의학석사 학위논문

Incidence, Diagnosis and Prognosis of Cardiac Amyloidosis

심장 유전분증의 발병률, 진단 및 예후에 대한 연구

2012 년 10 월

서울대학교 대학원

의학과 석사과정

이 민 호

A thesis of the Degree of Master of Science

심장 유전분증의 발병률, 진단 및 예후에 대한 연구

Incidence, Diagnosis and Prognosis of Cardiac Amyloidosis

October 2012

The Department of Internal Medicine,

Seoul National University

College of Medicine

Min-Ho Lee

심장 유전분증의 발병률, 진단 및 예후에 대한 연구

지도 교수 손 대 원

이 논문을 의학석사 학위논문으로 제출함
2012년 10월

서울대학교 대학원
의학과 내과학전공
이 민 호

이민호의 의학석사 학위논문을 인준함
2012년 12월

위 원 장 _____ (인)
부위원장 _____ (인)
위 원 _____ (인)

Incidence, Diagnosis and Prognosis of Cardiac Amyloidosis

by
Min-Ho Lee

A thesis submitted to the Department of Medicine in partial fulfillment of the requirements for the Degree of Master of Science in Medicine (Internal Medicine) at Seoul National University College of Medicine

December 2012

Approved by Thesis Committee:

Professor _____Chairman
Professor _____Vice chairman
Professor _____

ABSTRACT

Introduction: Cardiac involvement is frequent in systemic amyloidosis and is the most important determinant of clinical outcome. The aims of this study were to assess the incidence and prognosis of cardiac amyloidosis and discuss diagnostic issues related to cardiac amyloidosis.

Methods: We retrospectively studied all patients diagnosed with systemic amyloidosis who presented to our institution from January 1999 to December 2011.

Results: Of the 129 patients with systemic amyloidosis,cardiac amyloidosis was diagnosed in 62 patients. At a mean of 3 years' follow-up of the patients with systemic amyloidosis, there was statisticallysignificant difference in mortality between patients with cardiac amyloidosis and the rest of the patients (38.3% vs. 14.2%, log rank p = 0.014). And decreased LV function was theonly factor independently associated withsurvivalin cardiac amyloidosis patients in both univariate and multivariate analysis(HR3.936, 95% CI1.247-12.425, p = 0.020). In the diagnosis of monoclonal gammopathy, serum or urine PEPis not sensitive enough to be used clinically compared to serum FLC assay (35.8%vs. 96.4%).

Conclusions: In systemic amyloidosis, cardiac involvement is the most important determinant ofprognosis and decreased LV function was independently associated withsurvivalin cardiac amyloidosis patients.

Keywords: Cardiac amyloidosis, systemic amyloidosis, monoclonal gammopathy

Student number; 2011-21852

CONTENTS

LIST OF TABLES AND FIGURES

INTRODUCTION

Amyloidosis is a clinical disorder caused by extracellulardeposition of insoluble abnormal fibrils, derived from aggregationof misfolded normally soluble protein[1,2]. Many different proteins can formamyloid fibrils, and the types of amyloidosis are classified onthe basis of the amyloidogenic protein as well as by the distributionof amyloid deposits as either systemic or localized[3]. In systemic amyloidosis, amyloid depositsare present in the viscera, blood vessel walls, and connectivetissues. In contrast, in localized disease, the deposits are confinedto specific foci or to a particular organ or tissue.

The heart is notinfrequently involved in systemic amyloidosis. However, diagnosis of cardiac involvement is not easy and frequently underdiagnosed. Making an early diagnosis of cardiac amyloidosis iscritical because, once clinically significant heartdisease is present, the prognosis is extremely poor.

The gold standard test for diagnosis of cardiac amyloidosis is endomyocardial biopsy[4], but cannot be performed in every patient because of its invasiveness. Thus, in clinical practice, diagnosis of cardiac amyloidosis is often made in patients with systemic amyloidosis when echocardiographic findings suggest infiltrative cardiomyopathy[5-8].Recently, cardiovascularmagnetic resonance imaging (CMR) with late gadoliniumenhancement (LGE) sequences was shown to be useful for thediagnosis of cardiac involvement in systemic amyloidosis[9-13].

In the present study, we assessed the incidence and prognosis of cardiac amyloidosis and discuss diagnostic issues related to cardiac amyloidosis.

MATERIALS AND METHODS

Study Population

We retrospectively studied all patients diagnosed as systemic amyloidosis who presented to the Seoul National University Hospital, Korea from January 1999 to December 2011. This study was approved by theinstitutional review board at our institution. Patients were followed up and evaluated for development of clinical events, using electronic medical records.

Methods

Detection of the presence of monoclonal gammopahty and diagnosis of systemic amyloidosis. For the detection of the presence of monoclonal gammopathy, protein electrophoresis (PEP) for the presence of M protein or immunofixation electrophoresis (IEP), free light chain (FLC) assay in serum and/or urine were used. Diagnosis of systemic amyloidosis wasbased on histologic confirmation of tissue deposition of amyloid. At the time of histologic confirmation, specimens were stained with Congo red and diagnosis of amyloidosis was made when thedeposition of amorphous material which showed apple-green birefringenceunder the polarized microscope was detected[14]. Immunohistochemical stains using antibodies directedagainst serum amyloid P component, transthyretin (TTR), kappa and lambda light chains, and serum amyloid A were performed simultaneously[15].

Diagnosis of cardiac amyloidosis. Diagnosis of cardiac amyloidosis was made when 1) amyloid deposition was demonstrated in the myocardium by the endomyocardial biopsy, or 2) cardiac involvement either in echocardiography or CMR was suggested in patient with systemic amyloidosis. Echocardiography was performed in all patients with systemic amyloidosis. In the echocardiographic findings, cardiac involvement was suggested when mean LVthickness > 12 mm (average of end-diastolic septaland inferolateral walls in the parasternal long-axis view)[16] and standard 12-lead electrocardiograms (ECG) showed low voltage QRS (defined as a QRS amplitude <0.5 mV in all limb leads). When CMR was performed, cardiac involvement was suggested when there was global or subendocardial LGE of the myocardium.

Other biomarkers. Cardiactroponin-I(cTNI, reference normal: < 0.5 ng/mL), B-type natriuretic peptide (BNP, reference normal: ≤ 100 pg/ml) or pro-type natriuretic peptide (pro-BNP, reference normal: 0-84 pg/ml for men under 50 years; 0-194 pg/ml for men above 50 years; 0-155 pg/ml for women under 50 years; 0-222 pg/ml for women above 50 years) were measured.

Diagnosis of other organ involvement in amyloidosis. The 10th International Symposium on Amyloid andAmyloidosis was held 18-22 April 2004, in Tours,France. In anticipation of this meeting, 13 leaders inthe field were invited to submit their institutionalcriteria, from which the current guidelines were developed. We adopted these guidelines for the diagnosisof organ involvement in amyloidosis[16].

Statistical Analysis

Data analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, Illinois). Discrete data are summarized as frequencies, while continuous variables as mean ± SD. Chi-square or Fisher's exact test were used for comparison of categorical variables. The Kolmogorov-Smirnov test was used for normality test. Student's t-test was used for comparison of normally distributed continuous variables. In case of non-normal distribution, Mann-Whitney U test, Wilcoxon signed rank test were used. Survival estimates andcumulative event rates were estimated using the Kaplan-Meier method.Risk factors for survival were evaluated by both, univariate and multivariate analysis using Cox proportional hazards model.When verifying the analyses results with stepwise forward Cox's regression, a p value of 0.10 was used to exclude or include the variables. A p value of < 0.05 was considered statistically significant.

RESULTS

Patients

Baseline characteristics of the patients with systemic amyloidosis and cardiac amyloidosis are summarized in Table 1−2. From January 1999 to December 2011, 129 patients were newlydiagnosed with systemic amyloidosis. Among them, 76 patients (58.9%) were male, mean age was 57.2±11.5. Hypertension was found in 34 patients (26.4%), DM in 11 (8.5%), dyslipidemia in 7 (5.4%), chronic kidney disease (CKD) in 25 (19.2%) and smoking history in 2 (1.6%). Cardiac involvement was found in 62 patients (48.1%) and kidney was second most commonly involved organ (n = 49, 40.0%).

Baseline characteristics were not different between patients with cardiac involvement (n = 62) and without cardiac involvement(n = 67) except for theage and CKD.Patients with cardiac involvement were older and had less CKD than patients without cardiac involvement (60.1 ±9.7 vs. 54.5 ± 12.4, p = 0.006; 8.1% vs. 29.9%, p = 0.002). The mean follow−up periods were 725± 944.9 days, vs 999.5±993.0 days(p = 0.111) in patient with and without cardiac involvement, respectively.

Diagnostic characteristics

Table 3 shows the characteristics of the patients with systemic amyloidosis (n = 129). Light chain (AL)amyloidosiswas present in 127 (98.4%) andsenile

systemic amyloidosis (SSA) in 2 (1.6%). Among the patients with AL amyloidosis, 32 patients (25.2%) were kappa light chain type, and 75 patients (59.1%) were lambda light chain type. There were positive findings of serum or urine PEP in 43 of 120 patients (35.8%), serum or urine IEP in 43 of 103 (41.7%), serum FLC assay in 81 of 84 (96.4%). Laboratory, ECG, echocardiographic and CMR findings in cardiac amyloidosis are shown in detail in Table 4. In patients with cardiac amyloidosis (n = 62), AL amyloidosis was present in 60 (96.8%) and SSA in 2 (3.2%). Among the patients with cardiac involvement in AL amyloidosis, 11 cases (19.6%) were kappa light chain type and 45 cases (80.4%) were lambda light chain type.

In the laboratory findings, 26 of 27 patients (96.3%) had elevation of BNP or pro-BNP. Endomyocardial biopsy was available in 30 patients and positive pathology compatible with cardiac amyloidosis was present in 29 patients (96.6%). There was low voltage QRS at ECG in 53 of 62 patients (85.5%)(Figure 1). Echocardiography was available in all patients. Among them, increased LVwall thickness was present in 60patients (96.8%), decreased LV function in 31 (50.0%), pericardial effusion in37 (60.7%) and diastolic dysfunction in 42 (68.9%)(Figure 2). CMR was also available in 15 patients and positive finding was present in 13 (86.7%)(Figure 3). In detail, 29 patients were diagnosed with cardiac involvement by endomyocardial biopsy, and among the rest of the patients (n = 33), cardiac involvement was suggestedby the echocardiographic findings in 29 patients and both in echocardiographic and CMR findingsin 4 patients.

Survival and Prognosis

At a mean of3 years' follow-up of the patients with systemic amyloidosis, death had occurred in 17 cases in patients with cardiac involvement (n = 62) and 8 patients without cardiac involvement (n = 67). There werestatisticallysignificant differences in mortality at a mean of3 years' follow-up (38.3% vs. 14.2%, log rankp = 0.014) (Figure 4).

Regarding to the effect of treatment (chemotherapy, autologous stem cell transplantation and cardiac transplantation) on the prognosis, in patients with systemic amyloidosis, death had occurred in 20 cases in treatment group (n = 100) and 5 cases in no-treatment group (n = 29). There was no statisticallysignificant difference in mortality between the groups (25.6% vs. 20.9%, log rankp = 0.771) (Figure 5). In addition, no significant effect of treatment on the prognosis was also noted in patients with cardiac amyloidosis, at a mean of3 years' follow-up. Death had occurred in 14 cases in treatment group (n = 52) and 3 cases in no-treatment group (n = 10) (37.4% vs. 33.3%, log rankp = 0.316) (Figure 6).

In univariateanalysisof the patients with cardiac involvement, decreased LV function was the only significant variable associated with survival. After multivariate analysis, decreased LV function was theonly factor independently associated withsurvival, with a hazard ratio of 3.936 (p = 0.020; 95% confidenceinterval, 1.247-12.425) (Table 5)

Table 1. Baseline characteristics in patients with amyloidosis

	Systemic amyloidosis (n = 129)	With cardiac involvement (n = 62)	Without cardiac involvement (n = 67)	*p value
Age, years	57.2 ± 11.5	60.1 ± 9.7	54.5 ± 12.4	0.006
Male, n (%)	76 (58.9%)	32 (51.6%)	44 (65.7%)	0.112
HTN, n (%)	34 (58.9%)	18 (29.0%)	16 (23.9%)	0.552
DM, n (%)	11 (8.5%)	3 (4.8%)	8 (11.9%)	0.210
Dyslipidemia, n (%)	7 (5.4%)	3 (4.8%)	4 (6.0%)	> 0.999
Smoking History, n (%)	2 (1.6%)	1 (1.6%)	1 (1.5%)	> 0.999
CKD, n (%)	25 (19.4%)	5 (8.1%)	20 (29.9%)	0.002
Treatment, n (%)	100 (77.5%)	52 (83.9%)	48 (71.6%)	0.139
Mean follow-up, days	867.8 ± 976.1	725.5 ± 944.9	999.5 ± 993.0	0.111

* p value between with cardiac involvement and without cardiac involvement

CKD, chronic kidney disease

Table 2. Frequency of organ involvement in patients with systemic amyloidosis

Systemic amyloidosis (n = 129)	
Involved organs, n (%)	
Heart	63 (48.8%)
Kidney	49 (40.0%)
Gastrointestinal tract	20 (15.5%)
Soft tissue	10 (7.8%)
Liver	9 (7.0%)
Lung	5 (3.9%)
Nerve	1 (0.8%)

Table 3. Patients' laboratory characteristics in systemic amyloidosis

Systemic amyloidosis (n = 129)	
Types, n (%)	
AL amyloidosis	127 (98.4%)
SSA	2 (1.6%)
Subtypes of AL amyloidosis (n = 107)	
Kappa light chain, n (%)	32 (25.2%)
Lambda light chain, n (%)	75 (59.1%)
Laboratory characteristics	
Positive of serum or urine PEP (n = 120)	43 (35.8%)
Positive of serum or urine IEP (n = 103)	43 (41.7%)
Positive of serum FLC assay (n = 84)	81 (96.4%)
Positive of immunohistochemistry (n = 63)	43 (68.3%)

AL, amyloid light chain; SSA, senile systemic amyloidosis; PEP, protein electrophoresis; IEP, immunofixationelectrophoresis, FLC, free light chain.

Table 4. Patients' laboratory, ECG, echocardiographic and CMRcharacteristics in cardiac amyloidosis

Cardiac amyloidosis (n = 62)	
Types of amyloidosis (n = 62)	
AL amyloidosis, n (%)	60 (96.8%)
SSA, n (%)	2 (3.2%)
Subtypes of light chain (n = 56)	
Kappa light chain, n (%)	11 (19.6%)
Lambda light chain, n (%)	45 (80.4%)
Laboratory characteristics, n (%)	
Elevation of cTNI (n = 18)	0 (0%)
Elevation of BNP or pro-BNP (n = 26)	25 (96.2%)
Endomyocardial biopsy (n = 30)	
Positive pathology, n (%)	29 (96.6%)
ECG characteristics(n = 62)	
Low voltage QRS, n (%)	53 (85.5%)
Echocardiographic characteristics (n = 62)	
Positive echocardiography, n (%)	60 (96.8%)
LV EF < 50%, n (%)	31 (50.0%)
Presence of pericardial effusion, n (%)	37 (60.7%)
Presence of diastolic dysfunction, n (%)	42 (68.9%)
CMR characteristics(n = 15)	
Positive CMR, n (%)	13 (86.7%)

AL, amyloid light chain; SSA, senile systemic amyloidosis; cTNI, cardiactroponin-I; BNP, B-type natriuretic peptide; pro-BNP, pro-B-type natriuretic peptide; B2MG, beta-2-microglobulin; PEP, protein electrophoresis; IEP, immunofixation electrophoresis, FLC, free light chain; LV EF, Left ventricular ejection fraction; CMR, cardiovascular magnetic resonance imaging

Table 5. Prognosis valuables for cardiac amyloidosis

Univariate Analysis		Multivariate Analysis	
Variables	p value	Hazard Ratio (95% CI)	p value
Low voltage QRS	0.602	0.506 (0.137−1.869)	0.307
Increased LV wall thickness	0.681	0.276 (0.028−2.720)	0.270
Decreased LV function	0.030	3.936 (1.247−12.425)	0.020
Pericardial effusion	0.486	1.368 (0.520−3.596)	0.525
Diastolic dysfunction	0.754	1.036 (0.361−2.973)	0.947

LV, Left ventricular

Figure 1. ECG in a patient with cardiac amyloidosis. Note the low voltage QRS in the limb leads.

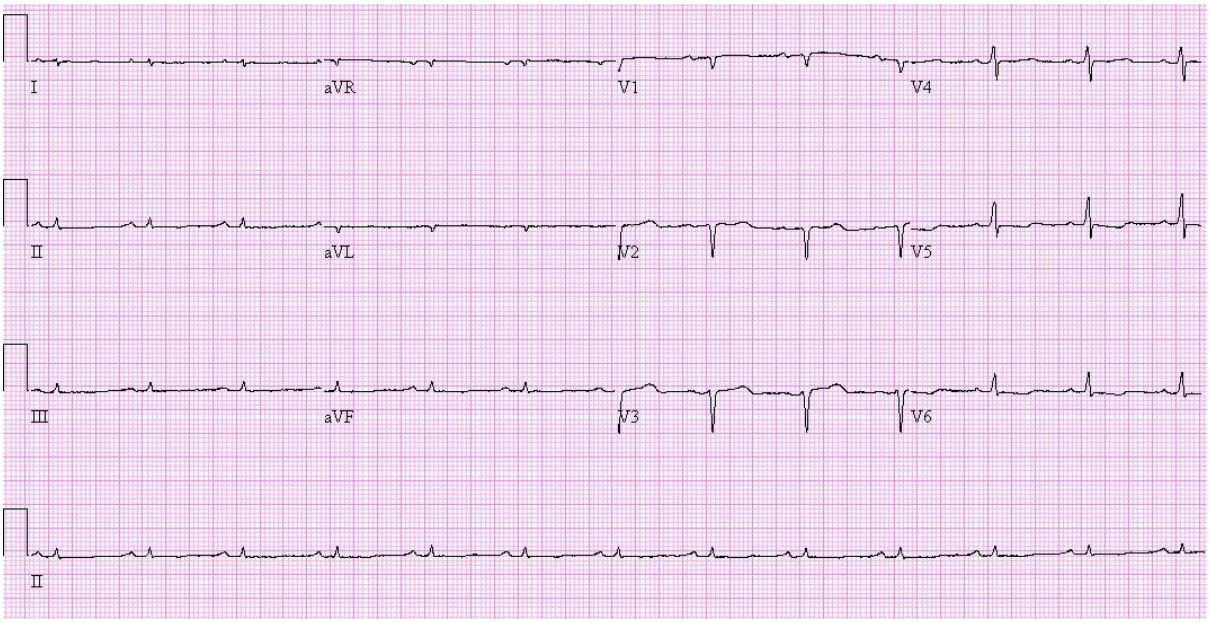


Figure 2. Echocardiography in a patient with cardiac amyloidosis.Top left and right, parasternal long-axis and apical four chamber view demonstrates concentric left ventricular thickening with small amount of pericardial effusion. Bottom left and right, transmitral doppler flow shows a pseudonormalization pattern with increased E/E' ratio.

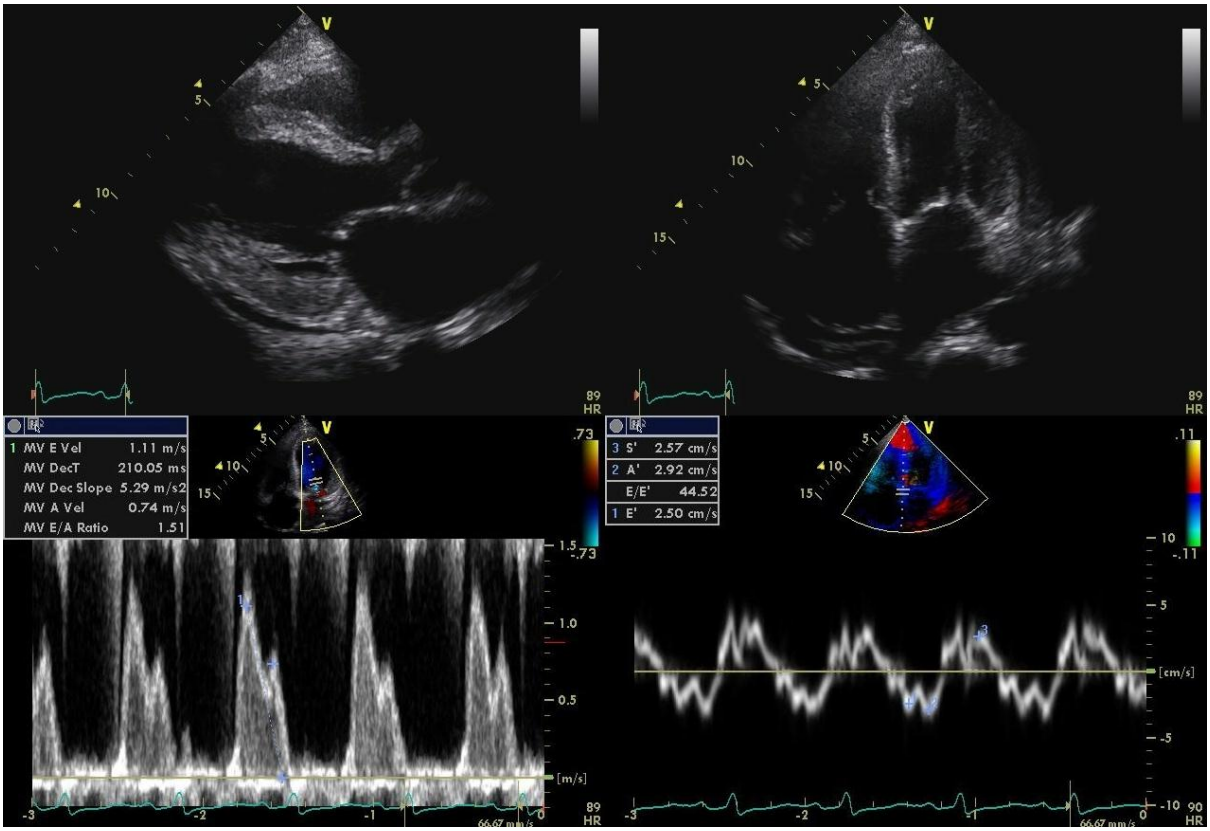
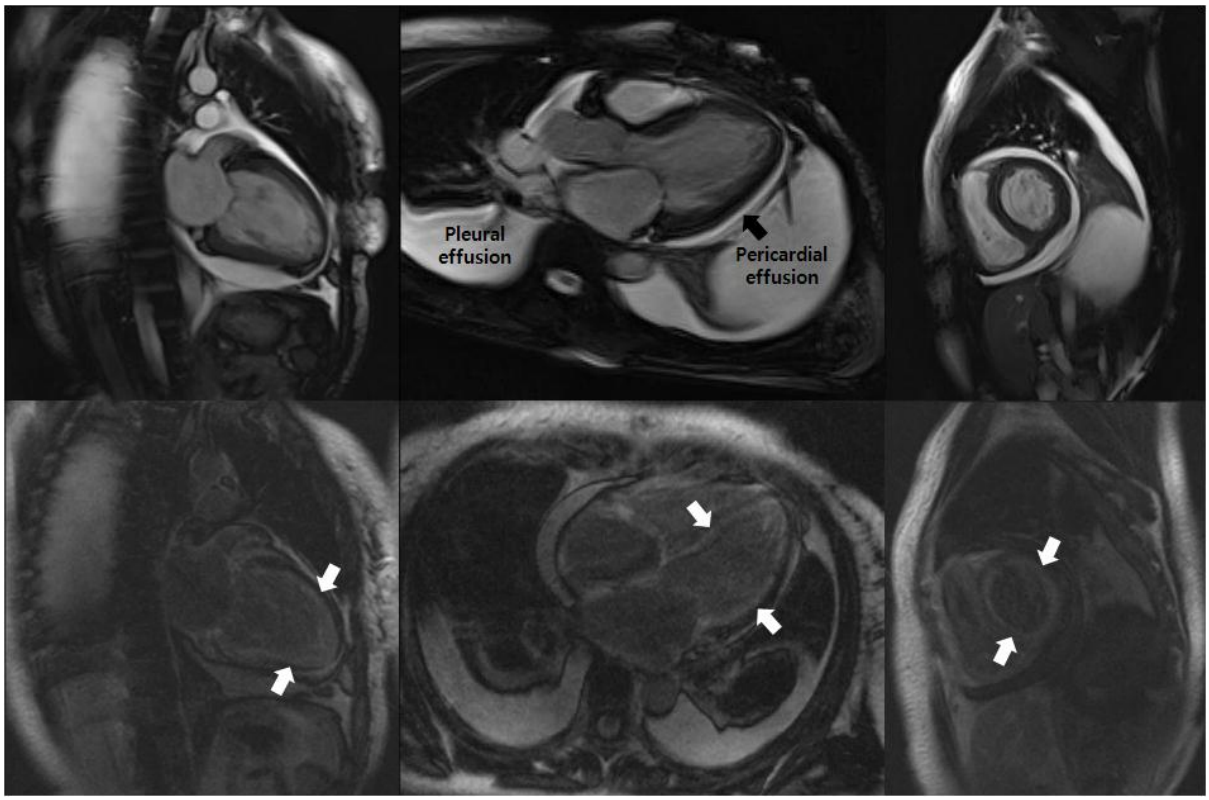
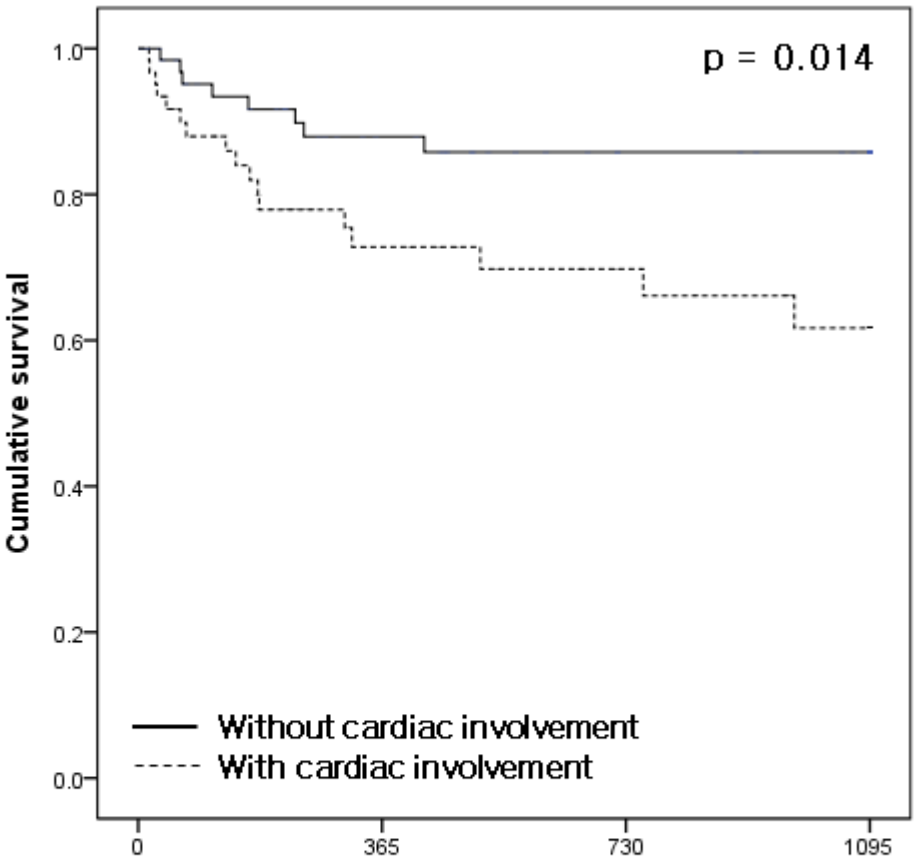


Figure 3. CMR in a patient with cardiac amyloidosis. Top row shows diastolic frames from cines (vertical long axis, horizontal longaxis, and short axis, respectively) showing a thickened left ventricular wall and presence of pericardial effusions. Bottom row shows LGE images in the same planes. The vertical and horizontal longaxis image demonstrates global subendocardial hyperenhancement ofboth ventricles, both atria and the interatrial septum(white arrows).



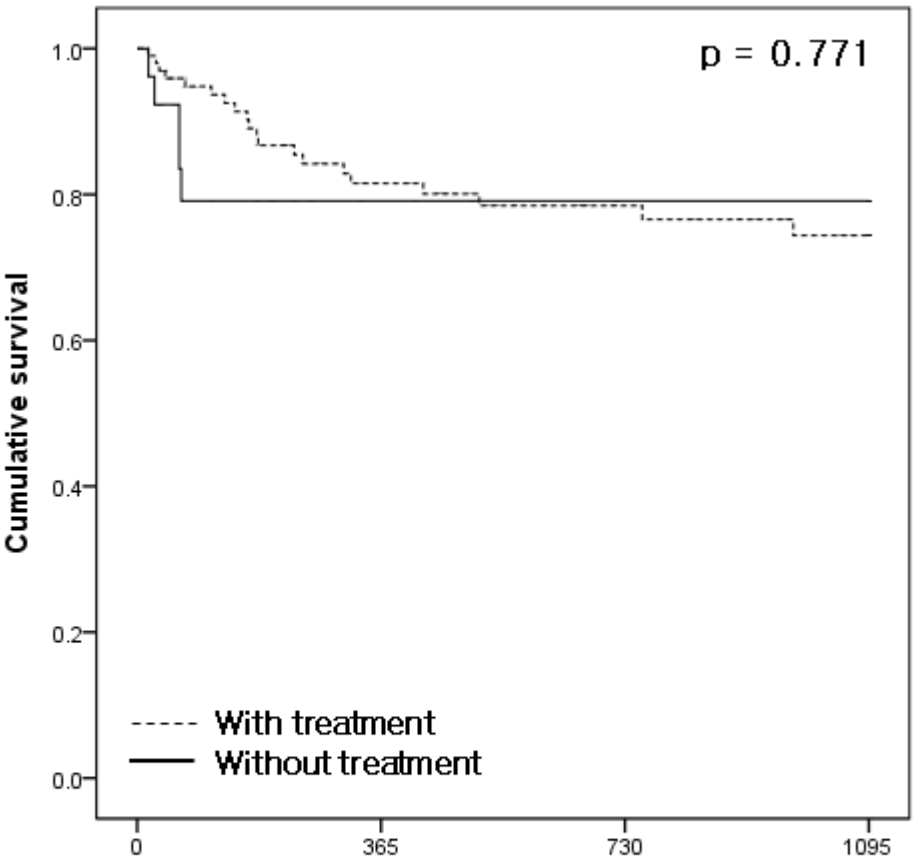
CMR, cardiovascular magnetic resonance imaging;LGE, late gadoliniumenhancement

Figure 4. Kaplan-Meier survival curves of patients with systemic amyloidosis with versus without cardiac involvement.



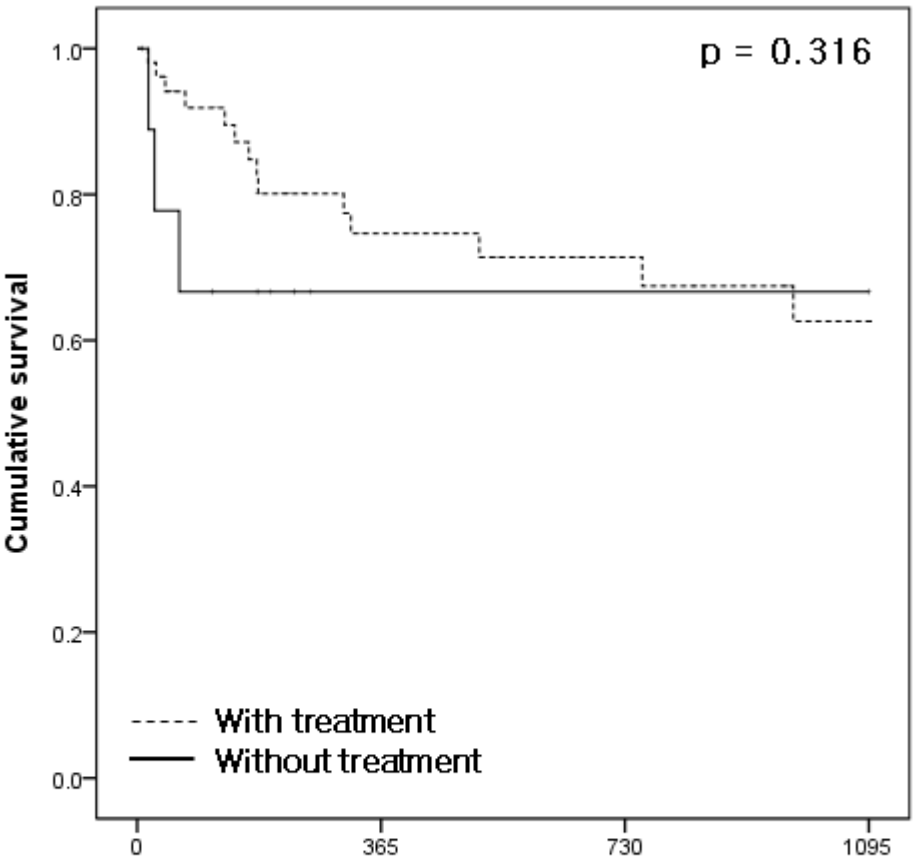
No. at Risk				
With cardiac involvement	62	27	19	14
Without cardiac involvement	67	42	29	24

Figure 5. Kaplan-Meier survival curves of patients with systemic amyloidosis with versus without treatment.



No. at Risk				
With treatement	100	58	41	32
Without treatment	29	11	7	7

Figure 6. Kaplan-Meier survival curves of patients with cardiac amyloidosis with versus without treatment.



No. at Risk				
With treatement	52	26	18	13
Without treatment	10	1	1	1

DISCUSSION

Cardiac involvement is frequent in systemic amyloidosisand is a major determinant of treatment optionsand prognosis[17].Cardiac involvement is observed in about 50% of the patients with AL amyloidosis[18] and is the cause of death inapproximately half of patients with AL amyloidosis[19]. And fewer than 5% of the patients with AL amyloidosis involving the heart have clinically isolated cardiac disease[20]. In our study, cardiac involvement was demonstrated in 48.8% cases of systemic amyloidosis, mostly by the AL amyloidosis, only 2 patients was proven to be SSA, and there was no patient with isolated cardiac involvement.

Diagnostic Issues in Systemic Amyloidosis

Once a tissue diagnosis of amyloidosis has been established,confirmation of AL amyloidosis, which is the most frequent type of systemic amyloidosis with cardiac involvement, requires demonstration of a monoclonal gammopathy. Presence of monoclonal gammopathy can be demonstrated by the bone marrow biopsy showing predominanceof kappa or lambda producing plasma cells or by the presence of amonoclonal light chain in the serum or urine. Between PEP and IEP/FLC assay, IEP or FLC assay is favored because of the high sensitivity compared to PEP.

In the present study, we confirmed the very high sensitivity of serum FLC assay in the diagnosis of AL amyloidosis with the sensitivity of 96.4% in contrast to low sensitivity in serum or urine PEP (35.8%). This finding is supported by several studies[21,22]. Morris et al reported that in study of 31 AL amyloidosis

patients, serum and urine PEP was positive in 30%, serum IEP in 67%, urine IEP in 83%,serum and urine IEP in 90%, absolute clonal light chain ≥ 100 mg/Lin 87%, and abnormal kappa lambda ratio with increased clonal light chain in 97%[23]. Normal FLC assay result in thepresence of biopsy-proven amyloidosis should lead toa thorough search for SSA or familial amyloidosis.

Diagnostic Issues in Cardiac Amyloidosis

Although the gold standard for diagnosis of cardiac amyloidosis is endomyocardial biopsy,ECG is considered a key player to orient diagnostic suspicion of cardiac amyloidosis, with low voltageQRS providing a particularly valuable noninvasive clue.Dubrey et al reported that more than 70% of the patients with AL cardiac amyloidosis exhibited low voltage amplitudes[20] and in another series, Murtagh et al found that only 46% of the patients with primary systemic amyloidosis and biopsy-proven cardiac involvement exhibited lowvoltage amplitudes[24].

The most common echocardiographic feature is thickening of the LV wall[5,8,25-28]. The combination of increased LV mass in the absence of high ECG voltages may be more specific for infiltrative diseases, of which amyloid is the most common[25,29]. High sensitivity (72% to 79%) and specificity (91% to 100%) have been reported for this combination[27,29]. In the present study, low voltageQRS was present in 84.1% and increased LVwall thickness was present in 96.8% of the patients.

CMR imaging now has an established role in the diagnosis of cardiac involvement. Although, CMR was available only in small number of the patients in

the present study, LGE in aglobal or subendocardial distributionwas present in 13 of 15 (86.7%) patients, similar to the study of Perugini[13]. He reported that gadolinium enhancement by CMR was detected in 16 of 21(76%) patientswith histologically proven systemic amyloidosis andechocardiographic diagnosis of cardiac involvement[13].Subsequent studies have substantiatedthe diagnostic value of CMR with LGE in identifying cardiacinvolvement, and suggested that the presence of LGE may confers prognostic information[12,30,31].

Survival and Prognosis in Cardiac Amyloidosis

The prognosis of the amyloidosis varies, but it isgenerally poor if the disease is untreated.Among various prognostic factors, the extentof cardiac involvementis the most important determinant of clinical outcome[17,32,33]. In the present study, the survival is worse in patients with cardiac involvement than without cardiac involvement and 1-year, 2-year and 3-year survival of the patients with cardiac involvement were 72.8%, 69.8% and 61.7%, respectively. And 82.3% patients were treated with chemotherapy, 19.4% with autologous stem cell transplantation and 4.8% with cardiactransplantation. The survival rates of our study were markedly better than in the study of Kyle, who reported a 1-year survival of approximately 30%[34] and similar to the previous study of Kristen, who reported 1- and 3-year survival of 68% and 63%[32], respectively. Deaths were more in patients noteligible for high-dose chemotherapy and autologous stemcell transplantation indicating a marked beneficial effect ofthis potentially curative treatment approach on survival.High-dose melphalan chemotherapy andautologous stem cell

transplantation is generally accepted asa therapeutic approach to improve survival[35-37] andquality of life[38]in AL amyloidosis.

Previously proposed associations with poor prognosis in cardiac amyloidosis include reduced EF, increased LV wall thickness on echocardiography, low voltage QRSin ECG, and the type of amyloidosis (with worse prognosis in AL compared with TTR type)[32]. In addition, the degree of diastolic dysfunction[33] and suppression of amyloidogenic serum light chains by chemotherapy, and lower baseline values and greater reductions in pro-BNP have been associated with improved outcome[39,40]. In the present study, only decreased LV function was associated with survival with marginal significancein both univariate and multivariate analysis.

Study Limitations

First, given the rarity of systemic amyloidosis and cardiac amyloidosis, patient numbers were relatively small although we reviewed 13-years' medical records from our institution. Therefore, some detailed comparisons were outside the scope of this study, and further work is needed for this. Second, a large loss to follow-up of our study may be a particular source of bias. For example, in case of the patients with systemic amyloidosis, 61 in 129 patients (47.3%) and with cardiac amyloidosis, 25 in 62 patients (40.3%) were lost to follow-up. Third, cardiac histology was only present in a subset of patients, and the decision to perform a cardiac biopsy was made on clinical grounds, which may introduce bias. Finally, though CMR shows promise for diagnosing cardiac amyloidosis if echocardiographic features are suspicious, CMR was only available in 24.2% of the patients with

cardiac amyloidosis in our study. Therefore some issues related to CMR were not discussed enough.

REFERENCE

1. Merlini G, Westermark P. The systemic amyloidoses: clearer understanding of the molecular mechanisms offers hope for more effective therapies. J Intern Med 255:159-78;2004.
2. Selkoe DJ. Folding proteins in fatal ways. Nature 426:900-4;2003.
3. Westermark P, Benson MD, Buxbaum JN, et al. Amyloid fibril protein nomenclature -- 2002. Amyloid 9:197-200;2002.
4. Duston MA, Skinner M, Shirahama T, Cohen AS. Diagnosis of amyloidosis by abdominal fat aspiration. Analysis of four years' experience. Am J Med 82:412-4;1987.
5. Cueto-Garcia L, Tajik AJ, Kyle RA, et al. Serial echocardiographic observations in patients with primary systemic amyloidosis: an introduction to the concept of early (asymptomatic) amyloid infiltration of the heart. Mayo Clin Proc 59:589-97;1984.
6. Falk RH, Plehn JF, Deering T, et al. Sensitivity and specificity of the echocardiographic features of cardiac amyloidosis. Am J Cardiol 59:418-22;1987.
7. Klein AL, Hatle LK, Burstow DJ, et al. Doppler characterization of left ventricular diastolic function in cardiac amyloidosis. J Am Coll Cardiol 13:1017-26;1989.
8. Klein AL, Hatle LK, Taliercio CP, et al. Serial Doppler echocardiographic follow-up of left ventricular diastolic function in cardiac amyloidosis. J Am Coll Cardiol 16:1135-41;1990.
9. Fattori R, Rocchi G, Celletti F, Bertaccini P, Rapezzi C, Gavelli G. Contribution of magnetic resonance imaging in the differential diagnosis of cardiac amyloidosis and symmetric hypertrophic cardiomyopathy. Am Heart J 136:824-30;1998.
10. Maceira AM, Joshi J, Prasad SK, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 111:186-93;2005.
11. vanden Driesen RI, Slaughter RE, Strugnell WE. MR findings in cardiac amyloidosis. AJR Am J Roentgenol 186:1682-5;2006.
12. Vogelsberg H, Mahrholdt H, Deluigi CC, et al. Cardiovascular magnetic resonance in clinically suspected cardiac amyloidosis: noninvasive imaging compared to endomyocardial biopsy. J Am Coll Cardiol 51:1022-30;2008.
13. Perugini E, Rapezzi C, Piva T, et al. Non-invasive evaluation of the myocardial substrate of cardiac amyloidosis by gadolinium cardiac magnetic resonance. Heart 92:343-9;2006.
14. Arbustini E, Verga L, Concardi M, Palladini G, Obici L, Merlini G. Electron and immuno-electron microscopy of abdominal fat identifies and characterizes amyloid fibrils in suspected cardiac amyloidosis. Amyloid 9:108-14;2002.
15. Hawkins PN, Lavender JP, Pepys MB. Evaluation of systemic amyloidosis by scintigraphy with 123I-labeled serum amyloid P component. N Engl J Med 323:508-13;1990.
16. Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus

opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol 79:319-28;2005.
17. Kyle RA, Greipp PR, O'Fallon WM. Primary systemic amyloidosis: multivariate analysis for prognostic factors in 168 cases. Blood 68:220-4;1986.
18. Dispenzieri A, Lacy MQ, Kyle RA, et al. Eligibility for hematopoietic stem-cell transplantation for primary systemic amyloidosis is a favorable prognostic factor for survival. J Clin Oncol 19:3350-6;2001.
19. Falk RH, Skinner M. The systemic amyloidoses: an overview. Adv Intern Med 45:107-37;2000.
20. Dubrey SW, Cha K, Anderson J, et al. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. QJM 91:141-57;1998.
21. Dispenzieri A, Lacy MQ, Katzmann JA, et al. Absolute values of immunoglobulin free light chains are prognostic in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. Blood 107:3378-83;2006.
22. Akar H, Seldin DC, Magnani B, et al. Quantitative serum free light chain assay in the diagnostic evaluation of AL amyloidosis. Amyloid 12:210-5;2005.
23. Morris KL, Tate JR, Gill D, et al. Diagnostic and prognostic utility of the serum free light chain assay in patients with AL amyloidosis. Intern Med J 37:456-63;2007.
24. Murtagh B, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. Am J Cardiol 95:535-7;2005.
25. Hamer JP, Janssen S, van Rijswijk MH, Lie KI. Amyloid cardiomyopathy in systemic non-hereditary amyloidosis. Clinical, echocardiographic and electrocardiographic findings in 30 patients with AA and 24 patients with AL amyloidosis. European Heart Journal 13:623-7;1992.
26. Nishikawa H, Nishiyama S, Nishimura S, et al. Echocardiographic findings in nine patients with cardiac amyloidosis: their correlation with necropsy findings. J Cardiol 18:121-33;1988.
27. Rahman JE, Helou EF, Gelzer-Bell R, et al. Noninvasive diagnosis of biopsy-proven cardiac amyloidosis. J Am Coll Cardiol 43:410-5;2004.
28. Siqueira-Filho AG, Cunha CL, Tajik AJ, Seward JB, Schattenberg TT, Giuliani ER. M-mode and two-dimensional echocardiographic features in cardiac amyloidosis. Circulation 63:188-96;1981.
29. Carroll JD, Gaasch WH, McAdam KP. Amyloid cardiomyopathy: characterization by a distinctive voltage/mass relation. Am J Cardiol 49:9-13;1982.
30. Ruberg FL, Appelbaum E, Davidoff R, et al. Diagnostic and prognostic utility of cardiovascular magnetic resonance imaging in light-chain cardiac amyloidosis. Am J Cardiol 103:544-9;2009.
31. Syed IS, Glockner JF, Feng D, et al. Role of cardiac magnetic resonance imaging in the detection of cardiac amyloidosis. JACC Cardiovasc Imaging 3:155-64;2010.
32. Kristen AV, Perz JB, Schonland SO, et al. Non-invasive predictors of survival in cardiac amyloidosis. Eur J Heart Fail 9:617-24;2007.

33. Klein AL, Hatle LK, Taliercio CP, et al. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis. A Doppler echocardiography study. Circulation 83:808-16;1991.
34. Kyle RA, Greipp PR. Amyloidosis (AL). Clinical and laboratory features in 229 cases. Mayo Clin Proc 58:665-83;1983.
35. Perz JB, Schonland SO, Hundemer M, et al. High-dose melphalan with autologous stem cell transplantation after VAD induction chemotherapy for treatment of amyloid light chain amyloidosis: a single centre prospective phase II study. Br J Haematol 127:543-51;2004.
36. Skinner M, Sanchorawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med 140:85-93;2004.
37. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. Blood 99:4276-82;2002.
38. Seldin DC, Anderson JJ, Sanchorawala V, et al. Improvement in quality of life of patients with AL amyloidosis treated with high-dose melphalan and autologous stem cell transplantation. Blood 104:1888-93;2004.
39. Lachmann HJ, Gallimore R, Gillmore JD, et al. Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy. Br J Haematol 122:78-84;2003.
40. Palladini G, Lavatelli F, Russo P, et al. Circulating amyloidogenic free light chains and serum N-terminal natriuretic peptide type B decrease simultaneously in association with improvement of survival in AL. Blood 107:3854-8;2006.

국문 초록

서론:전신성 유전분증에서 심장 침범은 흔하게 관찰되며, 심장 침범 여부는 임상 경과에 가장 중요한 영향을 미치는 인자이다. 이 연구의 목적은 심장 유전분증의 발병률과 예후를 확인하고 심장 유전분증 진단과 관련된 쟁점에 대하여 논의하는 데에 있다.

방법:우리는 본 연구를 위하여 1999 년 1 월부터 2011 년 12 월까지 서울대병원에서 전신성 유전분증을 진단받은 모든 환자를 후향적으로 연구하였다.

결과:상기 기간 동안 전신성 유전분증으로 진단된 129 명의 환자 중에, 62 명은 심장 유전분증으로 진단되었다. 전신성 유전분증 환자에 대하여 3 년의 추적 관찰 기간 동안, 심장 침범이 있는 경우, 없는 경우보다 통계적으로 유의하게 사망률이 높았다. (38.3% vs. 14.2%, log rank p = 0.014). 또한, 단변량 및 다변량 분석 결과, 좌심실 기능 감소는 통계적으로 유의하게 독립적으로 사망률을 높일 수 있음이 확인되었다 (HR 3.936, 95% CI 1.247−12.425, p = 0.020). 또한, 단클론성 감마병증 진단과 관련하여, 혈청 혹은 소변을 검체로 하는 단백영동검사는 유리형 경쇄 분석 검사만큼 민감도가 높지 않았다. (35.8% vs. 96.4%)

결론:전신성 유전분증에서, 심장 침범의 여부는 예후의 가장 중요한 결정 인자이며, 좌심실 기능 감소는 독립적으로 심장 유전분증 환자의 사망률을 높인다.

주요어: 심장 유전분증, 전신성 유전분증, 단클론성 감마병증

학 번: 2011-21852