Current Trends in Immunology
Vol. 23, 2022

Mini-Review

Cutaneous presentations associated with multiple myeloma: a brief overview

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ABSTRACT

To the best of our knowledge, published literature describing different cutaneous manifestations in patients with multiple myeloma (MM) is limited. Skin conditions, which appear as a rare extramedullary finding, generally occur in approximately 1% of the patients with relapsed or progressive MM. Therefore, cutaneous manifestations accompanying MM indicate a poor prognosis, with significantly reduced overall survival and progression-free survival rates. However, although rare, they may also present as the first manifestation of MM. Nevertheless, cutaneous findings in MM patients are probably overlooked and unrecognized because of their different clinical and histological presentations. Both the rarity of specific cutaneous involvement and occurrence of many distinct nonspecific dermatoses in MM, create a difficulty for dermatologists to suspect MM and in diagnosing MM-related skin lesions. Therefore, increasing recognition of these rare specific and nonspecific cutaneous manifestations of MM is important for accurate and urgent management.

KEYWORDS: multiple myeloma, hematologic malignancy, extramedullary involvement, cutaneous manifestations.

1. Introduction

Multiple myeloma (MM) is a rare malignancy that accounts for about 1-2% of all cancers and just over 18% of hematological malignancies [1, 2]. Its incidence is approximately 5 per 100,000 per year and has tended to increase in recent years due to the overall ageing of the population [3, 4]. It mostly affects older people of both sexes, with 90% of cases occurring in patients over 50 years of age. The incidence progressively increases with age and the median age at diagnosis of patients is 70 years, but it can be seen in younger patients as well [3-6].

This malignant hematologic disorder is a plasma cell dyscrasia characterized by abnormal increase of monoclonal immunoglobulins. The atypical immature monoclonal plasma cells proliferate abnormally mainly confined in the bone marrow and can cause prominent skeletal destruction. Otherwise, MM can also manifest as an extramedullary disease in which clonal plasma cells infiltrate at anatomic cites distant from the bone marrow, especially in advanced disease [2-4].

Signs and symptoms of MM tend to be variable and nonspecific. In the vast majority of cases, the common clinical presentations of MM are represented by the acronym CRAB symptoms (hyper*c*alcemia, *r*enal insufficiency, *a*nemia, and *b*one lesions). However, a variety of other clinical manifestations may also be observed in a significant proportion of patients with MM [7, 8]. In a study by Talamo *et al*. evaluating the existing symptoms that lead to the diagnosis of MM, it was shown that 20% of the patients had non-CRAB and 6% had both CRAB and non-CRAB clinical features. The authors grouped MM-related

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symptoms into a total of 14 categories, 4 CRAB and 10 non-CRAB manifestations (in decreasing order of frequency, neuropathy, extramedullary involvement, hyperviscosity syndrome, amyloidosis, bleeding/coagulopathy, systemic symptoms, primary plasma cell leukemia, infections, cryoglobulinemia, secondary gout). Taken together, it has been suggested that non-CRAB symptoms do not adversely affect the prognosis in MM [7].

To the best of our knowledge, limited medical literature with just only a few case series and case reports have exhaustively discussed cutaneous manifestations in MM. In this article, certain specific and nonspecific cutaneous findings associated with overt MM are overviewed.

2. Classification of cutaneous manifestations in multiple myeloma

It is estimated that extramedullary involvement in MM may be present in approximately 4% of cases and only less than 1-2% of cases demonstrate cutaneous involvement [9]. Owing to the fact that pathophysiologic mechanisms are not yet fully elucidated in detail, there is a paucity of knowledge in cutaneous manifestations of MM. When evaluating the literature to define the main characteristics of cutaneous involvement in MM, it has been identified that this rare finding occurs most commonly in males in the age range of 30 and 80 years with IgG and IgA MM [4, 10]. The median time from diagnosis to skin involvement is approximately 2.2 years. In addition, the median overall survival of patients with MM from the time of skin involvement has ranged from 8 to 9 months in previous studies [4, 11, 12].

Cutaneous involvement in MM is most commonly seen as a direct spread of the disease from an adjacent neoplastic lesion or, less frequently, may result from lymphatic or hematological metastatic extension [5, 8]. Cutaneous metastasis in MM without underlying bone tumors is very rare [2]. Various cutaneous findings that may be present during the course of MM due to the disease process itself and/or treatment have been described in the literature [8, 9]. Most authors have mentioned that this variable spectrum of skin diseases can be classified as specific or non-specific manifestations and categorized into three types: A) direct infiltration of the skin by malignant plasma cells (plasmacytomas); B) cutaneous findings owing to the abnormal level of proteins that the malignant plasma cells produce (amyloidosis, cryoglobulinemia); and C) paraneoplastic processes (e.g., scleredema, scleromyxedema, necrobiotic xanthogranuloma, Sweet's syndrome, pyoderma gangrenosum, small-vessel vasculitis, erythema elevatum diutinum, neutrophilic dermatosis, subcorneal pustular dermatosis, normolipemic plane xanthomas) [10-13].

A) Specific cutaneous involvement in MM (secondary extramedullary plasmacytoma)

Specific dermatologic manifestations associated with MM are very uncommon and include extramedullary plasmacytomas or cutaneous infiltration by MM as direct extension from underlying osteolytic bone tumors. This rare manifestation is observed as cutaneous or subcutaneous waxy, dome-shaped, usually erythematous or violaceous, occasionally skin-colored papules, nodules or plaques with variable sizes from 1 to 5 cm in diameter [3-5]. It usually affects the trunk, extremities, and less frequently, scalp, face and neck. Although cutaneous MM may present at any time or in any stage of the disease, specific skin lesions usually appear in the advanced stages of MM as a sign of high tumor burden with a life expectancy of less than one year after diagnosis [3, 8]. It mostly occurs in patients with known MM and is associated with disease relapse or progression. Remarkably, although it rarely occurs, it can be observed at an early stage or even be the first manifestation of the disease, especially in the aggressive forms of myeloma [8, 14]. Therefore, cutaneous involvement in MM has been generally attributed as an indicator of poor prognosis. Since most of the patients have extensive plasmacytic infiltration of more than one organ at autopsy, the opinion that cutaneous involvement reflects an aggressive biology is getting stronger. Despite aggressive novel treatments, including stem cell transplantation, the clinical course is progressive in most patients. Indeed, skin lesions may partially respond to systemic chemotherapy of the underlying MM as well as local radiation therapy and dermatologist-prescribed treatments for symptomatic relief. However, many treatments including new agents and stem cell transplantation, have shown only transient activity in MM patients with skin involvement [2].

Although the mechanisms that contribute to extramedullary spread of clonal plasma cells are not fully understood, changes in the expression of adhesion molecules such as CD44, VLA-4, CD54 and CD56 by MM cells during the course of the disease may be the possible causes [15]. It has been suggested that the skin-homing of MM cells may be associated with high C-C motif chemokine receptor 10 expression at the time of diagnosis with a lack of surface expression of C-X-C chemokine receptor type 4 along disease progression. In addition, increased expression of CD44, decrease of intercellular adhesion molecule-1/CD54 and the lack of expression of CD56 by MM cells in the progressive disease can be the mechanisms that drive the escape of plasma cells from bone marrow to the skin [2, 15]. Interestingly, there have been rare cases with secondary extramedullary plasmacytoma involving surgical sites such as pacemaker implantation, venous catheter insertion or fracture sites. Although the mechanism of these formations at trauma sites is not fully understood, the direct spreading of clonal plasma cells from surgical area may be the possible one. It is thought that trauma to skin or subcutaneous tissue will result in higher levels of local strong immune cell attractant called stroma cell-derived factor-1, which is a ligand for C-X-C chemokine receptor type 4. As a consequence, local inflammatory mediators released after surgery may contribute to the clonal expansion of the plasma cell population [16, 17].

In the literature review of MM with skin involvement, it has been shown that IgG is the most commonly involved, followed by IgA, free light chains, IgD, IgM and more less frequently, some rare types of monoclonal heavy chains [12]. Kois *et al*. reported that cutaneous involvement is more likely in patients with IgA monoclonal immunoglobulin; however, other authors showed that IgD monoclonal immunoglobulin is related with the development of metastatic plasmacytomas [6, 12, 18]. Requena *et al*. demonstrated that those with light chain disease alone and cutaneous involvement of IgD subtype manifest a more aggressive course [10].

Histopathologically, the neoplastic infiltrate consisting of immature plasmablasts with atypical features in cutaneous MM may show two different patterns as nodular (more common) and diffuse interstitial. Amyloid deposits may also be detected. Immunohistochemically, tumor cells stain positive for CD79a, CD138 and EMA, and negative for CD19 and CD20. In some cases of secondary plasmacytoma, CD43 and CD56 may be abnormally positive [5, 19]. Interestingly, heterotopic expression of T-cell markers CD3 and CD4 has been described for plasmablastic MM [14]. Thus, correlation between the immunoglobulin profile of cells in cutaneous lesions and serum immunoelectrophoresis studies is necessary for diagnostic confirmation [4, 10]. Although clinicopathological correlation is helpful to distinguish cutaneous MM from other malignant and reactive plasma cell-rich infiltrates, correct diagnosis can be challenging due to variable morphologic appearances (plasmacytic, plasmablastic, and lymphoplasmacytic variants) of MM cutaneous involvement [14, 17]. Furthermore, other inflammatory and various infectious conditions which exhibit dense plasma cell infiltrates (e.g., syphilis, Borrelia, atypical mycobacteria, deep fungal infections) must also be excluded [3, 4].

B) Cutaneous findings related to the abnormal level of proteins that the malignant plasma cells produce (e.g., *amyloidosis, cryoglobulinemia*)

Amyloidosis*:* Systemic light chain (AL) amyloidosis is a rare but serious comorbidity of MM. It occurs in 5-10% of cases and predominantly affects the kidney, heart, liver, peripheral nerves, and gastrointestinal system. The kappa free light chain subtype was found to be slightly more common in patients with MM-related cutaneous AL amyloidosis. Clinically, its skin manifestations are heterogeneous and may present with specific and nonspecific lesions. It is typically characterized by cutaneous manifestations including petechia and haemorrhages (periorbital bruising called Racoon sign), and macroglossia [20-22]. In a brief review of 32 patients by Andrei *et al*., bullous lesions were identified in 56% of patients, purpura/ecchymosis in 25%, and skin papules/nodules in 15% [20]. On the other hand, blistering skin lesions mimicking bullous pemphigoid or IgG-pemphigus foliaceus are considered as rare according to some reports illustrating the exhaustive and variable spectrum of dermatologic manifestations of MM-associated amyloidosis [21-24]. In a previous study, Rubinow and Cohen defined the histopathological features of skin specimens in a

group of 38 patients with primary and MM-related amyloidosis. The authors found that histological features were similar in both primary and MM-related amyloidosis, regardless of clinically affected or unaffected skin [25].

To our knowledge, only a small number of studies are available on the outcomes of AL amyloidosis with cutaneous involvement, which can be observed in 25% of MM cases [20, 22]. Andrei *et al*. suggested that AL amyloidosis-associated MM with cutaneous involvement has a worse prognosis and that histopathological dermal involvement may reflect extensive organ involvement [20].

Cryoglobulinemia: Crystalglobulinemia, a rare form of type I cryoglobulinemia, is characterized by the deposition of serum paraproteinemic immunoglobulins and crystallized paraproteins in the vasculature causing systemic occlusive vasculopathy. This condition requiring urgent intervention is generally associated with significant morbidity and mortality, with survival ranging from a few weeks to a year from the time of diagnosis. Due to microvascular occlusion, thrombosis and ischemia, it may be presented with multiple organ disorders including skin manifestations particularly in areas of relative stasis or cooling (e.g., livedo reticularis, acrocyanosis, cold urticaria, palpable/ nonpalpable petechiae/purpura, ecchymoses, necrosis and/or tender noninflammatory necrotic ulcers), and also kidney impairment, polyarthropathy, peripheral neuropathy and gastrointestinal ulcerations [26-31]. In a unique patient with cryocrystalglobulinemia, Wee *et al*. identified cryocrystalglobulins in the stratum corneum and epidermis, indicating transepidermal elimination of the crystals as a new finding. They mentioned that excessive proteolysis of interstitial collagen by upregulated transforming-growth factor-b3 and increased matrix metalloproteinases activity in MM facilitates this condition. Some structural aberrations such as non-fucosylated oligosaccharides and abnormal N-glycosylation of IgG crystal globulins causing protein misfolding and insoluble crystals as well as the cryo-precipitated arrays are a starting point for additional crystallization and result in greater thrombogenesis [31]. Interestingly, rare patients with MM-associated cryoglobulinemia may manifest with both thrombotic microangiopathy and leukocytoclastic vasculitis [32].

C) Particular paraneoplastic processes

Follicular hyperkeratotic spicules: One of the most common cutaneous manifestations of MM is multiple cutaneous follicular hyperkeratotic spicules. It is a very typical paraneoplastic sign of MM observed mostly in white male patients. These follicular spicules appear as hyperkeratotic horns in the follicular openings especially over the nose, forehead, face, and scalp. The horny follicular yellow spicules are firm on palpation and appear as "stuck-on" to the skin. They can usually be easily removed without any pain or bleeding, or topical keratolytics (such as retinoids, urea, salicylic acid) can be applied. Although a new onset of cutaneous hyperkeratotic spicules could be the initial presentation of MM, it must be considered as a possible sign of disease progression or relapse in advanced stage of myeloma [33-37]. Various hypotheses exist in the pathogenesis of spicule formation, such as a possible change in normal keratinization caused by the underlying hematological malignancy and/or autoantibody activity in monoclonal immunoglobulin that alters the keratinization process. In several of the reported cases, it has been shown that these follicular spicules contained cryoglobulins and monoclonal myeloma dysprotein identical to the serum protein precipitating into the follicular infundibulum [36, 37].

Necrobiotic xanthogranuloma: This non-Langerhans cell histiocytosis is a chronic and slowly progressive cutaneous finding rarely associated with MM. Hematologic malignancy usually occurs years after the onset of necrobiotic xanthogranuloma. It usually appears as yellowish orange-red, soft, partially ulcerated plaques with telangiectasia, primarily involving the infraorbital area. It may also affect the eyes, gastrointestinal and respiratory tracts. Immunosuppresive treatment of necrobiotic xanthogranuloma-associated MM does not always lead to cutaneous healing [38].

Small-vessel vasculitis: The development of small-vessel vasculitis in some patients with MM has been more frequently linked to cryoglobulinemia, infections and drugs. Although the occurrence of paraneoplastic vasculitis in the course of MM is uncommon, it has been reported that it can also be seen in progressive MM [39-41]. IL-6 levels were found to be high in the serum of patients with MM, possibly as a result of their increased expression

by bone marrow stromal cells and bone cells. The association between small-vessel vasculitis and MM could be attributed to elevated IL-6 levels, which contribute to increased neutrophil efflux and induce synthesis and production of surface endothelial adhesion molecules [39].

Pyoderma gangrenosum: It has been mentioned that ulcerative pyoderma gangrenosum is most commonly associated with IgA monoclonal gammopathy. IgA paraprotein may play a role in the pathogenesis of pyoderma gangrenosum by impairing neutrophil chemotaxis, reducing leukocyte chemotaxis and delaying leukocyte migration [42].

Diffuse plane normolipemic xanthomatosis: This uncommon cutaneous entity seen together with MM manifests clinically as yellow to orange colored, mostly asymptomatic patches and plaques symmetrically distributed over the face, neck and upper trunk. It has been shown that in almost all cases of MM-associated normolipemic xanthomatosis, hematological dyscrasias are discovered only after the appearance of cutaneous findings. When a hematological condition is responsible for the formation of xanthomatous lesions, a diffuse cutaneous involvement and low C4 and C1 inhibitory serum levels are generally observed. It has been suggested that monoclonal IgG-induced immune complexes directed against low-density lipoproteins leading to lipid accumulation in the skin and subsequently phagocytosis by macrophages play a role in the pathogenesis of this entity [43].

3. Other cutaneous comorbidities associated with MM

Besides the rarity of cutaneous involvement in MM, the reported skin conditions have been variable and relatively nonspecific as mentioned above. Nonspecific lesions may be noticed by a dermatologist as the first manifestation of MM, thus facilitating early diagnosis and prompt treatment. In some cases reported in the literature, it has been observed that both specific and nonspecific cutaneous presentations may occur simultaneously. These associations are sometimes considered incidental or certain hypotheses that have been proposed in connection with the pathogenesis [19, 42]. It can be thought that the exact incidence of cutaneous involvement may be higher than expected, taking into account the autopsy results revealing different extramedullary organ involvements (such as spleen, lymph nodes and liver) in approximately 70% of MM cases. Indeed, this is likely because many physicians are less concerned with cutaneous lesions specifically [42, 44]. It is believed that the cutaneous comorbidities are usually neglected and unrecognized among patients with MM due to their different clinical and histological presentations [45].

In a retrospective study from a Korean population evaluating the cutaneous comorbidities in patients with MM, it was determined that 24.6% of 1438 patients had more than one cutaneous presentation. Among these, infectious cutaneous disorders were seen most frequently, most of which caused herpes zoster infection. It has been mentioned that herpes zoster, which was mostly observed in MM patients who were younger and had undergone stem cell transplantation, is a good prognostic indicator, while the presence of malignant skin tumor is a bad prognostic indicator. Patients with cutaneous comorbidities were significantly younger and received more treatment with stem cell transplantation than those without any skin condition, but no difference was detected in terms of gender, heavy chain disease, light chain disease, serum b2-microglobulin and serum albumin levels. Overall survival was comparable between the patients with and without cutaneous comorbidities. The presence or absence of a non-specific skin lesion did not affect the overall survival rate, while the presence of a specific skin lesion reduced it [45]. On the other hand, Woo *et al*. mentioned that as a result of retrospective study evaluating 1228 patients with MM (1.14% with skin lesions), cutaneous involvement characterized by erythematous nodule, multiple lesions and histopathological absence of a grenz zone, significantly reduced overall survival [12].

Actually, due to the chronic nature of disease and cumulative toxicities of numerous treatment combinations (e.g., conventional chemotherapy drugs, corticosteroids, immunomodulating agents, interferon, monoclonal antibodies, proteasome inhibitors, histone deacetylase inhibitors, and stem cell transplants), the appearance of a number of cutaneous manifestations associated with MM treatments can be expected [45, 46]. Maculopapular rash has been most commonly observed as

drug-induced skin reactions (mostly associated with thalidomide, bortezomib or multidrug treatments) in patients with MM, followed by acneiform eruption, exfoliative dermatitis, leukocytoclastic vasculitis, Stevens–Johnson syndrome and toxic epidermal necrolysis. It has been demonstrated that the risk of drug-induced skin reactions were less related with heavy chain disease and the age of diagnosis of MM, while it was more frequently associated with kappa light chain disease [45].

In literature, several treatment-related disorders with MM have been reported as the sequelae of immunosuppression (e.g., infections, neoplasms) as well as the sequelae of bone marrow transplant (e.g., graft-versus-host-disease, drug eruptions, thrombocytopenic lesions). It is unknown whether circulating monoclonal immunoglobulins, cytokines, or other unidentifiable factors released from the malignant plasma cell clones play a role in inducing these cutaneous lesions [13]. In a study by Bayer-Garner and Smoller in which 2357 pathology reports were analyzed to find patients who had skin biopsy, it was found that 284 patients with MM yielded 472 skin biopsy specimens (mean of 1.7/patient). The skin samples taken within the first two months after transplant most frequently demonstrated sequelae of the transplant, Grover's disease, drug reactions, chemotherapy effect, thrombocytopenic effect, cutaneous eruption of lymphocyte recovery, and Sweet's syndrome. Moreover, other biopsy specimens taken after two months following transplantation demonstrated primarily graft-versus-host disease, drug eruptions, and Sweet's syndrome but also revealed irrelevant conditions (e.g. papulosquamous lesions, infections, neoplastic lesions, nevi, vasculitis, and nonspecific changes) [9].

Secondary primary malignancies have also been described as predictable complications following chemotherapy agents for MM treatment (lenalidomide etc.) [2]. As expected, the occurrence of secondary primary malignancies among cancer patients is not unusual. However, there is scarce data focusing on the association between secondary primary malignancies and MM. Large population-based studies of patients with MM demonstrated an elevated risk for non-melanoma skin cancer but not for melanoma compared to the general population. On the other hand, some studies have shown that the incidence of melanoma increases in certain conditions causing immunosuppression [47-49].

In summary, MM has a wide spectrum of specific and nonspecific dermatological manifestations. Both the rarity of specific cutaneous involvement and presence of mostly nonspecific manifestations in MM pose a challenge for dermatologists to suspect MM in the presence of a skin lesion. Therefore, a high degree of clinical doubt, detailed medical history and histopathological correlation are mandatory for early and accurate diagnosis [2-4]. Interestingly, a few cases of condyloma-like perianal or vulvar lesions in MM-associated nodular cutaneous amyloidosis have been reported [50-52]. Additionally, Martorell *et al*. presented a patient with cutaneous involvement of MM that presented as a single acral lesion mimicking acral-lentiginous melanoma [53]. In another patient with refractory IgG lambda MM and a medical history of lower extremity squamous cell carcinoma, newly developing tumoral lesions were initially thought to be squamous cell carcinoma, but were later evaluated as cutaneous MM with histopathological correlation. Thus, the authors emphasized the importance of simple physical and histopathological examinations, as some familiar lesions can sometimes hide more dangerous situations [19].

4. Conclusion

Although MM has a wide spectrum of presentation with rarely specific cutaneous involvement and mostly nonspecific dermatological manifestations, there is a scarcity of medical literature published to date regarding the subject matter. Cutaneous findings in MM patients are probably overlooked and unrecognized because of their different clinical and histological presentations. Both the rarity of specific cutaneous involvement and presence of many distinct nonspecific dermatoses in MM may result in overlooking the underlying MM. Therefore, clinicians should continue to share unique patient presentations of this entity to raise awareness of cutaneous involvement in MM, to better understand its pathogenesis, and to determine its association with prognostic factors.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

ABBREVIATIONS

MM	: multiple myeloma
CRAB	: hypercalcemia, *r*enal insufficiency, *a*nemia, and *b*one lesions
VLA-4	: very late antigen 4
EMA	: epithelial membrane antigen
AL amyloidosis	: amyloid light chain amyloidosis
C4	: complement 4
C1	: complement 1

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