Clinical and Experimental Rheumatology 2003; 21: 343-346.

Clinical outcome and survival of secondary (AA) amyloidosis

F. Tanaka, K. Migita, S. Honda, T. Fukuda[1], M. Mine[2], T. Nakamura[3], S. Yamasaki, H. Ida, A. Kawakami, T. Origuchi, K. Eguchi

First Department of Internal Medicine, Nagasaki University Graduate School of Biochemical Sciences, Sakamoto, Nagasaki; [1]First Department of Internal Medicine, Kurume University School of Medicine; [2]Department of Internal Medicine, Isahaya Health Insurance Hospital; [3]Faculty of Environmental Studies, Nagasaki University, Japan.

Fumiko Tanaka, MD; Kiyoshi Migita, MD; Seiyo Honda, MD; Takaaki Fukuda, MD; Masanobu Mine, MD; Tsuyoshi Nakamura, MD; Satoshi Yamasaki, MD; Hiroaki Ida, MD; Atsushi Kawakami, MD; Tomoki Origuchi, MD; Katsumi Eguchi, MD.

Please address correspondence and reprint requests to: Katsumi Eguchi, MD, First Department of Internal Medicine, Nagasaki University Graduate School of Biochemical Sciences, Sakamoto 1-7-1, Nagasaki 852-8501, Japan.
E-mail: eguchi @ net. nagasaki-u. ac. jp

Received on March 4, 2002; accepted in revised form on January 10, 2003.

Key words: Secondary amyloidosis, serum amyloid A protein, rheumatic disease.

ABSTRACT

Objective

In order to predict the clinical outcome of secondary (AA) amyoidosis patients with rheumatic diseases, we studied the clinical features at presentation of AA amyloidosis.

Methods

We investigated the clinical characteristics and survival of 42 patients with biopsy-proven AA amyloidosis who were followed up in our department from 1983 to 2001

Results

A presenting factor which adversely influenced clinical outcome was a raised serum creatinine concentration at the time AA amyoidosis was diagnosed. Eight of 42 patients survived for 10 years or more after the presentation of AA amyloidosis, while 24 patients had died within 10 years. At the diagnosis of AA amyloidosis, cardiac involvement was detected in 11 of 24 non-survivors, whereas it was not detected in any of the 8 long-term survivors. Estimated survival at 5 years was 31.3% in those who had cardiac involvement, and was 63.3% in those who had no cardiac involvement at the presentation of AA amyloidosis.

Conclusion

Our results indicate that clinical outcome is related to renal function and cardiac involvement at the time AA amyloidosis is diagnosed. Amyloid-related cardiac involvement is one of the unfavorable predictive factors in AA amyloidosis patients.

Introduction

Secondary (AA) amyloidosis which can complicate chronic inflammatory disorders is a disease characterized by extracellular deposition of amyloid A (AA) protein (1, 2). In AA amyloidosis, AA amyloid fibrils deposited in organs are derived from the circulatory acute phase reactant, serum amyloid A protein (SAA) (3,4). The natural history of AA amyloidosis is typically progressive, leading to organ failure and death, when the underlying inflammatory diseases remain active (5). The median survival period of patients with AA amyloidosis has been reported to be 24.5 months (6). Therefore, the long-term survival of AA amyloidosis patients is rare, and the factors affecting long-term survival remain unknown. More recently, Joss *et al.* reviewed AA amyloidosis and demonstrated that albuminuria and impaired renal function (creatinine clearance) are poor prognostic factors (7). This study is an analysis of 42 patients with AA amyloidosis over an 18-year period, its aim being to identify any clinical or laboratory factors that can predict long-term survival.

Materials and methods

Patients

The clinical records of 42 patients with biopsy-proven AA amyloidosis who were followed from 1983 to 2001 by the First Department of Internal Medicine, Nagasaki University School of Medicine were reviewed. When clinical features that may raise suspicion of the existence of amyloidosis, such as proteinuria, renal dysfunction, weight loss and diarrhea, were observed in patients with rheumatic diseases, routine screening including tissue biopsy were undertaken with the informed consent of the patients.

The presence of amyloid was histologically confirmed by positive Congo Red staining and sensitivity to pre-treatment with $KMNO_4$ (8). Any patient whose clinical chart diagnosis was secondary amyloidosis not confirmed by biopsy was excluded from this study. All patients were followed from diagnosis to death within 60 days of this study. The patient's charts were examined, and clinical data at the diagnosis of amyloidosis were recorded. Survival was calculated from the date that amyloid was first demonstrated histologically until the date of death or the most recent check-up for those still living.

In accordance with previous studies (9, 10), we considered the following parameters as indicators of amyloid-related cardiac involvement: the lack of other obvious predisposing factors such as hypertension, valvular disease or ischemic heart disease plus one of the following criteria: (1) congestive heart failure, (2) abnormal electrocardiographic findings (findings suggestion of a past myocardial infarction, poor R

wave progression, abnormal Q wave, QS pattern, conduction block), and (3) abnormal echocardiographic findings (findings of thickened right and left ventricular (LV) myocardium with normal LV cavity dimensions, diffuse hyper-refractile "sparkling granular" appearance). An autopsy was performed in 5 patients who were diagnosed as having amyloid-related cardiac involvement and amyloid deposits were confirmed in the heart tissues of all five.

Statistical analysis

The Cox proportional hazards model was used to determine the variables that influenced survival. Survival curves were estimated by means of the Kaplan-Meier technique.

Results

Patient profile

Over the course of the 20-year study period, 42 patients with AA amyloidosis were seen in our department. Table I gives the sex and age at onset of rheumatic diseases and the age at the diagnosis of amyloidosis of the patients. In our study, the median time between the first symptoms of the underlying rheumatic diseases and histological diagnosis of AA was 9.93 ± 8.68 years. As shown in Table II, the underlying diseases which developed AA amyloidosis were rheumatoid arthritis (RA) (n = 36), juvenile RA (n = 3), adult onset Still's disease (n = 1), Takayasu's aortitis (n = 1), and mixed connective tissue disease (MCTD) (n = 1).

To identify the factors which were associated with poor survival, we investigated the patients' clinical parameters and survival by Cox analysis. As shown in Table III, a high serum creatinine level was significantly associated with a poor outcome (p = 0.02). In contrast, other parameters were not correlated with survival. Ultimately, eight patients survived for 10 years or more after the histological diagnosis of AA amyloidosis. In contrast, 24 patients died within 10 years of the diagnosis of AA amyloidosis.

Comparison of these two groups showed that cardiac involvement including congestive heart failure was not confirmed at the onset of AA amyloidosis in long-term survivors (> 10 years). In contrast, cardiac involvement was observed in 50% of the non-survivor group (<10 years). A total of 8 patients were supported with dialysis therapy; two patients among the long-term survivors (> 10 years) received regular dialysis therapy without serious cardiac involvement for more than seven years. The causes of death of 27 patients are shown in Table IV. Of 27 deaths, 5 were related to cardiac problems, 4 were caused by renal insufficiency, 4 were due to infections, 5 were caused by gastrointestinal bleeding, and 2 could be characterized as sudden death.

Table I. Background of patients with secondary amyloidosis.

No. of patients	42 (male 7; female 35)
Underlying disease onset age of males	42.9 ± 22.2 (yrs.)
Underlying disease onset age of females	44.6 ± 15.8 (yrs.)
Patient's age at the diagnosis of amysoidosis of males	51.3 ± 19.5 (yrs.)
Patient's age at the diagnosis of amyloidosis of females	55.3 ± 19.8 (yrs.)
Median time between the diagnosis of underlying diseases and AA amyloidosis	9.93 ± 8.68 (yrs.)

Table II. Diseases underlying secondary amyloidosis.

Disease	No. of patients
Rheumatoid arthritis	36
Juvenile rheumatoid arthritis	3
Adult onset Still's disease	1
Takayasu' s aortitis	1
Mixed connective tissue disease	1
Total	42

Table III. Causes of death in secondary amyloidosis (n = 27).

Cause of death	No. of patients
Heart failure	5
Renal failure	4
Gastrointestinal bleeding	5
Infection	4
Sudden death	2
Ileus	1
Lung cancer	1
Acute pancreatitis	1
Unknown	4

Table IV Survival parameters in secondary amyloidosis

Survival parameter	Hazard ratio (95% CI)	P-value
Age (year)	1.02 (0.99-1.05)	0.07
Hemoglobin (mg/dl)	0.74 (0.89-1.07)	0.23
Platelet (104/mm^3)	0.99 (0.96-1.01)	0.41
Albumin (g/dl)	1.18 (0.89-1.45)	0.21
Serum creatinine (mg/dl)	1.23 (1.04-1.47)	0.02
CRP(mg/dl)	1.00 (0.88-1.12)	0.97
Mean survival after diagnosis of secondary amyloidosis (years)		Mean ± SD 5.56 ± 4.69

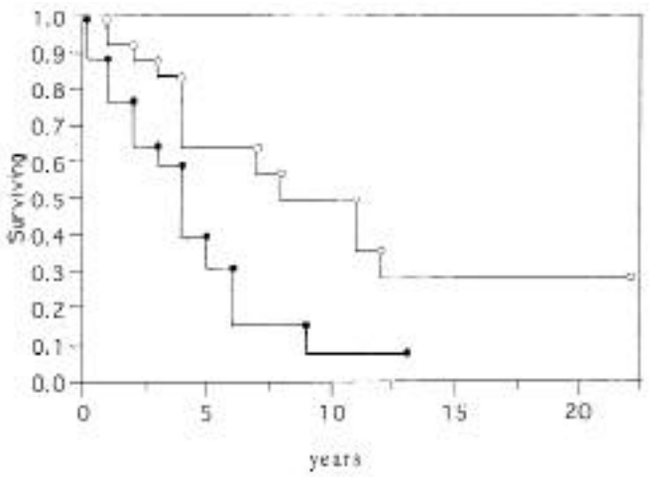

Fig. 1. Survival rate of patients with (❍; n = 17) or without (●; n = 25) cardiac involvement.

Survival

Figure 1 shows the survival curve of the 17 AA amyloidosis patients with cardiac involvement and the 25 AA amyloidosis patients without cardiac involvement using the Kaplan-Meier technique. The median survival of the patients with cardiac involvement was 3.96 ± 3.28 years, with 31.3% surviving for 5 years.

The median survival period of the patients without cardiac involvement was 6.64 ± 3.28 years, with 63.6% surviving 5 years. The presence of cardiac involvement was significantly associated with poor survival in the patients with AA amyloidosis ($p = 0.017$).

Discussion

In patients with rheumatic diseases, secondary amyloidosis has been recognized as a serious complication affecting their prognosis (11). The natural history of AA amyloidosis is typically progressive, leading to multiple organ failure (6). Long-term survival among patients with AA amyloidosis is uncommon, and there are few parameters that have been shown to indicate the prognosis of this disease.

In assessing the prognosis of patients with AA amyloidosis, it is important to identify the risk factors affecting the survival of these patients. Of 42 patients with AA amyloidosis followed at the Nagasaki University School of Medicine, 8 patients survived 10 years or more. Our study confirmed that the serum creatinine concentration is an important predictive factor for the survival of AA amyloidosis patients. Additionally, in a comparison of 8 patients who survived for 10 years or more, and 24 patients who did not survive for 10 years, we found that patients without cardiac involvement were more likely to survive 10 years, and the lack of cardiac involvement appears to be a favorable prognostic factor.

Renal involvement has been considered to be the most critical problem in patients with amyloidosis (6, 12, 13). Gertz *et al.* analyzed 64 patients with AA amyloidosis and demonstrated that renal dysfunction at presentation is strongly associated with shorter survival (6). They showed that a serum creatinine value of > 2.0 mg/dl at presentation was associated with a poorer survival. The median survival of patients with a serum creatinine level > 2.0 mg/dl was 11.2 months compared to patients with a serum creatinine level < 2.0 mg/dl who had a median survival of 56.9 months. More recently, Joss *et al.* identified albuminuria and creatinine clearance as prognostic factors in 43 patients with AA amyloidosis. To support these findings, our data showed that increased serum creatinine levels were associated with a poorer survival in 44 patients with AA amyloidosis.

Although the life expectancy of patients with amyloidosis and undergoing dialysis treatment is poor, a few patients can expect a long survival with dialysis therapy. Interestingly, Gertz *et al.* demonstrated that of 37 patients with primary amyloidosis 31 died, and that 15 of these died as a result of cardiac amyloidosis, while the long-term survivors showed normal echocardiograms (14).

In our study, two patients survived more than 10 years under hemodialysis therapy which was continued for more than 7 years without serious cardiovascular accident. When both the renal and the cardiac systems begin to fail, dialysis treatment can no longer be continued. It is considered that serious cardiac complications are infrequent in AA amyloidosis at presentation, compared to AL amyloidosis (15,16). Although heart failure is directly responsible for death in only a minority of patients, the cases of patients with heart failure might be complicated by organ failure of other types, and death may be due to renal failure, G-I bleeding or infection. Therefore these causes of death indirectly might be related to the presence of cardiac involvement.

AA amyloidosis occurs in chronic inflammatory diseases, and the amyloid fibrils are derived from the acute phase reactant, serum amyloid A protein (SAA) (1-4). Amyloid deposition has been thought to be irreversible, but the clinical symptoms can dramatically improve if remission of the underlying inflammatory diseases can be brought about (1, 4, 17). More recently, Gillmore *et al.* demonstrated that amyloidotic organ function was stabilized or improved, and that outcome is favorable in AA amyloidosis when the SAA concentration is maintained below 10 mg/l (17).

In our patients experiencing long-term survival, underlying inflammatory diseases (RA, aortitis, and MCTD) were intensively controlled by steroid and/or immunosuppressants (data not shown), and chronic inflammation and SAA elevations were eradicated, with the further accumulation of amyloid deposits being prevented. This could be the reason these patients survived for more than 10 years without suffering serious organ failure.

In summary, we show that long-term survival in rheumatic patients with AA amyloidosis is not unusually rare. Cardiac involvement and impaired renal

function at presentation were underrepresented in the 10-year survivors and appears to be an unfavorable prognostic factor.

References

1. DHILLON V, WOO P, ISENBERG D: Amyloidosis in the rheumatic diseases. *Ann Rheum Dis* 1989; 48: 696-701.
2. HUSEBEKK A, SKOGEN B, HUSBY G, MARHAUG G: Transformation of amyloid precursor SAA to protein AA and incorporation in amyloid fibrils *in vivo*. *Scand J Immunol* 1985; 21: 283-7.
3. STEEL DM, WHITEHEAD AS: The major acute phase reactants: C-reactive protein, serum amyloid P component and serum amyloid A protein. *Immunol Today* 1944; 15:81-8.
4. CUNNANE G: Amyloid precursors and amyloidosis in inflammatory arthritis. *Curr Opin Rheumatol* 2001; 13: 67-73.
5. GERTZ MA,KYLE RA: Amyloidosis: Prognosis and treatment. *Semin Arthritis Rheum* 1994; 24: 124-138.
6. GERTZ MA, KYLE RA: Secondary systemic amyloidosis: Response and survival in 64 patients. *Medicine* 1991; 70: 246-56.
7. JOSS N, MCLAUGHLIN K, SIMPSON K, BOULTON-JONES JM: Presentation, survival and prognostic markers in AA amyloidosis. *Q J Med* 2000; 93: 535-42.
8. CHASTONAY P, HURLIMANN J: Characterization of different amyloids with immunological techniques. *Pathol Res Pract* 1986; 181: 657-63.
9. ARISTARCO GS, CLAUDIO LPC, ABDUL JT, JAMES BS, THOMAS TS, EMILIO RG: M-mode and two-dimensional echocardiographic features in cardiac amyloidosis. *Circulation* 1981; 63: 188-96.
10. GRACIA R, SAEED SM: Amyloidosis. Cardiovascular manifestations in five illustrative cases. *Arch Intern Med* 1968; 121: 259-66.
11. HUSBY G: Amyloidosis and rheumatoid arthritis. *Clin Exp Rheumatol* 1985; 3: 173-80.
12. HAZENBERG BP, VAN RIJSWIJK MH: Clinical and therapeutic aspects of AA amyloidosis. *Clin Rheumatol* 1994; 8: 661-90.
13. CUNNANE G: Amyloid precursors and amyloidosis in rheumatoid arthritis. *Clin Rheumatol* 1999; 13: 615-28.
14. GERTZ MA, KYLE RA: Dialysis support of patients with primary systemic amyloidosis. *Arch Intern Med* 1992; 152: 2245-50.
15. KYLE RA, GREIPP PR: Amyloidosis (AL). Clinical and laboratory features in 229 cases. *Mayo Clin Proc* 1983; 58: 665-83.
16. SIMONS M, ISNER JM: Assessment of relative sensitivities of noninvasive tests for cardiac amyloidosis in documented cardiac amyloidosis. *Am J Cardiol* 1992; 69: 425-7.
17. GILLMORE JD, LOVAT LB, PERSEY MR, PEPYS MB, HAWKINS PN: Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. *Lancet* 2001; 358: 24-9.