

Unusual Multiple Myeloma Cutaneous Manifestation Following Nonmyeloablative Allogeneic Stem Cell Transplantation

Sukanthini Subbiah, MD¹
 Florence O'Connell, MD²
 Kathy B. Kobraei, MD²
 Francisco A. Ramos-Caro, MD²
 Jan S. Moreb, MD¹

¹Department of Medicine; ²Division of Dermatology and Cutaneous Surgery; University of Florida, Gainesville, Florida

Introduction

Skin involvement in multiple myeloma (MM) has been described, but is uncommon.¹⁻⁴ 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 skin rash in these patients including graft versus host disease (GVHD), drug reaction, vasculitis, or cellulitis. Thus, our case emphasizes the need to include myeloma in the differential diagnosis of erythematous skin rash.

Case Report

A 52-year-old Caucasian male with known immunoglobulin A (IgA) lambda MM stage IIIA of approximately 1½ year duration presented with multiple lytic lesions, hypercalcemia, elevated creatinine, and anemia. His β 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 from diagnosis. He achieved very good partial remission, which lasted approximately 11 months when he relapsed. At this point, he was treated with bortezomib, doxorubicin,⁵ and 100-mg/day thalidomide 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 CR. He then proceeded with the planned allogeneic peripheral blood SCT. The nonmyeloablative chemotherapy regimen consisted of antithymocyte globulins, busulfan, and fludarabine.⁶ His total transplant cell dose was 7.04×10^6 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, non-tender, papulovesicular rash on bilateral lower extremities with some distributed violaceous plaques (Figure 1). He underwent punch biopsies at 2 sites. The differential diagnosis included vasculitis such as Henoch-Schonlein purpura,⁷ GVHD, and cutaneous involvement by myeloma.

Address correspondence to:

Jan S. Moreb, MD, 1600 SW Archer Rd., PO Box 100277, Dept of Medicine, University of Florida, Gainesville, FL 32610; Phone: 352-2737499; Fax: 352-392-8530; E-mail: morebjs@medicine.ufl.edu.



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

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 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.⁸ 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 1×10^8 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 case, skin manifestation was not plasmacytoma, but rather diffuse erythematous rash with a wide range of

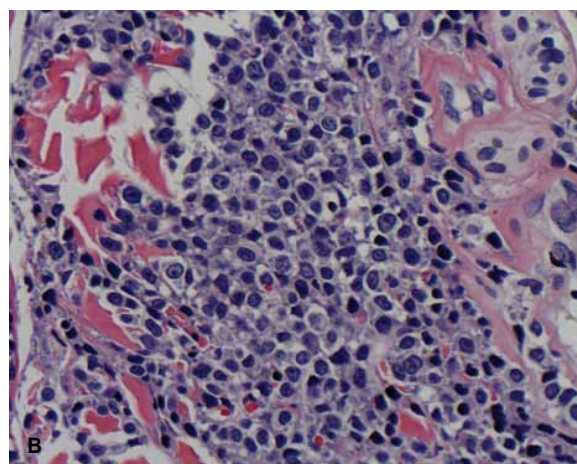
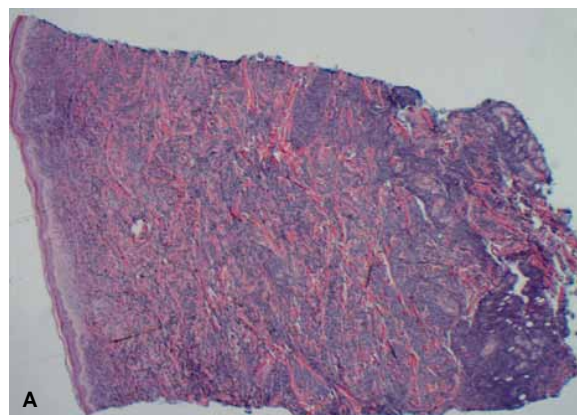


Figure 2. Skin biopsy results: At low power (A), they show histologic evidence for extensive infiltration of the upper and deep dermis, while at high power (B), atypical large and immature plasma cells can be recognized.

differential diagnoses. Nevertheless, the biopsy proved myelomatous involvement. A thorough study by Requena and colleagues¹ elucidated 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.^{2–4} 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 patient with advanced MM.

Several reports have indicated an increased incidence of extramedullary relapses of MM after allo-SCT,⁹⁻¹² especially in those patients who are either heavily pretreated or who have high-risk features such as deletion of chromosome 13.¹² These extramedullary relapses occurred late after transplant and involved different sites including the skin, but mainly skin plasmacytomas. Interestingly, most of the published data show similar responses to treatment for medullary and extramedullary relapses.

Thus, our patient is unique by 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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