

# Systemic amyloidosis associated with chronic lymphocytic leukemia/ small lymphocytic lymphoma

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**To clarify the presentation and course of patients with chronic lymphocytic leukemia (CLL) and amyloidosis. Mayo databases were interrogated for patients who carried a diagnosis of amyloidosis and CLL evaluated at Mayo Clinic, Rochester from January 1974 to October 2012. Charts were abstracted and data analyzed. Of the 33 patients identified, 20 (61%) were diagnosed with AL and 13 (39%) with non-AL. Only four patients had immunoglobulin light chain amyloidosis (AL) that could be solely attributed to the CLL clone; another six had both a plasma cell clone and a CLL clone that shared the same light chain. Median overall survival was 15.6 months for patients with AL and 58.1 months for patients with non-AL. For patients with AL management involved chemotherapy targeted toward monoclonal plasma cells, lymphocytes or both, and for patients with non-AL no specific amyloid treatment was administered. AL is a rare complication of CLL, but in this elderly population of patients non-AL is nearly as common. Distinguishing between these two groups is essential since patients with non-AL amyloidosis have better outcomes and they do not require cytotoxic chemotherapy to treat their amyloidosis. *Am. J. Hematol.* 88:375–378, 2013. © 2013 Wiley Periodicals, Inc.**

## Introduction

Amyloidosis collectively refers to the extracellular tissue deposition of fibrils composed of low molecular weight subunits of various proteins, many of which circulate as normal constituents of plasma. Immunoglobulin Light chain amyloidosis (AL) is characterized by the progressive deposition of immunoglobulin (Ig) light chains, leading to organ-wide amyloid fibril deposits and organ dysfunction. It is typically associated with an underlying clonal plasma cell dyscrasia. Non AL amyloidosis can be familial, when it is caused by germline mutations in various precursor protein genes, or acquired which is frequently associated with chronic inflammatory diseases. Both AL and non-AL amyloidoses have very rarely been reported in association with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), mostly in the form of case reports or in small case series that included other B-cell lymphoproliferative disorders, such as Waldenstrom's macroglobulinemia (WM) and non-Hodgkin's lymphoma (NHL) including CLL/small lymphocytic lymphoma [1–7]. Here, we present a series of 33 patients with CLL or SLL and AL or non-AL amyloidosis, seen at the Mayo Clinic from 1974 through 2012. We compare the clinical and laboratory characteristics on presentation as well as treatment and outcomes.

## Patients and Methods

Between January 1974 and October 2012, 5,848 patients with amyloidosis were evaluated at the Mayo Clinic, Rochester. Our amyloidosis database was queried for the diagnosis of CLL or SLL and separate electronic data retrieval from the medical record was also performed. A total of 33 patients were identified, all of whom had authorized the use of their medical records for research in accordance with Minnesota privacy statutes. This retrospective chart review was approved by the Institutional Review Board of the Mayo Clinic. In all cases, amyloidosis was diagnosed after tissue biopsy and apple-green birefringence when stained with Congo red stain and viewed under polarized light and/or visible amyloid fibrils on electron microscopy. In 27 cases, amyloid was further classified with the use of immunofluorescence, immunohistochemistry, or liquid chromatography mass spectrometry (Figure 1). Patients were classified as having AL

amyloidosis if immunoglobulin light chains were identified after amyloid typing in at least one organ/tissue biopsy. In the remaining six cases, two patients were presumed to have and were treated as systemic AL amyloidosis based on clinical judgment, biopsy proven amyloid deposition in two or more sites and bone marrow involvement with a clonal lymphoid and plasma cell process. Three patients were presumed to have non-AL amyloidosis based on single organ involvement and bone marrow biopsy with no evidence of clonal plasma cells at the time of diagnosis. One patient was found to have familial amyloidosis based on detection of transthyretin (TTR) gene mutation by polymerase chain reaction testing of peripheral blood. The diagnosis of CLL or SLL was confirmed after review by an experienced hematopathologist in our institution and was based on established diagnostic criteria [8]. The diagnosis of SLL was based on a combination of limited bone marrow involvement by monoclonal lymphocytes, absence of peripheral lymphocytosis on diagnosis and biopsy proven lymph node involvement in at least one site [8].

Patients were evaluated for organ involvement using history, physical examination, blood, and urine laboratory investigations, echocardiography and tissue biopsies according to standard criteria [9]. Three patients were lost to follow-up after their initial visit to Mayo. Survival was estimated by the method of Kaplan–Meier. All statistics were done using JMP software (SAS, Carey, NC).

## Results

Out of 33 patients, 18 (55%) were diagnosed with AL and 13 (27%) with non-AL and six (18%) patients had undetermined amyloid type (two of which were presumed to have AL). CLL was diagnosed in 28 patients and SLL

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**TABLE I. Characteristics of 33 Patients with AMYLOIDOSIS and CLL**

	AL amyloidosis (N = 18)	Non AL amyloidosis (N = 9) <sup>a</sup>	Undetermined amyloid type (N = 6) <sup>b</sup>
N (%); median (range)			
Age <sup>c</sup>	67.5 (49–82)	71 (61–81)	70 (50–92)
Gender, M:F	11:7	8:1	5:1
Time from diagnosis of CLL, months (range) <sup>d</sup>	16 (–15.6–164.5)	40.9 (–7.6–265.4)	48.3 (0.1–129.8)
Follow-up duration, months	40.1 (0.6–173.3)	78.1 (21.6–320)	110 (43.8–216.4)
PS	1 (0–3)	0 (0–2)	0 (0–2)
OS, months, (range)	38.9 (1.4–65.1)	61.4 (31–112)	49.9 (3.6–64.6)
Number of Organs Involved	2.5 (1–6)	2 (1–3)	2 (0–3)
>2 organs involved	9 (50%)	1 (11%)	3 (50%)
Cardiac involvement	10 (55%)	7 (78%)	3 (50%)
Renal involvement	14 (78%)	2 (22%)	2 (33%)
Nervous System involvement <sup>e</sup>	4 (22%)	4 (44%)	0
GI <sup>f</sup> involvement	5 (28%)	0	1 (17%)
Liver involvement	3 (17%)	0	0
Lung involvement	1 (6%)	0	0
Skin or Soft tissue involvement	3 (17%)	2 (22%)	2 (33%)
Heavy chain IgA/IgG/IgM/None/Not done	0/6/1/13/0	0/2/0/4/7	NR
Light Chain Kappa/lambda/Not done	11/9/0	1/4/8	NR
Involved FLC			
Kappa restricted patients			
K (mg/dL) (Not Done)	42.4 (4)	1.29 (6)	NR
K/L ratio <sup>g</sup>	40.4	0.74	NR
Lambda restricted patients			
L (mg/dL) (Not Done)	33.4 (1)	1.15 (6)	NR
K/L ratio <sup>g</sup>	0.16	0.74	NR

CLL: Chronic lymphocytic leukemia, SLL: Chronic lymphocytic leukemia/small lymphocytic lymphoma, OS: overall survival, PS: performance status, GI: gastrointestinal system, NR: not reported.

<sup>a</sup> Hereditary transthyretin (TTR), N = 1 patient, Insulin type, N = 1 patient, senile/TTR amyloid N = 11 patients.

<sup>b</sup> Two presumed to have AL.

<sup>c</sup> On diagnosis of amyloidosis.

<sup>d</sup> Negative number indicates that the diagnosis of amyloidosis predated the diagnosis of CLL.

<sup>e</sup> Including peripheral and autonomic nervous system.

<sup>f</sup> Including stomach, small and large intestine.

<sup>g</sup> All but one patient (lambda restricted) for which data was available had an abnormal k/l ratio.

in five. CLL predated the diagnosis of amyloidosis in all but two patients, one with AL and one with TTR amyloidosis.

Patients with non-AL were older, as expected, and had a longer interval from the diagnosis of their CLL (Table I) until recognition of amyloidosis. Although the median number of organs involved was the same for both the AL and non-AL patients, AL patients were more likely to have three or more organs involved. The heart and kidneys were the organs most commonly involved in both groups. Cardiac involvement was noted in 11 (55%) AL and in nine (69%) non-AL patients.

Of the 18 patients with AL that had typing results available, four had a CLL clone only and the remaining 14 had both a CLL and plasma cell clone (Figure 1), two of whom had sufficient plasma cells and organ impairment (hypercalcemia, renal failure, anemia or lytic lesions) to be classified as having coexisting MM. In six patients, the lymphoid and plasma cell clones expressed the same light chain, in three patients the light chain status for both the lymphoid and plasma cell clone was not known and the remaining patients expressed different light chains. Cases of AL amyloidosis were almost equally divided between kappa and lambda restriction.

Cases with non-AL that had amyloid typing were comprised mostly of patients with TTR amyloid (seven of nine patients). One patient had insulin type amyloid and she was a type I diabetic who had been on insulin for more than 50 years prior to diagnosis.

Information on treatment was available for 19 patients with AL (Table II). In four patients CLL was thought to be the cause of the systemic free light chain deposition based on less than 1% plasma cells in their bone marrow and matching light chain expression between CLL and amyloid. Two patients had lambda restricted CLL, one had kappa restricted CLL, one had a biclonal CLL with the lambda com-

ponent being more abundant and causing lambda type AL. Three patients received treatment directed both toward their CLL and plasma cell clones (Table II). In these cases there was either a separate indication to treat the CLL (e.g., B symptoms, cytopenias) or both clones were thought to be responsible for systemic amyloid deposition. Twelve of the 19 patients received treatment directed toward their abnormal plasma cell clone, with melphalan and dexamethasone being the most common regimen (n = 8 patients). Follow-up information was available on five patients from this group (Table II).

Patients with non-AL were either observed or managed supportively after their diagnosis. Detailed follow up data were available for three patients. One patient is doing well 18 years after diagnosis of his non-AL which involved joints only. One patient died 5 years after his diagnosis because of rapid progression of his underlying CLL and the third patient is doing poorly 5 years after his diagnosis because of reasons unrelated to amyloidosis.

The median overall survival (OS) of the non-AL patients was 61.4 months as compared to 38.9 months for AL patients (Figure 2). Median OS of patients with cardiac involvement was 10.9 months for the AL and 56.6 months for the non-AL patients, respectively.

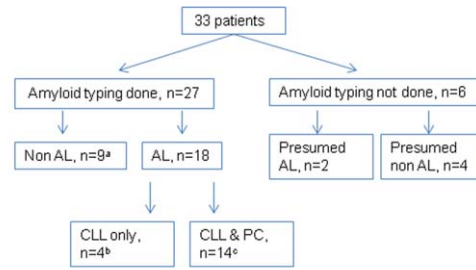
**Discussion**

Amyloidosis in association with CLL is a very rare occurrence, accounting for 0.6% of all amyloidosis patients seen at our institution over a period of four decades. Among our series of 33 patients with concomitant systemic amyloidosis and CLL, we demonstrated amyloidosis non-AL type in a third of patients, underlying the importance of amyloid typing. AL in this setting is more commonly caused by a coexisting plasma cell clone, although in four cases it was a result of systemic deposition of immunoglobulins

TABLE II. Characteristics of Patients with CLL and AL Reported in the Literature

Reference	Age	Cause of AL	Isotype	Organ involvement	Treatment	Outcome	OS, months
Current series	80	CLL	IgM-lambda	Heart, renal, GI	Chlorambucil followed by rituximab for relapsed disease	NR	52 (alive)
	71	CLL	IgG-lambda	Renal, skin	Pentostatin and cyclophosphamide and rituximab	NR	4 (dead)
	62	CLL	IgG-lambda	Renal	Fludarabine and rituximab	Renal Response	27 (alive)
	73	CLL	NR	Heart, renal	No treatment	NR	9 (dead)
	49	CLL+PC	kappa	Peripheral nerves	CHOP-R + bortezomib-ASCT	VGPR (CHOP), CR (ASCT) stable organ disease	26 (alive)
	57	CLL+PC	IgG-kappa	Heart, renal, liver, GI	Bendamustine and lenalidomide	No hematologic response, organ progression	52 (dead)
	63	CLL+PC	IgG-kappa CLL, IgG-Lambda PC	Autonomic nervous system	Lenalidomide and bendamustine	NR	1 (alive)
	82	PC	kappa	Heart, renal, peripheral nerves, GI	Melphalan and dexamethasone	No hematologic/organ response	4 (alive)
	71	PC	lambda	Renal, liver	Melphalan and dexamethasone	VGPR, liver response, renal progression	65 (dead)
	71	PC	IgG kappa CLL, IgG-lambda PC	Renal, skin, soft tissues	Melphalan and dexamethasone	VGPR, renal response	41 (dead)
	81	PC	IgG lambda CLL-IgG kappa PC	Heart, renal, lungs	Melphalan and dexamethasone	No hematologic response, organ progression	9 (dead)
	64	PC	Kappa CLL, IgA kappaPC	Heart, renal, GI	Bortezomib → ASCT	CR, renal response, cardiac progression	20 (alive)
[1]	68	NR	NR	Renal, GI	ASCT	VGPR	96 (alive)
[1]	72	NR	NR	Renal, GI	Fludarabine	LFU	94 (NR)
[5]	54	CLL	IgM-kappa	Renal	Fludarabine, Rituximab	CR, organ response	12 (Alive)
[6]	64	PC	IgG-kappa	Renal	Melphalan	Progression	24 (Alive)
[7]	75	NR	Not found	Lung	NR	NR	NR
[7]	70	NR	IgM-kappa	Lung	NR	NR	NR

CLL: chronic lymphocytic leukemia, AL: immunoglobulin light chain amyloidosis, NR: Not reported, ASCT: autologous stem cell transplant, VGPR: very good partial response, CR: complete response, PC: Plasma cells.



\* Types of non-AL included insulin (n=1), senile/TTR (n=7), hereditary TTR (n=1)  
 \* Two patients with lambda (l) light chains, one with kappa (k) and one with biclonal CLL (k and l)  
 \* 6 patients had the same light chain expressed from their lymphoid and plasma cell clones.

Figure 1. Patient distribution based on amyloid typing. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

produced solely by CLL cells. In this small group of patients seen over the course of four decades, the OS of the AL patients with CLL was rather poor, with a median of 38.9 months.

Systemic amyloidosis has rarely been associated with CLL despite the fact that up to a-third of CLL cases have abnormal serum free light chain ratios [10,11]. Two possible reasons that these light chains do not cause amyloid may be that the level of the circulating free light chain tends to be low [10,11] and that CLL clones are more often kappa than lambda [12]. Lambda light chains are more amyloidogenic than kappa light chains, resulting in lambda AL being twice as common as kappa AL [13]. In our series, all but one patient with AL caused by CLL had lambda light chain positive CLL and amyloid. The high prevalence of an abnormal serum immunoglobulin free light chain ratio and increase free light chains in general in patients with CLL brings into question whether a subset of these patients may have undiagnosed AL. Another interesting observation that may link CLL/SLL to plasma cell disorders is that in CLL/SLL lymph nodes, normal plasmacytoid lymphocytes in the SLL microenvironment with cytoplasmic reactivity to the immunoglobulin free light chain shared by the CLL are more prevalent than those with cytoplasmic reactivity not shared by the CLL cells [11]. This suggests that persistent immune stimulation leading to ongoing polyclonal B-cell activation may play a central role in the development and progression of these malignancies [14].

Whereas most patients with non-AL did not receive treatment because they had senile systemic amyloidosis or were managed supportively, treatment for patients with AL varied. Although the majority of patients were treated with regimens typically used against plasma cell clone, four patients were treated with classic CLL regimens and three patients were treated with regimens targeting both monoclonal lymphocytes and plasma cells. An extensive review of the literature reveals that various treatment strategies have been implemented when amyloidosis is found in association with lymphoproliferative disorders. In a series of 50 patients with AL associated with WM treatment included both alkylator-based treatment, such as melphalan, chlorambucil or CHOP [2]. In a report of 16 cases with AL and B-cell lymphoproliferative disorders, treatment was almost equally divided between autoSCT, alkylator-based regimens or regimens using fludarabine or cladribine [1]. In a report of six cases of AL and NHL, treatment involved autoSCT in two patients, rituximab as a single agent in two patients, melphalan in one patient and cyclophosphamide based treatment in one patient [4]. Finally, in a case series involving 10 patients with AL and NHL, treatment was directed toward the underlying lymphoma in all patients except in one who received alkylator-based treatment [3]. Organ response in these reports and in our study was

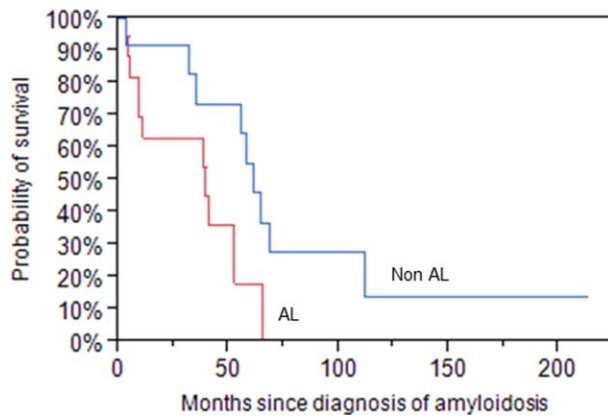


Figure 2. Kaplan-Meier curves according to amyloidosis type. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

variable although in all cases some extent of hematologic response was required to achieve stable organ disease or organ response. In our series one patient had organ progression despite CR and one patient had VGPR and stable organ disease. AutoSCT in patients with lymphoproliferative disorder associated AL has yielded mixed outcomes: one patient achieved PR and had stable neuropathy [3], five patients achieved VGPR and renal response [1] and one patient achieved CR with stable disease after long term follow up [4]. Based on these data one could extrapolate that autoSCT-based approach may be beneficial in patients with CLL-associated AL.

The major limitations of this study are its retrospective nature, the small number of patients and the limited follow up. Another limitation is that amyloid typing was not available for six patients, all of which were diagnosed before 1991, when current tests used to type amyloid were not available or not routinely performed. Despite these limitations these results emphasize that amyloid typing is crucial in order to distinguish between AL and non-AL amyloid. In

the case of AL, it should not be assumed that plasma cells are solely responsible for light chain production as our data and that of other reports of low grade lymphomas and AL have demonstrated.

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