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Cutaneous comorbidities in patients with multiple myeloma

A 10-year retrospective cohort study from a Korean population

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Abstract

Multiple myeloma (MM) is a common hematologic malignancy characterized by the presence of the clonal proliferation of tumor cells. Studies on cutaneous comorbidities in Asian patients with MM have yet to be conducted.

This study aimed to analyze the prevalences, characteristics, overall survivals, and risk factors of various cutaneous comorbidities in patients with MM.

A retrospective cohort study using medical records from January 1, 2008, to December 31, 2017, in patients with MM was conducted.

Of 1438 patients with MM, 354 patients (24.61%) had one or more cutaneous comorbidities. Among them, herpes zoster infection was found to be the most common cutaneous comorbidity. The development of herpes zoster was found to be a possible candidate for good prognostic factor for overall survival [hazard ratio, 0.62; 95% confidence interval (95% CI), 0.44–0.86], while the occurrence of cutaneous malignant tumor was found to be a possible candidate for poor prognostic factor for overall survival (hazard ratio, 3.13; 95% CI, 1.76–5.56).

The development of some cutaneous comorbidities heralds the prognostic importance in patients with MM. A better understanding of the prevalences, clinical characteristics, and risk factors of various cutaneous comorbidities in patients with MM may help clinicians identify the clinical course and prognosis of the disease.

Abbreviations: MM = multiple myeloma, OS = overall survival, SCT = stem cell transplantation.

Keywords: cohort study, cutaneous comorbidities, herpes zoster, Korean, malignant tumor, multiple myeloma

1. Introduction

Multiple myeloma (MM) is a common malignant disorder characterized by the clonal proliferation of aberrant plasma cells that produce monoclonal immunoglobulins.[1] The abnormal proliferation of the malignant antibody, which forms plasma cells, causes various unusual clinical manifestations in patients with MM. The common clinical presentations of MM are explained by "CRAB"; symptoms include hypercalcemia, renal dysfunction, anemia, and lytic bone lesions.[2] In addition to these clinical presentations, various cutaneous manifestations can be observed in patients with MM. However, the cutaneous comorbidities are usually neglected and underdiagnosed among patients with MM. Therefore, there are limited data regarding cutaneous disorders in patients with MM. To date, only 3 articles have been conducted regarding the issues of cutaneous disorders in patients with MM.[3,4] Previous studies of cutaneous disorders in MM have only included patients who have undergone histological examination.[3] In addition, most of the studies have only investigated the prevalences of specific cutaneous comorbidities in the Caucasian population.[3,4]

To date, little remains known about the cutaneous comorbidities of MM in Asian population. This study aims to study the prevalences, overall survival (OS), and characteristics of various cutaneous comorbidities in MM as well as to elucidate the possible risk factors for the development of specific cutaneous comorbidities in patients with MM by using the most recent Asian data. Moreover, the present study intends to include the patients with MM with cutaneous comorbidities who were also clinically diagnosed by the specialized dermatologists, which might be helpful for identifying more diverse cutaneous comorbidities in patients with MM.

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2. Materials and methods

The inclusion criteria were Korean patients who were diagnosed with MM during January 1, 2008, to December 31, 2017 at Yeouido St. Mary's Hospital and Seoul St. Mary's Hospital in Seoul. The diagnosis of MM was defined on the basis of the following diagnostic criteria by international myeloma working group[5]: presence of serum or urinary monoclonal protein; clonal bone marrow plasma cells ≥ 10%; and evidence of end-organ damage that can be associated with underlying plasma cell proliferative disorder. The medical records of all 1740 patients initially identified as being diagnosed with MM were reviewed. The patients with monoclonal gammopathy of undetermined significance, smoldering MM, plasma cell leukemia, systemic amyloidosis, Waldenström macroglobulinemia, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes were excluded. And loss to follow-up, defined as patients who were referred for second-opinion or had no record of death, were excluded in the analysis. Among the included patients, the clinical and pathologic tissue sections of patients with cutaneous comorbidities were additionally analyzed. However, patients with cutaneous manifestations secondary to systemic infection such as bacteremia and fungemia were not included as having cutaneous comorbidities in this study. This study was approved by the Ethics Committee of the Yeouido St. Mary's Hospital.

IBM SPSS version 21.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses. The comparison between 2 groups according to the presence or absence of cutaneous comorbidities was performed using an independent *t* test for continuous variables and Chi-square test for categorical variables. In order to analyze the influence of various cutaneous comorbidities on OS in patients with MM, Cox proportional hazard models were performed after adjusting for other covariables. Subgroup analyses to determine the risk factors associated with the development of specific cutaneous comorbidities were conducted using logistic regression analysis. A *P* value of less than .05 was considered to be statistically significant.

3. Results

3.1. Baseline characteristics of the patients with MM

Initially, 1740 patients with MM were identified. Of these, 102 patients with monoclonal gammopathy of undetermined significance, 48 patients with smoldering MM, 30 patients with systemic amyloidosis, 12 patients with Waldenström macroglobulinemia, 92 patients with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes, and 18 patients who were loss to follow-up were excluded. Finally, 1438 patients with MM were identified and included in the current analysis.

Among the 1438 patients with MM, 354 (24.61%) were identified as having more than one cutaneous comorbidity. The demographic characteristics of patients with MM are summarized in Table 1. All patients were Korean. The mean age of the MM patients who had cutaneous comorbidities (mean age, 60.25 years) was younger than the mean age of those who did not have cutaneous comorbidities (mean age, 63.52 years, $P < .001$). Patients with cutaneous comorbidities received more treatment with stem cell transplantation (SCT) than those without cutaneous comorbidities ($P < .001$). However, no statistically significant differences were noted between the 2 groups regarding sex ($P = .06$), heavy chain disease ($P = .33$), light chain disease ($P = .26$), serum β2-microglobulin level ($P = .16$), and serum albumin level ($P = .85$) (Table 1).

3.2. Prevalences of various cutaneous comorbidities in patients with MM

Of the 354 patients with MM with cutaneous comorbidities, 458 cutaneous comorbidities were diagnosed. Among them, a total of 152 patients (33.18%) were undertaken the skin biopsies for accurate diagnosis. Two hundred thirty-nine patients (67.51%) had 1 cutaneous comorbidity, while 80 patients (22.60%) had 2 cutaneous comorbidities. Nineteen patients (9.89%) had more than 3 different cutaneous comorbidities. The prevalences of

Table 1

Baseline characteristic of the patients with multiple myeloma (n = 1438).

	Cutaneous comorbidity (−)	Cutaneous comorbidity (+)	*P*
Number of patients	1084	354	
Age at MM diagnosis	63.52 ± 11.40	60.25 ± 12.20	**<.001**
Sex (male)	555 (51.19)	202 (57.06)	.06
SCT (yes)	368 (33.94)	173 (48.87)	**<.001**
Heavy chain			.33
No	203 (18.73)	78 (22.04)	
IgA	224 (20.67)	74 (20.90)	
IgD	37 (3.41)	17 (4.80)	
IgG	601 (55.44)	177 (50.00)	
IgE	2 (0.18)	0 (0.00)	
IgM	17 (1.57)	8 (2.26)	
Light chain			.26
No	0 (0.00)	1 (0.28)	
lambda	476 (43.9)	150 (42.37)	
kappa	608 (56.1)	203 (57.34)	
ISS stage			.02
Grade 1	158 (14.6)	65 (18.36)	
Grade 2	507 (46.8)	137 (38.70)	
Grade 3	419 (38.7)	152 (42.93)	
B2-microglobulin, mg/L	4.87 ± 3.61	5.18 ± 3.59	.16
Albumin, g/dL	3.25 ± 1.10	3.24 ± 1.07	.85

Data are presented as number (%) or mean. The comparison between 2 groups was performed using independent *t* test for continuous variables and Chi-square test for categorical variables. Ig = immunoglobulin, ISS = international staging system, MM = multiple myeloma.

Bold value indicates a statistically significant difference with a *P* value of less than .001.

Table 2

Prevalences of various cutaneous comorbidities in patients with multiple myeloma.

Cutaneous comorbidities	No. (%)
Infectious cutaneous disorders	223 (48.69)
Herpes viral infection	144 (31.45)
Dermatophyte infection	50 (10.92)
Viral warts	17 (3.71)
Bacterial infection	11 (2.40)
Parasitic disorder	1 (0.21)
GVHD of the skin	27 (5.90)
Acute GVHD	20 (4.37)
Chronic GVHD	7 (1.53)
Tumors	52 (11.35)
Benign tumors	35 (7.65)
Malignant tumors	17 (3.70)
Eczema	60 (13.10)
Contact dermatitis	18 (3.93)
Xerotic eczema	21 (4.58)
Seborrheic dermatitis	20 (4.37)
Lichen simplex chronicus	1 (0.22)
Drug-induced skin disorders	49 (10.70)
Drug eruption	45 (9.83)
SJS/TEN	4 (0.87)
Other inflammatory skin disorders	47 (10.26)
Pruritic dermatoses	24 (5.23)
Urticaria	12 (2.62)
Rosacea	4 (0.87)
Sweet syndrome	2 (0.44)
Psoriasis	2 (0.44)
Erythema nodosum	1 (0.22)
Granuloma annulare	1 (0.22)
Erythema elevatum diutinum	1 (0.22)

GVHD = graft-versus-host disease, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis.

various cutaneous comorbidities in MM are summarized in Table 2. The infectious cutaneous disorders were the most frequent cutaneous comorbidities in patients with MM.

This study included 8 patients with a previous history of cutaneous comorbidities before the diagnosis of MM, 3 patients with long-standing eczema, 2 patients with cutaneous plasmacytoma, 1 patient with herpes zoster, 1 patient with erythema elevatum diutinum, and 1 patient with urticaria. Because of these notable skin manifestations, patients had earlier opportunities to receive further laboratory evaluation of their MM. Therefore, cutaneous manifestations were helpful presenting signs for the diagnosis of MM in those patients.

3.3. Differences of OS in a subgroup of patients with MM

Generally, OS between patients with and without cutaneous comorbidities was not statistically different ($P = .38$, Fig. 1). However, OS between patients with and without herpes zoster ($P = .048$) and malignant tumor ($P < .001$) was significantly different. Except for the 2 comorbidities, the presence or absence of other cutaneous comorbidities was not associated with the differences in OS between 2 groups.

The cutaneous manifestations of MM are further subcategorized into specific skin lesion, which includes the cutaneous plasmacytoma, and nonspecific skin lesions, which includes the xathoma, Sweet syndrome, and erythema elevatum diutinum. Although the presence of specific skin lesion was associated with the decreased OS ($P < .001$), the presence or absence of nonspecific skin lesion was not associated with any differences in OS between the 2 groups ($P = .11$).

3.4. Factors affecting OS in patients with MM with cutaneous comorbidities

In order to identify the factors affecting OS among patients with MM with cutaneous comorbidities, a subgroup analysis was conducted. The higher ISS stage has been identified as a risk factor for OS in patients with cutaneous comorbidities. In addition, treatment with SCT and kappa light chain disease have been identified as protective factors. The development of malignant tumor was identified as a possible candidate for poor prognostic factor after adjusting the covariables [hazard ratio (HR), 3.13; 95% confidence interval (95% CI), 1.76–5.56; Table 3]. On the contrary, the development of herpes zoster was observed as a possible candidate for good prognostic factor after adjusting covariables (HR, 0.62; 95% CI, 0.44–0.86).

3.5. Clinical characteristics and factors associated with the occurrence of various cutaneous comorbidities in patients with MM

3.5.1. Infectious cutaneous disorders in patients with MM.

Of 144 patients with herpes viral infection, 123 patients had herpes zoster infection and 21 patients had herpes simplex

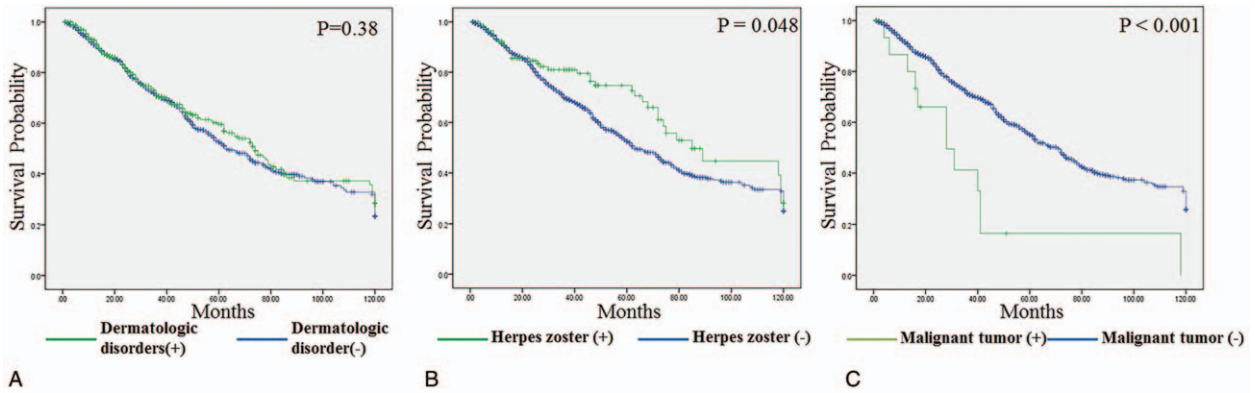

Figure 1. Kaplan–Meier analysis of overall survival curve in patients with multiple myeloma according to the presence of (A) cutaneous comorbidities, (B) herpes zoster, and (C) malignant tumor.

Table 3

Subgroup analysis of patients with multiple myeloma with various cutaneous comorbidities (n = 354).

	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at MM diagnosis	1.01 (0.99–1.02)	.079		
Sex (male)	0.92 (0.66–1.29)	.623		
SCT (yes)	0.55 (0.39–0.78)	**.001**		
Heavy chain				
No	1.0 (Reference)			
A, D, G, E, M	1.07 (0.71–1.62)	.103		
Light chain				
Lambda	1.0 (Reference)			
Kappa	0.69 (0.49–0.97)	**.030**		
ISS stage		**.013**		
Grade 1	1.0 (Reference)			
Grade 2	2.46 (1.29–4.67)	.006		
Grade 3	2.57 (1.36–4.89)	.004		
B2-microglobulin (<5.5)	0.81 (0.58–1.13)	.217		
Albumin (<3.5)	0.99 (0.70–1.38)	.930		
Dermatological outcomes				
Infectious cutaneous disorder	0.62 (0.44–0.86)	**.005**	0.63 (0.45–0.88)	**.007**
Herpes zoster	0.68 (0.48–0.98)	**.037**	0.75 (0.52–1.09)	**.048**
Postherpetic neuralgia	1.09 (0.42–2.82)	.866		
Disseminated herpes zoster	0.99 (0.35–2.80)	.986		
Herpes simplex infection	0.77 (0.33–1.78)	.541		
Dermatophyte infection	0.71 (0.41–1.23)	.218		
Viral warts	0.46 (0.17–1.25)	.128		
GVHD of the skin	0.92 (0.50–1.70)	.782		
Benign tumor	0.54 (0.25–1.16)	.116		
Malignant tumor	3.13 (1.76–5.56)	**<.001**	2.85 (1.60–5.08)	**<.001**
Eczematous disorder	0.63 (0.37–1.09)	.097		
Drug-induced skin reaction	0.83 (0.49–1.39)	.474		
Inflammatory skin disorders	1.01 (0.60–1.71)	.963		

Multivariate; adjusted by SCT only because of rule for 10.

CI = confidence interval, GVHD = graft-versus-host disease, HR = hazard ratio, SCT = stem cell transplantation.

Bold value indicates a statistically significant difference with a *P* value of less than .05.

infection. Herpes zoster infection was the most common disorder found in the patients. The dermatomal involvement site was most commonly involved in T dermatome (61 patients, 49.59%), followed by L dermatome (16 patients, 13.00%). Dissemination of the herpes zoster was observed in 13 patients (10.56%). Of these 13 patients, 8 (61.54%) had been treated with a combination of thalidomide and dexamethasone or thalidomide for the previous 6 months. Postherpetic neuralgia was noted in 17 patients (13.82%). The incidence rate of grade 3/4 neutropenia and thrombocytopenia[6] at the time of development of herpes zoster was 12.19% (15/123 patients) and 15.44% (19/123 patients), respectively. Chemotherapy was conducted in 27 patients (21.95%) with herpes zoster, and SCT was conducted in 76 patients (61.78%) with herpes zoster. Among them, the development of herpes zoster occurred within 1 year of SCT in 44 patients (58.22%). The mean onset time of development of herpes zoster within 1 year of SCT was 110 days (range 3–360 days). The treatment of SCT was associated with an increased risk of herpes zoster in patients with MM [odds ratio (OR), 2.19; 95% CI, 1.40–3.44; Table 4]. The age of MM diagnosis was associated with a decreased risk of development of herpes zoster in patients with MM (OR, 0.97; 95% CI, 0.96–0.99).

Among dermatophyte infections, tinea pedis (38 patients, 60.32%) was the most common subtype followed by tinea unguium (18 patients, 28.57%), tinea corporis (4 patients, 6.35%), and tinea cruris (3 patients, 4.76%). The concomitant sites of infection for dermatophyte were observed in 13 patients. Chemotherapeutic regimens were ongoing in 17 patients (34.00%) with dermatophyte infection at the time of diagnosis. None of the patients showed grade 3/4 neutropenia at the time of diagnosis of dermatophyte infection, whereas grade 3/4 thrombocytopenia was observed 13% of patients with dermatophyte infection.

With regards to cutaneous bacterial infection, furuncle was observed in 5 patients and abscess was also found in 6 patients. At the time of diagnosis of bacterial infections, chemotherapeutic regimens were being conducted in 4 patients (36.36%). However, grade 3/4 neutropenia and thrombocytopenia were not observed at the time of diagnosis of cutaneous bacterial infection. Regarding viral warts infection, viral warts on the extremities were seen in 14 patients, and genital warts were found in three patients. At the time of diagnosis, chemotherapeutic regimens were ongoing in 8 patients (57.14%) with viral warts, and SCT was conducted in 3 patients (21.42%). Grade 3/4 neutropenia and thrombocytopenia was observed in 5 patients (35.71%) and 4 patients (28.57%) at the time of diagnosis of viral warts, respectively. The treatment of SCT was associated with a decreased risk of the development of viral warts in patients with MM (OR, 0.25; 95% CI, 0.07–0.90; Table 4).

3.5.2. Graft-versus-host disease of the skin in patients with MM. Graft-versus-host disease (GVHD) of the skin was observed in 27 patients. Of these patients, acute GVHD of the skin was observed in 20 patients (74.07%), and chronic GVHD of the skin was observed in 7 patients (25.93%; Fig. 2). Among the 1 to 4 grading scale of acute GVHD of the skin, grade 1 was the most

Table 4

Factors associated with selected cutaneous comorbidity in univariate analyses (n = 354).

	Herpes zoster		Postherpetic neuralgia		Disseminated herpes zoster		Herpes simplex		Dermatophyte infection		Viral warts	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age	0.98 (0.96–0.99)	.026*	1.03 (0.98–1.08)	.226	0.96 (0.91–1.02)	.189	0.97 (0.92–1.05)	.217	1.03 (0.99–1.05)	.057	0.99 (0.95–1.04)	.799
Sex (male)	0.80 (0.51–1.24)	.311	0.57 (0.20–1.60)	.282	1.25 (0.37–4.19)	.715	0.85 (0.61–1.37)	.623	1.48 (0.78–2.83)	.233	0.65 (0.23–1.82)	.409
SCT (yes)	2.19 (1.40–3.44)	.001*	0.66 (0.23–1.85)	.427	7.86 (0.98–63.03)	.052	1.48 (0.92–2.14)	.145	0.70 (0.38–1.32)	.273	0.25 (0.07–0.90)	.033*
SCT (below 1 y)	1.12 (0.58–1.97)	.284	1.65 (0.59–4.66)	.340	1.26 (0.38–4.25)	.705	1.04 (0.27–4.02)	.812				
Heavy chain												
No	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
A, D, G, E, M	0.77 (0.46–1.30)	.336	1.66 (0.44–6.22)	.454	0.63 (0.18–2.28)	.485	0.78 (0.47–1.31)	.567	1.67 (0.72–3.89)	.236	1.14 (0.31–4.13)	.846
Light chain												
lambda	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
kappa	0.85 (0.55–1.33)	.474	1.60 (0.55–4.65)	.388	1.16 (0.35–3.89)	.807	0.98 (0.94–1.22)	.782	0.78 (0.42–1.44)	.423	1.11 (0.39–3.18)	.849
ISS stage		.791		.513		.256		.475		.134		.738
Grade 1	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
Grade 2	1.14 (0.60–2.15)	.691	1.12 (0.57–2.04)	.574	0.41 (0.05–3.13)	.390	1.11 (0.46–1.98)	.245	0.61 (0.28–1.33)	.209	1.11 (0.28–4.45)	.880
Grade 3	1.24 (0.67–2.31)	.499	1.13 (0.58–2.07)	.582	1.57 (0.30–8.09)	.593	1.12 (0.57–2.17)	.372	0.44 (0.20–0.98)	.045	0.70 (0.16–3.03)	.637
β2-MG (<5.5)	1.59 (1.01–2.49)	.051	1.07 (0.37–3.13)	.899	0.37 (0.11–1.25)	.111	0.86 (0.53–1.27)	.247	1.96 (1.00–3.81)	.059	0.90 (0.32–2.53)	.836
Albumin (<3.5)	1.08 (0.70–1.69)	.725	1.48 (0.51–4.30)	.472	0.51 (0.15–1.71)	.276	1.42 (1.13–1.74)	.578	1.30 (0.69–2.44)	.422	0.92 (0.33–2.59)	.871

	GVHD of the skin		Drug-induced skin reaction		Benign tumor		Malignant tumor		Eczematous disorder		Other inflammatory skin disorders	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age	0.96 (0.93–0.99)	.023*	0.97 (0.94–0.99)	.042*	1.02 (0.99–1.05)	.243	0.99 (0.96–1.04)	.787	1.01 (0.99–1.04)	.309	1.01 (0.98–1.03)	.742
Sex (male)	1.31 (0.58–2.94)	.520	1.66 (0.88–3.14)	.120	1.10 (0.50–2.45)	.810	1.08 (0.40–2.90)	.881	1.28 (0.72–2.28)	.400	1.15 (0.59–2.24)	.690
SCT (yes)	9.56 (2.82–32.36)	<.001*	0.83 (0.45–1.52)	.549	0.50 (0.22–1.14)	.098	0.56 (0.20–1.54)	.257	1.06 (0.60–1.85)	.851	0.75 (0.39–1.46)	.393
SCT (below 1 y)	5.49 (0.55–54.46)	.146	1.65 (0.59–4.66)	.340	1.36 (0.28–4.48)	.705	1.26 (0.38–4.25)	.945				
Heavy chain									1.0 (Reference)		1.0 (Reference)	
no	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.43 (0.69–2.98)	.338	1.15 (0.51–2.60)	.742
A, D, G, E, M	0.77 (0.46–1.30)	.146	0.34 (0.18–0.64)	.001*	0.99 (0.38–2.54)	0.980	4.74 (0.62–36.30)	.134				
Light chain									1.0 (Reference)		1.0 (Reference)	
Lambda	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.05 (0.59–1.86)	.867	0.79 (0.41–1.53)	.487
Kappa	0.85 (0.55–1.33)	.070	2.55 (1.28–5.08)	.008*	1.82 (0.78–4.28)	0.168	0.64 (0.24–1.70)	.370		.273		.419
ISS stage		.586		.188		0.316		.435	1.0 (Reference)		1.0 (Reference)	
Grade 1	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)		0.60 (0.29–1.27)	.182	0.73 (0.31–1.71)	.464
Grade 2	1.98 (0.54–7.29)	.302	1.82 (0.64–5.13)	.260	2.35 (0.65–8.49)	.192	0.46 (0.11–1.90)	.282	0.56 (0.27–1.17)	.126	0.56 (0.23–1.33)	.189
Grade 3	1.77 (0.48–6.50)	.389	2.48 (0.91–6.77)	.077	1.46 (0.39–5.47)	.579	0.96 (0.29–3.24)	.947	1.05 (0.59–1.85)	.872	0.68 (0.35–1.32)	.256
β2-MG (<5.5)	0.84 (0.38–1.84)	.657	0.66 (0.36–1.20)	.174	2.39 (0.98–5.81)	.054	1.47 (0.53–4.07)	.458	1.66 (0.92–2.99)	.091	1.39 (0.71–2.74)	.337
Albumin (<3.5)	0.53 (0.24–1.17)	.117	1.32 (0.71–2.45)	.375	0.86 (0.39–1.88)	.702	1.51 (0.65–2.71)	.049*	1.30 (0.69–2.44)	.422	0.92 (0.33–2.59)	.871

β2-MG = β2-microglobulin, GVHD = graft-versus-host disease, ISS = international scoring stage, SCT = stem cell transplantation.
The asterisks indicate a statistically significant difference with a *P* value of less than .05.

common, manifested by pruritic maculopapular erythema covering less than 25% of the body surface area, followed by grade 2 and 3. Acute GVHD of the skin frequently occurred after 10 days of the transplant (Table 5). Among patients with chronic GVHD of the skin, 5 of 7 patients (71.43%) had a history of receiving prior SCT. In addition, 2 patients exhibited the sclerotic type of chronic GVHD of the skin, while others exhibited the nonsclerotic type. Treatment with SCT is associated with an increased risk of GVHD of the skin (OR, 9.56; 95% CI, 2.82–32.36). In addition, the age at MM diagnosis was associated with a decreased risk of GVHD of the skin (OR, 0.96; 95% CI, 0.93–0.99).

3.5.3. Drug-induced skin reactions in patients with MM. Among 49 patients with drug-induced skin reactions, maculopapular rash was the most commonly observed type of drug eruptions followed by acneiform eruption (n = 31), exfoliative dermatitis (n = 5), and leukocytoclastic vasculitis (n = 3). The

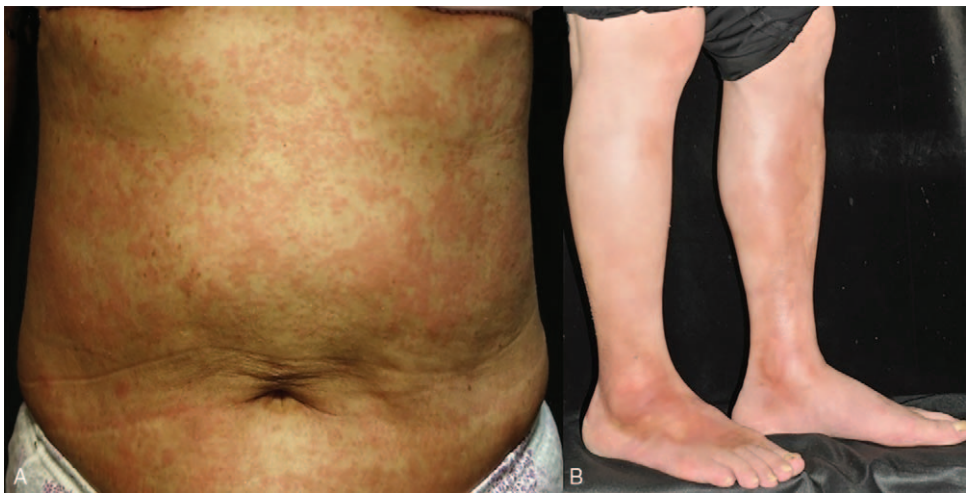

Figure 2. Skin manifestations of the GVHD of the skin. (A) Acute GVHD of the skin. (B) Chronic GVHD of the skin.

Table 5

Distribution of the patients with GVHD of the skin according to the clinical stage and days after transplant.

	Days after transplant				
	<10	10–50	50–100	>100	Total
Acute GVHD					
Stage 1	1	2	5	0	8
Stage 2	0	5	2	0	7
Stage 3	1	2	2	0	5
Stage 4	0	0	0	0	0
Chronic GVHD	0	0	1	6	7
Total	2	9	10	6	27

GVHD = graft-versus-host disease.

most common inducible drug was thalidomide (17 patients, 34.69%), followed by bortezomib (13 patients, 26.53%), possibility of multidrug (5 patients, 10.20%), and lenalidomide (4 patients, 8.16%). In addition, cases of pamidronate, ciprofloxacin, oxycodone/naloxone, and steroid-induced skin disorders were also observed. Among them, Stevens–Johnson syndrome (SJS) was observed in patients treated with bortezomib and thalidomide, respectively. Developments of toxic epidermal necrolysis (TEN) were observed in patients treated with allopurinol and thalidomide, respectively.

The decreased risks of development of drug-induced skin reactions in patients with MM were associated with the age of MM diagnosis (OR, 0.97; 95% CI, 0.94–0.99) and heavy chain disease (OR, 0.34; 95% CI, 0.18–0.64). The kappa light chain disease was associated with an increased risk of drug-induced skin reactions in patients with MM (OR, 1.82; 95% CI, 0.78–4.28).

3.5.4. Benign and malignant tumors in patients with MM. Among benign tumors, epidermal cyst (n = 10) was the most common type, followed by seborrheic keratosis (n = 9), lipoma (n = 5), capillary hemangioma (n = 3), xanthelasma (n = 1), lentigine (n = 1), corn (n = 1), xanthogranuloma (n = 1), dermatofibroma (n = 1), poroma (n = 1), soft fibroma (n = 1), and chondroid syringoma (n = 1). Interestingly, 4 of 9 patients with seborrheic keratosis showed the Leser–Trélat sign. Cutaneous plasmacytoma (n = 16) was the most common malignant tumor, followed by basal cell carcinoma (BCC) (n = 1). The lower serum albumin level was associated with an increased risk of malignant tumor in patients with MM (OR, 1.51; 95% CI, 0.65–2.71).

3.5.5. Other inflammatory skin disorders in patients with MM. Pruritic dermatosis was observed in 24 patients with MM. Prurigo was found in 13 patients followed by prurigo simplex (n = 8) and prurigo nodularis (n = 3). Urticarial eruption was observed in 12 patients with MM. Rosacea (n = 3) was the most commonly observed chronic inflammatory skin disorders, followed by psoriasis (n = 2; Fig. 3). The development of erythema nodosum, generalized perforating granuloma annulare, and erythema elevatum diutinum was observed in each patient.

4. Discussion

Of the cutaneous comorbidities observed in patients with MM, infectious cutaneous disorders were the most common. Among them, prevalance of herpes zoster was the highest among several cutaneous comorbidities. Moreover, development of herpes zoster was found to be a possible candidate for good prognostic factor for OS in MM. As it was also found in this study that the treatment with SCT is associated with an increased risk of herpes zoster, and the treatment with SCT is associated with increased OS in MM patients,[7] it is suspected that the therapeutic effect of SCT is related with the finding from this study that occurrence of herpes zoster can be a candidate for good prognostic factor for OS in MM. In addition to herpes zoster, dermatophyte infection, herpes simplex infection, and viral wart were also commonly encountered infectious cutaneous disorders in Korean patients with MM. Although a detailed statistical analysis regarding the immunocompromised host status and development of cutaneous infections was not performed, the immune status of the host can be a possible risk factor for the development of cutaneous infection in oncologic patients.[8] Therefore, further research to investigate the possible relationship between immunocompromised host status and localized cutaneous infection must be performed in the future.

In this study, a total of 541 patients (37.62%) with MM underwent SCT. Among them, 27 (4.99%) developed GVHD of the skin. Although GVHD has been known as a major complication of SCT that affects the OS in patients treated with SCT,[9] development of GVHD of the skin did not affect the OS in our patient group. In addition, the age of MM diagnosis was found to be a protective factor for development of GVHD of the skin in this study. The fact that SCT is generally performed in a young age group may explain this observation.[10]

Among various inflammatory skin rash, the diagnosis of cutaneous drug-induced skin reactions can be considered only after precise characterization of the type of eruption. Although various presentations of cutaneous drug-induced skin reactions do exist, the morphology of vast majority of cutaneous drug-induced skin reactions in patients with MM is maculopapular, followed by acneiform. In addition, the time of onset of cutaneous drug-induced skin reactions might occur within a few weeks to 3 months following the initiation of potential causative agents. In the case of thalidomide, most patients developed their drug-induced skin reactions within first month of the initiation of thalidomide.[11] Moreover, the peripheral eosinophilia and eosinophilic infiltration from skin biopsy can help to differentiate drug-induced skin reactions from other inflammatory skin rash of MM. Among various medications, thalidomide was found to be the most common causative drug for cutaneous drug eruption in patients with MM, and severe drug eruption including SJS and TEN after using thalidomide was also observed in our study. Paradoxically, thalidomide has long been used to treat TEN due to its immunomodulatory and anti-inflammatory properties. These findings are consistent with the previous report from Hall et al.[11] Therefore, careful caution should be paid when treating with thalidomide in patients with MM.

In this study, it was found that development of cutaneous malignant tumor was associated with the decreased OS. The cutaneous plasmacytoma and BCC were the only observed malignant tumors in our patient group. Bayer-Garner and Smoller[3] reported a total of 17 cases of BCC in patients with MM. They explained that the increased incidence of BCC in these patients group might be due to the immunocompromised state of the MM patient. However, the prevalence of BCC was found to be relatively low in our study. As the ethnic differences in the prevalence of BCC do exist due to the photoprotective nature of melanin,[12] it is believed that this could be in part explain the relatively low incidence of BCC in our MM patient group. However, the prevalence of cutaneous plasmacytoma (1.11%) was similar when compared with a previous study.[13]

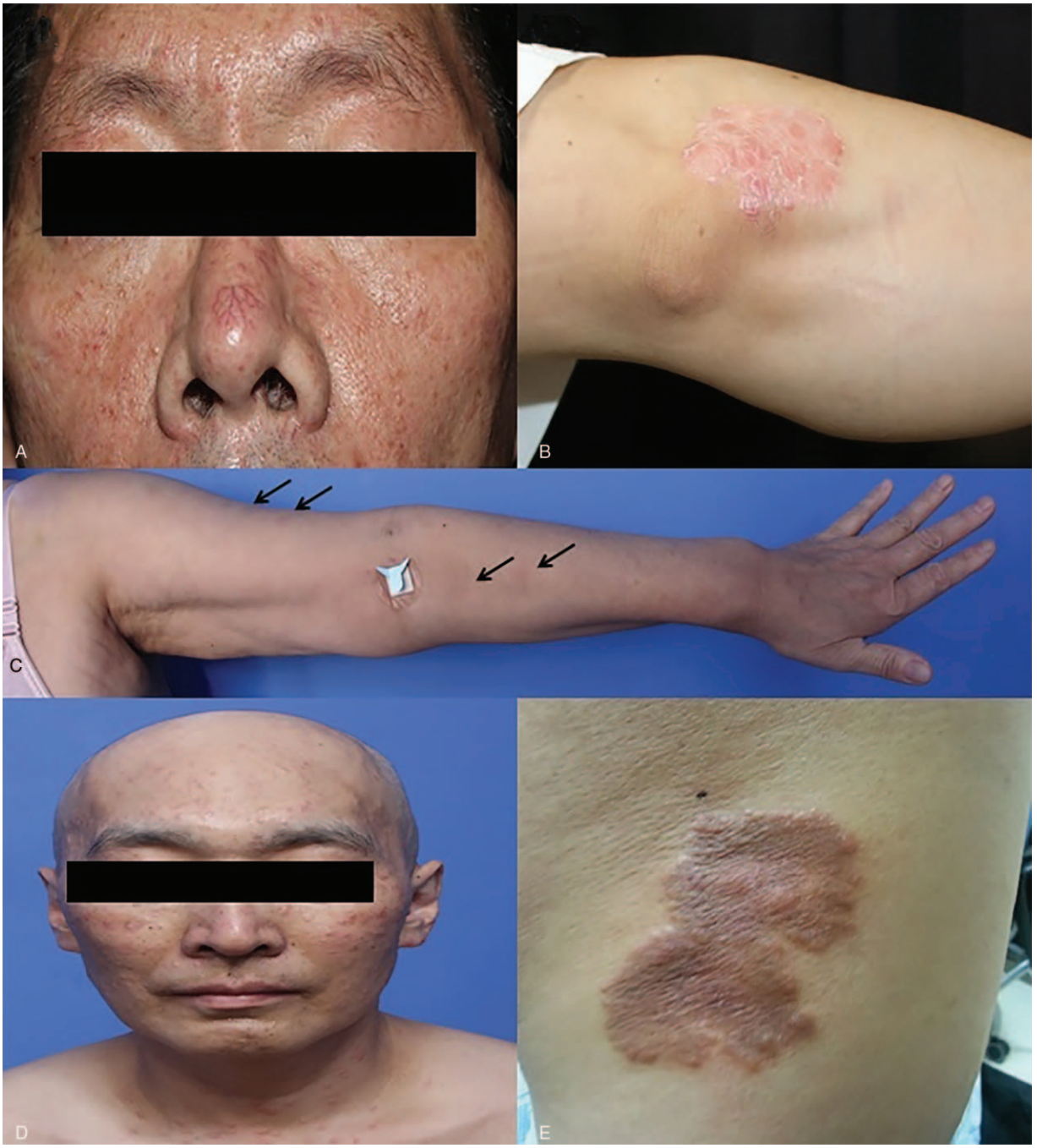

Figure 3. Clinical photographs of chronic inflammatory skin disorders in patients with MM including (A) rosacea, (B) psoriasis, (C) erythema nodosum, (D) generalized perforating granuloma annulare, and (E) erythema elevatum diutinum.

In general, the cutaneous manifestations of MM can be divided into specific and nonspecific lesions.[14] The specific cutaneous manifestations relate to the lesion that are histopathologically distinct for malignant plasma cell infiltration. With regards to the specific cutaneous manifestations of MM, cutaneous plasmacytoma was the only observed cutaneous comorbidity in Korean patients with MM, which is consistent with the previous reports.[13] Moreover, it was found that the development of specific cutaneous manifestation was associated with the decreased OS. Regarding the nonspecific cutaneous manifestations of MM, the nonspecific manifestations of MM due to deposition of abnormal protein can be observed as amyloidosis and cryoglobulinemia.[4] However, the developments of amyloidosis and cryoglobulinemia were not found in our patient group. The other nonspecific cutaneous manifestations of MM, which are considered paraneoplastic, have been described from the previous literature as following: xanthomas, scleredema, pyoderma gangrenosum, leukocytoclastic vasculitis, erythema elevatum diutinum, Sweet syndrome, and subcorneal pustular dermatosis.[14–18] Among them, xathoma, erythema elevatum diutinum, and Sweet syndrome were also observed in our patient group. Two cases of Sweet syndrome were also found in our

patient group. Although the exact pathogenesis for development of Sweet syndrome in patients with MM must be further elucidated, Bayer-Garner et al[18] suggested that it may be due to the secondary effect of increased levels of granulocyte colony stimulating factor in a patient with MM.

With regards to the inflammatory skin disorders, simultaneous occurrence of psoriasis and MM was observed in 2 patients. Although there has been 1 case report describing the remission of psoriasis in patients with MM after SCT,[19] all 2 patients included in our study did not show the complete remission of psoriasis even after the SCT. Therefore, further large-scaled study is needed to further examine this relation. Although rarely observed in our patient group, the development of rosacea and generalized granuloma annulare in patients with MM has not been reported in the previous literature. Interestingly, rosacea was observed in 3 patients with MM in the present study. Among 4 subtypes of rosacea, all patients exhibited the erythematotelangiectatic type. Although further studies are needed to confirm this association, it is suspected that the hyperviscosity in MM may disturb the microcirculation of blood vessel and affect the development of rosacea in a susceptible patient.[20] It is supposed that the possible relationship between various cutaneous comorbidities and MM should be always considered in order to identify still unraveled nonspecific cutaneous comorbidities in patients with MM.

This study has 2 potential limitations: First, due to its retrospective design, our data may underestimate the degree of the actual prevalence of some cutaneous comorbidities in patients with MM. Second, only 1 variable was adjusted in subgroup analyses because of the rule of ten. Therefore, a further large-scaled prospective study is needed.

In conclusion, the present retrospective cohort study revealed that infectious cutaneous disorder was found to be the most common cutaneous comorbidity in Korean patients with MM. The prevalence of herpes zoster infection was the highest among various infectious cutaneous disorders. In addition, the occurrence of herpes zoster was found to be a possible candidate for good prognostic factor, whereas malignant tumor was identified as a possible candidate for poor prognostic factor in patients with MM. Factors that may influence the prevalence of specific cutaneous comorbidities are as follows: increased risk of herpes zoster was observed in patients with younger age and treated with SCT; increased risk of drug-induced skin disorders was observed in patients with kappa light chain disease; decreased risk of drug-induced skin disorders was observed in patients with older age and heavy chain disease; increased risk of malignant tumor was found in patients with low serum albumin level; and decreased risk of viral warts was observed in patients treated with SCT.

It is suggested that the findings from the present study may provide insight into the medical impact of cutaneous comorbidities in patients with MM. In fact, the occurrence of some cutaneous comorbidities in MM is associated with the pathogenetic and prognostic importance in patients with MM. Therefore, a better understanding of the prevalence, clinical characteristics, and risk factors of various cutaneous comorbidities in patients with MM may enhance awareness of the disease and provide proper management for patients with MM.

Author contributions

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Writing - original draft: Yu Ri Woo.
Writing - review & editing: Chang-Ki Min, Dong-Wook Kim, Hyun Jeong Park.

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