κ and λ Light Chain Disease: Survival Rates and Clinical Manifestations

By C. Shustik, D. E. Bergsagel, and W. Pruzanski

Ninety-seven patients with light chain disease (LCD) were studied. The median survival from diagnosis was 30 mo for 52 patients with κ-LCD and 10 mo for 45 patients with λ-LCD ($p < 0.0007$). A lower proportion of κ-LCD patients (15.7%) than λ-LCD patients (42.2%) died within the first 6 mo after diagnosis. The survival of the remaining patients with κ-LCD was still much longer than of those with λ-LCD ($p = 0.022$). The shorter survival of λ-LCD patients could not be ascribed to an increased incidence of recognized manifestations indicating a poor prognosis (e.g., anemia, hypercalcemia, azotemia, low albumin, the extent of osteolytic lesions, or proteinuria), the incidence of amyloidosis, the clinical stage of the disease at diagnosis, or the response to treatment, and remains unexplained. A comparison of the clinical manifestations of LCD with those of other myelomas revealed some differences. LCD patients were slightly younger than IgA and IgG patients but older than IgD patients. A 1:1 ratio of males to females was similar to the ratios in IgA and IgG myeloma, but differed from the 3:1 ratio reported for IgD myeloma. Plasma-cell leukemia developed in 7/97 LCD patients, an incidence that was higher than has been reported in other myelomas. The initial BUN was ≥30 mg/100 ml in 54 of 95 LCD patients, an incidence that was higher than has been reported for IgA and IgG myeloma, but lower than the incidence in IgD myeloma. The incidence of amyloidosis in LCD (23 of 97 patients) was similar to that reported for IgA and IgG myeloma, but less than the incidence in IgD myeloma.

PLASMA-CELL NEOPLASMS secreting only κ or λ light chains (light chain disease, LCD) are thought to be more aggressive and to have a shorter survival than myelomas secreting other types of M components.[1,2] Significant differences in the therapeutic response and the survival time of the λ-type (λ-LCD) relative to the κ-type (κ-LCD) have also been reported by some investigators,[3] but were not confirmed by others.[4,5] These studies did not involve a large number of patients and different criteria were applied in the analysis. Whereas in one report all patients, regardless of the survival time or the duration of therapy, were analyzed,[3] in another only those patients who survived more than 6 mo were recorded,[4] thus excluding all early deaths.

The observation that patients with κ-LCD survive longer than those with λ-LCD[3] has been confirmed by subsequent studies.[6,7] However, the reasons for the shorter survival of patients with λ-LCD have not been identified.

We have surveyed 97 well-documented patients with LCD. The purpose of this study was to determine if the shorter survival of λ-LCD patients could be related to a higher incidence of recognized clinical manifestations indicating a

From the Immunoglobulin Diagnostic and Research Centre, Departments of Medicine, the Wellesley and Princess Margaret Hospitals, University of Toronto, Toronto, Ont., Canada.

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Address for reprint requests: W. Pruzanski, M.D., the Wellesley Hospital, Toronto, Ont., Canada M4Y 1J3.

poor prognosis (e.g., anemia, the extent of osteolytic lesions, hypercalcemia, azotemia, and the amount of protein excreted per 24 hr),[8] other manifestations such as amyloidosis, or response to treatment. In addition, the clinical picture of LCD was compared with that observed in other myelomas.

MATERIALS AND METHODS

Our laboratory receives sera and urines of myeloma patients from most of the hospitals in this area for immunodiagnostic studies. From this material we selected patients in whom we were able to detect homogeneous free κ or λ light chains (Bence Jones protein) in the serum and/or urine, and we demonstrated the absence of an M component containing a heavy chain. Of these patients, 106 satisfied the diagnostic criteria for LCD. We were able to collect detailed clinical information about 97 of these patients; 47 were treated by one of the authors. The remaining 50 patients were similarly investigated and treated in other University Hospitals. The analysis of these data forms the basis of this report. The sera and urines were tested for total protein by the biuret method and by cellulose acetate electrophoresis. Cryoglobulin and pyroglobulin tests were done by routine techniques. Each serum was tested immunoelectrophoretically using antisera against Ig, IgG, IgA, IgM, IgD, IgE, F_c, and Fab fragments, κ and λ light chain proteins, and free κ and λ light chains. The concentration of IgG, IgA, IgM, and IgD was estimated using immunoquantitation plates. When required, each urine was concentrated from 50 to 500 times and tested immunoelectrophoretically using antisera against both types of light chains and against F_c fragment. All of these tests were done as previously described.[9] Amyloidosis was verified by Congo Red staining of histologic specimens and by polarized light microscopy. In several instances the amyloid substance was examined by electron microscopy.

The myeloma staging system used in the paper has been described in detail.[8] Briefly, stage I represents patients with a low myeloma cell mass. The criteria are hemoglobin above 10.5 g/100 ml, normal serum calcium, urinary light chain protein excretion below 4.0 g/24 hr, and no skeletal lesions, or only a solitary osteolytic lesion. All of these criteria must be fulfilled for a diagnosis of stage I disease. Stage III indicates patients with a high myeloma cell mass. One or more of the following criteria must be present: hemoglobin below 8.5 g/100 ml, serum calcium above 12 mg/100 ml, advanced osteolytic lesions, urinary light chain protein excretion above 12 g/24 hr. Stage II is intermediate. Each stage is subdivided into (A) blood urea nitrogen below 30 mg/100 ml, and (B) BUN equal to or greater than 30 mg/100 ml.

The response to therapy was evaluated by monitoring the amount of light chain protein excreted in the urine per 24 hr. Reduction to 50% or less of the quantity recorded before therapy was defined as an objective response. Since no palpable plasmacytomas were encountered in the present series, and very few significant spikes were observed in serum electropherograms, these criteria of response were not feasible.

Actuarial survival curves were prepared by the method of Kaplan and Meier.[10] The significance of differences in the survival curves was tested by the method of Gehan.[11]

RESULTS

The general characteristics of the patients with LCD in this study are shown in Table 1. There were 52 patients with the κ-type of light chain protein (κ-LCD) and 45 with the λ-type (λ-LCD). The median, mean, and range of ages at diagnosis were similar for the two groups of patients. The ratio of males to females was essentially 1:1 in both groups.

The median survival from diagnosis was 30 mo for patients with κ-LCD and 10 mo for patients with λ-LCD (Table 1 and Fig. 1). The median interval from symptomatic onset to diagnosis was 4 mo for patients with κ-LCD and 6 mo for patients with λ-LCD. The number of patients over 70 yr of age at diagnosis was somewhat higher in the group with λ-LCD (17 of 45) than in κ-LCD (12 of 52). When the survival of patients less than 70 yr of age was considered, the im-

Table 1. General Characteristics of Patients With κ- and λ-LCD

	κ-LCD	λ-LCD	Total
No. of patients	52	45	97
Age at diagnosis (yr)			
Range	23–86	30–82	23–86
Median	60	62	61
Mean	60.4	62.0	61.1
Males/females	26/26	23/22	49/48
Survival from diagnosis, median (mo)*	30	10	

*The difference between the survival of κ-LCD and λ-LCD patients is significant at $p < 0.0007$.

proved survival of patients with κ-LCD was significantly better than those with λ-LCD ($p = 0.005$). Even after the patients who died within 6 mo of diagnosis were excluded (15.7% of κ-LCD and 42.2% of λ-LCD), the survival of patients with κ-LCD was still much longer than for those with λ-LCD ($p = 0.022$), and the survival curves of the two groups became widely separated after 48 mo.

Certain clinical manifestations are known to be of prognostic significance in patients with plasma-cell myeloma.[8] For this reason we compared the initial values of the six prognostic factors shown in Table 2 for patients with κ-LCD and λ-LCD. It will be noted that the initial hemoglobin, blood urea nitrogen, serum albumin, serum calcium, the amount of protein excreted per 24 hr, and the severity of the skeletal lesions in the two groups of patients were very similar.

These prognostic factors can be used to stage patients.[8] The clinical stages of the patients in this study are shown in Table 3. The proportion of stage III disease was similar for patients with κ-LCD and λ-LCD. A greater proportion of patients with κ-LCD were stage II (46% versus 36%) and a smaller proportion were stage I (19% versus 29%). The percentage of patients presenting with a BUN ≥ 30 mg/100 ml was slightly greater in patients with κ-LCD (35% versus 29%). Thus, the improved survival of patients with κ-LCD cannot be ex-

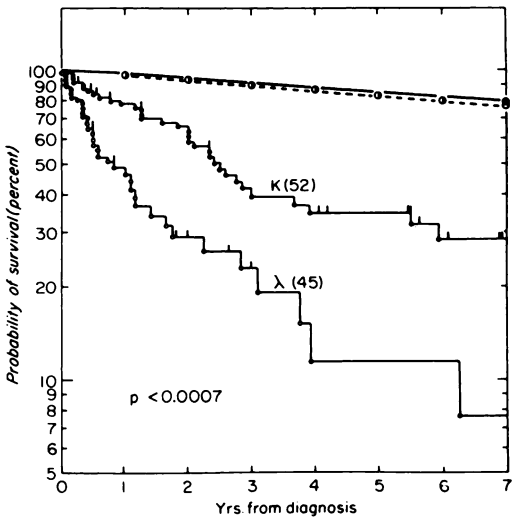

Fig. 1. Survival of patients with κ- and λ-LCD. In this and other figures actuarial survival curves were prepared by the method of Kaplan and Meier[10] and the significance of the differences in the survival of the two groups was calculated by the method of Gehan.[11] Patients withdrawn alive prior to the seventh year are shown in all figures by a vertical bar above the curve. The survival curves in the upper portion of the figure indicate the survival of a normal population of the same age distribution as the patients with κ-LCD ○——○ and λ-LCD ○---○.

Table 2. Comparison of Prognostic Manifestations in Patients With κ- and λ-LCD*

		No. of Patients	
		κ-LCD	λ-LCD
Hemoglobin (g/100 ml)	≤ 8.5	9	9
	8.6–10.4	11	11
	≥ 10.5	32	25
Blood urea nitrogen (mg/100 ml)	≤ 20	20	23
	21–39	18	11
	≥ 40	13	10
	Unknown	1	1
Serum albumin (g/100 ml)	< 2.0	1	1
	2.0–2.9	11	8
	≥ 3.0	39	36
	Unknown	1	—
Serum calcium (mg/100 ml)	≤ 10.4	34	29
	10.5–11.9	4	3
	≥ 12.0	9	7
	Unknown	5	6
Bence Jones proteinuria (g/24 hr)	≤ 4.0	29	21
	4.0–11.9	11	13
	≥ 12.0	4	6
	Unknown	8	5
Skeletal lesions	None	6	5
	Osteoporosis	11	12
	Solitary osteolytic lesion	3	0
	A few osteolytic lesions	0	1
	Many osteolytic lesions	32	27

*All values recorded prior to treatment.

plained on the basis of the stage of the disease or the severity of azotemia at presentation. It is also of interest to note that in stages I and II (Fig. 2), and for those with azotemia (Fig. 3), patients with λ-LCD died at a faster rate than κ-LCD patients. The survival curves for κ- and λ-LCD patients with stage III disease were not significantly different (Fig. 2). Nonazotemic patients with λ-LCD died at a very rapid rate initially; after the first year the death rate slowed, and the survival curve appeared to parallel the curve for patients with κ-LCD (Fig. 3).

Amyloidosis was detected during the course of the disease or at autopsy in 13 patients with κ-LCD (25%) and in 10 with λ-LCD (22%). Kidneys, liver, and spleen were involved in more than half of these patients. Amyloid was also

Table 3. Clinical Stages of Patients With κ- and λ-LCD at Diagnosis[8]

	κ-LCD			λ-LCD		
Stage	A	B	Total (%)	A	B	Total (%)
I	8	2	10 (19)	12	1	13 (29)
II	20	4	24 (46)	12	4	16 (36)
III	6	12	18 (35)	8	8	16 (36)
Totals	34	18	52	32	13	45
(%)	(65)	(35)	(100)	(71)	(29)	(100)

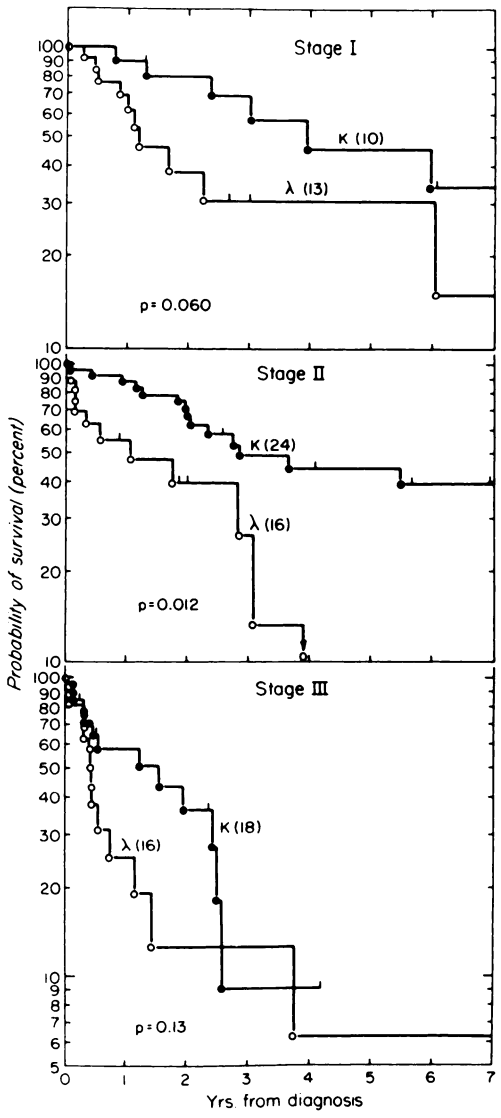

Fig. 2. Survival of patients with κ- and λ-LCD by clinical stage.

found in the skin, tongue, gastrointestinal tract, heart, synovium, salivary glands, muscles, and thyroid. The presence of amyloidosis did not affect the survival of patients with κ-LCD, but shortened the survival of patients with λ-LCD (Fig. 4). The difference in the survival of patients with amyloidosis and κ-LCD, as compared to those with amyloidosis and λ-LCD, was highly significant (p = 0.0021). However, the presence or absence of amyloidosis did not explain the better survival of patients with κ-LCD, for the survival of patients without amyloidosis was considerably longer for κ-LCD than for λ-LCD (p = 0.019).

The patients with LCD were treated in a variety of ways (Table 4). Approximately 80% of both groups of patients were treated with an alkylating agent,

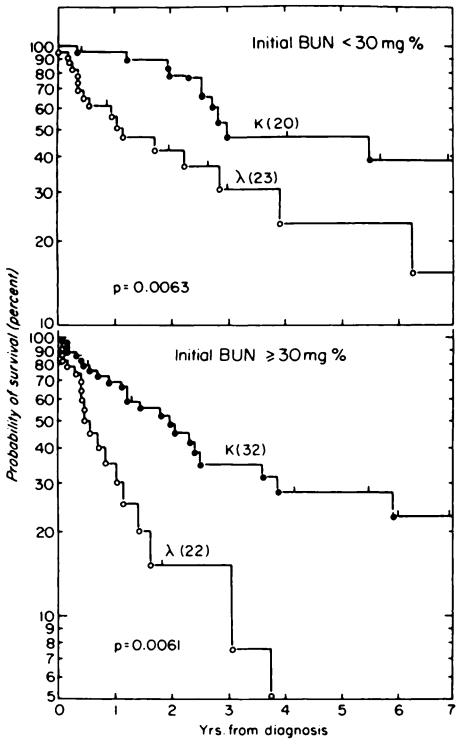

Fig. 3. Survival of patients with κ- and λ-LCD by initial blood urea nitrogen (BUN).

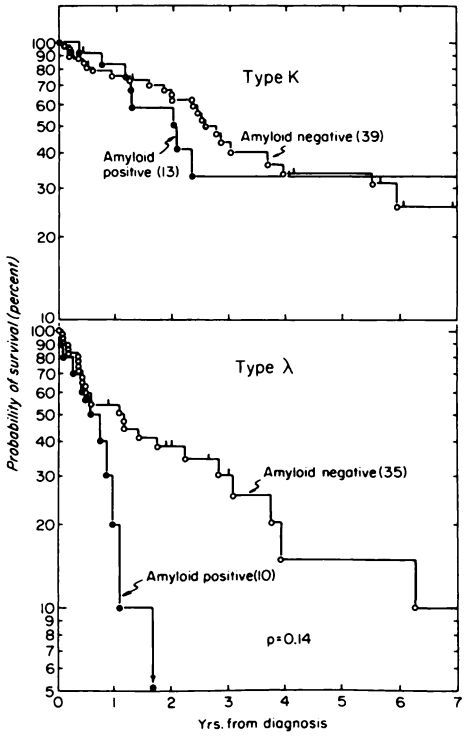

Fig. 4. The effect of amyloidosis on the survival of LCD patients.

Table 4. Treatment of Patients With κ- and λ-LCD

Treatment	κ-LCD	λ-LCD	Total
No treatment	8 (15)*	9 (20)	17 (18)
Steroids, urethane, or radiotherapy only	2 (4)	1 (2)	3 (3)
Alkylating agents† without steroids	17 (33)	15 (33)	32 (33)
Alkylating agents† with steroids	25 (48)	20 (45)	45 (46)
Patients treated with alkylating agents: no. of responders/no. evaluable	17/33 (52)	13/22 (59)	30/55 (55)

*Numbers in parentheses are percentages.

†Alkylating agents used are melphalan, cyclophosphamide, or chlorambucil.

with, or without the addition of corticosteroids. Of the evaluable patients treated with an alkylating agent, 52% of those with κ-LCD and 59% of those with λ-LCD were classified as "responders." When the survival of only those patients treated with alkylating agents was considered, we found that patients with κ-LCD survived significantly longer than those with λ-LCD ($p = 0.005$). It is unlikely that the difference in the survival of these two groups of patients can be ascribed to differences in treatment policies or the responsiveness of the two tumor types to alkylating agents.

Other Clinical Features

Four patients with κ-LCD and one with λ-LCD presented with severe renal failure; four others with κ-LCD and three with λ-LCD manifested the nephrotic syndrome. Two patients with κ-LCD presented with a classical adult Fanconi syndrome.

Four patients had a previous history of cancer: lung, breast, kidney, and tongue were the primary sites involved in these patients. In addition, one patient had pernicious anemia, and another, Hashimoto's thyroiditis.

Proteinuria was found in all patients, but the amount of Bence Jones protein excreted per 24 hr varied greatly (Table 2). Electrophoresis of the urine invariably showed spikes, usually of γ or β mobility (Table 5). We wondered if the mobility of the light chain protein would be affected by the presence or absence of amyloidosis, and therefore we analyzed these two groups separately. It will be noted that in the group of patients without amyloidosis the Bence Jones protein had a mobility faster than γ in 59% of patients with κ-LCD and in 34% of those with λ-LCD. In the group with amyloidosis the respective values were 45% and 75%.

Marrow aspiration prior to therapy showed no increase in plasma cells in seven patients with κ-LCD and six with λ-LCD. There was a moderate increase of 5%-50% plasma cells in 12 patients with κ-LCD and 8 with λ-LCD, and in the remainder the marrow plasmacytosis exceeded 50%. Two patients with κ-LCD and five with λ-LCD developed plasma-cell leukemia, with total leukocyte counts ranging from 4900 to 37,000/μl, and the percentage of plasma cells from 7% to 25%. One patient with κ-LCD developed a terminal acute myeloblastic leukemia, and another presented with Di Guglielmo's erythroleukemia.

The total serum protein was low in more than one-third of the patients in each group and higher than normal in only 5%. Low IgG and IgA concentra-

Table 5. Immunologic Data in Patients With κ- and λ-LCD*

Test	κ-LCD		λ-LCD	
IgG (mg/100 ml)				
<600	17		23	
600–1400	28		19	
>1400	3		1	
IgA (mg/100 ml)				
<50	17		22	
50–150	19		14	
>150	12		7	
IgM (mg/100 ml)				
<30	24		23	
30–90	19		15	
>90	5		15	
Serum electrophoresis				
Normal	14†	6‡	10†	2‡
Hypogammaglobulinemia	15	6	7	3
γ-spike	5	1	14	2
β-spike	5	0	3	1
α_2-spike	0	0	1	2
Electrophoretic mobility of the urinary Bence Jones protein				
γ	15	6	21	3
β	16	7	8	3
α_2	4	0	3	3
α_1	0	0	0	1
Not tested	4	0	3	0

*Assayed before the beginning of therapy.
†Patients without amyloidosis.
‡Patients with amyloidosis.

tions were noted in one-third of κ-LCD, and in more than 50% of the patients with λ-LCD (Table 5). The IgM serum concentrations were low in half of the patients in both groups. An elevation of one or more immunoglobulins was noted in less than 10% of the patients in each group.

Serum protein electrophoresis in κ-LCD showed spikes of γ or β mobility in 21% of the patients, hypogammaglobulinemia in 40%, and a normal electrophoretic pattern in 39%. For λ-LCD the respective proportions were 51%, 22%, and 27%. All but two of the spikes were small, not exceeding 0.3 g/100 ml. Two patients with λ-LCD had spikes of approximately 2.0 g/100 ml; in one the light chain protein was a tetramer[12] and in the second the light chain protein had polymerized spontaneously to produce high molecular weight molecules of various sizes.

DISCUSSION

Light chain disease, or multiple myeloma with excretion of homogenous light chains only, comprises 10%–20% of all myelomas. The diagnosis of LCD depends on the availability of specific antisera against five known classes of immunoglobulins and against free and bound light chains. Previously reported series describing LCD[13,14] may have included some patients with IgD or IgE

myeloma, and some obviously have included patients with IgG M components.[13]

In our series of 97 patients, LCD occurred with equal frequency in males and females, as in IgG and IgA myeloma, but in clear distinction from IgD myeloma, which is found three times more commonly in males.[15] Forty-seven per cent of the patients were younger than 60 yr at the time of diagnosis, as compared with 65% in IgD myeloma[15] and only one-quarter to one-third of IgA or IgG myeloma patients.[16]

The survival of κ-LCD patients in our group was much longer than that of λ-LCD. Survival was not influenced by the sex or age of the patients at diagnosis. The shortened survival of patients with λ-LCD could not be explained by differences in the incidence of azotemia or amyloidosis, which was almost equal in both groups. The occurrence of amyloidosis caused a marked shortening of survival in patients with λ-LCD but did not affect the survival of patients with κ-LCD. The adverse effect of amyloidosis on the survival of patients with λ-LCD was not sufficient to explain their poorer survival, for the survival of patients without amyloidosis was also shorter for λ-LCD than for κ-LCD.

Our study did not support the observation that patients with λ-LCD have a higher incidence of azotemia[6] and a lower therapeutic response rate.[3] On the contrary, the proportion of responders with λ-LCD (59%) was not different from that with κ-LCD (52%). Similar observations were made by Alexanian et al.,[17] who reported high response rates in both κ-LCD (77%) and λ-LCD (73%) when combinations of melphalan with steroids, and sometimes with procarbazine, were used. In our series, survival was significantly shorter in λ-LCD, even after exclusion of all early deaths. These results are in accordance with the results of others.[3,6] There is no explanation as yet of the significantly shorter survival of the patients with λ-LCD. No differences in the degree of anemia, blood urea nitrogen, calcium and albumin, Bence Jones proteinuria, the severity of skeletal lytic lesions, the frequency of amyloidosis or the therapeutic response to alkylating agents were observed in patients with κ-LCD or λ-LCD. Similarly, we were unable to explain the shorter survival of patients with λ-LCD on the basis of the stage of the disease when therapy was started. Thus, the cause of the short life span of the patients with λ-LCD remains to be found. An increased growth fraction and a faster growth rate of the malignant cells could explain the shortened survival of λ-LCD patients, but these parameters have not yet been studied.

Subjective complaints of LCD patients were similar to those in other myelomas. Organomegaly or lymphadenopathy was detected in approximately 20% of the patients, an incidence much lower than in IgD myeloma.[15] Osteolytic lesions were as common as in IgD myeloma[15] but more frequent than in other classes.[1,16]

Anemia was detected before initiation of chemotherapy in proportion similar to IgG and IgA myeloma (47%) but lower than in IgD myeloma (61%).[15,18] Plasma-cell leukemia developed in seven patients with LCD, and this incidence was considerably higher than the incidence reported among myeloma patients producing other M components.[19]

Azotemia was noted in a proportion much higher than in IgG or IgA myeloma,[8] but lower than in IgD.[15,16] Thus our study did not confirm the observa-

tion[6] that azotemia was more frequent in λ-LCD. Also hypercalcemia seemed to be as frequent as in other myelomas.[1,16,20] The electrophoretic pattern of the serum was distinctly different from other myelomas. High spikes exceeding 2.0 g/100 ml were noted in the sera of only two patients with λ-LCD. The frequency of amyloidosis was similar to that observed in patients with IgA and IgG myeloma, but lower than in patients with IgD myeloma.[15,21] Since the electrophoretic mobility of the urinary light chain proteins in patients with amyloidosis was reported to be faster than in myeloma without amyloidosis,[22] the mobility of the urinary light chain protein was analyzed separately in patients with and without amyloidosis. No differences were found in κ-LCD, whereas in λ-LCD with amyloidosis 75% of the light chain proteins had faster than gamma mobility, as compared to 34% in those without amyloidosis.

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