Ann Hematol (2009) 88:59–66
DOI 10.1007/s00277-008-0554-0

ORIGINAL ARTICLE

Multiple myeloma-associated amyloidosis is an independent high-risk prognostic factor

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Received: 14 October 2007 / Accepted: 27 June 2008 / Published online: 22 July 2008

Abstract Several prognostic factors have been recognized in patients with multiple myeloma (MM). Among the most important are: the serum levels of β2-microglobulin, albumin, and LDH; the labeling index; and an abnormal karyotype. Patients with amyloidosis (AL) have poor prognosis; however, little is known concerning the prognostic significance of AL associated to MM. In 201 consecutive patients with de novo MM, we performed a fat-pad biopsy needle aspiration (FPBNA) that was stained with Congo red. Sixty eight (34%) patients had AL and a poorer prognosis disease: lower performance status, presence of B symptoms, higher LDH and calcium values, and worse response to chemotherapy. Cox regression model for overall survival detected three variables having independent prognostic significance: the presence of AL (RR=3.4, $P<0.004$), serum albumin levels <3.5 g/dl (RR 3.2, $p<0.005$), and patients not achieving complete remission or very good partial remission (RR 2.9, $p<0.02$). In 28% of patients with de novo MM, FPBNA was useful to detect incidental amyloidosis. During follow-up, 69% of these patients had symptoms of AL. Excluding 16 patients with obvious symptoms of AL at diagnosis, overall survival was worse in patients who developed later symptoms of AL. MM-associated AL represents a poorer prognosis disease even in the absence of symptoms at diagnosis, and this specific association may be considered as an independent high-risk prognostic factor. The routine study of periumbilical fat-pad tissue should be mandatory in all patients with MM.

Keywords Multiple myeloma · Amyloidosis · Prognostic factors

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Introduction

Multiple myeloma (MM) is a clonal malignant disease of plasma cells characterized by the production of a monoclonal immunoglobulin, anemia, lytic bone lesions, and renal failure [13].

Several prognostic factors have been recognized for this disorder; however, the most important are: the serum level of β2-microglobulin, albumin, and LDH [10]; the labeling index [20]; and abnormal karyotypes [23].

Systemic amyloidosis (AL) is a rare disorder characterized by the deposition of amyloid fibrils in different tissues. AL is part of the spectrum of monoclonal gammopathies that includes: MM, Waldenstrom's macroglobulinemia, heavy chain disease, and monoclonal gammopathies of unknown significance (MGUS) [11]. The natural evolution of AL shows that it is a progressive disease and that 80% of the patients are dead within 2 years after diagnosis [12]. Approximately 12% to15% of patients with MM develop AL during the course of the disease and up to 30% have subclinical amyloid deposits whenever fat-pad biopsy needle aspiration (FPBNA) and Congo red staining are routinely performed [3].

Amyloid stained with Congo red gives pathognomonic red-green birefringence when viewed under crossed polarized light and is the most commonly used method for the detection of amyloid deposits and has been the diagnostic gold standard for more than 40 years [18].

In general, patients with AL have a poor prognosis, with a median overall survival of one or 2 years [7, 8]. To date, however, little is known about the prognostic significance of AL associated to MM.

We report herein our experience in 201 patients with MM in whom FPBNA was done at diagnosis in order to search the prognostic significance of AL in these patients.

Materials and methods

From January 1989 to January 2000, we studied a total of 201 patients with MM. Diagnosis of MM was made using the conventional criteria [9].

Written informed consent was obtained from each patient before any procedure in accordance with the Ethics and Research Committee of La Raza Medical Center, and in accordance with the Declaration of Helsinki of 1975.

Fat-pad biopsy needle aspiration was done in all patients according to a previously reported technique [24]. Briefly, fat samples were obtained by aspiration from an aseptic and locally anesthetized periumbilical site using a 22- to 25-gauge biopsy needle. The fat was compressed between two clean glass slides and sent for staining and interpretation with an expert pathologist. The slides were dried and then fixed for 10 min in 10% formalin. After rinsing for10 min in a distilled water bath, they were stained with fresh 1% alkaline Congo red, and then counterstained with hematoxylin and dehydrated in alcohol and xylene. The biopsies were examined by light and polarized microscopy for the presence of Congo red deposits and green birefringence. All samples were analyzed by the same pathologist during the study. All fat biopsies were examined immediately in order to assess the presence of visible fragments of adipose tissue on the slides. In the case of absence of fat, the biopsy was repeated until enough fat material was available.

In addition, serum samples were obtained at diagnosis to determine LDH, β-2 microglobulin, albumin, calcium, phosphorus, creatinine, and liver function tests. Serum and urine electrophoresis and immunofixation, as well as bone marrow aspiration and bone X-ray studies were taken at diagnosis. Non-secretory MM was considered when the patient had more than 10% of plasma cells on bone marrow examination, and evidence of end-organ damage: hypercalcemia, renal insufficiency, anemia, or lytic bone lesions. In all patients having non-secretory MM, response was evaluated by both bone marrow aspiration and bone marrow biopsy. Bone marrow karyotype was obtained in only 38 patients. After diagnosis of MM, chemotherapy was started according to the current protocols in our department.

Criteria for response

The criteria to evaluate response for MM were as follows: complete remission (CR) was defined as the absence of paraprotein in serum and urine conventional electrophoresis and immunofixation as well as the presence of 5% or less plasma cells in the marrow. Very good partial remission (VGPR) was defined as a decrease of 90% in the serum paraprotein level. Partial remission (PR) was considered whenever a 50% decrease of the serum paraprotein level and/or a 90% decrease in the urine Bence Jones protein were obtained. Minimal response was considered when the patient achieved a decrease of 25% in the serum paraprotein level.

In the case of non-secretory MM, CR was defined as the presence of less than 5% of plasma cells in bone marrow smear/biopsy and absence of symptoms and signs of end-organ damage.

Statistical analysis

Comparison of the categorical and interval variables between the groups was made using X^2 test or Mann–Whitney U test, respectively.

Probabilities of disease-free survival (DFS) and overall survival (OS) were calculated using the method of Kaplan–Meier. Univariate comparisons were made using the log-rank test. DFS was defined as the time between remission and relapse or last follow-up. OS was considered as the time elapsed from diagnosis to death (despite the cause of dead), or until the last-documented contact with the patient. All quoted p values are from two-sided tests, and values of less than 0.05 were considered significant. Cox proportional hazard model for DFS and OS was performed using the following covariates: age, gender, M protein, clinical stage, performance status (Karnofsky), LDH (< or > 450 UI/l), β2-microglobulin (< or >3.5 mg/l), serum albumin (< or >3.5 g/

dl), chemotherapy schedule, response to treatment, and presence of amyloid deposits (with or without symptoms of amyloidosis at diagnosis).

In order to evaluate if the presence of AL had any prognostic value even in the absence of symptoms, we performed additional univariate and multivariate analysis excluding those patients with positive FPBNA and clinical data of amyloidosis.

Results

Table 1 shows the baseline characteristics of the patients included in the study.

As in the majority of Latin-American countries, most of the patients (78%) were classified as having a Durie-Salmon stage III. Forty patients (20%) with stage II or III MM, had, in addition, plasmocytoma of the bone. The frequency of MM-associated plasmocytoma was similar between the groups. Sixty-eight of 201 patients (34%) had AL; 16 (8%) of them never had symptoms or clinical signs of AL, in 36 (18%) the symptoms appeared during follow-up (the median time to develop clinical findings of amyloidosis in this cohort was 14 months, range 6 to 30 months), and the other 16 (8%) were positive to Congo red in FPNBA and had classical clinical findings of AL at the time of diagnosis.

The individuals with MM associated AL had a higher frequency of Bence Jones proteinuria, anemia (hemoglobin <10 g/dl), hypercalcemia (>10.6 mg/dl), increase in serum alkaline phosphatase (> 100 UI/l), decrease in serum albumin (<3.5 g/l), increase serum LDH levels (>450 UI/l), and worse performance status (Table 1).

Table 2 shows the chemotherapy given and response to chemotherapy according to the presence (whether or not having symptoms of AL at diagnosis) or absence of amyloid deposits in the FPBNA. Chemotherapy treatments included melphalan-prednisone regimen (n=89, 44%), VMCPA chemotherapy (vincristine, melphalan, cyclophosphamide, prednisone, and adryamicin) (n=76, 38%), and VAD (vincristine, adryamicin, and dexamethasone) (n=36, 18%).

The group of patients with MM-associated AL (whether or not having symptoms of AL at diagnosis) had a worse

Table 1 Clinical baseline characteristics of the patients included in the study

Characteristic	Amyloid + with symptoms at dx[a] N=16 (8%)	Amyloid + no symptoms at dx[b] N=52 (26%)	Amyloid −[c] N=133 (66%)	P value
Age, mean (sd) years	56.9 (12.3)	58.6 (9.0)	60.2 (8.4)	0.4
Gender, N (%)				
Male	9 (56)	26 (50)	70 (52.5)	0.8
Female	7 (44)	26 (50)	63 (47.5)	
M protein, N (%)				
IgG	7 (44)	23 (44)	72 (54)	
IgA	5 (31)	16 (31)	29 (22)	0.5
LCD[d]	2 (12.5)	11 (21)	25 (19)	
Non secretory	2 (12.5)	2 (4)	7 (5)	
Durie-Salmon, N (%)				
IIA	1 (6.2)	7 (13.5)	28 (21)	
IIB	1 (6.2)	1 (2)	6 (4.5)	0.2
IIIA	6 (37.5)	25 (48)	60 (45)	
IIIB	8 (50)	19 (36.5)	39 (29.5)	
Karnofsky <60% N (%)	9 (56)	17 (33)	40 (30)	0.5
Bence Jones protein + N (%)	10 (62.5)	25 (48)	50 (37.5)	0.5
Serum M spike mean (SD) g/dl	5.3 (1.1)	4.8 (2.1)	4.6 (1.9)	0.3
Total proteins in urine >5 g/24 h, N (%)	6 (37.5)	5 (9.5)	0	0.07
Hemoglobin <10 g/dl, N (%)	10 (62.5)	25 (48)	54 (40.5)	0.0001
Serum calcium >10.6 mg/dl N(%)	7 (44)	23 (44)	35 (26)	0.0001
Serum creatinine mean (SD) mg/dl	1.4 (0.4)	1.2 (0.5)	1.4 (0.5)	0.04
Serum alkaline phosphatase > 100 UI/l, N (%)	4 (25)	8 (15)	8 (6%)	0.01
Serum albumin <3.5 g/l, N (%)	8 (50%)	35 (67%)	46 (34.5)	0.0001
High LDH[e] (>450 UI/l), N (%)	9 (56)	26 (50)	53 (40)	0.0001
β2-microglobulin >3.5 mg/l, N (%)	13 (81)	12 (75)	106 (80)	0.0001

[a] Both, positive FPBNA and clinical data of amyloidosis at diagnosis
[b] FPBNA positive; no symptoms of amyloidosis at diagnosis
[c] Amyloid negative
[d] Light chain disease
[e] Lactid dehydrogenase

Table 2 Initial treatment given and response to chemotherapy according to the presence (with or without symptoms at diagnosis) or absence of amyloidosis associated to myeloma

Characteristic	Amyloid + with symptoms at dx[a] *N*=16 (8%)	Amyloid + no symptoms at dx[b] *N*=52 (26%)	Amyloid–[c] *N*=133 (66%)	*P* value
Initial treatment				
MP	6 (37.5)	23 (44)	60 (45)	
VMCPA	6 (37.5)	19 (36.5)	51 (38.5)	0.9
VAD	4 (25)	10 (19)	22 (16.5)	
Response to treatment				
CR[d]	0	3 (6)	10 (7.5%)	
VGPR[e]	1 (6.2)	5 (9.5)	13 (10%)	<0.001
PR[f]	6 (37.5%)	20 (38.5)	83 (62.5%)	
Failure	9 (56.2%)	24 (46)	27 (20%)	

[a] Both, positive FPBNA and clinical data of amyloidosis at diagnosis
[b] FPBNA positive; no symptoms of amyloidosis at diagnosis
[c] Amyloid negative
[d] Complete remission
[e] Very good partial remission
[f] Partial remission

response to chemotherapy compared with the group without AL; particularly, patients with AL achieved lower PR rates and higher treatment failures.

In 16 patients who had clinical AL and a positive FPBNA at diagnosis, six patients (9%) had nephrotic syndrome, three more patients (4.5%) had pancytopenia (two of them hepatomegaly and splenomegaly as well), and in five patients echocardiography showed indirect data compatible with cardiac AL. Thirty-six additional patients who had a positive FPBNA, developed clinical data of AL during follow-up (Table 3).

Survival data

Disease-free survival

After a median follow-up of 36 months (range 12 to 199 months), the median DFS for all patients was 30 months (95% CI 25.4 to 34.6 months).

In the univariate analysis, the serum albumin levels (< or >3.5 g/dl), β2-microglobulin (< or >3.5 mg/l), the response to treatment (CR+VGPR vs PR and failure), and the presence or absence of AL were statistically significant (Table 4).

Overall survival

Some variables showed statistical significance such as the response to treatment. Those patients who achieved CR or VGPR had a median OS of 53 months. On the other hand, those individuals who achieved PR or those who did not respond to chemotherapy had a median OS of 34 and 27 months, respectively ($p<0.002$, Fig. 1, Table 4). Of interest, the median OS for patients who had AL was 13 months compared with 64 months for those without AL ($p<0.004$, Fig. 2). This finding was independent if the patients had clinical symptoms of AL or not at diagnosis. Individuals with serum levels of albumin (< or >3.5 g/dl) had a median OS of 20 and 36 months, respectively ($p<0.003$). Also, those patients with high serum levels of LDH at diagnosis had a median OS of 27 months in comparison to those with normal values (median OS 35 months, $p<0.002$). Finally, β2-microglobulin levels > or <3.5 mg/l was another important prognostic factor because median OS was 23 and 34 months, respectively ($p=0.04$, Table 4).

Table 3 Clinical diagnosis of amyloidosis in 68 patients with multiple myeloma

Signs and symptoms of amyloidosis	Positive FPBNA at diagnosis *N*=68 (%)
At diagnosis:	16 (23.5%)
Nephrotic syndrome	6 (9)
Pancitopenia	3 (4.5)
Hepato-splenomegaly	2 (3)
Cardiac amyloidosis	5 (7)
After follow-up:	36 (53%)
Neuropathy	10 (15)
Nephrotic syndrome	5 (7)
Cardiac amyloidosis	8 (12)
Arthropaty	4 (6)
Chronic diarrhea (malabsortion)	4 (6)
Skin amyloid infiltration	5 (7)
No clinical amyloid demonstrated (other than FPBNA)	16 (23.5)

FPBNA Fat pad biopsy needle aspiration

Table 4 Survival analysis of 201 patients with multiple myeloma

Variable	Univariate analysis				Cox regression model			
	DFS median (months) (95%CI)	*P* value	OS median (months) (95%CI)	*P* value	DFS HR (95%CI)	*P* value	OS HR (95%CI)	*P* value
Albumin								
< 3.5 g/l	22 (18.8–25.1)	0.04	20 (7.9–32.1)	0.003	2.6 (1.3–4)	0.04	3.2 (1.1–7.7)	0.005
> 3.5 g/l	30 (23.8–36.1)		36 (17.4–54.6)					
β2-micro								
< 3.5 mg/l	21.1 (14.7–35.7)	0.04	34 (16.4–51.8)	0.04	1.5 (0.6–2.6)	0.05	1.6 (0.8–4.5)	0.03
>3.5 mg/l	13.9 (4–38.5)		23 (13.3–32.7)					
LDH								
<450 UI/l	40 (21.3–58)	0.06	35 (9.7–60.3)	0.002		0.4		0.08
>450 UI/l	27 (23–31)		27 (14.8–39.2)		0.2 (0.1–1.0)		1.2 (0.6–2.9)	
CR+VGPR	42 (37.3–48.4)		53 (41.1–64.9)					
PR	24.2 (19.1–29.4)	0.001	34 (27–41)	0.002	2.2 (0.6–3.1)	0.03	2.9 (1.3–4.5)	0.03
Failure	6.9 (3.7–10.0)		27 (8.7–45.3)					
Amyloid +	29 (15–64)	0.01	13 (5–56)	0.004	3.8 (1.8–4.2)	0.03	3.4 (1.1–8.4)	0.004
Amyloid −	53 (22.3–83.4)		64 (37.8–90.2)					

HR hazard ratio, *β2-micro* β2-microglobulin, *LDH* lactic dehydrogenase, *CR* complete remission, *VGPR* very good partial remission, *PR* partial remission, *Amyloid +* patients with multiple myeloma associated amyloidosis, *Amyloid –* patients with multiple myeloma without amyloidosis

Because it is obvious that patients with amyloidosis associated to MM have worse prognosis, we performed survival curves excluding 16 patients who had MM and classical symptoms of AL at diagnosis. Interestingly, overall survival was better for patients with MM and no AL (median: 53 months, 95% C.I. 39.4–66.6) in comparison to patients with MM and positive FPNBA who never developed clinical data of amyloidosis (median 24 months, 95% C.I. 15.2–32.8), and patients with MM and AL in whom symptoms of amyloidosis appeared after follow-up (median 16 months, 95% C.I. 5.6–26.4), $P<0.0003$ (Fig. 3).

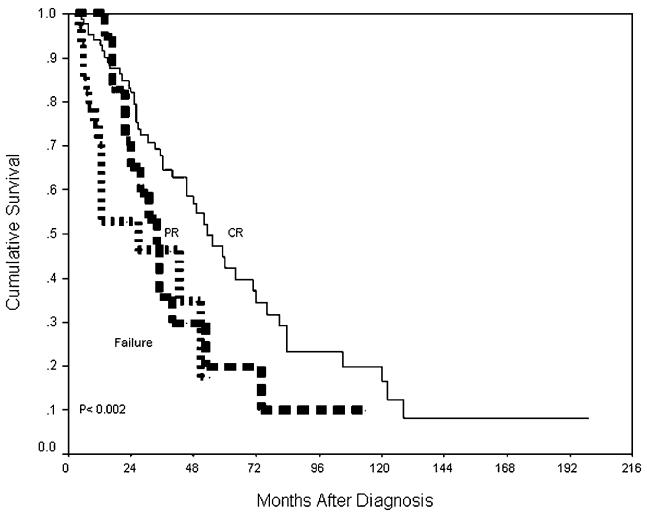

Fig. 1 Overall survival according to the response achieved with chemotherapy. *CR* denotes complete remission plus very good partial remission. *PR* partial remission

Cox regression analysis

Cox regression model for DFS showed that four variables may be considered as independent prognostic factors: individuals having serum albumin levels <3.5 g/dl had a hazard ratio (HR) of 2.6 ($p<0.04$); patients with β2-microglobulin levels >3.5 mg/l (HR 1.5, $p<0.05$); individuals not achieving neither CR nor VGPR (HR 2.2, $P<0.03$), and patients with MM-associated amyloidosis (HR 3.8, $P<0.03$) (Table 4). Cox regression model for overall survival detected four variables having independent prognostic significance: the presence of amyloidosis (HR=3.4, $P<0.004$, Fig. 4), serum albumin levels < 3.5 g/dl (HR=3.2, $p<0.005$), patients who did not achieve CR or VGPR (HR=2.9, $p<0.03$), and levels of β2-microglobulin levels >3.5 mg/l (HR=1.6, $p<0.03$).

Cox regression model for overall survival was done excluding 16 patients who had AL associated to MM and clinical symptoms since diagnosis. Of interest, the analysis detected that patients who had serum albumin <3.5 g/dl (HR 2.3, $P<0.01$) and subclinical amyloidosis (HR 2.6, $P<0.001$) had worse prognosis.

Discussion

In the present study, we found that the presence of amyloid deposits in patients with MM is an independent adverse prognostic factor, regardless of the presence or absence of amyloid symptoms at the time of diagnosis.

Median survival of patients with AL amyloidosis is 1–2 years; however, fewer than 5% of these patients survive

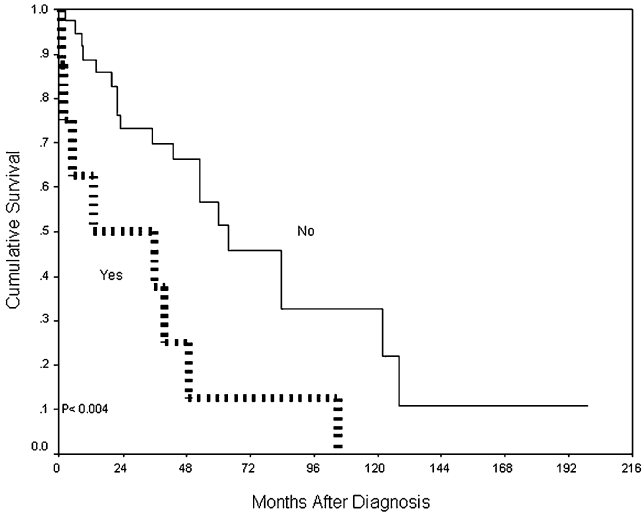

Fig. 2 Overall survival according to the presence or absence of amyloid deposits in the fat aspiration biopsy. *Yes* presence of amyloid deposits, *No* absence of amyloid deposits

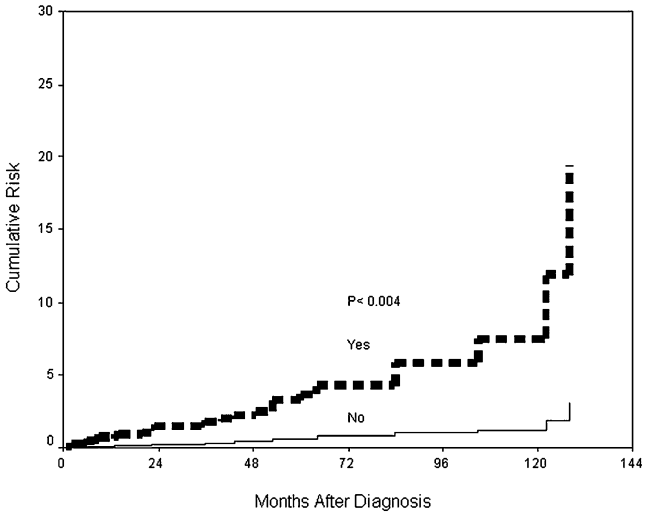

Fig. 4 Cox proportional hazard risk of death over time according to the presence or absence of amyloid deposits in the fat aspiration biopsy. *Yes* presence of amyloid deposits, *No* absence of amyloid deposits

10 or more years [14]. Palladini and colleagues recently reported an improvement in progression-free survival and overall survival in the order of 3.8 and 5.1 years, respectively, with the use of melphalan and dexamethasone in patients with AL amyloidosis [16, 17].

It is well-known that the most important prognostic factor in patients with AL is the presence or absence of cardiac involvement. Those patients with congestive heart failure as a consequence of cardiac amyloid deposition, survive from 4 to 6 months compared with a median survival of 30 months in those individuals with no cardiac failure [6]. Other poor prognostic factors include renal failure, liver involvement, a large whole-body amyloid deposit (as evaluated on serum amyloid P component [SAP] scintigraphy), and autonomic neuropathy [10, 15, 19]. In our group, more than half of the patients who had at diagnosis a positive FPBNA for amyloidosis had these adverse prognostic factors. In addition, this group belonged to a higher risk group because of poorer performance status, higher LDH values, and worse response to chemotherapy (Tables 1 and 2).

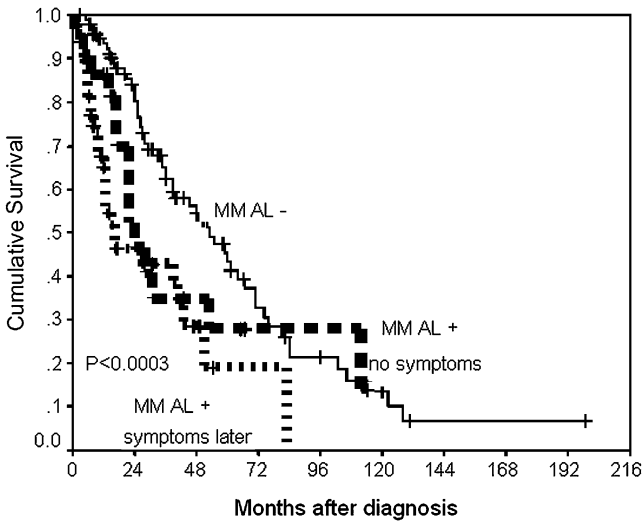

Fig. 3 Overall survival in multiple myeloma patients according to the absence of amyloidosis (*continuous line*), Congo red positivity at diagnosis and development of amyloid symptoms after follow-up (*dotted line*), and Congo red positivity at diagnosis without symptoms of amyloidosis (*dashed line*)

The response to therapy is another important prognostic factor in AL. The median survival time in responders is around 89.4 months and 14.7 months in non-responders [5]. In our study, we demonstrated that patients who achieved CR or VGPR had better survival than individuals not having at least VGPR. These findings are in agreement with a previous report on 25 patients with MM-related AL who had a median survival of 28 months in patients who responded to treatment vs 7.5 months for patients without response [4]. In the same direction, it has been informed that patients achieving complete hematological response with autologous stem cell transplantation have a higher organ-response rate and overall survival [21].

There are only few studies dealing with the prognostic relevance of AL in patients with MM. Some authors [1] demonstrated that patients who have coexisting AL with MM have a poorer prognosis, with a median survival of 1.1 years vs 2.9 years in patients without AL. In this particular group of patients, the coexistence of MM and AL was seen in 18% of individuals.

In concordance with our findings, another study [3] showed that when routine fat-pad biopsies and Congo red staining are made, subclinical AL is present at high frequencies (35%) among patients with MM; however, in

contrast to our results, these authors suggested that the clinical and therapeutic value of a positive fat pat biopsy result appears to be non-significant and with no prognostic relevance. These differences could be explained because our patients were treated with conventional chemotherapy and those of Desikan's series underwent autologous stem cell transplantation. Another explanation for this discrepancy is the fact that our patients with MM-associated amyloidosis belonged to a higher risk group because they had a worse prognostic pattern, namely, higher LDH (68% vs 40%), hypercalcemia, B symptoms, lower performance status (Karnofsky score less than 60% in 53%), and a higher rate of treatment failure (48.5% vs 20%).

It is important to note that in our study the presence of amyloid deposits in the FPNBA conferred a worse prognosis to the patients, regardless of the presence of amyloid symptoms at the time of myeloma diagnosis or during follow-up. Because most of the reports are in agreement that patients with amyloidosis associated to multiple myeloma have poor prognosis, we investigated the outcome of those patients who had Congo red deposits in fat biopsy but no symptoms or signs of amyloidosis at the time of diagnosis. We made the univariate and multivariate analysis excluding 16 patients who had symptoms of amyloidosis and a positive FPNBA (those of worse prognosis).

Of interest, patients with underlying amyloidosis who developed symptoms after follow-up (positive FPNBA and no amyloid symptoms at diagnosis) had worse overall survival than those who never had symptoms, and worse than patients with myeloma with no amyloidosis. Thus, we can assume that the presence of amyloid in the biopsy even in the absence of symptoms confers a poor prognosis.

In our study, 52 of 68 (76%) patients with fat-pad positive biopsy had clinical data compatible with AL. At diagnosis, only 16 of 68 (23.5%) patients had findings of AL; however, during follow-up, 36 (53%) additional patients developed signs or symptoms of AL, most of them corroborated with a second biopsy. With these data, we can speculate that FPBNA is a good procedure for the diagnosis of AL associated with multiple myeloma and that the positivity of the biopsy can precede the development of the amyloid syndrome.

Our findings are of interest because if a FPNBA is performed in every patient with MM without symptoms of AL, 28% (52 of 185 patients) will have underlying amyloidosis. In addition, according to our study, during the follow-up of patients with unexpected Congo red positivity, 69% will eventually manifest symptoms or clinical signs of amyloidosis.

The natural history of the disease in these two cohorts of patients (MM patients with subclinical AL and MM individuals with clinical manifestations of AL) is not known. Some investigators [22] believe that AL deposits can be clinically insignificant in some patients with MM, and for this reason the treatment choice is not a matter of discussion. Based in our findings, we feel like others [2], that the coexistence of both entities is a clear indication of a more intensive treatment such as hematopoietic stem cell transplantation in most of the patients. Therefore, it is crucial to recognize the presence of AL in patients with MM in order to offer a better survival and maybe a better quality of life.

In summary, our study indicates that MM-associated amyloidosis represents a poorer prognosis disease and an independent high-risk prognostic factor. Our study also suggests that the routine study of periumbilical fat-pad tissue should be mandatory in all patients with MM because the presence of subclinical amyloidosis also confers a poor prognosis.

Acknowledgments We thank Dr. Sergio Giralt from M.D. Anderson Cancer Center, for his contribution in the critical review of the manuscript. The authors declare that the treatments described in the article comply with the current law of the Mexican Republic including all ethical aspects.

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