**Case Series**
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# The Cutaneous Involvement of Multiple Myeloma as an Indicator of Unfavorable Evolution: Series of Three Cases

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## Abstract

Cutaneous myeloma, a rare clinical presentation of multiple myeloma, is usually associated with high burden of malignant cells and poor prognosis. Three cases who were diagnosed with multiple myeloma and exhibited cutaneous involvement with a wide range of clinical manifestations. We emphasize the morphologic and immunohistochemical patterns of this rare presentation. The use of new therapies associated double or triple regimens in the treatment of myeloma showed significant improvements in progression-free survival, but relapse with cutanea infiltration suggests a pattern of aggressiveness that is still unclear and generally refractory to conventional therapies. The pathophysiology and the findings and markers that might be associated with prognosis based on the review of recent literature.

**Keywords:** Multiple myeloma • Cutaneous infiltration • Extra medullary myeloma

## Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the uncontrolled proliferation of plasma cells in the bone marrow and the subsequent overabundance of monoclonal paraproteins. Extramedullary involvement in MM (EEMM) is an uncommon presentation, with an estimated incidence ranging from 6% to 7.5% in recent studies [1].

EEMM is defined as the infiltration of clonal plasmacytic cells at sites that are anatomically distant from the bone marrow and the adjacent soft tissues in patients with MM. Unlike the clonal plasmacytic infiltration observed in the local invasion of structures adjacent to the bone marrow, EEMM exhibits a more immature and plasmablastic cell profile, which underlies its aggressive clinical behavior and poorer prognosis [2-5].

Cutaneous involvement, which is a particularly rare manifestation of EEMM, occurs in 1% to 4% and usually presents as a late complication in patients treated with several therapeutic regimens. Cutaneous involvement is also observed as a late-stage presentation in patients with extensive tumor burden (bone marrow plasmacytosis > 60%), high International Staging System (ISS) scores, and poor prognosis at the time of diagnosis according to the cytogenetic evaluation [3]. The definitive diagnosis of cutaneous infiltration is based on the histopathological examination of skin lesions in patients with a previous diagnosis of MM [4-7].

Although significant advances and new therapeutic approaches have changed the outlook of MM, mainly due to the implementation of new therapies in this patients with cutaneous manifestations still experience unfavorable outcomes and poor response to adjuvant therapies, including protease inhibitors [8,9].

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Proteasome inhibitors of first and second generation, monoclonal antibody and lenalidomide have represented a breakthrough in the treatment of MM, providing longer survival. Nevertheless, in our experience, the use of these new drugs has not translated into additional survival benefit, underscoring the role of skin involvement as a poor prognostic factor [6,8,10].

In this report, we present three cases of MM with cutaneous involvement which followed a fatal disease course despite the use of new therapies in the triple drugs protocols. To the best of our knowledge, this is the first case series of patients with MM who developed cutaneous involvement despite treatment with proteasome inhibitors and new treatment to the myeloma: anti-CD38, lenalidomide and thalidomide.

## Case Series

### Case 1

SFO, a 55-year black male patient was diagnosed with symptomatic MM based on an serum immunoglobulin (Ig) G kappa chain protein level of 5.6 g/dL and had Durie–Salmon stage III A disease (lytic lesions on lumbosacral spine), cytogenetic with 13q deletion and an ISS score of 3 (albumin, 2.5 g/dL; B2-microglobulin, 4.7 g/dL) at presentation. Complete response (CR) according to the International Working Myeloma Foundation (IWMF) was achieved with four cycles of treatment with cyclophosphamide, dexamethasone, and bortezomib. Subsequently, the patient underwent hematopoietic stem cell transplantation (HSCT) with the infusion of 12 × $10^6$ $CD34^+$ cells/kg following preconditioning with melphalan (200 mg/$m^2$). After the HSCT, the patient has maintained CR with bortezomib and quarterly monitoring for monoclonal protein levels. Four months later, the patient exhibited an elevation of the monoclonal peak of the heavy-chain protein and a subcutaneous nodule with progressive growth in the left axillary region (describe the lesions from the dermatological point of view) shown in Figure 1A-1B (Figure 1). The radiological investigation of sudden spinal cord compression revealed bone plasmacytoma at the level of T12. Decompressive laminectomy was performed, and the skin lesion biopsy confirmed the presence of cutaneous infiltration by MM, leading to the diagnosis of extramedullary plasmacytoma of cutaneous involvement. The patient was initiated third-line treatment with daratumumab, bortezomib, and dexamethasone but did not achieve clinical improvement; the plasmacytoma

in the left axillary lesion grew as well. The patient was worsening renal function and skin lesions, associated with septic shock. The time interval from the cutaneous presentation to death was 6 months.

## Case 2

NRD, a 76-year white male was diagnosed with IgA-lambda MM and had Durie–Salmon stage IIIA disease (lytic lesions in costal arches and lumbosacral spine), cytogenetic with t(4;11) and an ISS score of 2 at the time of diagnosis. He was initiated treatment with melphalan, prednisone, and bortezomib and achieved CR 7 months later. In August 2016, he presented with disease progression based on a compression fracture of T12 due to progression and was initiated treatment with lenalidomide and dexamethasone. The persistent disease progression according to the IWMF criteria remained unchanged despite the switch in treatment to carfilzomib, lenalidomide, and dexamethasone. Due to worsening of renal function and high lambda light-chain protein levels, treatment with daratumumab, melphalan, and dexamethasone was initiated. However, after three cycles, the patient experienced worsening renal function, cardiovascular decompensation, and the appearance of cutaneous nodules (hematological lesions) on bilateral forearms and legs (Figure 2A). The histopathological examination of the fine-needle aspiration biopsy of the skin lesions using Wright–Giemsa staining revealed signs of cutaneous plasmacytosis (Figure 2B), confirming cutaneous infiltration of MM. The patient progressed to multi-organ failure 60 days after the onset of cutaneous lesions (Figure 2).

## Case 3

MSP, a 50-year patient was diagnosed with IgA MM and had Durie–Salmon stage IIIB disease (lytic lesions in basin and lumbosacral column, renal insufficiency, and hypercalcemia), cytogenetic with 17p deletion and an ISS score of 3 (albumin, 2.0 g/dL; B2-microglobulin, 10 mg/dL). The patient was initiated treatment with thalidomide and dexamethasone and achieved partial response based on stable heavy- and light-chain monoclonal protein levels according to the IWMF criteria. Two months later, the patient was diagnosed with progressive disease and initiated treatment with bortezomib,

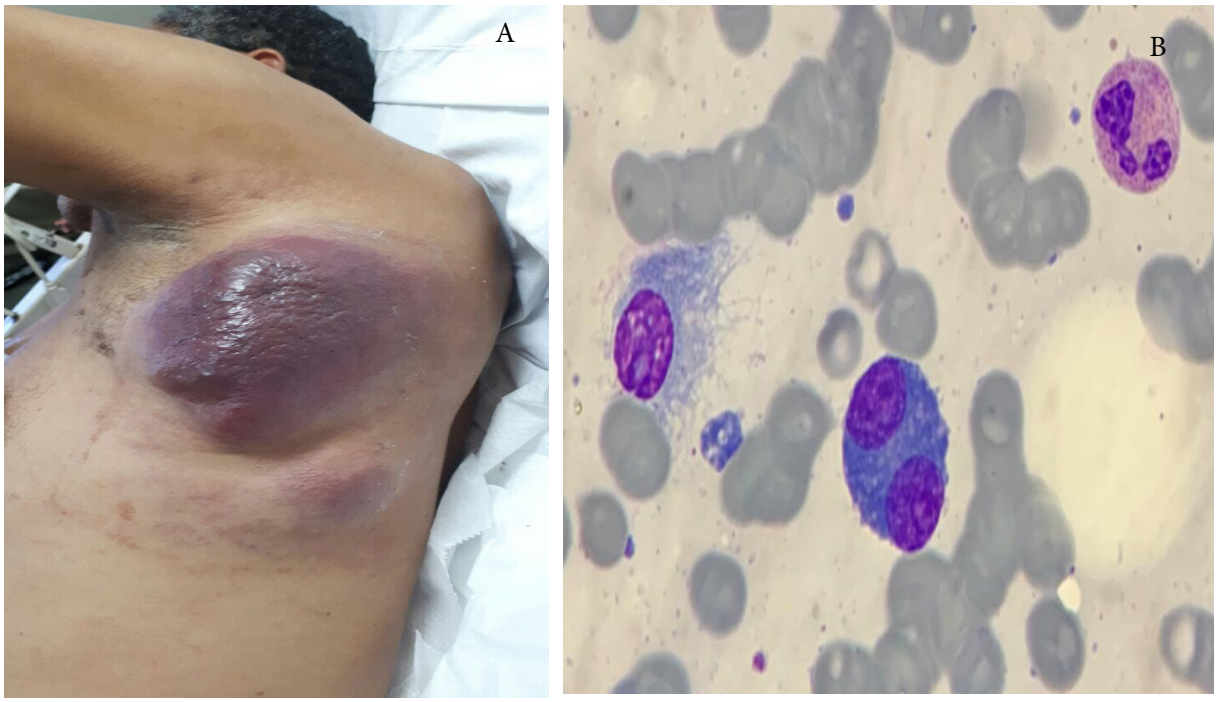


**Figure 1. (A)** Multiple subcutaneous nodules detected in a patient with multiple myeloma and **(B)** Giemsa staining shows plasmacytic cells in the biopsy specimen of the skin lesion (magnification, 100X).

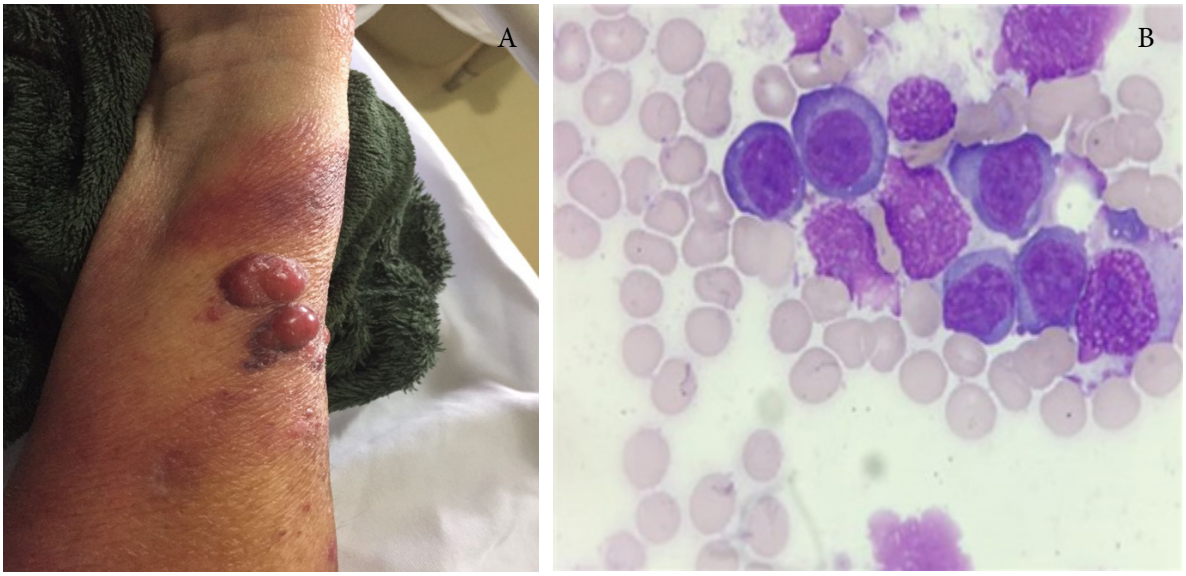


**Figure 2. (A)** Cutaneous nodules in a patient with refractory multiple myeloma and **(B)** Wright–Giemsa staining shows plasmacytosis in the fine-needle aspirate (magnification, 100X).

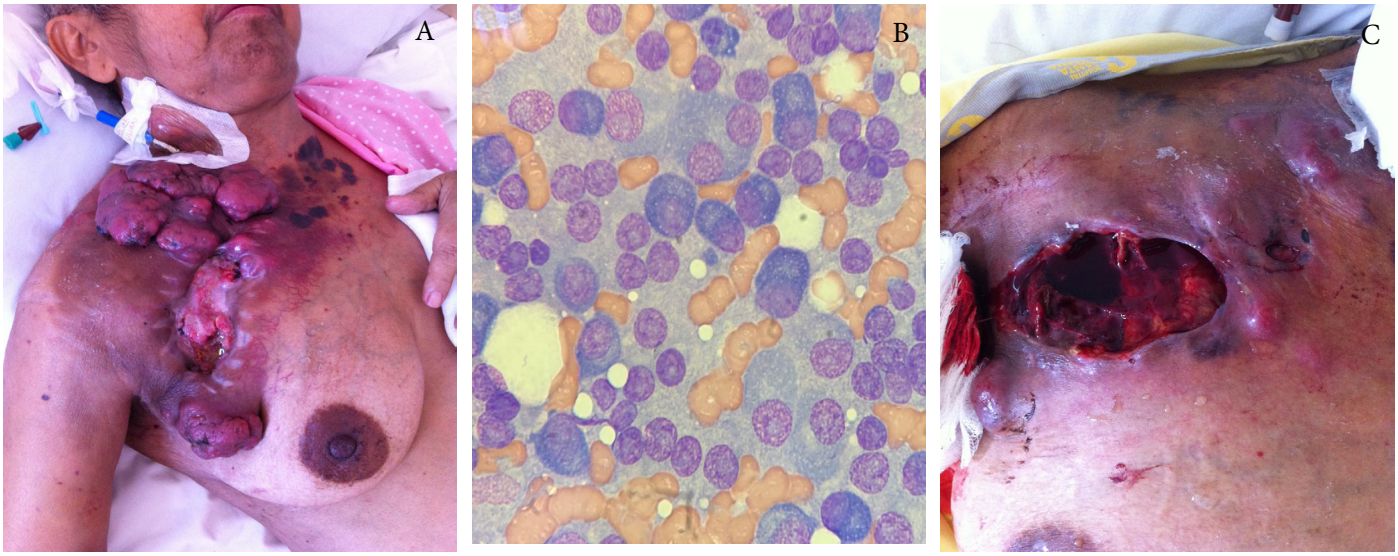


**Figure 3. (A)** Nodules in upper limb were confirmed as extramedullary plasmacytoma based on the aspirated specimen stained with Wright–Giemsa (magnification, 100X), **(B)** Detected plasm cell and **(C)** Ulceration and necrosis of the extramedullary plasmacytoma lesions detected after chemotherapy.

cyclophosphamide and dexamethasone; autologous HSCT was also indicated. However, 2 months later, the patient developed supraclavicular cutaneous nodules and lesions in bilateral limbs (describing dermatological lesions) indicating rapid progression (Figure 3A). The histopathological evaluation of the biopsy sample of the cutaneous lesions was compatible with extramedullary plasmacytoma (Figure 3B). A higher-potency chemotherapy regimen containing melphalan, vincristine, cyclophosphamide, and methylprednisolone was chosen. However, the patient did not exhibit clinical response to MM and the ulceration of the cutaneous lesions (Figure 3C), which worsened. The patient died in August 2012 (Figure 3).

## Discussion

MM is caused by the clonal proliferation of plasma cells that secrete light- and heavy-chain Ig proteins and usually involves the spinal cord although extramedullary cutaneous involvement may occur in advanced stages of the disease [8].

Plasma cell myeloma (PCM) involving skin is rare and occurs in the 1% a 4% of patients with PCM. This infiltration may be primary, such as that observed in isolated extramedullary plasmocytomas, or may occur secondary to MM. In the current literature, there is a description of this manifestation, occurred in the older individual, nearly 75 years, and is more frequent in men. Al the cases had bone marrow involvement preceding the cutaneous lesions. Cytogenetic analysis shows multiple hyperdiploid abnormalities, with higher prevalence of 13q, 11q and rb-1 deletion in aggressive clinical cases. The follow-up of cases shows short-term disease-related death in the vast majority of patients [11-14].

The extramedullary cutaneous lesions are characterized by a wide variety of histopathological presentations and are categorized as interstitial and nodular types. The nodular pattern is characterized by plasma cells in the dermis, whereas the interstitial pattern is characterized by plasma cells forming fine strands between the collagen bands [7,15]. Cutaneous extramedullary lesions have been described in all subtypes of MM, regardless of the secretory proteins involved, and the IgG subtype is the most commonly described and is followed by the IgA subtype [8,9,16,17].

Cutaneous involvement represents a rare complication of MM, described mainly in isolated case reports or small case series. The pathophysiology remains unclear; however, some studies suggest that a reduction in the expression of adhesion molecules, such as very late antigen-4 and CD44, is associated with the loss of CD56 expression, which can facilitate the hematogenous circulation of clonal plasma cells due to their reduced homing in the bone marrow. It has been supposed that biologically unique sub-clones that have the ability to migrate to the skin may be selected, in particular, by high-dose chemotherapy used before hematopoietic stem cell transplantation [18].

Immunohistochemical analyses show that the CD138 marker is positive and may be associated with CD38 and CD79. The lesions are negative for CD19 and CD20 but may be positive for CD56 [4,19,20]. Currently, there are no standardized therapeutic approaches for the clinical management of the secondary cutaneous infiltration of the MM due to the unfavorable outcome. In the current series of three patients, despite the use of latest therapeutic regimens for MM, the median survival was 6 months following the diagnosis of skin infiltration [1,2,5,8]. We concluded that skin affection is a rare EEMM and tends to occur in patients with multiple myeloma in late stages of the disease and cases involving poor cytogenetic.

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## Statement of Ethics

Written informed consent was obtained from patients at the time of diagnosis of the oncological condition as well as authorization to publish the details of their medical case and any accompanying images. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images. The CARE LIST was applied in series of cases. This study was reviewed and approved by IMESP approval number CAAE: 65300422.6.0000.8101.

## Author Contributions

Concept: Flávia Zattar Piazera. Manuscript writing and final approval: Rafael de Sá Vasconcelos, Marcelo Jorge Carneiro, Alexandre Nonino, Jorge Vaz Pinto Neto, Luiz Henrique Athaides Ramos, Selma Maria Kuckelhaus.

## Data Availability Statement

The authors declare and make available all the data described in this article upon request of editors and reviewers, when requested.

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There were no sponsors involved in this report. The information described comes from reviewed data from the medical records and clinical evolution of the case throughout the established treatment.

## Conflict of Interest

The authors have no conflicts of interest to declare.

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