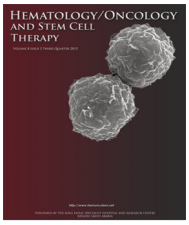
Hematol Oncol Stem Cell Ther (2019) 12, 71–81

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/hemonc



Cutaneous light chain amyloidosis with multiple myeloma: A concise review

Mirela Andrei [a], **Jen Chin Wang** [b,*]

[a] *Division of Hematology & Oncology, Saint Mary's Regional Medical Center, Lewiston, ME, USA*
[b] *Division of Hematology & Oncology, Brookdale University Hospital Medical Center, Brooklyn, NY, USA*

Received 14 January 2018; received in revised form 9 July 2018; accepted 3 September 2018
Available online 21 September 2018

KEYWORDS
Cutaneous amyloidosis;
Immunoglobulin light-chain amyloidosis;
Multiple myeloma

Abstract
Objective/Background: Cutaneous immunoglobulin (Ig) amyloid light-chain (AL) amyloidosis associated with overt multiple myeloma (MM) is rare and optimal treatment is not well defined. The recently developed highly efficacious MM therapy has brought on a new set of challenges to this field for consideration. The goal of this paper is to describe the characteristics of cutaneous manifestations of systemic AL amyloidosis associated with MM according to age, sex, race, Ig type, plasma cell percentage, and cytogenetic and fluorescent *in situ* hybridization studies along with their outcomes.
Methods: An electronic search of the PubMed database was performed to obtain key literature in AL amyloidosis and MM, using the following search terms: multiple myeloma, immunoglobulin light chain amyloidosis, and cutaneous amyloidosis. The search results were narrowed by selecting studies in English. Results were confined to the following articles types: case reports, case series, and systematic reviews.
Results: We identified 32 cases from the PubMed database search and examined their potential relevance. We found the following: (a) higher prevalence in women (two-thirds) and white population; (b) IgG and IgA were equally distributed with lambda (λ) light chain occurring in 53–66% of cases; (c) majority of cases (56%) presented as hemorrhagic bullous lesions, followed by purpura/ecchymosis in 25% of cases; and (d) majority (64%) died within 6 months since diagnosis.

* Corresponding author at: Division of Hematology & Oncology, Brookdale University Hospital Medical Center, 1 Brookdale Plaza, Brooklyn, NY 11212, USA.
E-mail address: jcwang0005@gmail.com (J.C. Wang).

https://doi.org/10.1016/j.hemonc.2018.09.003

Conclusions: We reviewed the constellation of the cutaneous manifestations of AL amyloidosis with concurrent MM. We found a female predominance, and more than half presented as hemorrhagic bullous lesions. There is a preponderance of λ light chains over kappa (κ) light chains, both as a free light chain (15% vs. 4%) and as an intact Ig (38% vs. 24%; absolute number of 14 vs. 7 patients, respectively). In the subgroup of patients with bullous skin lesions, λ light chain was present in eight cases and κ light chain in seven cases. All κ light chain subtypes presented with bullous lesions and no other cutaneous types of lesions. They carried very poor prognosis with majority of cases surviving only 6 months, much worse than overall patients with AL amyloidosis without myeloma or myeloma without amyloidosis.

Contents

Introduction

Any organ can be affected by amyloid light-chain (AL) amyloidosis. The site of deposition may be related to the interaction of insoluble fibrils, resistance to proteolytic degradation and tissue glycosaminoglycans, or specific cell-surface receptors [1,2]. Rubinow and Cohen [3] described the histopathologic findings of skin biopsy in a group of 38 patients with primary and multiple myeloma (MM)-associated amyloidosis. The most common finding was amyloid deposition in the dermis and subcutaneous tissue, especially in their small blood vessels (arterioles, venules, capillaries). In seven biopsies, the amyloid was detected between the collagen bundles and in some cases close to the dermoepidermal junction. Amyloid infiltration into the sweat glands was found in nine biopsies, followed by fat cell infiltration in eight biopsies, and only one biopsy positive for hair follicle shaft involvement. Histologic findings were similar in primary and MM-associated amyloidosis regardless of clinically involved or uninvolved skin. Cutaneous lesions secondary to myeloma-associated AL amyloidosis are a heterogeneous collection of specific and nonspecific lesions. Bullous manifestation is reported as a rare and distinct clinical subtype. We have previously published a case of cutaneous hemorrhagic bullous lesions occurring as a result of immunoglobulin G (IgG) κ myeloma-associated AL amyloidosis [4]. Now, 8 years later this patient has a bone marrow biopsy-confirmed relapse of MM, but without skin involvement. Using a case presentation format, we present a concise review of the cutaneous amyloidosis manifestations secondary to overt myeloma and an analysis of the prognosis and treatment for MM along with other parameters, including Ig type, plasma cell percentage, and cytogenetic and fluorescent *in situ* hybridization (FISH) analysis.

Case history

A 59-year-old African-American woman was initially diagnosed at the age of 51 with IgG κ MM-associated AL amyloidosis when she presented with bilateral breasts bullous hemorrhagic skin lesions. Skin biopsy with special stains confirmed the abundant amyloid deposits. Laboratory evaluation was significant for mild normocytic anemia, elevated serum-free κ light chains (6090 mg/dL), positive urine κ light-chain assay (6220 mg/dL), and multiple lytic bone lesions on skeletal survey. Bone marrow biopsy confirmed that she was monoclonal CD138 positive, with IgG κ plasma

Table 1 Characteristics of all the patients that were analyzed.

Cutaneous manifestations	Age/sex/race	Multiple myeloma-associated amyloidosis	ALs: light-chain type	Bone marrow biopsy: plasma cell (%)	Cytogenetic/fluorescent *in situ* hybridization	Treatment	Survival	Author/Study
Hemorrhagic bullous breast lesion	51/F/AA	IgG κ	κ	50	46 XX; monosomy 13; t(6; 7)	RVD (PR); doxorubicin, cyclophosphamide, bortezomib, lenalidomide, dexamethasone → ASCT (VGPR)	Alive	Agheli [4]
Condyloma-like lesions; purpuric, pedunculated lesions	66/M/W	M spike	NR	75	NR	Melphalan, dexamethasone (no response); cyclophosphamide, thalidomide, dexamethasone	Few months	López et al. [5]
Hemorrhagic bullous amyloidosis	72/F/W	IgA λ	λ	20	NR	NR	NR	Bieber et al. [6]
Hemorrhagic bullous amyloidosis	73/F/W	IgA λ	λ	42	NR	NR	NR	Bieber et al. [6]
Bullous skin amyloidosis	62/F/NR	IgA κ	κ	13	NR	Alkylating agents, prednisone	Few months	Robert et al. [7]
Bullous skin amyloidosis	55/F/NR	NR	NR	100	NR	Vincristine, adriablastin, methyl-prednisolone	NR	Robert et al. [7]
Bullous skin amyloidosis	63/F/NR	IgG κ	κ	NR	NR	None	Few days	Robert et al. [7]
Palmodigital purpura	69/F/W	λ	λ	37.5	NR	NR	NR	Vella et al. [8]
Pellagra	64/M/J	BJ	BJ	NR	NR	Niacin	6 mo	Itami et al. [9]
Scleroderma amyloidosum	48/F/W	IgA λ	λ	NR	NR	Melphalan, prednisolone	NR	Casper et al. [10]
Bullous dermatosis	70/M/W	IgA λ	λ	>20	NR	Dapsone	2 y	Barnadas et al. [11]
Vesiculobullous eruption	63/M/W	IgA κ	κ	NR	NR	Cyclophosphamide, mitozantrone, prednisone, dapsone	18 mo	Wong et al. [12]
Purpura; diffuse hematomas; macroglossia	60/M/I	NR	NR	NR	NR	NR	NR	Saoji et al. [13]
Cutaneous amyloid elastosis	69/F/NR	IgG λ	λ	20	Hyperdiploid karyotype	Melphalan, bortezomib, dexamethasone	4 mo	Marchand et al. [14]
Papulous periorbital ecchymosis	43/F/AA	λ	λ	75	NR	Dexamethasone	2 wk	Mason et al. [15]
Periorbital ecchymosis	58/M/W	IgG λ	λ	15–20	Hyperdiploidy (+3, +6, +9); t(6; 14)	Bortezomib, dexamethasone → high-dose melphalan → ASCT → maintenance lenalidomide	CR at 2.5 y	Colucci et al. [16]
Lichen amyloidosis	60/M/NR	NR	NR	NR	NR	Corticosteroids	NR	Greaves [17]
Periorbital papules, purpura	48/F/W	BJ	BJ	70	NR	NR	5 mo	Oliveira et al. [18]
Bullous, purpuric lesions	45/F/I	NR	NR	42	NR	CT	NR	Behera et al. [19]
Nail dystrophy, bullous amyloidosis	61/M/J	IgG λ	λ	NR	NR	CT, ASCT prior to amyloidosis development	3 mo	Fujita et al. [20]
Petechial periorbital bleeding, macroglossia	44/F/W	λ	λ	35	NR	VAD	NR	Becker et al. [21]
Alopecia, erythematous papules	54/F/W	BJ	BJ	50	NR	None	1 mo	Perloff [22]

(*continued on next page*)

Table 1 (*continued*)

Cutaneous manifestations	Age/sex/race	Multiple myeloma-associated amyloidosis	ALs: light-chain type	Bone marrow biopsy: plasma cell (%)	Cytogenetic/fluorescent *in situ* hybridization	Treatment	Survival	Author/Study
Cutaneous nodules, left breast skin induration	48/F/W	BJ	BJ	12	NR	None	5 mo	Perloff [22]
Bullous amyloidosis- axilla	81/F/W	IgG λ	λ	80	NR	None	5 d	Trump et al. [23]
Bullous amyloidosis	68/M/W	IgG κ	κ	15	NR	NR	NR	Westermark et al. [24]
Bullous amyloidosis	83/F/W	IgA λ	λ	NR	NR	NR	3 y	Westermark et al. [24]
Bullous amyloidosis	55/F/W	λ	λ	NR	NR	Melphalan, prednisolone	14 mo	Westermark et al. [24]
Bullous amyloidosis	50/M/W	BJ	BJ	Increased	NR	Vincristine, cyclophosphamide, prednisolone	9 mo	Holden et al. [25]
Bullous amyloidosis	61/F/W	IgG λ	λ	Increased	NR	Chlorambucil, prednisolone	NR	Holden et al. [25]
Bullous amyloidosis	74/M/W	IgA κ	κ	42	NR	Melphalan, prednisone	>19 mo	Beacham et al. [26]
Bullous amyloidosis	74/F/J	κ	κ	21.8	NR	NR	NR	Isobe et al. [27]
Papules, xanthoma-like	52/M/AA	No serum M spike	NR	10	NR	Melphalan, corticosteroids	NR	Reem et al. [28]

Note. AA = African American; AL = amyloid light chain; ASCT = autologous stem cell transplant; BJ = Bence Jones; CR = complete remission; CT = chemotherapy; d = day; I = Indian; J = Japanese; mo = month; NR = not reported; PR = partial remission; prognosis = time of death since diagnosis; RVD = lenalidomide, bortezomib, dexamethasone; VAD = vincristine, doxorubicin (Adriamycin), dexamethasone; VGPR = very good partial response; W = white; wk = week; y = year.

cell comprising 50% of cellularity. No chromosomal abnormalities were identified on conventional cytogenetic studies. FISH was positive for monosomy of chromosome 13 (loss of rb1 and LAMP1) in 10.3% of cells, and t(6; 7), indicating overexpression of BCL1, and cyclin D1 (CCND1/IGH) rearrangement in 5.8% of the cells. Induction therapy initially consisted of four cycles of RVD (REVLIMID, VELCADE, and dexamethasone) with only partial response. Very good partial response was achieved with six cycles of five-drug combination chemotherapy (liposomal doxorubicin, cyclophosphamide, bortezomib, lenalidomide, and dexamethasone) that was followed by high-dose consolidative chemotherapy supported with autologous hematopoietic stem cell transplantation (April 2011). She continued to have stable disease when enrolled on clinical trial with VELCADE, Cytoxan, Chloroquine, and dexamethasone from November 2011 to January 2013. Because of disease progression, the regimen was changed to pomalidomide and dexamethasone in October 2013. In January 2014, carfilzomib was added due to lack of response to the aforementioned regimen. Pomalidomide was changed to Cytoxan in February 2014 because of toxicity. Afterward she was enrolled in two clinical trials: daratumumab from April to June 2014, and then REVLIMID and ABRAXANE from August to October 2014. She continued to have stable disease until October 2014, when she was started on high-dose carfilzomib, bendamustine, and dexamethasone due to disease progression and achieved very good partial response. Maintenance therapy with carfilzomib and dexamethasone was continued with serial monitoring of serum protein electrophoresis/immunofixation and serum-free light chain analysis. Her treatment was complicated by left lower extremity venous thromboembolism for which she received ELIQUIS. Serum-free κ light chain level increased slowly and in March 2016 it was 69.2 mg/dL, with a faint band in the κ region on serum immunofixation electrophoresis. In addition to disease progression, she developed symptomatic hypercalcemia (15.6 mg/dL) and mild kidney insufficiency requiring hospitalization. Elotuzumab with REVLIMID and dexamethasone was initiated in April 2016, which achieved stable disease. The disease then progressed with severe cytopenia, and κ chain level increased to 4057 (κ:λ ratio, 513). A second bone marrow biopsy performed 8 years later in February 2017 was hypocellular with overall cellularity of 15%, with CD138, κ-restricted plasma cells representing 85%. Karyotyping was normal. FISH showed t(11; 14)/CCDN1-IGH translocation (3.5% of cells). Bone marrow staining for amyloidosis was negative. She was then treated with panobinostat plus bortezomib and dexamethasone and partial response was achieved; no cutaneous lesions were found.

Material and methods

PubMed records reporting a diagnosis of systemic cutaneous AL amyloidosis associated with MM, including case reports, case series, and systematic reviews, were reviewed and data found suitable were analyzed (Table 1) [5—28]. Cases other than those in English were excluded, as were cases of localized cutaneous amyloidosis and systemic cutaneous amyloidosis without MM. A total of 32 cases were eventually identified.

Results

Age, sex, and race

Median age at diagnosis was 61 years (range, 43—83 years) with two-thirds of women and one-third of men (20 females and 12 males; Fig. 1). None of the patients were younger than 40 years. This is different from MM, which had a median age of 69 [29]. Most patients were white (n = 19); interestingly, only three patients were black (43-year-old female, 51-year-old female, and 52-year-old male).

Multiple myeloma subtype

The serum protein electrophoresis showed an M spike in 84% of the patients (4 cases were not reported and in one case there was no M spike; Fig. 2). Of those patients, 62% had a monoclonal intact Ig and 38% had a free monoclonal light chain in the serum [17% patients had unspecified Bence Jones (BJ) protein]. IgG and IgA MM were found in equal numbers; lambda (λ) chain was present in 14 cases and κ light chain in seven cases, respectively (in 4 cases these were not reported, 1 case had no M spike, 1 case reported only as having an M spike, and 5 cases had BJ protein). Upon excluding the unspecified subtypes of light chains, λ free light chain was slightly higher than κ light chain, present in 66.6% of cases with skin manifestations. There were 18 patients in the subgroup of patients with bullous skin lesions (56% of all patients): λ chain was present in eight, κ light chain in seven, not reported in two, and BJ in one case. By excluding the two not reported and one BJ, λ free light chain was present in 53.3% of bullous lesions cases. An analysis of one large review of 869 cases of MM seen at Mayo

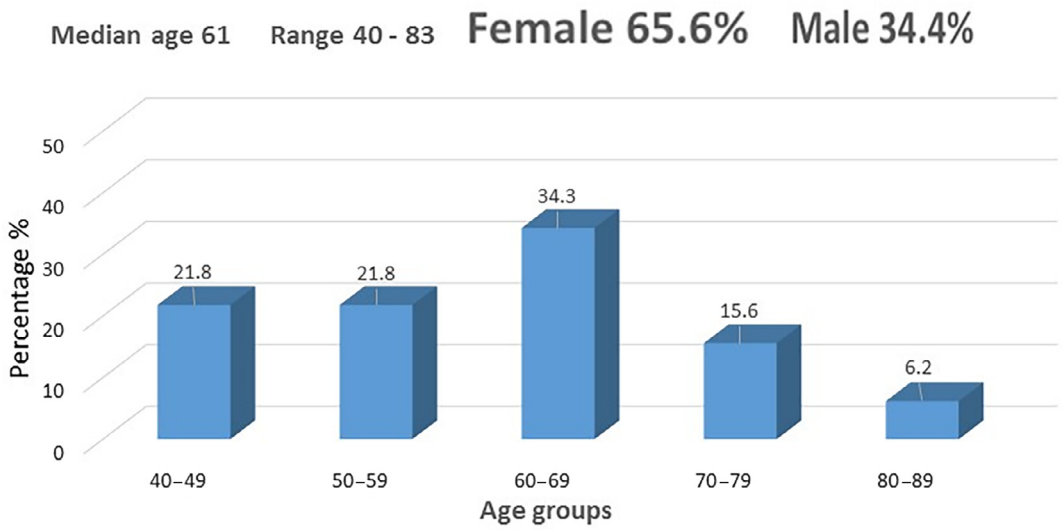


Fig. 1 Age and sex distribution of 32 cases of systemic cutaneous amyloid light-chain amyloidosis secondary to multiple myeloma. Age (range) in years.

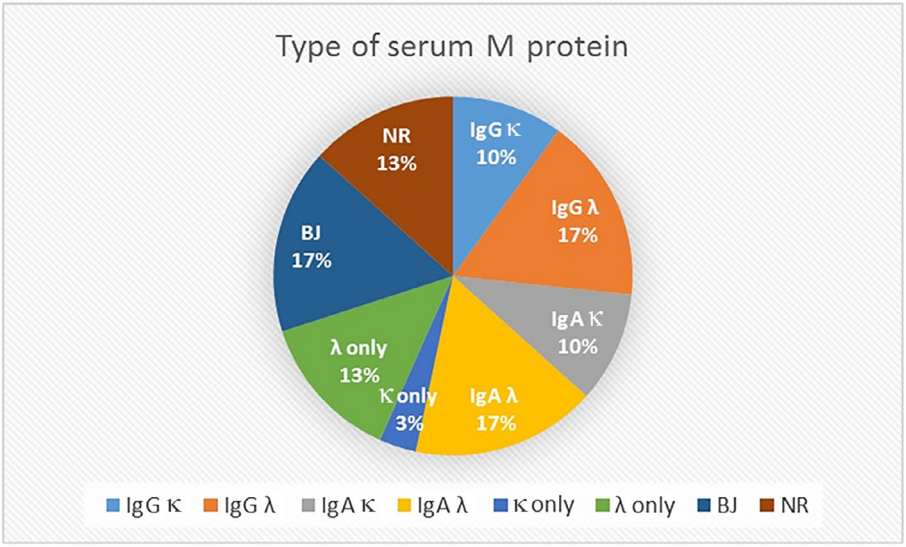


Fig. 2 Type of serum M protein in cutaneous systemic amyloid light-chain amyloidosis secondary to multiple myeloma: 84% of patients had an M spike. BJ = Bence Jones; Ig = immunoglobulin; NR = not reported.

Clinic showed that 61% of the patients were men; 59% had IgG, with predominant κ light chain (60%) [30].

AL amyloidosis light-chain subtype

Fig. 3 reflects that the λ free chain is the more common idiotype in cutaneous AL amyloidosis associated with MM, both as a free light chain (15% vs. 4%) and as an intact Ig (38% vs. 24%). The absolute numbers of λ and κ light chains are 14 and 7, respectively. Of note, in MM, a 4:1 ratio is reported for κ:λ in patients with heavy-chain myeloma, whereas a 1:4 ratio is reported for κ:λ in patients with light-chain myeloma [31].

Bone marrow plasma cells involvement

The reported percentage of bone marrow plasma cell (BMPCs) is the highest percentage of plasma cells from the aspirate or biopsy at the time of biopsy. Fig. 4 shows the number of patients and the equivalent percentage of BMPCs among patients with cutaneous systemic AL amyloidosis secondary to MM. The mean BMPCs is 38.6%, with 42.8% of patients having a plasma cell percentage between 10% and 30%. Because of the small number of patients and incomplete data, it is unclear whether there is a correlation between type of monoclonal Ig and plasma cell burden. However, there is a preponderance of higher BMPCs associated with free monoclonal light-chain subtype. The mean percentage of BMPCs in MM patients was 52.9% in an analysis done by Lee et al. [32].

Cytogenetic and molecular analysis

Cytogenetic and molecular data, however, for the most part were absent.

Clinical features

Cutaneous manifestations of systemic AL amyloidosis associated with overt myeloma in 32 patients are shown in Fig. 5.

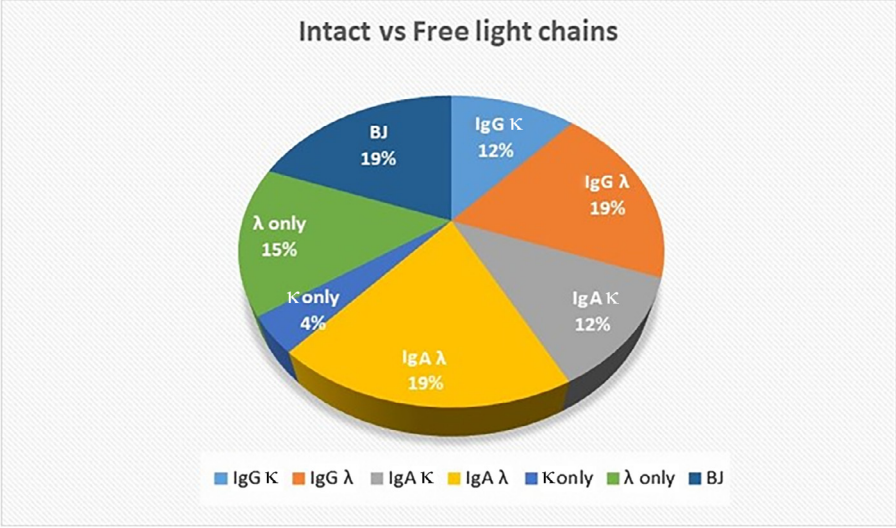


Fig. 3 Intact immunoglobulin versus free light chains only: 62% had a monoclonal intact immunoglobulin and 38% had a free monoclonal light chain in the serum. In the amyloid light-chain amyloidosis light-chain subtype, λ was the more common subtype (14 patients of the 21). BJ = Bence Jones; Ig = immunoglobulin.

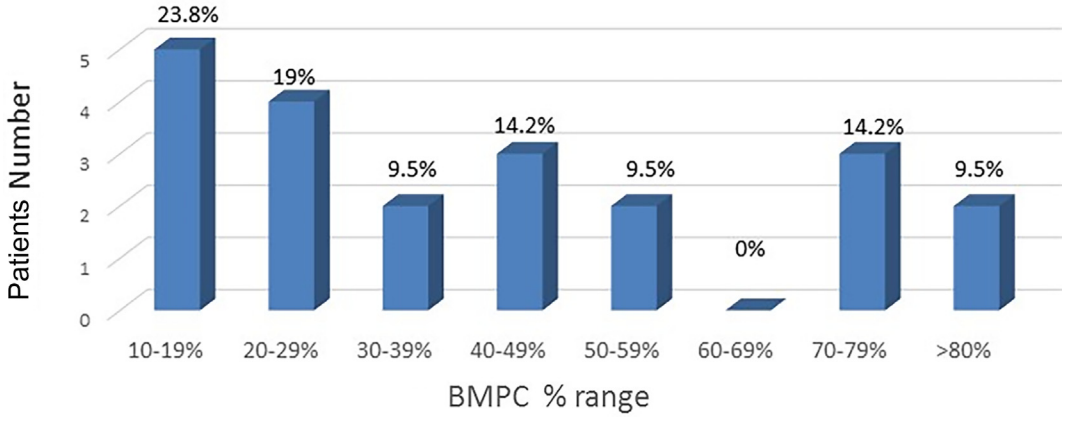


Fig. 4 The number of patients and its equivalent percentage of bone marrow plasma cell (BMPC) proliferation among patients with cutaneous systemic amyloid light-chain amyloidosis secondary to multiple myeloma.

Despite being reported rarely, we found that the bullous skin lesions are common findings in MM-associated AL amyloidosis: 18 of 32 patients had hemorrhagic bullous lesions, followed by purpura/ecchymosis in eight. Subgroup analysis of cutaneous presentation and light-chain type was consistent with λ light-chain predominance: 14 patients of the 21 reported subtypes of free light chain had the λ subtype and seven had the κ subtype (Fig. 6).

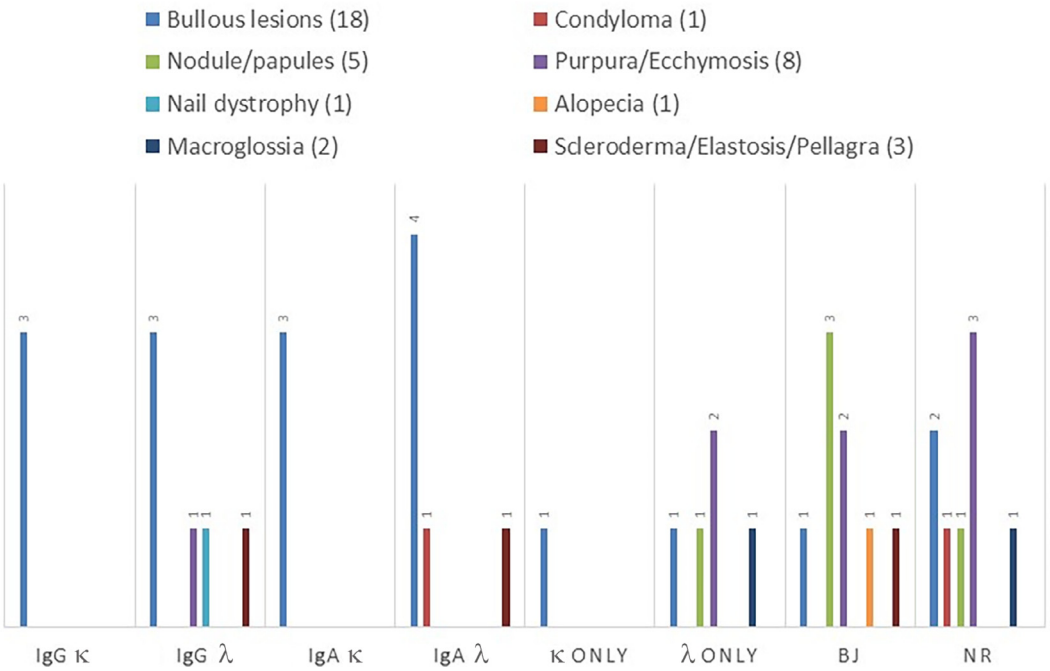


Fig. 5 Correlation between cutaneous manifestations and myeloma immunoglobulin (Ig) subtype of systemic amyloid light-chain amyloidosis secondary to multiple myeloma in 32 patients. BJ = Bence Jones; NR = not reported.

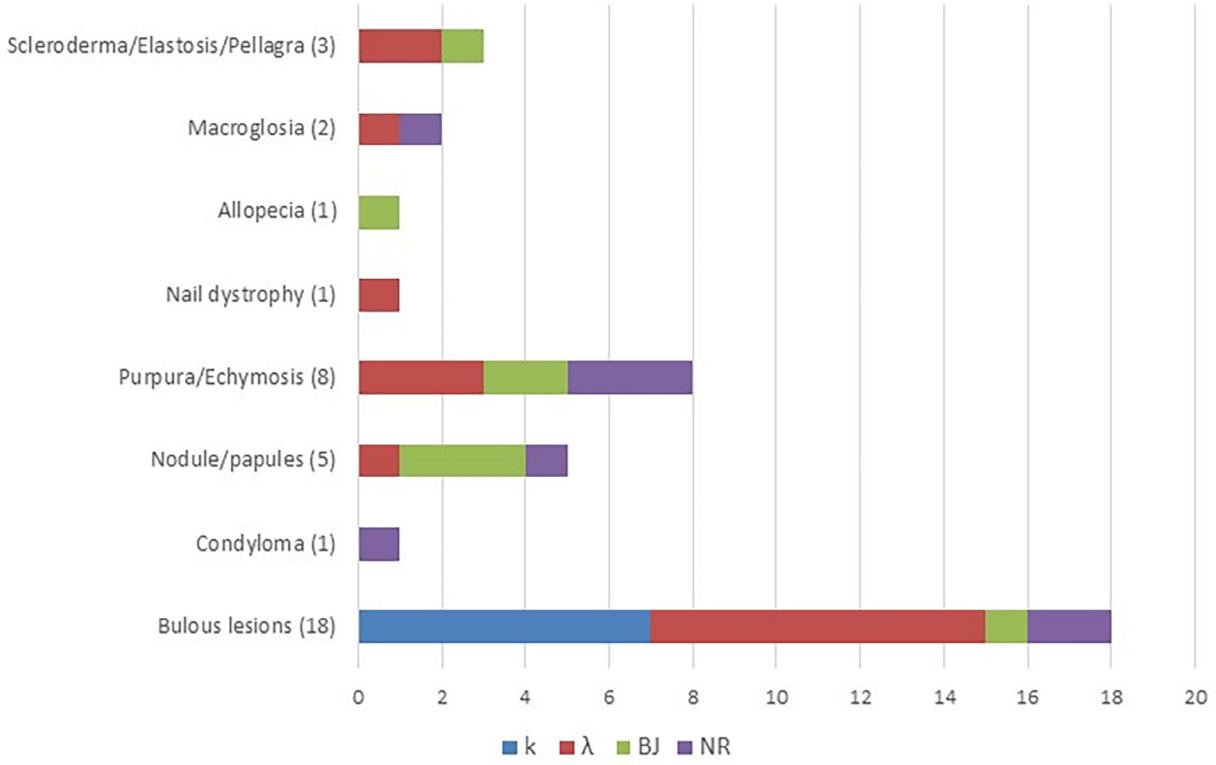


Fig. 6 Correlation between cutaneous manifestations and immunoglobulin light-chain subtype of systemic ALs amyloidosis secondary to multiple myeloma in 32 patients. BJ = Bence Jones; Ig = immunoglobulin; NR = not reported.

Treatment

In our review of the 32 patients, 19 had available treatment data and received different therapeutic regimens: in general, melphalan-based treatment or RVD, VAD (vincristine, doxorubicin, and dexamethasone) regimens (Table 1). Only two patients received autologous peripheral blood stem cell transplant: our patient who is still alive at 8 years postdiagnosis [4] and a 58-year-old man who achieved complete remission at 2.5 years after the diagnosis [22].

Survival

Of the 19 patients for whom data were available, 17 have died, with most of them in the first 6 months since diagnosis (11/17 patients; Fig. 7). The overall prognosis appears to be poor for patients with AL amyloidosis associated with myeloma compared with those with myeloma without amyloidosis. In the emerging era of novel drug regimens, MM survival improved significantly with the median cohort overall survival (OS) increasing to 43 months in 2008 from 30 months between 1980 and 2001 [33]. The median cohort OS is expected to improve with better scientific understanding, targeted therapy, and precision medicine. A retrospective analysis of 46 patients by Dinner et al. [34] found that patients with AL amyloidosis with myeloma-associated end-organ damage or higher degree of BMPC infiltration have a worse outcome than those with smoldering myeloma (1-year OS 39% vs. 81%; $p = .005$). Further studies showed a median OS of 10.6 months for patients with AL amyloidosis with active myeloma, 16.2 months for AL patients with smoldering myeloma, and 46 months for patients with AL amyloidosis only [35]. AL amyloidosis comprises many manifestations with the predominantly involved organs being the kidney, heart, liver, peripheral nerves, and gastrointestinal tract. To the best of our knowledge, there have been no large studies reporting the outcome for the subgroup of patients with AL amyloidosis with myeloma and cutaneous involvement.

Our present study found that the patients with AL amyloidosis-associated myeloma with skin involvement had even worse prognosis. This might be in part because patients

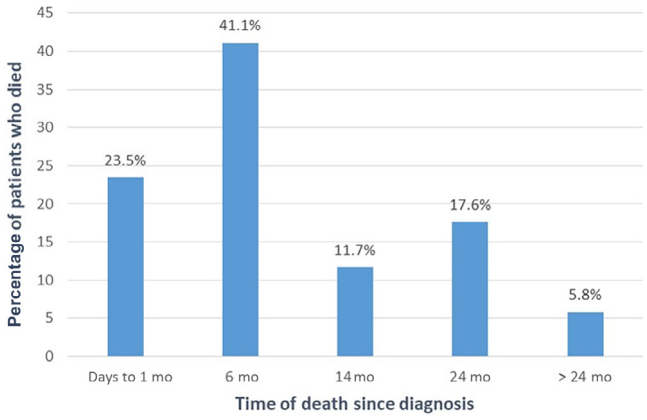


Fig. 7 Survival analysis: most patients died in the first 6 months since diagnosis.

are sick at the time of diagnosis and ability to tolerate chemotherapy compromises survival. It remains a matter of debate if additional possible mechanisms are responsible for poor outcome such as difference in the biology of the plasma cell clone, anatomical distribution, whole body amyloid load, retention of amylogenic free light chains in the circulation as a result of renal impairment; correlation between the histologic regressions of amyloid with normalization of serum-free light chain; late detection due to possible indolent AL amyloidosis with skin involvement that slowly progresses to MM. Thus, we will need to include and investigate more cases to answer this question definitely. Of note, AL amyloidosis with extensive organ involvement also had an OS of 6 months; hence, myeloma-associated AL amyloidosis with dermal involvement might possibly reflect an extensive organ involvement that translates into a poor prognosis. Whether this is due to amyloid fibril resistance to proteolytic degradation and tissue glycosaminoglycans or specific cell-surface receptors will need to be studied further.

Discussion

Systemic AL amyloidosis and MM are intimately connected through their cell of origin and the cutaneous manifestations seen between these are indistinguishable. Several reports describe a wide constellation of skin manifestations of systemic AL amyloidosis, with the most common findings being petechia, purpura, ecchymosis, and macroglossia [36]. Macroglossia was recorded in 30% of people in an analysis of 1388 Mexican individuals with systemic AL amyloidosis [37]. Other more common cutaneous lesions are the macular and papular types and the rare nodular form: a 45-year-old woman with macroglossia and eyelids/lower chest papular eruptions [38], a 75-year-old man with diffuse body nodular lesions (2—5-cm nodules over the scalp and trunk, and few lesions on the extremities) [39]. Bullous lesions, scleroderma, or condyloma-like picture, alopecia, or nail dystrophy can also be an initial presentation. AL amyloidosis-associated bullous skin lesions have been reported previously: a 51-year-old man with monoclonal λ light-chain amyloidosis with periorbital purpura and hemorrhagic bullae [40]; a 63-year-old woman with periorbital and peribuccal petechiae and hemorrhagic bullae of the breasts and abdomen [41]; a 56-year-old black man with subepidermal bullous skin amyloidosis [42]. Ruzicka et al. [43] reported a case of a 45-year-old woman with chest bullous amyloidosis in addition to a review of bullous amyloidosis cases previously reported in the literature (associated or not with MM). Therefore, AL amyloidosis without overt myeloma can also present as bullous hemorrhagic lesions. The prognosis of AL amyloidosis varies considerably depending on the extent of organ involvement and treatment approach. Median survival may be as short as 4—6 months, with cardiac failure and infection being the main causes of death [44]. By contrast, patients with limited organ involvement can expect a median OS over 5 years [45]. The first-line regimes for AL amyloidosis and patient survival are high-dose melphalan and autologous stem cell transplantation (OS, 6.3 years) [46], high-dose melphalan (median OS, 22.2 months), melphalan plus high-dose dexamethasone (median OS, 56.9 months [47]; range, 6—43 months [48]).

MM is rarely associated with skin lesions, with cutaneous plasmacytoma being the most specific form as reported by Harati et al. [49]. A retrospective analysis of 115 patients by Kois et al. [50] reported nonthrombocytopenic purpura as the most common cutaneous manifestation.

It is extremely rare for AL amyloidosis to progress to MM when compared with MM because patients with AL amyloidosis do not live enough to develop MM. Rajkumar et al. [51] described a case series of six patients with AL amyloidosis who progressed to MM. It was noted that a subgroup of patients with fairly indolent AL amyloidosis can progress to MM, especially those without significant cardiac or hepatic involvement. Although the majority of MM patients do not have associated systemic AL amyloidosis, approximately 15% of Ig light chains have the capacity to transform into insoluble, B-sheet fibrillary protein [52]. In one study of 494 cases of primary systemic amyloidosis, only 13% of cases were associated with MM; other monoclonal gammopathies were associated specifically with monoclonal gammopathy of undetermined significance and smoldering myeloma (15% and 3% of cases, respectively) [53].

In fact, two main groups of monoclonal-related skin lesions were described: one group as a direct sequence of malignant process, due to either plasma cell proliferation with subsequently increased serum monoclonal Ig or direct infiltration of plasma cells in the skin; the second group was skin lesions associated with an M component. López et al. [5] illustrated the wide and variable constellation of common and less common dermatologic features of myeloma-associated amyloidosis. Bullous skin lesions are considered rare cutaneous manifestations. In our review, of the 32 patients, 18 (56%) presented with bullous lesions, eight (25%) with purpura/ecchymosis, and five (15%) with skin papules or nodules.

AL amyloidosis is a disease of elderly with the median age at diagnosis of 64 years and approximately 70% male predominance [54,55]. All races can be affected, but there are little data about whether the incidence varies by ethnicity. Our analysis showed a median age of diagnosis of 61 years for patients with systemic AL amyloidosis associated with overt myeloma, and female predominance.

In systemic AL amyloidosis, the clonal plasma cells express light chains of the λ isotype more frequently than the κ isotype, with a ratio of approximately 3:1 [56].

We found that IgG and IgA MM were equally distributed; 62% of patients had a monoclonal intact Ig and 38% had a free monoclonal light chain in the serum. There is a preponderance of λ light chains over κ light chains (14 vs. 7, respectively) in patients with cutaneous AL amyloidosis with MM. In the subgroup of patients with bullous skin lesions, λ light chain was present in eight cases and κ light chain in seven cases. All κ light-chain subtypes presented with bullous lesions and no other cutaneous types of lesions. Whether λ light-chain subtype is the predominant subtype remains a matter of debate because this study is limited by its retrospective analysis, the small of patients analyzed, and about one-third of light-chain subtypes not being reported. The extent of BMPCs is wide, with 42.8% of patients having a plasma cell percentage between 10% and 30%.

What determines the particular cutaneous manifestation in a given individual depends on several factors, some of which are understood, whereas others are not. Substantial emerging data indicate that organ tropism is partially related to function of light-chain variable region (IGVL) as well as to some chromosome abnormalities. The recent article by Kourelis et al. [57] provides deep insight into a concept that the IGVL gene family is partially responsible for different organ tropism. Prior investigations have demonstrated that t(11; 14) is an important prognostic factor, which is being seen in about half of AL patients (15% in patients with MM) [58]. An abstract presented at *ASH 2015* showed that the t(11; 14)-positive AL group tended to have shorter OS when compared with negative AL cases. By contrast, in MM patients, the positive group tended to have superior OS [59]. However, the significance of t(11; 14) in AL associated with MM was not addressed.

The past few years have seen significant progress in the management of patients with MM. The prognosis of AL associated with MM remains poor and the treatment has not yet been well defined. Bahlis et al. [60] recommended to proceed directly to stem cell transplantation in transplant-eligible patients, omitting induction therapy, as analysis of some studies that included only AL amyloidosis showed no OS benefit with induction chemotherapy.

Conclusions

In this review, we analyzed the spectrum of cutaneous manifestations of AL amyloidosis associated with overt myeloma. The present findings suggest that the prevalence of bullous amyloidosis is likely to be underestimated. The analysis showed a predominance of AL amyloidosis in white people with the λ free light-chain subtype being slightly more common among patients with cutaneous AL amyloidosis associated with MM. All κ light-chain subtypes presented with bullous lesions and no other cutaneous types of lesions. With consideration of BMPCs' involvement, there is a preponderance of higher BMPCs associated with free monoclonal light-chain subtype. Interestingly, many cutaneous features are similar and what dictates the amyloidogenic potential of Ig light chains, the type, and the level of organ involvement continues to be an active area of interest. This study is limited by its retrospective analysis, lack of sufficient data, and the small number of patients analyzed, all of which may limit the interpretation of the results. Although the number of reported cases we were able to analyze based on available clinical and laboratory information is small, the results of this paper suggest that λ free light-chain subtype MM is more commonly associated with AL amyloidosis in patients with skin manifestations, and this should stimulate further clinical research.

Conflicts of interest

We declared that no competing interest or conflict exists.

References

[1] Stevens FJ, Kisilevsky R. Immunoglobulin light chains, glycosaminoglycans, and amyloid. Cell Mol Life Sci 2000;57:441—9.

[2] Yan SD, Zhu H, Zhu A, Golabek A, Du H, Roher A, et al. Receptor dependent cell stress and amyloid accumulation in systemic amyloidosis. Nat Med 2000;6:643—51.
[3] Rubinow A, Cohen AS. Skin involvement in generalized amyloidosis. A study of clinically involved and uninvolved skin in 50 patients with primary and secondary amyloidosis. Ann Intern Med 1978;88:781.
[4] Agheli A, Becker M, Becker G, Chaudhry MR, Wang JC. Response of hemorrhagic bullous skin lesions of the breast secondary to primary systemic amyloidosis to a five-drug combination chemotherapy: a case report and literature review. Exp Hematol Oncol 2012;1:19.
[5] López L, Gonzalez K, Navarrete G, Novales J, Guarneros A, Cortez B, et al. Multiple myeloma and systemic amyloidosis. Int J Dermatol 2008;47:165—7.
[6] Bieber T, Ruzicka T, Linke RP, von Kries R, Goerz G, Braun-Falco O. Hemorrhagic bullous amyloidosis: a histologic, immunocytochemical, and ultrastructural study of two patients. Arch Dermatol 1988;124:1683.
[7] Robert C, Aractingi S, Prost C, Verola O, Blanchet-Bradon C, Blanc F, et al. Bullous amyloidosis: report of 3 cases and review of the literature. Medicine (Baltimore) 1993;72:38—44.
[8] Vella F, Simone B, Antonaci S. Palmodigital purpura as the only skin abnormality in myeloma-associated systemic amyloidosis. Br J Dermatol 2003;120:917.
[9] Itami A, Ando I, Kukita A, Nagai K. Pellagra associated with amyloidosis secondary to multiple myeloma. Br J Dermatol 1997;137:829.
[10] Casper C, Scharffetter-Kochanek K, Bohlen H, Linke RP, Krieq T, Hunzelmann N. Light chain multiple myeloma with peripheral leucocytosis presenting as scleroderma amyloidosum of the Alambda-type. Br J Dermatol 1999;140:1172—4.
[11] Barnadas MA, Gelpi C, Martinez L, Curell R, Martino R, Alomar A. Acquired bullous dermatosis associated with Ig A multiple myeloma: a case report. J Cutan Pathol 2010;37:1174.
[12] Wong DA, Hunt MJ, Stapleton K. Ig A multiple myeloma presenting as an acquired bullous disorder. Australas J Dermatolol 1999;40:31—4.
[13] Saoji V, Chaudhari S, Gohokar D. Primary systemic amyloidosis: three different presentations. Indian J Dermatol Venereol Leprol 2009;75:394—7.
[14] Marchand A, Levaltier X, Croue A, Arbeille B, Ifrah N, Martin L. Cutaneous amyloid elastosis revealing multiple myeloma with systemic amyloidosis. Acta Derm Venereol 2013;93:204—5.
[15] Mason AR, Rackoff EMJ, Pollack RB. Primary systemic amyloidosis associated with multiple myeloma: a case report and review of the literature. Cutis 2007;80:193—200.
[16] Colucci G, Alberio L, Demarmels Biasiutti F, Lämmle B. Bilateral periorbital ecchymoses. An often missed sign of amyloid purpura. Hamostaseologie 2014;34:249—52.
[17] Greaves MW. Myelomatosis following lichen amyloidosis. Proc R Soc Med 1963;56:791—2.
[18] Oliveira EV, Pozetti AC, Pozetti EM, Antonio JR, Michalany NS. Primary systemic amyloidosis associated with multiple myeloma. An Bras Dermatol 2012;87:119—22.
[19] Behera B, Pattnaik M, Sahu B, Mohanty P, Jena S, Mohapatra L. Cutaneous manifestations of multiple myeloma. Indian J Dermatol 2016;61:668—71.
[20] Fujita Y, Tsuji-Abe Y, Sato-Mtsumura KC, Akiyama M, Shimizu H. Nail dystrophy and blisters as sole manifestations in myeloma-associate amyloidosis. J Am Acad Dermatol 2006;54:712—4.
[21] Becker MR, Rompel R, Plum J, Gaiser T. Light chain multiple myeloma with cutaneous AL amyloidosis. J Dtsch Dermatol Ges 2008;6:744—5.
[22] Perloff JK. Some unusual cutaneous, cardiac and gastrointestinal manifestations of systematized amyloidosis associated with multiple myeloma. J Mt Sinai Hosp NY 1954;21:195—208.
[23] Trump DL, Allen HA, Olson J, Wright J, Humphrey RL. Epidermolysis bullosa acquisita: association with amyloidosis and multiple myeloma. JAMA 1980;243:1461—2.
[24] Westermark P, Ohman S, Domar M, Sletten K. Bullous amyloidosis. Arch Dermatol 1981;117:782—4.
[25] Holden CA, Weston MJ, MacDonald DM. Trauma-induced bullae; the presenting feature of systemic amyloidosis associated with plasma cell dyscrasia. Br J Dermatol 1982;107:701—6.
[26] Beacham BE, Greer KE, Andrews BS, Cooper PH. Bullous amyloidosis. Am Acad Dermatol 1980;3:506—10.
[27] Isobe T, Hata S, Murakami M, Kadowaki S, Fujita T. Bullous amyloidosis associated with Bence Jones proteinemia without proteinuria. Jpn J Med 1984;23:254—7.
[28] Reem AR, Valiollah A, Maodo N. Papular cutaneous amyloidosis associated with multiple myeloma. Sci J Clin Med 2016;5:16—9.
[29] SEER Stat Fact Sheets: Myeloma. Available at: <http://seer.cancer.gov/statfacts/html/mulmy.html> [last accessed September 9, 2018].
[30] Kyle RA. Multiple myeloma: review of 869 cases. Mayo Clin Proc 1975;50:29—40.
[31] Kapadia AB. Multiple myeloma: a clinicopathologic study of 62 consecutively autopsied cases. Medicine (Baltimore) 1980;59:380—92.
[32] Lee N, Moon SY, Lee JH, Park HK, Kong SY, Bang SM, et al. Discrepancies between the percentage of plasma cells in bone marrow aspiration and BM biopsy: impact on the revised IMWG diagnostic criteria of multiple myeloma. Blood Cancer J 2017;7:e530.
[33] Drawid A, Kaura S, Kiely D, Hussein MA, Kaman M, Gilra N, et al. Impact of novel therapies on multiple myeloma survival in US: current and future outcomes. J Clin Oncol 2015;33:e63.
[34] Dinner S, Witteles W, Witteles R, Lam A, Arai S, Lafayette R, et al. The prognostic value of diagnosing concurrent multiple myeloma in immunoglobulin light chain amyloidosis. Br J Haematol 2013;161:367—72.
[35] Kourelis TV, Kumar SK, Gertz MA, Lacy MQ, Buadi FK, Hayman SR, et al. Coexistent multiple myeloma or increased bone marrow plasma cells define equally high-risk populations in patients with immunoglobulin light chain amyloidosis. J Clin Oncol 2013;31:4319—24.
[36] Breathnach SM. Amyloid and amyloidosis. J Am Acad Dermatol 1988;18:1—16.
[37] Hernandez-Reyes J, Galo-Hooker E, Ruiz-Delgado GJ, Ruiz-Arguelles GJ. Systemic immunoglobulin light-chain amyloidosis (AL) in Mexico: a single institution, 30-year experience. Rev Invest Clin 2012;64:604—8.
[38] Kumar S, Sengupta RS, Kakkar N, Sharma A, Singh S, Varma S. Skin involvement in primary systemic amyloidosis. Mediterr J Hematol Infect Dis 2013;5:e2013005.
[39] Vyas K, Morgaonkar M, Gupta S, Jain SK. Primary systemic amyloidosis with unusual dermatological manifestations: a rare case report. Indian J Dermatol 2016;61:216—8.
[40] Bluhum JF, Johnson SC, Norback DH. Bullous amyloidosis: case report with ultrastructural studies. Arch Dermatol 1980;116:1164—8.
[41] Pramatov K, Lazarova A, Mateev G, Popov A. Bullous hemorrhagic primary systemic amyloidosis. Int J Dermatol 1990;29:211—3.
[42] Johnson TM, Rapini RP, Hebert AA, Lowe L, Verani R, Evanoff G. Bullous amyloidosis. Cutis 1989;43:346—52.
[43] Ruzicka T, Schmoeckel C, Ring J, Linke RP, Braun-Falco O. Bullous amyloidosis. Br J Dermatol 1985;113:85—95.
[44] Kyle RA, Gertz MA, Greipp PR, Witzig TE, Lust JA, Lacy MQ, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med 1997;336:1202—7.
[45] Dispenzieri A, Kyle RA, Gertz MA, Therneau TM, Miller WL, Chandrasekaran K, et al. Survival in patients with primary

systemic amyloidosis and raised serum cardiac troponins. Lancet 2003;361:1787—9.
[46] Cibeira MT, Sanchorawala V, Seldin DC, Quillen K, Berk JL, Dember LM, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. Blood 2011;118:4346—52.
[47] Jaccard A, Moreau P, Leblond V, Leleu X, Benboubker L, Hermine O, et al. High dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med 2007;357:1083—93.
[48] Palladini G, Perfetti V, Obici L, Caccialanza R, Semino A, Adami F, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. Blood 2004;103:2936—8.
[49] Harati A, Brockmeyer NH, Altmeyer P, Kreuter A. Skin disorders in association with monoclonal gammopathies. Eur J Med Res 2005;10:93—104.
[50] Kois JM, Sexton FM, Lookingbill DP. Cutaneous manifestations of multiple myeloma. Arch Dermatol 1991;127:69—74.
[51] Rajkumar SV, Gertz MA, Kyle RA. Primary systemic amyloidosis with delayed progression to multiple myeloma. Cancer 1998;82:1501—5.
[52] Ozaki S, Abe M, Wolfenbarger D, Weiss DT, Solomon A. Preferential expression of human lambda-light-chain variable-region subgroups in multiple myeloma, AL amyloidosis, and Waldenström's macroglobulinemia. Clin Immunol Immunopathol 1994;71:183—9.
[53] Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 1995;32:45—59.
[54] Kyle RA, Greipp PR. Amyloidosis (AL). Clinical and laboratory features in 229 cases. Mayo Clin Proc 1983;58:665.
[55] Kyle RA, Greipp PR, O'Fallon WM. Primary systemic amyloidosis: multivariate analysis for prognostic factors in 168 cases. Blood 1986;68:220.
[56] Abraham RS, Ballman KV, Dispenzieri A, Grill DE, Manske MK, Price-Troska TL, et al. Functional gene expression analysis of clonal plasma cells identifies a unique molecular profile for light chain amyloidosis. Blood 2005;105:794—803.
[57] Kourelis TV, Dasari S, Theis JD, Ramirez-Alvarado M, Kurtin PJ, Gertz MA, et al. Clarifying immunoglobulin gene usage in systemic and localized immunoglobulin light-chain amyloidosis by mass spectrometry. Blood 2017;129:299—306.
[58] Hayman SR, Bailey RJ, Jalal SM, Ahmann GJ, Dispenzieri A, Gertz MA, et al. Translocations involving the immunoglobulin heavy-chain locus are possible early genetic events in patients with primary systemic amyloidosis. Blood 2001;98:2266—8.
[59] Suzuki K, Kasuga M, Miyazaki K, Meshitsuka S, Abe Y, Yoshiki Y, et al. Difference of treatment outcomes in AL amyloidosis and multiple myeloma with/without translocation (11;14). Blood 2015;126:4224 [Abstract].
[60] Bahlis NJ, Lazarus HM. Multiple myeloma-associated AL amyloidosis: is a distinct therapeutic approach warranted? Bone Marrow Transplant 2006;38:7—15.