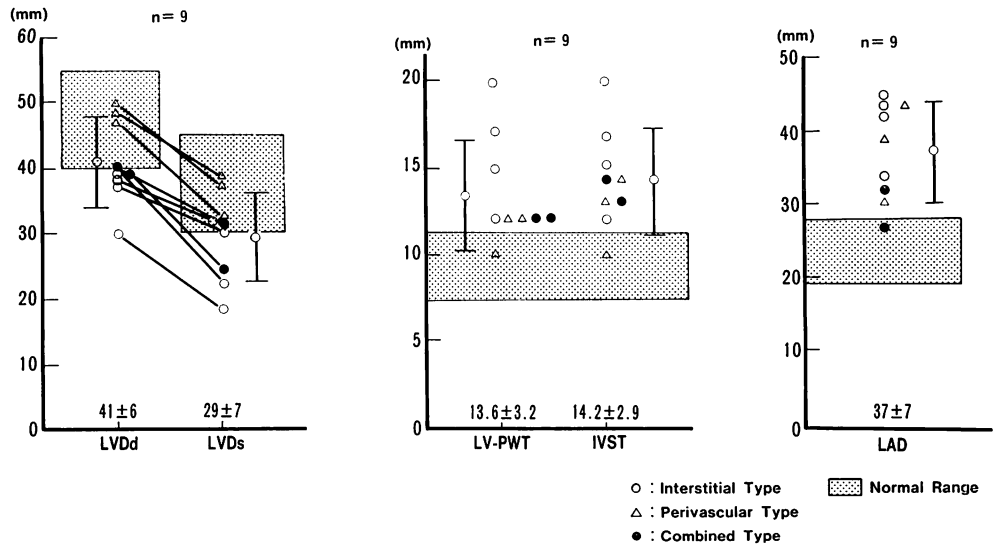

Fig. 3. M-mode echocardiographic data obtained in nine patients with cardiac amyloidosis.

LVDd=left ventricular end-diastolic dimension; LVDs=left ventricular end-systolic dimension; LV-PWT=left ventricular posterior wall thickness; IVST=interventricular septal thickness; LAD=left atrial dimension.

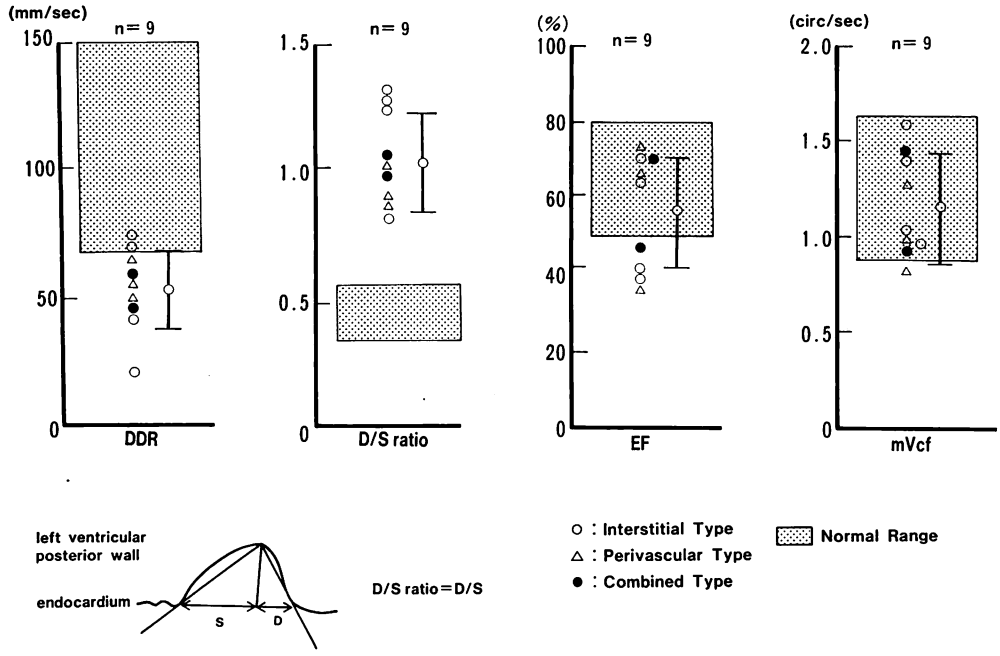

Fig. 4. M-mode echocardiographic data obtained in nine patients with cardiac amyloidosis and measurement method of the D/S ratio.

DDR=diastolic descent rate of the anterior mitral valve leaflet; EF=ejection fraction; mVcf=mean velocity of circumferential shortening.

as Grade C-II or more. The "combined type" was defined as Grade M-II or more and Grade C-II or more.

Results

Clinical features

The clinical data are summarized in **Table 1.** All nine patients initially had or subsequently developed congestive heart failure. Initially, four cases were in New York Heart Association (NYHA) functional class III; five were in class II. The mean disease duration (±SD) was 1.7 ±1.1 years. Six patients died of congestive heart failure; two, chronic renal failure; and one, pneumonia. All nine patients had abnormal electrocardiograms; eight (89%) had low voltage. Chest radiography revealed cardiomegaly (CTR >55%) in eight patients (89%). None had histories of systemic arterial hypertension or evidence of obstruction of the aortic outflow tract.

M-mode echocardiography

Table 2 and **Figs. 3 & 4** summarize the M-mode echocardiographic data of the nine patients. LV end-diastolic dimension (LVDd) was normal in four patients; and decreased in five. LV end-systolic dimension (LVDs) was normal in six patients, and decreased in three. The thickness of the interventricular septum (IVST) was increased in eight patients (89%), and the thickness of the LV posterior wall (LV-PWT) was increased in eight patients (89%). None had asymmetrical septal hypertrophy (IVST/LV-PWT>1.3). Left atrial enlargement was observed in eight patients (89%). Ejection fraction (EF) was normal in five patients, and reduced in four. The mean rate of circumferential shortening (mVcf) was normal in eight patients; and decreased in one. The rate of early diastolic closure of the anterior leaflet of the mitral valve (DDR) was normal in two patients; and decre-

ased in seven (78%). All nine patients had increased D/S ratios.

Fig. 5 shows a representative example of the serial M-mode echocardiographic studies (Case 2). The thicknesses of the interventricular septum and LV posterior wall increased progressively. An increase in the D/S ratio was noted initially; then the decrease of ejection fractions and the mean rate of circumferential shortening (mVcf) gradually developed.

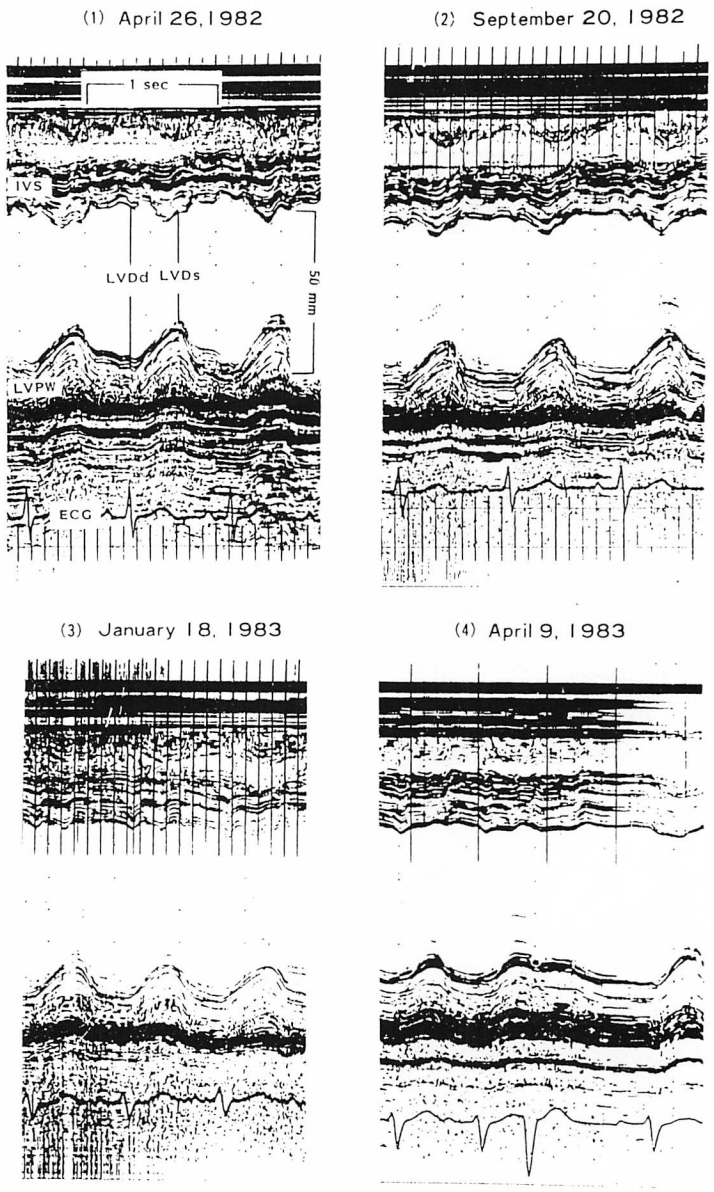

Fig. 5. A representative example of serial M-mode echocardiographic studies (Case 2). LVDd=left ventricular end-diastolic dimension; LVDs=left ventricular end-systolic dimension; IVS=interventricular septum; LVPW=left ventricular posterior wall; ECG=electrocardiogram.

Two-dimensional echocardiographic data

Six patients (67%) had pericardial effusion; small in five, and moderate in one. Only one patient (Case 1) had large mural thrombi in both atria (**Fig. 6**).

The most impressive two-dimensional findings, which were not apparent on M-mode echocardiography, however, were a hyperrefractile "granular sparkling" appearance of the thickened ventricular myocardium (**Fig. 7**). This uniform hyperrefractility was observed in five of the nine patients (55%). The hyperrefractile echoes in the interventricular septum exceeded in number those in other parts of the myocardium, and they often appeared in clusters.

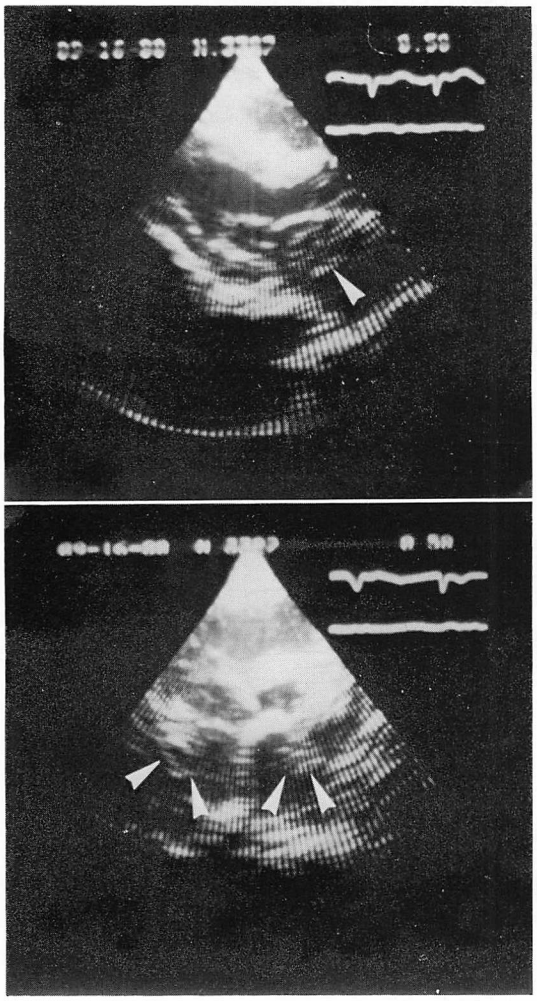

Fig. 6. Two-dimensional echocardiograms obtained in a case with large mural thrombi in both atria (Case 1).

Upper: long-axis view; lower: short-axis view. Arrows indicate mural thrombi.

Correlation with necropsy findings

Table 2 summarizes the necropsy findings of all subjects. Five cases (Cases 1, 2, 4, 5 and 6) had "rubbery" non-compliant hearts. The average heart weight (±SD) was 462±102 g with a range from 290 to 590 g. Four cases (Cases 1, 3, 4 and 7) were of the "interstitial type"; three (Cases 2, 8 and 9), the "perivascular type"; and two (Cases 5 and 6), the "combined type". There was no correlation between amyloid deposit types and the hyperrefractile "granular sparkling" appearance. Histologically, scattered amyloid deposits were observed in four patients who had "granular sparkling" appearances in their thickened ventricular myocardium on two-dimensional echocardiography. The histopathological findings of one case (Case 6) having a "granular sparkling" appearance without scattered amyloid deposits included moderate amyloid deposits and a moderate degree of interstitial fibrosis.

Discussion

Systemic amyloidosis is a progressive disease which often involves the heart[4,6], and it is reported that approximately one-third of amyloidosis patients have cardiac-related deaths[4]. Characteristically, when cardiac amyloid deposits are extensive, they cause myocardial dysfunction manifested as congestive heart failure and, ultimately, death[1,3,4]. The clinical presentation was congestive heart failure in all patients in the present study.

Autopsy studies have demonstrated consistent findings in patients with cardiac amyloidosis[3,5,6]. The heart weight is increased. The myocardium is involved more often than is the pericardium or epicardium; both the atria and ventricles may be diffusely or focally affected. Usually, there is marked thickening of the myocardial wall, re-

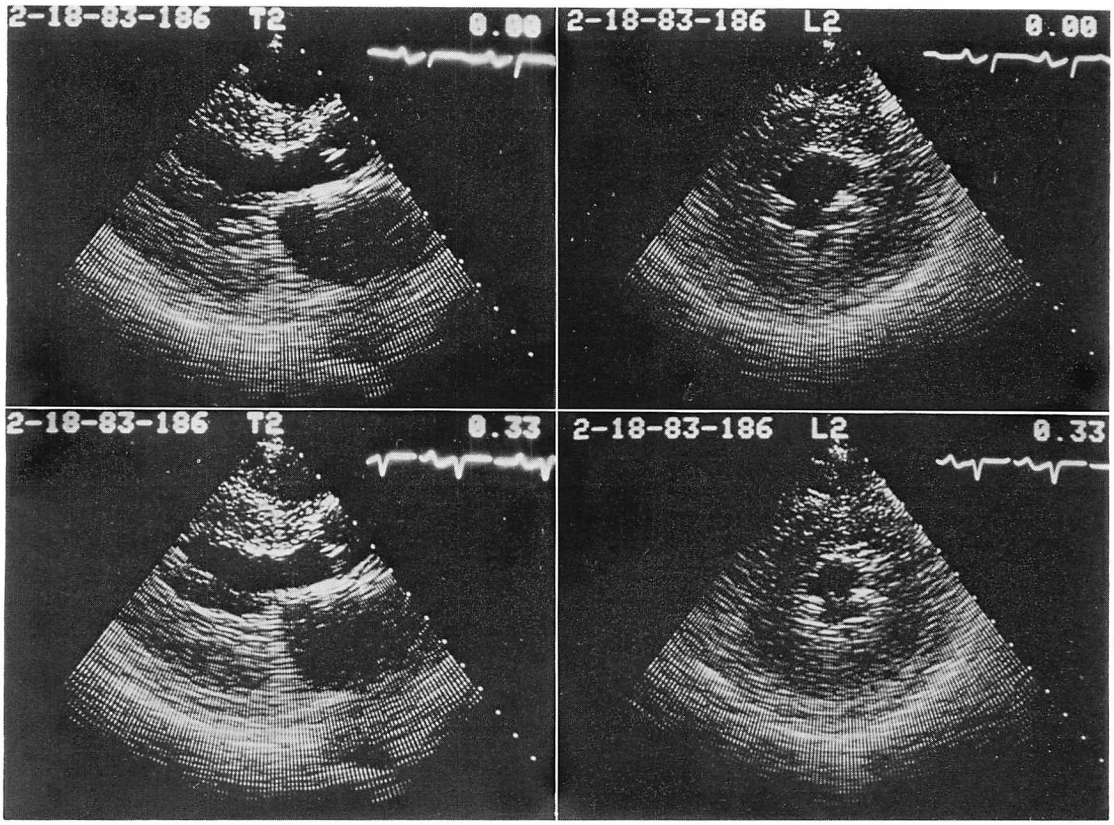

Fig. 7. Two-dimensional echocardiograms obtained in a case with a hyperrefractile "granular sparkling" appearance of the thickened ventricular myocardium (Case 4).

sulting in a stiff and non-compliant ventricle. The LV cavity is often normal in size, and the left atrium is dilated, presumably as a result of diminished left ventricular compliance[9].

Cardiac amyloidosis may mimic constrictive pericarditis clinically and hemodynamically[1,3,20,21]. Constrictive pericarditis should be excluded by exploratory thoracotomy[12]. All patients had electrocardiographic abnormalities similar to those previously described[3,4,7].

M-mode echocardiography

M-mode echocardiography revealed, as anticipated, that LV internal dimension was not enlarged in these patients[3,7,8,12,22,23]. Four of nine M-mode echocardiograms (44%) showed normal end-diastolic LV dimensions; in five cases (56%) they were reduced. The left atrium, however, was mildly to moderately enlarged in eight of the nine patients (89%), presumably as a consequence of diminished LV compliance.

Increased thickness of the interventricular septum and the LV posterior wall was noted in the majority of patients (89%). Although asymmetrical septal hypertrophy (IVST/PWT ratio >1.3) was reported in one-fourth of cardiac amyloidosis cases by Siqueira-Filho et al[12], none of the patients in the present study had asymmetrical septal hypertrophy.

Interstitial infiltration by amyloid compresses the myocardial fibers, which then undergo necrosis or atrophy. Extensive deposition destroys the muscle cells entirely, leaving empty amyloid rings or solid sheets of amyloid[24]. The degree of consequent impairment of LV function de-

Table 2. Echocardiographic and necropsy findings in patients with cardiac amyloidosis

Case	LVDd (mm)	LVDs (mm)	IVST (mm)	LV-PWT (mm)	LAD (mm)	EF (%)	mVcf (circ/s)	DDR (mm/s)	D/S ratio*
1	37	30	12	12	43	40	1.05	42	1.23
2	48	39	14	12	43	88	0.78	67	1.00
3	39	22	15	15	42	62	1.60	72	1.25
4	38	31	17	20	44	39	0.97	21	1.30
5	39	24	13	12	27	70	1.48	49	0.92
6	40	31	14	12	31	46	0.93	60	1.07
7	30	18	20	17	33	70	1.42	70	0.79
8	49	30	13	12	30	73	1.29	50	0.89
9	49	37	10	10	38	62	1.01	58	0.87
mean	41	29	14.2	13.6	37	56	1.21	54	1.04
±SD	±6	±7	±2.9	±3.2	±7	±15	±0.37	±16	±0.19

*D/S ratio=by the method of Fujino et al (Fig. 4)[18].

Abbreviations: LVDd=left ventricular end-diastolic dimension; LVDs=left ventricular end-systolic dimension; IVST=diastolic thickness of the interventricular septum; LV-PWT=diastolic thickness of the left ventricular↗

pends on the magnitude of cardiac involvement and the stage of the disease. Global LV contractility by ejection fraction (EF), or by the mean rate of circumferential shortening (mVcf), was reduced in 44% or 22%, respectively. Global LV distensibility by the rate of early diastolic closure of the anterior leaflet of the mitral valve (DDR), or by the D/S ratio, was impaired in 78% or 100%, respectively. Thus, M-mode echocardiography showed a greater reduction in diastolic than systolic regional LV function.

Serial M-mode echocardiograms indicated that cardiac amyloidosis is manifested initially more as diastolic than systolic LV failure, confirming previous hemodynamic findings[25]. The final stages in the natural history of this disease are marked by severe impairment of both systolic and diastolic regional and global LV functions[13].

Two-dimensional echocardiography

Evaluation by the two-dimensional technique confirmed all the M-mode echocardiographic findings.[12] Pericardial effusion, more easily visualized and better appreciated by this technique, was detected in six patients (67%). There was no correlation between pericardial effusion and the clinical findings, especially congestive heart failure. Two-dimensional echocardiography provided additional features not appreciated using the M-mode technique; for example, papillary muscle hypertrophy, thickened valves or a thickened interatrial septum[8,12,15]. The most interesting and characteristic finding was a diffuse hyperrefractile "granular sparkling" in the thickened myocardium[12,15,22], observed in five of the nine patients (55%).

This constellation of two-dimensional echocardiographic findings; namely thickened ventricular and septal walls with "granular sparkling" in the myocardium, a normal or small LV cavity, and enlarged atria, is virtually diagnostic of cardiac amyloidosis[12]. On the basis of the two-dimensional echocardiographic findings, biopsies is recommended, which results in the correct diagnosis of this disease[7,13].

Correlative echocardiography and histopathology

The echocardiographic evaluation of the functional and anatomical features in the present study was in good agreement with the pathological findings. In some cases of systemic amyloidosis two-dimensional echocardiography has demonstrated hyperrefractile myocardial echoes,

Table 2. Cont'd.

Pericardial effusion	Granular sparkling appearance	Heart weight (g)	Amyloid deposit type	Amyloid mass deposits
(+)	(+)	510	IS	(+)
(+)	(+)	550	PV	(+)
(−)	(−)	370	IS	(−)
(−)	(+)	550	IS	(+)
(+)	(−)	500	CB	(−)
(−)	(+)	415	CB	(−)
(+)	(+)	380	IS	(+)
(+)	(−)	290	PV	(−)
(+)	(−)	590	PV	(−)
		462 ±102		

↘posterior wall; LAD=left atrial dimension; EF=ejection fraction; mVcf=the mean rate of circumferential fiber shortening; DDR=diastolic descent rate of the anterior mitral valve leaflet; IS=interstitial type; PV=perivascular type; CB=combined type.

so-called "granular sparkling" appearance, which has been considered a characteristic feature of cardiac amyloidosis[12,15,22]. However, the underlying histopathological basis for the hyperrefractile myocardial echoes has not yet been established. Bhandani and Nanda[15] reported that hyperrefractile myocardial echoes corresponded to amyloid deposits, without concomitant fibrosis or calcification in specimens of two cases of cardiac amyloidosis which were examined in vitro[15]. Another in vitro study of autopsied heart specimens of familial amyloidosis subjects showed that hyperrefractile myocardial echoes were due to nodules containing amyloid and collagen in varying proportions[26]. In the present study, four cases with hyperrefractile " granular sparkling" appearance histologically had scattered amyloid deposits. In one subject who had a hyperrefractile "granular sparkling" without scattered amyloid deposits, a moderate quantity of amyloid was deposited in the perivascular and interstitial regions, and a moderate degree of interstitial fibrosis was observed histopathologically.

Conclusion

The echocardiographic features of cardiac amyloidosis included thickened septal and ventricular walls with a "granular sparkling" appearance, a normal or small LV cavity, and enlarged atria. The "granular sparkling" corresponded histopathologically to scattered amyloid deposits in most patients. Cardiac involvement in systemic amyloidosis can be accurately and non-invasively assessed by M-mode and two-dimensional echocardiography.

心アミロイドーシスの心エコー図所見と病理学的所見の対比検討

虎の門病院　循環器センター内科
西川英郎，西山信一郎，西村重敬，近藤邦夫
今井　進，加藤健一，中西成元，関　　顕
三重大学医学部　第一内科
井坂直樹，山門　徹，中野　赳，竹沢英郎

要　　約

剖検にて確診された9例の心アミロイドーシスの病理学的所見と心エコー図所見の対比検討を行った．全例，心不全を有し，剖検にて心へのアミロイド沈着を認めた．

M モード心エコー図所見は，(1) 心内径の狭小化ないしは正常，(2) 壁厚の増加 (89%)，(3) 左房拡大 (89%)，(4) 左室拡張能の低下 (DDR：78%，D/S 比：100%) および左室収縮能の低下 (mVcf：22%，EF：44%) であった．早期には拡張能の低下が主で，収縮能は比較的よく保たれていたが，末期には収縮能の異常も著明になった．

断層心エコー図所見は，心嚢水貯留 (67%) と特徴的な granular sparkling (55%) であった．この高屈折エコーは病理組織学的に散在性のアミロイドの塊状沈着にほぼ一致し，血管型ないし間質型といった沈着様式とは相関しなかった．

このように，全身性アミロイドーシスの心病変は，M モードならびに断層心エコー図にて非観血的に評価でき，かつ病理組織像の推測が可能であった．

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