

# Unusual Multiple Myeloma Cutaneous Manifestation Following Nonmyeloablative Allogeneic Stem Cell Transplantation

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## Introduction

Skin involvement in multiple myeloma (MM) has been described, but is uncommon.<sup>1-4</sup> It usually presents in the form of plasmacytoma or nodular skin lesions that involve a well-demarcated area of the skin. We describe a case of unusual cutaneous involvement in a patient with relapsed MM after nonmyeloablative allogeneic stem cell transplantation (allo-SCT) that presented as a diffuse erythematous rash without any evidence of nodularity. Typically, there is a wide differential diagnosis for such a skin rash in these patients, including graft versus host disease (GVHD), drug reaction, vasculitis, and cellulitis. Thus, our case emphasizes the need to include myeloma in the differential diagnosis of erythematous skin rash.

## Case Report

A 52-year-old white man with known immunoglobulin A (IgA) lambda MM stage IIIA of approximately 1½ years' duration presented with multiple lytic lesions, hypercalcemia, elevated creatinine, and anemia. His  $\beta$ 2-microglobulin was 2.6 mg/L and his cytogenetics/fluorescence in situ hybridization analysis showed normal karyotype with no evidence of chromosome 13q abnormalities. He underwent vincristine, doxorubicin, and dexamethasone (VAD) chemotherapy followed by autologous stem cell transplantation (auto-SCT) within 4 months of diagnosis. He achieved very good partial remission, which lasted approximately 11 months until he relapsed. At this point, he was treated with bortezomib (Velcade, Millennium Pharmaceuticals), doxorubicin,<sup>5</sup>

and 100-mg/day thalidomide (Thalomid, Celgene) without dexamethasone due to his diabetes. In the meanwhile, a matched unrelated donor (MUD) was being identified through the National Marrow Donor Program. Despite a very good initial response to the combination chemotherapy, the patient showed disease progression after 5 cycles and consequently received 1 cycle of hyper-CVAD (cyclophosphamide + VAD) part A, with which he achieved near complete remission. He then proceeded with the planned allogeneic peripheral blood SCT. The nonmyeloablative chemotherapy regimen consisted of antithymocyte globulins, busulfan, and fludarabine.<sup>6</sup> His total transplant cell dose was  $7.04 \times 10^6$  CD34+ cells/kg. The patient's GVHD prophylaxis included FK506 (tacrolimus), and blood levels were kept under 10 ng/mL. His post-transplant course was complicated by acute renal insufficiency, hypertension, and hemorrhagic cystitis. He engrafted his granulocytes (absolute granulocyte count  $>500/\mu\text{L}$ ) on day +17. Donor chimerism was 89% or higher in 3 cell lineages (T and B cells and granulocytes) by single tandem repeats on day +20. At the time of discharge following MUD transplant, he was noted to have mild skin rash of the lower extremities with +2 edema. Over the next 2 weeks, the skin rash became more prominent and confluent and did not resemble a GVHD rash. In addition, a nonpitting +4 edema developed up to the knees and was unresponsive to diuretics. The rash was treated with intravenous vancomycin (for staphylococcal cellulitis) and then oral sulfamethoxazole/trimethoprim (for possible nocardia or other gram-negative bacteria), with no response.

The patient was referred to the dermatology clinic where he was found to have a diffuse, erythematous, nontender, papulovesicular rash on the bilateral lower extremities with some distributed violaceous plaques (Figure 1). He underwent punch biopsies at 2 sites. The

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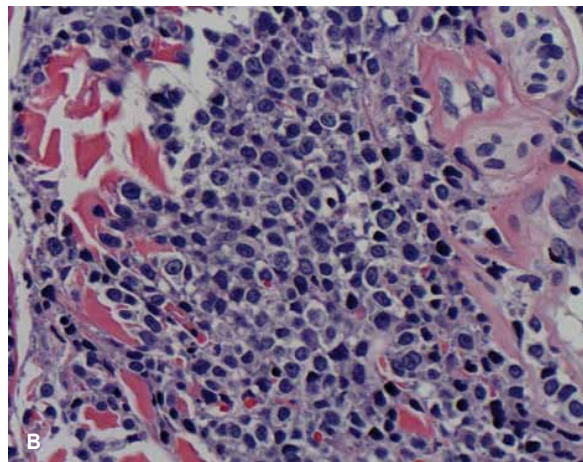
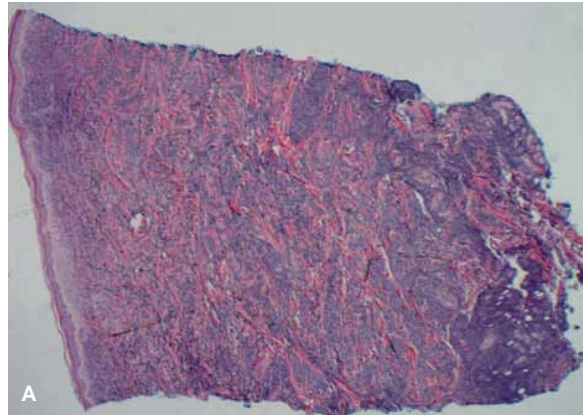


**Figure 1.** Photograph of skin rash on lower extremities. This is approximately a 2-week-old erythematous, nontender, papulovesicular rash on the bilateral lower extremities with some distributed violaceous plaques.

differential diagnosis included vasculitis such as Henoch-Schönlein purpura,<sup>7</sup> GVHD, and cutaneous involvement by myeloma. Histology revealed tissue involvement by plasma cells with extensive infiltrate involving the upper and deep dermis (Figures 2A and 2B). Immunohistochemistry was negative for CD3, CD20, and CD5, while slightly positive for CD10, mainly in the stroma and with some in the myeloma infiltrate. His myeloma assessment revealed an increase in IgA to 2,753 mg/dL and M-spike of 2.6 g/dL, and his serum free lambda light chain was elevated at 9.09 mg/dL. Repeat skeletal survey was stable. Tacrolimus was discontinued and an all-oral chemotherapy regimen was initiated including lomustine, etoposide, prednisone, and cyclophosphamide.<sup>8</sup> He responded dramatically with some mild tumor lysis syndrome and complete resolution of the rash. The patient then underwent donor lymphocyte infusion (DLI) with a total dose of  $1 \times 10^8$  CD3+ cells/kg. He did not develop any GVHD and was later started on lenalidomide (Revlimid, Celgene) 25 mg/day orally on days 1–21 every 28 days. Unfortunately, despite treatment, the patient had recurrence of MM with the same skin rash and expired approximately 2 months later.

## Discussion

Cutaneous involvement in MM is rare and is generally identified by nodular lesions or plaques. In this particular



**Figure 2.** Skin biopsy results: At low power (A), they show histologic evidence for extensive infiltration of the upper and deep dermis, while at high power (B), atypical large and immature plasma cells can be recognized.

case, the skin manifestation was not plasmacytoma, but rather a diffuse erythematous rash with a wide range of differential diagnoses. Nevertheless, the biopsy proved myelomatous involvement. A thorough study by Requena and colleagues<sup>1</sup> identified a number of MM patients with cutaneous involvement. These patients presented with either nodular lesions or plaques. Other reported cases in the literature do not describe a maculopapular rash as was seen in this particular patient.<sup>2–4</sup> Some of the described mechanisms behind cutaneous involvement in myeloma include direct extension via bony lesions, lymphatic distribution, or hematogenous spread.

The importance of histologic confirmation was evidenced in this case. When the patient developed the rash, the differential diagnosis was broad, particularly as this patient had recently undergone unrelated donor peripheral blood stem cell transplantation. As there are, to this

date, no reported cases of erythematous skin rash due to myeloma, myelomatous infiltrate was not initially present in the differential diagnosis in this case. Thus, our case shows the necessity of performing skin biopsy early when presented with suspicious cutaneous manifestations in a patient with advanced MM.

Several reports have indicated an increased incidence of extramedullary relapses of MM after allo-SCT,<sup>9-12</sup> especially in those patients who are either heavily pretreated or who have high-risk features such as deletion of chromosome 13.<sup>12</sup> These extramedullary relapses occurred late after transplant and involved different sites including the skin, but consisted mainly of skin plasmacytomas. Interestingly, most of the published data show similar responses to treatment for medullary and extramedullary relapses.

Thus, our patient is unique in the type of extramedullary relapse and its early timing after transplant. Although he demonstrated good response to chemotherapy, he never developed any signs of GVHD or graft versus myeloma effect and eventually succumbed to his disease with recurrence of the skin rash.

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# Review

## Extramedullary Disease in Multiple Myeloma

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Subbiah and colleagues<sup>1</sup> provide an intriguing account of a 52-year-old man with an extramedullary (EM) relapse of multiple myeloma (MM) soon after a nonmyeloablative (NMA) allogeneic stem cell transplant (allo-SCT). His relapse manifested as a diffuse, erythematous papulovesicular skin rash on bilateral lower extremities with biopsy-proven plasma cell infiltrate involving the upper and deep dermis, concurrent with biochemical progression of MM.

MM is characterized by uncontrolled clonal proliferation of plasma cells, mainly in bone marrow, and EM involvement is infrequent. EM disease can occur either at initial diagnosis of MM or later during the disease course.<sup>2-4</sup> In a recent study, an overall incidence of EM disease of 13% (7% at diagnosis and 6% during follow-up) was observed among 1,003 MM patients from a single institution at a median follow-up of 30 months from diagnosis.<sup>2</sup> Among those with EM disease, 7% were found to have plasma cell leukemia, which has been closely linked with EM disease in previous reports as well.<sup>5,6</sup> EM involvement commonly affects the pleura, lymph nodes, soft tissue, liver, skin, lungs, central nervous system (CNS), genitourinary system, breast, and pancreas, and involvement of multiple sites can occur.<sup>3,7,8</sup> The presence of EM involvement in MM indicates aggressive disease with shorter overall survival (OS) and progression-free survival,<sup>2</sup> especially when the EM tumor occurs at the same time as MM.<sup>3,9</sup> In a study of 19 patients with EM and extraosseous disease at various sites, the observed median OS was 15 months from diagnosis after treatment with conventional chemotherapy or thalidomide (Thalomid, Celgene) and/or high-dose therapy.<sup>3</sup> Another study observed an overall incidence of approximately 1% for CNS involvement in MM<sup>4</sup>; all but 1 patient died at a median of 5 months from the diagnosis of CNS involvement.

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Symptomatic myeloma presenting with EM involvement should be distinguished from a solitary nonosseous plasmacytoma. EM plasmacytoma is a soft tissue plasma cell tumor that arises outside the bone marrow. It is characterized by normal bone marrow, little or no monoclonal protein (mostly IgA), and no evidence of myeloma-related end organ damage.<sup>10</sup> The median age at diagnosis of EM plasmacytoma is approximately 60 years, with a strong male preponderance.<sup>11</sup> It usually occurs (>80%) in the upper aerodigestive tract,<sup>3,11</sup> producing symptoms such as epistaxis, rhinorrhea, and nasal obstruction. It frequently remains localized and has a favorable prognosis after treatment with radiation therapy and/or surgery. Cutaneous involvement with EM plasmacytoma (solitary or multiple) is rare,<sup>11</sup> and carries a favorable prognosis with a survival rate of greater than 90% at 5 years.<sup>12</sup> These patients require close surveillance and regular testing to determine if overt MM will develop.

### EM Disease Post-allogeneic Transplantation

Recent reports suggest higher rates of EM relapses, either alone or concurrent with systemic relapse, in MM patients undergoing allo- and autologous (auto)-SCT,<sup>8,13,14</sup> especially those receiving NMA (reduced intensity) therapy.<sup>15</sup> Although the mechanisms of EM relapse after allo-SCT are largely unclear, the potential reasons include a less potent graft versus myeloma (GVM) effect outside the bone marrow, clonal evolution of the tumor cell enabling independence from the supportive effect of the bone marrow microenvironment, and/or the escape of myeloma cells from the GVM effect of immunocompetent allogeneic T cells in extramedullary sites. A recent report observed a 9.3% incidence of isolated EM relapse and a cumulative 20.4% incidence of EM relapses among MM patients treated with sequential auto- and NMA allo-SCT.<sup>16</sup> The authors of this study suggest that a worsening disease status at transplant may be related to a higher incidence of EM relapse. In another study, where fewer patients were treated with the sequential transplantation approach and one-third had progressive disease at the time of allo-SCT, an even higher rate of EM relapse (37%) was observed, mainly involving the cranial and periorbital sites without medullary disease recurrence.<sup>15</sup> The presence of chromosome 13 deletion at diagnosis, a well-recognized poor prognostic factor in MM, has also been implicated in the increased incidence of EM relapse in several studies.<sup>4,8,16</sup> Although other risk factors such as increased tumor burden and stage of disease,<sup>3,4,16</sup> elevated lactate dehydrogenase levels,<sup>2-4,8,16</sup> type of immunoglobulin,<sup>3,16,17</sup> and the development of chronic graft versus host disease (GVHD)<sup>14-16</sup> have been linked to the development of EM disease and/or relapse, their exact role still remains

under investigation due to conflicting reports from various studies.

### Treatment

A GVM effect achieved by donor leukocyte infusion (DLI) has been described in patients with progressive or relapsed MM after allogeneic bone marrow transplantation,<sup>18,19</sup> and some reports suggest its efficacy even in EM disease relapse after allo-SCT.<sup>16,20</sup> In a subgroup of MM patients who underwent allo-SCT and received DLI, a treatment response was observed in 5 of 9 and 3 of 4 patients who developed bone marrow and EM relapse, respectively.<sup>8</sup> The use of thalidomide, an agent with antiangiogenic properties, has been described with variable efficacy in EM disease. Biagi and associates reported on 3 patients who developed EM disease after allo-SCT and were able to achieve complete resolution with thalidomide<sup>21</sup>; however, other reports have observed poor efficacy with thalidomide in EM disease.<sup>22-24</sup> Bortezomib (Velcade, Millennium Pharmaceuticals), a potent proteasome inhibitor, appears to be promising, with several clinical reports suggesting its effectiveness in EM relapse.<sup>25,26</sup> Minemura and coworkers reported on a group of 54 MM patients who relapsed after undergoing sequential auto- and allo-SCT, and observed no significant difference in the response rates and survival of those with EM disease relapse treated with DLI, chemotherapy with novel agents, and radiotherapy compared with those without EM disease,<sup>16</sup> a finding also corroborated by another study.<sup>8</sup>

### Skin Lesions in MM and Other Monoclonal Gammopathies

Skin involvement from MM is uncommon. Cutaneous lesions in MM usually appear as multiple erythematous nodules or papules, or plaques that show a nodular or diffuse interstitial pattern on histopathologic exam.<sup>27</sup> In descending order, these lesions appear on the trunk and abdomen, head and neck, and the extremities. Skin involvement in MM usually manifests itself later in the disease course when the tumor burden is high, and it is associated with a poor prognosis.<sup>27</sup> On the other hand, cutaneous eruptions are a frequent complication after allo-SCT, and most commonly occur due to immunologic reactions (GVHD), infections (staphylococcus aureus, herpes simplex virus type 1, varicella zoster virus, cytomegalovirus, Epstein-Barr virus), and drug reactions (cytotoxic drugs, antibiotics, and nonsteroidal anti-inflammatory drugs).<sup>28</sup> Among a subgroup of 247 patients who underwent transplantation (both autologous and allogeneic), 159 skin biopsies were obtained less than 2 months from the transplant.<sup>29</sup> The cutaneous manifesta-

tions included GVHD (31%), drug-related phenomenon (15%), infections (8%), bullous diseases (7%), papulo-squamous lesions (5%), and neoplasm (4%), while others had thrombocytopenia-related lesions, Sweet's syndrome, and other nonspecific diagnoses (30%).

An excellent review by Daoud and co-authors divided skin disorders associated with monoclonal gammopathies into 4 distinct groups.<sup>30</sup> Group 1 diseases (amyloidosis, cryoglobulinemia, plasmacytoma, osteosclerotic myeloma, Waldenström macroglobulinemia cutis) are characterized by infiltration and proliferation of skin by malignant plasma cells or a product of these plasma cells; group 2 diseases have a strong association with monoclonal gammopathies (scleromyxedema, scleredema, necrobiotic xanthogranuloma, plane xanthoma, Schnitzler syndrome, pyoderma gangrenosum, Sweet's syndrome, and erythema elevatum diutinum, among others); group 3 represents various dermatoses linked to paraproteinemia without a clear association; and group 4 comprises nonspecific cutaneous conditions, symptoms, and complications related to M protein.

In conclusion, this case serves to highlight several important clinical points. Disease relapse in MM can occur outside the bone marrow in diverse EM sites, including the skin. Although rare, tumor recurrence should be considered in the differential diagnosis of skin rash in patients with MM, especially in the context of aggressive disease, and a biopsy should be performed in order to correctly diagnose and guide treatment in these patients.

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