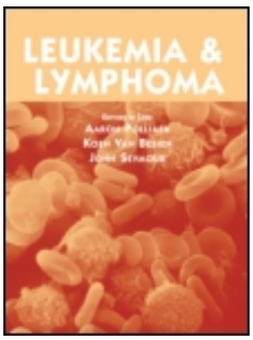

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Cutaneous involvement in multiple myeloma: a multi-institutional retrospective study of 53 patients

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ABSTRACT

Skin infiltration in multiple myeloma (skin MM) is a rare clinical problem. Only a few cases of skin involvement have been reported, primarily in single case reports. We analyzed and present the clinical outcomes, immunohistochemistry and cytogenetic features, and relevant laboratory data on 53 biopsy-proven skin MM cases. The median time from MM diagnosis to skin involvement was 2 years. There appears to be an overrepresentation of immunoglobulin class A (IgA) and light chain disease in skin MM. We found no correlation between CD56 negative MM and skin infiltration. We found that skin MM patients presented in all MM stages (i.e. ISS stages I to III), and there was no preferential cytogenetic abnormality. Patients with skin MM carry a very poor prognosis with a median overall survival (OS) of 8.5 months as time from skin involvement. Moreover, patients with IgA disease and plasmablastic morphology appear to have a worse OS.

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KEYWORDS
Cutaneous; diagnosis; myeloma; skin; treatment

Introduction

Multiple myeloma (MM) is a plasma cell dyscrasia characterized by the accumulation of malignant plasma cells, mainly in the bone marrow. The vast majority of patients with MM present with anemia, renal dysfunction, hypercalcemia, and/or lytic skeletal lesions. Although the bone marrow is the most common site affected by MM, extramedullary involvement of MM has a strong prognostic value.[1–4]

Skin infiltration in MM (skin MM) is a rare clinical problem, which usually manifests during end-stage disease. To date, only a few series of skin MM have been reported, and these are primarily case reports. [5–10] Hence, little is known about the features and outcomes of patients with skin MM. In this retrospective study, we report on the clinical and pathological characteristics, and outcomes of 53 pathologically confirmed skin MM cases.

Methods

Patient selection

This was a multi-institutional, retrospective study conducted in 24 centers from 13 countries in Europe (Belgium, Czech Republic, Denmark, France, Germany, Italy, the Netherlands, Poland, and Spain), South America (Argentina and Brazil), the United States, and Canada.

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The institutional review boards at each of the participating institutions approved the study. Patients were identified through a database search at each of the participating institutions. Patients with a pathological diagnosis of MM involving the skin were included in this analysis.

Data gathering

Clinical data included: age at MM diagnosis, sex, time from initial MM diagnosis to skin MM, number and type of therapies for MM prior to skin involvement, symptoms at skin MM diagnosis, number, and type of therapies received for skin MM, overall survival (OS) from MM diagnosis and skin MM diagnosis, and cause of death. Laboratory data at the time of skin MM diagnosis included: beta-2-microglobulin (B2M), albumin, and lactate dehydrogenase (LDH) levels. Pathological data included fluorescent *in situ* hybridization (FISH) abnormalities prior to skin MM diagnosis. There are no standard response criteria for skin MM. Therefore, for this study, we considered complete response (CR) as the complete resolution of skin lesions, partial response (PR) as a decrease in size >25% or number of lesions without complete resolution, stable disease (SD) as no new lesions or change in size of existing lesions, and progressive disease (PD) as a >25% increase in size or number of lesions.

Statistical analysis

Continuous and categorical variables are presented using descriptive statistics. Comparisons between categorical variables were performed using the chi-square test. Time from MM diagnosis to skin MM diagnosis (MM to skin MM) was defined as the time in months from the date of pathological diagnosis of MM to the date of a pathological diagnosis of skin MM. OS was defined as the time in months between the date of pathologic diagnosis of skin MM and the date of death or last follow-up. Time from MM to skin MM and OS were estimated using the Kaplan-Meier method. The log-rank test was used to compare OS estimates according to prognostic factors. Univariate survival analyses were performed using the log-rank test. p Values <0.05 were considered statistically significant. No multivariate analysis was attempted given the small sample size. STATA 13.1 (StataCorp LP, College Station, TX) was used for analysis.

Results

Fifty-three patients were included in this study; 32 (60%) were from Europe, 12 (23%) from Latin America, and 9 (17%) from the United States and Canada. The median time from MM to skin MM was 2.2 years (range 0–11 years; Figure 1). Clinical and laboratory characteristics of the patients are shown in Table 1. The median burden of bone marrow involvement at skin MM diagnosis was 21% (range 0–100%).

A third of the patients had more than five skin lesions, and the largest skin MM mass was 10 cm × 15 cm. In 18 patients, the skin MM lesion diameter was 5 cm or larger. The most common locations of skin MM were the chest, lower extremities, back, and buttocks (Table 2). A plasmablastic morphology could be recognized in skin biopsies from 20 out of 34 (59%) patients. Pathological characteristics of the patients are shown in Table 2.

The median number of therapies prior to skin MM was 3 (range 0–9). After a skin MM diagnosis, 52 patients (98%) received therapy; 73% received chemotherapy, 48% received proteasome inhibitors, 29% received immunomodulatory agents (IMIDs), 10% underwent radiotherapy, and 12% had autologous stem cell transplantation (SCT) (Table 3). Note: the numbers do not sum up to 100% due to overlapping categories. After first-line therapy, a total of 22% of investigated patients showed CR to treatment, 35% of patients had a PR, 11% of patients had SD, and 33% had PD. From the 52 patients who received initial therapy for skin MM, 38 patients (73%) went on to receive second-line therapy for skin MM, as follows: 53% received chemotherapy, 50% received IMIDs, 42% received proteasome inhibitors, 3% underwent radiotherapy, and 13% had autologous SCT. Responses to second-line therapy were as follows: CR = 3%, PR = 24%, SD = 21%, and PD = 52%. From the 38 patients who received second-line therapy for skin MM, 29 patients (56%) received third line of therapy; 52% received chemotherapy, 48% received IMIDs, 45% received proteasome inhibitors, 7% underwent radiotherapy, and 10% had autologous SCT. Responses to third-line therapy were as follows: CR = 9%, PR = 26%, and PD = 65%. The trend toward a higher rate of PD with each line of therapy for skin MM was statistically significant ($p < 0.001$). No treatment modality was associated with higher rates of CR or CR/PR (data not shown).

With a median follow-up of 24 months, the median OS from time of skin MM diagnosis was 8.5 months (range 0.4–108 months; Figure 2A). Causes of death were MM progression in 83%, infection in 14%, and pancreatic obstruction in 3% of the patients. In the univariate analysis, patients with IgA heavy chain disease and plasmablastic morphology were associated with worse OS (Figure 2B and C, respectively). Age (log-rank $p = 0.18$), sex ($p = 0.58$), light chain disease ($p = 0.89$), International Scoring System (ISS) stage ($p = 0.19$),

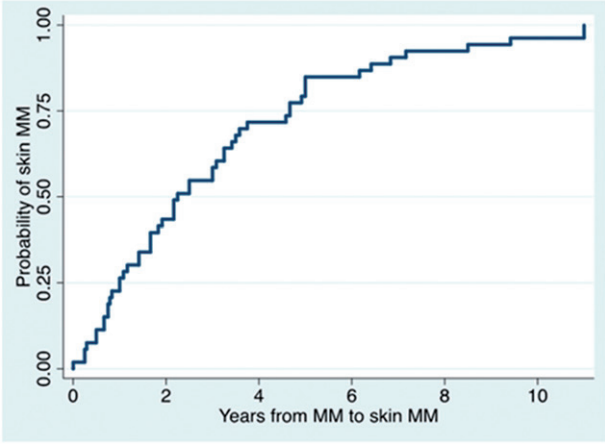

Figure 1. Kaplan–Meier estimates of time from multiple myeloma (MM) diagnosis to skin involvement (skin MM).

number of previous lines of MM therapy ($p = 0.37$), time from MM to skin MM ($p = 0.48$), CD56 expression ($p = 0.50$), complex cytogenetic abnormalities ($p = 0.89$) at diagnosis, and location of the lesions ($p > 0.05$ for each location) were not associated with worse OS.

Discussion

Skin involvement is a rare complication in patients with MM. This is the largest retrospective study focusing on this rare clinical presentation. The most striking results of our study are: (1) the median time from MM diagnosis to skin involvement is 2.2 years, indicative of more aggressive disease biology; (2) skin MM can be seen at any time during the course of the disease and at any stage of disease; (3) there is a trend toward a higher proportion of IgA heavy chain in patients with skin MM; (4) the median OS is short, at 8.5 months; (5) worse outcome is seen in patients with IgA heavy chain disease and plasmablastic morphology; and (6) there is an unmet need for improved therapies for skin MM patients.

In our cohort, the median age at skin MM diagnosis was 63, and there were no primary skin MM patients. The median time from initial MM diagnosis to skin MM was approximately 2 years, and a number of patients developed skin involvement shortly after systemic MM diagnosis. Also, 27.5% of our patients had ISS stage 1 disease at the time of skin MM diagnosis, suggesting no association between staging and likelihood of developing skin MM. In three patients, skin infiltration was accompanied by other extramedullary locations of MM. Overall, our study shows that skin involvement by MM might occur at any time during the course of the disease and not necessarily only during the late stages of disease. When it does occur earlier in the disease course, it represents a more de-differentiated, aggressive form of MM.

Table 1. Clinical and laboratory characteristics of patients with cutaneous involvement of multiple myeloma.

Characteristic	*N* (%) or median (range)
Median age at skin involvement (years)	63 (38–86)
Male sex	32 (60%)
Median lines of therapy before skin involvement	3 (0–9)
Chemotherapy	29 (58%)
Immunomodulators	24 (48%)
Proteasome inhibitors	21 (42%)
Radiotherapy	7 (14%)
Autologous stem cell transplant	17 (34%)
Allogeneic stem cell transplant	4 (8%)
Heavy chain disease	
IgG	21 (40%)
IgA	19 (36%)
IgD	1 (2%)
No heavy chain disease	12 (23%)
Light chain disease	
Kappa	37 (70%)
Lambda	16 (30%)
Laboratory data	
Serum albumin (g/L)	3.6 (1.9–4.6)
Serum beta-2-microglobulin (mg/dL)	3.1 (0.6–10.4)
Number of lesions	
1–5 lesions	34 (67%)
>5 lesions	17 (33%)
Location	
Chest	22 (44%)
Lower extremities	12 (24%)
Back/buttocks	11 (22%)
Face/neck	10 (20%)
Upper extremities	9 (18%)
International Scoring System stage	
Stage I	11 (27.5%)
Stage II	13 (32.5%)
Stage III	16 (40%)

Plasmacytic infiltrates in the skin typically present as red–violet spots, nodules or lumps, which can ulcerate, or as dome-shaped plates having a smooth surface (Figure 3).[11,12] In our study, a third of the patients had more than five lesions and a lesion diameter of ≥5 cm. The most common locations for skin MM lesions were the chest, lower extremities, back and buttocks; some lesions were located on the upper extremities and less often on the face. In one of our patients, skin infiltration appeared in the abdominal area where the patient had frequently been given repeated subcutaneous injections. In another patient, skin lesions were found in the amputation stump scar of the right leg. Therefore, trauma might play a role in skin homing by plasma cells. In most of our patients, skin lesions were just one of the signs of disease progression; however, in more than 20% of skin MM patients, the skin was the first or only site of progression.

Previous studies have shown that histopathological examination reveals the presence of clonal plasma cells in different layers of the skin in MM, while the epidermis is usually spared (Figure 4).[13,14] Often, cells with

Table 2. Pathological characteristics of patients with cutaneous involvement of multiple myeloma.

Characteristic	*N* positive/*N* tested (%)
Immunohistochemistry	
CD38/CD138	29/29 (100%)
IRF4/MUM1	4/4 (100%)
CD56	9/11 (82%)
CD79A	4/5 (80%)
CD45	1/3 (33%)
CD20	1/10 (10%)
EBER	0/2 (0%)
Fluorescent *in situ* hybridization	
Complex (3 + abnormalities)	10/23 (43%)
Deletion 13q	9/24 (38%)
Translocation (4;14)	6/24 (25%)
Deletion 17p	2/24 (8%)
Translocation (14;16)	2/24 (8%)
Translocation (11;14)	1/23 (4%)

Table 3. Response rate to each group of therapy.

Therapies	Number	CR	PR	SD	PD
First line ($n = 52$)					
IMID-based	15 (29%)	4 (27%)	7 (47%)	0	4 (27%)
PI-based	25 (48%)	6 (24%)	6 (24%)	3 (12%)	10 (40%)
Chemotherapy-based	5 (10%)	1 (20%)	1 (20%)	1 (20%)	2 (40%)
Radiotherapy	5 (10%)	0	2 (40%)	3 (60%)	0
ASCT	7 (12%)	3 (43%)	3 (43%)	1 (14%)	0
Second line ($n = 38$)					
IMID-based	19 (50%)	1 (5%)	5 (26%)	8 (42%)	5 (26%)
PI-based	16 (42%)	1 (6%)	5 (31%)	6 (38%)	4 (25%)
Chemotherapy-based	7 (18%)	0	1 (14%)	0	6 (86%)
Radiotherapy	1 (3%)	0	0	0	1 (100%)
ASCT	5 (13%)	0	1 (20%)	1 (20%)	3 (60%)
Third line ($n = 29$)					
IMID-based	14 (48%)	2 (14%)	4 (29%)	0	8 (57%)
PI-based	13 (45%)	3 (23%)	3 (23%)	0	7 (54%)
Chemotherapy-based	6 (20%)	0	2 (33%)	0	4 (67%)
Radiotherapy	2 (7%)	0	0	0	2 (100%)
ASCT	3 (10%)	0	1 (33%)	0	2 (67%)

The numbers do not sum up to 100% due to overlapping categories.
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; IMID, immunomodulator; PI, proteasome inhibitor; ASCT, autologous stem cell transplant.

atypical or immature morphology can be seen in skin lesions, even though mature plasma cells are simultaneously present in the bone marrow. In our study, we found a plasmablastic morphology in the skin infiltrates in approximately 60% of our patients, suggesting the aggressive nature of skin MM. This is consistent with previous reports.[15,16] However, as this plasmablastic morphology can be diagnostically misleading and may suggest lymphoma or sarcoma, pertinent immunohistochemistry, and molecular studies should be performed to prove the clonal nature of the tumor.

Overrepresentation of rare types of monoclonal protein is remarkable in previously published descriptions of skin MM. For example, some studies report a higher incidence of IgA MM among cases with skin involvement;[14,17] while others observed that the skin is more frequently involved in IgD MM and light chain disease.[18] Our data also show a trend for IgA and light chain disease cases, with kappa predominance, among skin MM patients.

It has been hypothesized that lack of CD56 expression might play a role in the pathophysiology of skin MM. In a small study, 6 out of 7 patients with skin MM patients showed a lack of CD56 expression.[19] In our study, we assessed CD56 expression in 11 skin samples, and found that 9 cases (82%) showed positive CD56 expression. This argues against a role for negative CD56 expression in the development of skin MM.

With a median follow-up of 24 months, the median OS was 8.5 months from the time of skin involvement, which is consistent with historical data.[14,19] The most common cytogenetic adverse factor was complex karyotype, which was present in approximately 40% of the patients. Almost half of the patients received proteasome inhibitors (42%) and/or immunomodulators (48%) before a skin MM diagnosis, and 58% of them were treated with conventional chemotherapy. The median number of prior lines of therapy was three, supporting the finding that skin MM appears mainly in advanced disease in heavily pretreated patients. In the univariate survival analysis, IgA heavy chain disease, and plasmablastic morphology were associated with worse patient outcomes. Both factors have been previously associated with worse outcomes in patients with MM.[20]

Nearly all patients received initial therapy for skin MM (98%), 73% received second-line therapy, and 56% received third line of therapy. There were some responders observed in the later lines of therapy, especially to novel drugs such as carfilzomib and pomalidomide. However, no drug superiority was observed in terms of response, although this may be explained by the small sample size, the heterogeneity of the treatments, and the significant trend toward a higher rate of PD with each line of therapy. Single reports have previously described transient effectiveness of traditional chemotherapy in the treatment of skin MM.[21,22] Novel agents, including bortezomib, thalidomide, and lenalidomide, have also had transient activity in skin MM.[23,24] Moreover, the efficacy of autologous or allogeneic SCT in skin MM, which was used by some patients in our study, remains unclear.[11,15] Finally, radiotherapy was not widely used by MM patients in our cohort, and although responses were observed, they were partial and transient. This is consistent with previous reports.[25]

Conclusions

Skin involvement is a rare complication of MM. Our study does not support an association with advanced disease

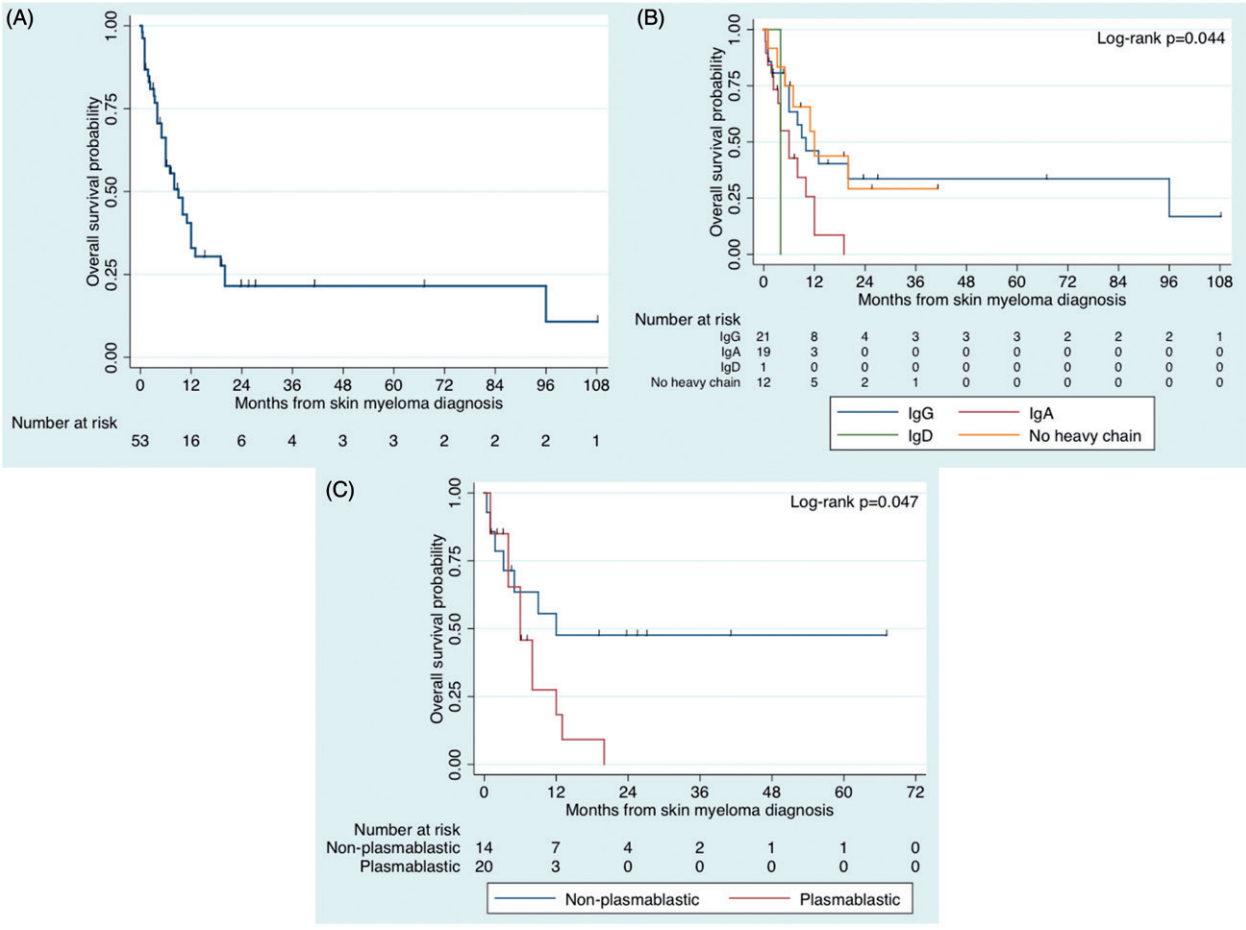

Figure 2. Kaplan–Meier estimates of overall survival since skin myeloma diagnosis (A), and according to immunoglobulin (Ig) heavy chain restriction (B), and plasmablastic morphology (C).

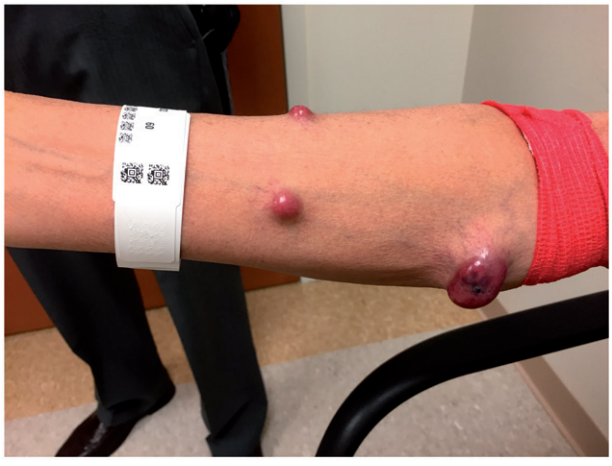

Figure 3. Skin involvement in MM.

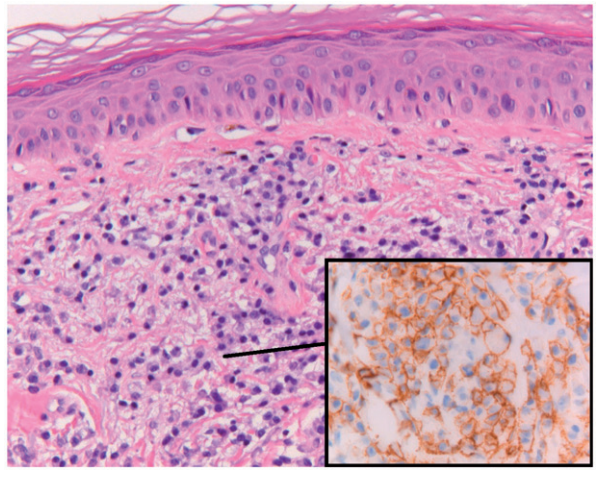

Figure 4. A dense infiltrate of CD138 + plasma cells in the dermis, with a normal epidermis.

or high tumor burden at diagnosis. There seems to be an overrepresentation of IgA heavy chain disease, light chain disease, and plasmablastic morphology in skin MM. Patients with skin MM carry a very poor prognosis with a median OS of 8.5 months as time from skin involvement. Currently, there is no standard of care for patients with skin involvement by MM. Therefore, with a median survival of less than a year from the time of diagnosis, skin MM remains a therapeutic challenge with poor prognosis.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at http://dx.doi.org/10.3109/10428194.2015.1128542.

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