

# Senile Systemic Amyloidosis Presenting With Heart Failure

## A Comparison With Light Chain–Associated Amyloidosis

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**Background:** Small deposits of amyloid are often found in the hearts of elderly patients. However, extensive deposition of transthyretin-derived amyloid fibrils in the heart (senile systemic amyloidosis [SSA]) can cause heart failure. The clinical features of SSA that involve the heart are ill defined, and the condition may be overlooked as a cause of heart failure. We sought to better define the clinical, echocardiographic, and electrocardiographic features of cardiac involvement in SSA and to compare them with the findings in patients with light chain–associated (AL) amyloidosis that affects the heart.

**Methods:** Eighteen consecutive patients with SSA and heart failure evaluated at a tertiary referral center for the diagnosis and treatment of amyloidosis were compared with 18 randomly selected patients with AL amyloidosis that involved the heart. All patients underwent a complete clinical and biochemical evaluation. Echocardiograms and electrocardiograms were interpreted by blinded investigators.

**Results:** Patients with SSA were older than those with AL amyloidosis and were all male. Proteinuria (protein output of  $>1$  g per 24 hours) was common in AL amyloidosis but was not present in SSA. Left ventricular wall thickness was greater in patients with SSA than those with AL amyloidosis, but despite thicker walls and older age, the severity of heart failure was less in the SSA group and the median survival was much longer (75 vs 11 months;  $P = .003$ ).

**Conclusions:** Senile systemic amyloidosis is a disorder of elderly men and is characterized by amyloidosis clinically limited to the heart. In contrast to the rapid progression of heart failure in AL amyloidosis, SSA results in slowly progressive heart failure. The difference in survival, despite evidence of more myocardial disease in the senile group, suggests that heart failure in AL amyloidosis may have a toxic component, possibly related to the circulating monoclonal light chain.

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THE TERM AMYLOIDOSIS DESCRIBES a group of diseases characterized by the deposition of a proteinaceous material in 1 or more organs. Although several different precursor proteins exist, all amyloid fibrils share a similar microscopic appearance; when stained with Congo red, all demonstrate an apple-green birefringence under polarized light. The biochemical differences in fibril structure depend on the precursor protein and may affect the clinical manifestations of the disease, both in terms of the specific organ involved and the clinical manifestations of such involvement. The most common type of systemic amyloidosis is light chain–associated (AL) amyloidosis, which is caused by a plasma cell dyscrasia. This type of amyloidosis is a rapidly progressive disease that affects multiple organs, including the heart in 50% of patients. The prognosis of patients with AL amyloidosis is poor when heart fail-

ure is present, with a median survival of 5 months from diagnosis.<sup>1</sup>

Less common than AL amyloidosis is a familial form associated with a point mutation in the transthyretin molecule (ATTR). The clinical presentation is usually polyneuropathy and/or cardiomyopathy,<sup>2,3</sup> and more than 100 variant transthyretin proteins with single amino acid substitutions have been described, most of which are amyloidogenic.<sup>4</sup> Patients with ATTR amyloidosis who have cardiac involvement may have an echocardiographic appearance indistinguishable from patients with AL cardiac amyloidosis but with a significantly longer survival time.<sup>5</sup> A mutation in ATTR is not a prerequisite for the formation of transthyretin-associated amyloid fibrils. In elderly patients, wild-type transthyretin may become structurally unstable, resulting in the development of misfolded intermediates that ultimately aggregate and precipitate as amyloid.<sup>6</sup> These fibrils form in many dif-

ferent organs, but they have a predilection for the heart.<sup>7-9</sup> Although cardiac deposits of wild-type transthyretin amyloid are not uncommonly found in small amounts at autopsy in elderly patients who had few or no cardiac symptoms,<sup>7</sup> wild-type transthyretin may occasionally be deposited in massive amounts in the heart. When this occurs, congestive heart failure occurs and senile cardiac amyloidosis is said to be present.<sup>2,8-12</sup>

The diagnosis of SSA is one of exclusion. It is based on the presence of amyloid in a tissue biopsy specimen in conjunction with the echocardiographic appearance of an infiltrative cardiomyopathy after the exclusion of a plasma cell dyscrasia and of a mutant transthyretin or other amyloidogenic protein.<sup>11</sup> The natural history is not well defined, in part because the disease often is not recognized before death. In a study of 18 patients with symptomatic SSA that involved the heart, the median survival was 60 months. This contrasted with a median survival of 5.4 months among 147 patients with AL amyloidosis and congestive heart failure who were evaluated at the same institution during the same period.<sup>11</sup> No details of the patients with AL amyloidosis used as controls were given, and the reasons for longer survival of patients with SSA compared with AL cardiac amyloidosis are unclear. However, the authors noted that no distinguishing features were found at the time of diagnosis that differentiated the patients with SSA from those with AL amyloidosis. Thus, it is unknown whether there is quantitatively less amyloid deposition in the heart in SSA or if there is less of a deleterious effect of the circulating amyloidogenic protein on cardiac myocytes in patients with SSA compared with those with AL amyloidosis. In this study, we describe the clinical and echocardiographic features of a consecutive group of patients with SSA and compare them with a well-defined group of patients with AL amyloidosis that affects the heart.

## METHODS

### PATIENT SELECTION

Between January 1, 1996, and January 31, 2002, 19 patients with SSA were evaluated at the Boston University Amyloidosis Treatment and Research Program. All patients had biopsy-proven amyloidosis confirmed by positive Congo red staining of tissue specimens. Patients underwent a detailed history and physical examination, standard blood tests, 24-hour urine collection, chest x-ray examination, 12-lead electrocardiography, and echocardiography with Doppler study. All patients were evaluated for a plasma cell dyscrasia by serum and urine immunofixation electrophoresis and by bone marrow biopsy with immunohistochemical examination to determine the presence of a monoclonal population of plasma cells. They were all evaluated by the same cardiologist (R.H.F.). Cardiac involvement was defined as a cardiac biopsy specimen that showed amyloid deposits (15 patients) or by a history of congestive heart failure with myocardial wall thickening on an echocardiogram without a history of significant hypertension or valvular or coronary disease, and a noncardiac biopsy specimen that showed amyloid deposition (fat pad biopsy specimen in 4). Heart failure was defined as jugular venous distention with or without peripheral edema and/or the presence of radiographic features of congestive heart failure. If monoclonal plasma cells were absent in the bone marrow and no monoclonal gammopathy

was detected in the serum or urine, AL amyloidosis was considered to have been excluded. After exclusion of AL amyloidosis, patients underwent screening for ATTR amyloidosis by isoelectric focusing of serum designed to detect the presence of mutant transthyretin.<sup>12,13</sup> If this result was positive, the transthyretin gene mutation was identified by direct DNA sequencing.<sup>14</sup> If both a clonal light chain and a variant transthyretin were excluded and the patient presented with amyloid cardiomyopathy at an advanced age, the diagnosis of SSA was made.

As a comparison group, we selected 18 patients with AL amyloidosis that involved the heart who had been evaluated during the same period. Since all patients with SSA had congestive heart failure, we used a large database to identify patients with AL amyloidosis who had cardiac amyloidosis and heart failure and randomly selected 18 of them who had been evaluated during the same period. The patients with AL amyloidosis had biopsy-proven amyloidosis, and all had a plasma cell dyscrasia with clonal plasma cells in the bone marrow and/or monoclonal gammopathy detected by immunofixation electrophoresis of serum or urine proteins. In 5 patients the diagnosis of amyloidosis was made by cardiac biopsy, and the remainder had a positive noncardiac biopsy specimen with typical echocardiographic abnormalities. All patient data were collected with the approval of the institutional review board of Boston University Medical Center.

## ELECTROCARDIOGRAPHY AND ECHOCARDIOGRAPHY

All patients had 12-lead electrocardiograms and echocardiograms performed at the time of initial evaluation. Echocardiograms were performed using a Hewlett-Packard array system, with M-mode and color Doppler recordings (Hewlett-Packard Company, Palo Alto, Calif). To assess any similarities or differences between patients with SSA or AL cardiac amyloidosis, the electrocardiograms and echocardiograms were reinterpreted by an observer who was blinded to the identity of the patient and the type of amyloidosis. The echocardiograms were coded and read in a random order. Measurements were made according to the American Society of Echocardiography guidelines.

### SURVIVAL DATA

Survival status was determined by the national Social Security Registry or by telephone contact with the patients or their families. Survival was calculated from the first onset of congestive heart failure symptoms, which had been established at the time of the initial visit to our institution.

### STATISTICAL ANALYSIS

Continuous data were compared using the *t* test. Dichotomous data from patients with SSA or AL amyloidosis were compared using 2-sided Fisher exact tests. Survival curves were calculated by Kaplan-Meier analysis and the log-rank test for equality of survival.  $P \leq .05$  was considered statistically significant.

## RESULTS

### CLINICAL FEATURES

One patient with SSA was excluded from further analysis because of concomitant aortic stenosis, which might have caused left ventricular hypertrophy. Thus, the data presented are from 18 patients with SSA. Patients with SSA were significantly older than those with AL amyloi-

**Table 1. Clinical Features of Patients With Senile Systemic Amyloidosis vs Light Chain–Associated Amyloidosis\***

Feature	SSA (n = 18)	AL Amyloidosis (n = 18)	P Value
Age, mean ± SD (range), y	73 ± 5 (67-86)	57 ± 9 (39-69)	<.001
Male sex	18	11	.01
Fat aspirate positive for Congo red, No (%)	4/15 (27)	14/15 (93)	<.001
Systolic blood pressure, mean ± SD, mm Hg	118 ± 23	108 ± 21	.18
Diastolic blood pressure, mean ± SD, mm Hg	72 ± 12	73 ± 12	.80
Orthostasis, No. (%)	1/16 (6)	4/18 (22)	.34
Amount of protein in 24-h urine sample, mean ± SD, mg	114 ± 150	4759 ± 6504	<.001
<1 g of protein in 24 h, No. (%)	15/15 (100)	33.3 (5/15)	<.001
Carpal tunnel syndrome, No. (%)	7/17 (41)	1/18 (6)	.02
Symptomatic neuropathy, No. (%)	2/7 (12)	3/18 (17)	.62
Macroglossia, No. (%)	0/17	6/18 (33)	.02

Abbreviations: AL, light chain–associated; SSA, senile systemic amyloidosis.

\*The denominator does not always equal 18 because not all patients underwent all investigations.

**Table 2. Electrocardiographic Features in Patients With Senile Systemic Amyloidosis vs Light Chain–Associated Amyloidosis\***

Feature	SSA, No./Total No. (%) (n = 18)	AL Amyloidosis, No./Total No. (%) (n = 18)	P Value
Sinus rhythm	9/14 (64)	15/16 (94)	.07
First-degree atrioventricular block	5/9 (56)	3/15 (20)	.19
Pacemaker	2/16 (12)	2/18 (11)	>.99
Low voltage (<5 mm in limb leads)	4/14 (29)	11/16 (69)	.07
Complete left bundle branch block	3/14 (21)	0/16	.09
Left anterior fascicular block	10/14 (71)	3/16 (19)	.009
Left posterior fascicular block	2/14 (14)	4/16 (25)	.90
Right bundle branch block	7/14 (50)	1/16 (6)	.01
Presence of any infarct pattern(s)	7/14 (50)	8/16 (50)	>.99

Abbreviations: AL, light chain–associated; SSA, senile systemic amyloidosis.

\*The denominator does not always equal 18 because not all patients underwent all investigations.

dosis ( $P<.001$ ) and exclusively male ( $P=.01$ ) (**Table 1**). The abdominal fat aspirate biopsy specimen stained positive for Congo red more often in the patients with AL amyloidosis (14/15) compared with patients with SSA (4/15) ( $P<.001$ ). Macroglossia ( $P=.02$ ) and proteinuria of more than 1 g in 24 hours ( $P<.001$ ) only occurred in AL amyloidosis. Carpal tunnel syndrome was more often found among patients with SSA ( $P=.02$ ), and there was no significant difference in the prevalence of symptomatic neuropathy or hepatomegaly. The mean supine blood pressure and the prevalence of orthostasis were similar. Only 2 patients had a history of hypertension, and in both cases it had been well controlled with medications.

### ELECTROCARDIOGRAPHIC FEATURES

Electrocardiographic data are given in **Table 2**. One of the 18 patients with SSA did not have an electrocardiogram available. In both the SSA and AL amyloidosis groups, 2 patients had a paced rhythm and were excluded from the analysis. Comparisons of the remaining electrocardiograms revealed that left anterior fascicular block was significantly more common in patients with SSA than those with AL amyloidosis ( $P=.009$ ). Half of the patients with SSA had right bundle branch block compared with only 1 of the 16 nonpaced patients with AL amyloidosis ( $P=.01$ ). Most patients with SSA had normal voltage, whereas two thirds of those with AL amyloidosis had low voltage ( $P=.07$ ). Patients with SSA were

less likely to be in sinus rhythm, although this finding did not reach statistical significance ( $P=.07$ ). Of the nonpaced patients with SSA who were not in sinus rhythm, 2 were in a junctional rhythm, 1 was in atrial flutter, and 2 were in atrial fibrillation. Other electrocardiographic features were not significantly different.

### ECHOCARDIOGRAPHIC FEATURES

The echocardiographic findings are given in **Table 3**. Patients with SSA had thicker left ventricular walls; the mean interventricular septum thickness was 17.8 mm in patients with SSA compared with 14.3 mm in the AL amyloidosis group ( $P=.002$ ). A similar difference in mean left ventricular posterior wall thickness was present: 17.9 mm in the SSA group and 15.3 mm in the AL amyloidosis group ( $P=.04$ ). Although the left ventricular end-diastolic dimensions were normal in all patients, patients with SSA had larger left ventricular internal dimensions during systole than those with AL amyloidosis (mean, 32.8 vs 28.1 mm;  $P=.05$ ). Other echocardiographic features did not differ between groups, including most Doppler indexes (**Table 4**).

### SURVIVAL

Despite the older age and greater left ventricular wall thickness among patients with SSA, the difference in survival was highly significant in favor of the SSA group, with a

**Table 3. Echocardiographic Measurements in Patients With Senile Systemic Amyloidosis vs Light Chain–Associated Amyloidosis\***

	SSA (n = 18)	AL Amyloidosis (n = 18)	P Value
LA (medial-lateral), mean ± SD, mm	42.8 ± 5.7	43.2 ± 5.9	.83
LA (superior-inferior), mean ± SD, mm	51.4 ± 7.2	49.0 ± 7.0	.31
LA (anterior-posterior), mean ± SD, mm	46.6 ± 9.1	41.4 ± 6.8	.05
IVS, mean ± SD, mm	17.8 ± 2.8	14.3 ± 3.0	.002
LVPW, mean ± SD, mm	17.9 ± 3.8	15.3 ± 3.1	.04
RA (medial-lateral), mean ± SD, mm	42.6 ± 5.1	45.0 ± 6.7	.23
RA (superior-inferior), mean ± SD, mm	47.8 ± 9.8	47.9 ± 9.2	.97
RV thickness >5 mm, No. (%)	12/15 (80)	14/17 (82)	>.99
Decreased RV function, No. (%)	2/13 (15)	1/11 (9)	>.99
LVEF ≤40%, No. (%)	4/16 (25)	4/18 (22)	>.99
LVIDd, mean ± SD, mm	44.5 ± 7.9	39.9 ± 8.6	.10
LVIDs, mean ± SD, mm	32.8 ± 4.7	28.1 ± 7.3	.05
Fractional shortening, mean ± SD, %	26 ± 8	28 ± 16	.63

Abbreviations: AL, light chain–associated; IVS, interventricular septum; LA, left atrium; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal dimension in diastole; LVIDs, left ventricular internal dimension in systole; LVPW, left ventricular posterior wall; RA, right atrium; RV, right ventricle; SSA, senile systemic amyloidosis.

\*The denominator does not always equal 18 because not all patients underwent all investigations.

**Table 4. Transmitral Doppler Measurements in Patients With Senile Systemic Amyloidosis vs Light Chain–Associated Amyloidosis\***

	SSA	AL Amyloidosis	P Value
Peak height of E wave, m/s	0.73 ± 0.17	0.87 ± 0.21	.03
Peak height of A wave, m/s	0.40 ± 0.20	0.51 ± 0.30	.20
E/A wave ratio	2.32 ± 1.04	2.03 ± 0.81	.35
E-wave deceleration time, ms	185 ± 63	157 ± 52	.16

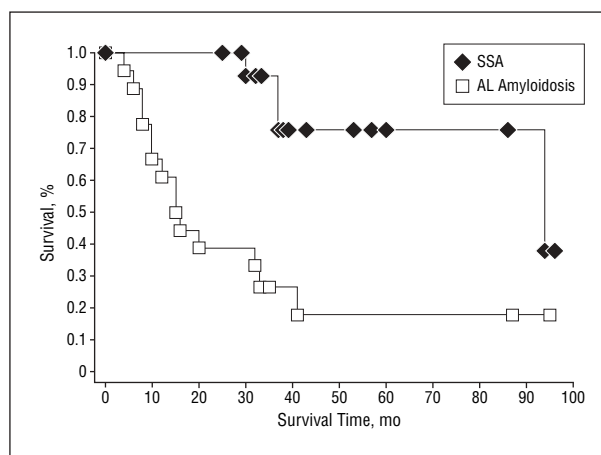
Abbreviations: AL, light chain–associated; SSA, senile systemic amyloidosis.  
\*Data are mean ± SD.

median survival of 75 months compared with 11 months in the AL amyloidosis group ( $P = .003$ ) (**Figure**). Of the 4 patients with SSA who died, 2 died of congestive heart failure, 1 of pneumonia that complicated congestive heart failure, and 1 of renal failure. The relationship of the renal failure to amyloidosis is unclear because no autopsy was performed.

Nine patients in the AL amyloidosis group had undergone intensive intravenous melphalan chemotherapy with autologous stem cell transplantation. Four of them had had complete hematologic responses (defined as the disappearance of bone marrow, serum, or urine evidence of plasma cell dyscrasia), and 1 patient experienced a partial hematologic response. This therapy may induce a prolonged clinical and hematologic remission,<sup>15,16</sup> and all 4 of the surviving patients with AL amyloidosis at the end of this study had received this treatment. Three patients with AL amyloidosis died shortly before or during stem cell collection, 1 of congestive heart failure and 2 of sudden arrhythmic death. Of the remaining patients, 1 patient received a heart transplant (considered a mortality equivalent for this analysis), 4 experienced sudden death, 5 died of congestive heart failure, and 1 patient died of sepsis.

#### COMMENT

This study documents that AL amyloidosis and SSA, although both producing infiltrative cardiomyopathy, dif-



**Figure.** Kaplan-Meier survival curve comparing survival in senile systemic amyloidosis (SSA) with light chain–associated (AL) amyloidosis. A statistically significant longer survival ( $P = .003$ ) occurred in the SSA group.

fer from one another in prognosis and the presence of associated noncardiac disease. Other than a frequent history of carpal tunnel syndrome, a striking finding of SSA was its clinical limitation to the heart. This contrasts with the frequent presence of non–cardiac amyloid–related disease, such as heavy proteinuria and macroglossia, in patients with AL cardiac amyloidosis. This observation indicates that in a patient with cardiac amyloidosis, the finding of either macroglossia or proteinuria should strongly suggest the diagnosis of AL amyloidosis and should prompt a vigorous search for plasma cell dyscrasia.

It is unclear why wild-type transthyretin has a predilection for the heart and why the patients with SSA did not experience macroglossia or nephrotic syndrome, but this observation confirms similar findings in an earlier study of SSA.<sup>11</sup> Similar to our findings, carpal tunnel syndrome was more likely to be present in patients with SSA, raising the question of whether the increased prevalence might be due to the older age of patients with SSA. All of the patients with SSA in our study were male, and only 1 of 18 patients with SSA was female in the study by Kyle et al.<sup>11</sup> The male predilection appears to be unique

to SSA; in contrast, mutant ATTR amyloidosis has close to a 50:50 male:female ratio, and this ratio in AL amyloidosis with cardiac involvement was 60:40 in one large series.<sup>1</sup> This intriguing observation raises the possibility of a factor in males that predisposes them to the deposition of wild-type transthyretin in the heart or, alternatively, suggests an inherent protective factor in females.

We also found that despite older age and echocardiographic evidence of thicker ventricles, survival was significantly longer among patients with SSA than for those with AL amyloidosis. These findings are concordant with the observations of Dubrey et al,<sup>5</sup> who showed that despite a similar degree of cardiac involvement, survival of patients with ATTR familial amyloidosis that involved the heart was better than among patients with AL amyloidosis. The greater left ventricular wall thickness in patients with SSA suggests a greater degree of myocardial infiltration because none of these patients had concomitant disease that would cause ventricular hypertrophy. If there is indeed more myocardial infiltration in patients with SSA, a factor other than mechanical disruption of ventricular architecture by amyloid deposits must be postulated to account for the worse heart failure and poorer survival in the patients with AL amyloidosis. One possibility is that there is a slower deposition of fibrils in SSA than AL amyloidosis, resulting in a compensatory mechanism, presumably due to hypertrophy. We believe that this is unlikely because no data suggest that myocyte hypertrophy is a feature of SSA. In our opinion, a more likely hypothesis is that the circulating light chains have a toxic effect on the heart in patients with AL amyloidosis. Animal studies have shown that the infusion of amyloidogenic light chains into isolated hearts from mice results in cardiac dysfunction,<sup>17</sup> probably mediated by an increase in cellular oxidant stress.<sup>18</sup> In addition, recent preliminary data show that resolution of light chain production after successful chemotherapy is associated with an early decrease in serum N-terminal pro-B-type natriuretic peptide and a corresponding increase in left ventricular fractional shortening despite unchanged wall thickness.<sup>19</sup> The authors attribute that finding to resolution of a cardiotoxic effect of circulating amyloidogenic light chains, a suggestion with which we concur. Our observation of significant survival differences between the 2 groups in the present study indirectly suggests that in addition to myocardial infiltration, light chain toxicity may be a factor in the extremely poor prognosis of patients with AL cardiac amyloidosis.

In summary, SSA is an infiltrative cardiomyopathy of elderly men with a slowly progressive course and a prognosis that contrasts favorably with the aggressive nature of AL amyloidosis of the heart. This disparity may stem from the different protein composition of the amyloid fibrils and perhaps from an intrinsic toxic effect of light chains. The absence of other major organ system involvement in SSA may be a cause of its underrecognition, particularly since this elderly population has a high prevalence of other heart diseases. Although currently no specific therapy is available, new compounds designed to stabilize transthyretin are being investigated and hold promise for a treatment designed to prevent amyloid formation and deposition.<sup>20,21</sup> The potential for new thera-

pies and the recognition that SSA with heart failure has a favorable prognosis underscores the importance of heightened awareness of this disease, which should lead to an increased likelihood of diagnosis. An accurate typing as SSA can permit a certain degree of reassurance to the patient faced with a diagnosis of SSA and will avoid the prescription of unnecessary and harmful chemotherapy.

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