Painful, plantar nodules in cutaneous macroglobulinosis: Successful treatment with rituximab and bendamustine

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INTRODUCTION

Waldenstrom macroglobulinemia (WM) is a chronic lymphoproliferative disorder characterized by a monoclonal IgM component secreted by the lymphoplasmacytoid cells. Cutaneous macroglobulinosis (CM), a specific cutaneous manifestation of WM, is a clinical condition that rarely appears on the affected patients. The most important finding of WM is the monoclonal spike electrophoresis.[1] Its clinical manifestation is related to tumoral infiltration, monoclonal IgM paraprotein, and deposition of IgM in the tissue.[2]

The symptoms of tumoral infiltration may be caused by the replacement of bone marrow, splenomegaly, and/or lymphadenopathy. High levels of IgM paraprotein can also lead to hyperviscosity syndrome, peripheral neuropathy, and immune complex vasculitis.[3] Dermatologic manifestations of WM are usually classified as specific and nonspecific.[4] Specific manifestation are sporadically reported and are subdivided in cell infiltrates or deposits of monoclonal component in cutis. Nonspecific manifestations are the consequence of hyperviscosity or cryoglobulinemia such as purpura, livedo reticularis, mucosal bleeding, and Raynaud phenomenon.[5]

We previously described a patient affected by WM who presented with new painful nodules localized to the soles of the feet and characterized by deposition of IgM paraprotein in the dermis.[6] In this report, we show the successful treatment of this patient and his clinical follow-up after 5 years.

Abbreviations used:

CM: cutaneous macroglobulinosis
WM: Waldenstrom macroglobulinemia

CASE REPORT

In December 2014, we reported the clinical case of a patient with WM with atypical CM. The case was characterized by extremely painful nodules covered by a thick, hyperkeratotic layer on the soles of the patient's feet that was treated with keratolytic agents without success (Fig 1).[6] Based on cutaneous symptomatology, the patient was sent back to the hematologist to assess a systemic therapy. He was otherwise in good health.[7] The systemic therapy consisted of a first-line treatment with rituximab, a monoclonal anti-CD20 antibody, cyclophosphamide, and dexamethasone. The therapy was suspended at the third administration because no laboratory or clinical responses had occurred and, in particular, the plantar lesions had increased in consistency.

Taking advantage of successful alkylating and purine analogue-like properties previously reported by Treon et al,[8] the patient was treated with rituximab and bendamustine. In particular, 6 cycles of rituximab (375 mg/mq) followed by bendamustine (75 mg/mq) were administered every 28 days, once daily for 2 consecutive days. This therapy was well tolerated with a good clinical and laboratory response and without any signs of myelosuppression. Plantar

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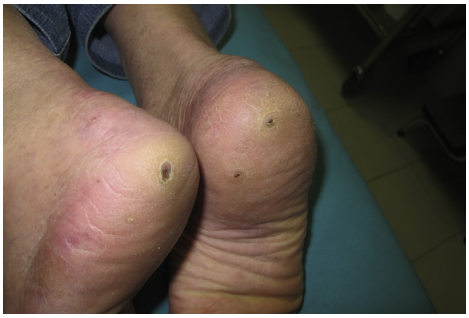

Fig 1. Extremely painful nodules covered by a thick, hyperkeratotic layer on the soles of patient's feet.

lesions progressively improved until they healed in about 3 months. The patient applied only emollient creams locally at the end of the treatment (Fig 2). Laboratory analysis found a reduction of the IgM-κ monoclonal protein from the initial value of 22.9 g/L to 3.02 g/L underlying the resolution of Bence-Jones proteinuria. The improvement was so influential on the patient's quality of life that he was able to start dancing again. The case described suggests that treatment with rituximab and bendamustine can lead to resolution of cutaneous lesions in CM, when the lesions are the only symptomatic manifestation in WM-affected patients. After 5 years, the patient shows no recurrence of plantar nodules (Fig 3).

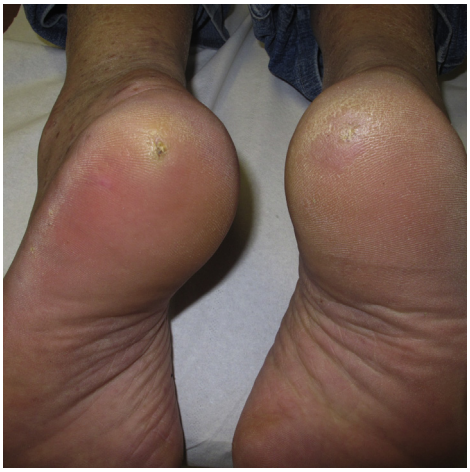

Fig 2. Improvement of the painful, plantar nodules in cutaneous macroglobulinosis treated with rituximab and bendamustine after 3 months.

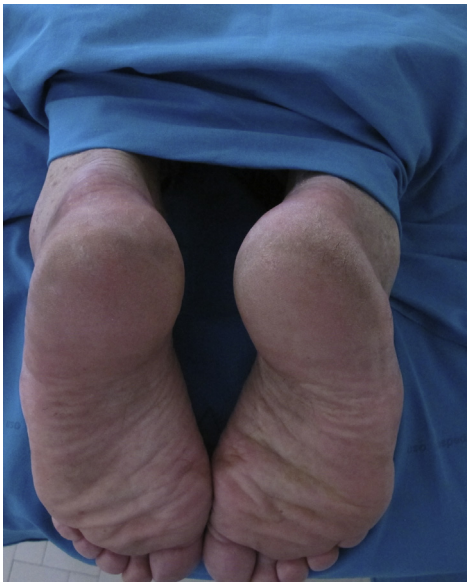

Fig 3. Clinical follow-up after 5 years of painful, plantar nodules in cutaneous macroglobulinosis treated with rituximab and bendamustine.

DISCUSSION

WM is a lymphoplasmacytic lymphoma with a monoclonal IgM paraprotein; it represents about 2% of all hematologic malignancies, and its incidence is 3.8 per million persons per year.[3]

Cutaneous manifestations of WM were reported for the first time in 1978 by Tichenor et al.[9] They can be divided in 2 main groups: specific and nonspecific.[10] A further subdivision can be made within the specific group of cutaneous manifestations between the skin lesions caused by neoplastic infiltration and skin lesions caused by the accumulation of monoclonal component.[11] With regard to neoplastic infiltration, only 16 cases are reported in the literature in which papules and purplish brown nodules, located on the trunk and face, are the most typical clinical presentations.[5] The histologic examination shows an infiltration of lymphoplasmacytoid cells and mature plasma cells localized within periadnexal, perivascular, and interstitial spaces of the dermis reaching the subcutaneous tissue. However, cutaneous manifestations caused by the accumulation of monoclonal IgM paraprotein are more polymorphic and depend on the accumulation level of the monoclonal IgM paraprotein themselves (Fig 4). These paraproteins, directed against a nonidentified antigen in the basement membrane,[11] result in clinically itchy papules or subepidermal bullous dermatosis.[10]

Finally, the monoclonal IgM component may be deposited in the dermis and form accumulations that clinically appear as translucent erythematous papules that are located on the limbs, buttocks, and torso. This presentation is rare, and the deposition of IgM-positive material within dermal blood vessels and extravascular dermis is reported only in 12 patients.[5] This material presents an intense eosinophilic staining on periodic acid–Schiff, whereas it is negative to Congo Red. Immunocytochemical

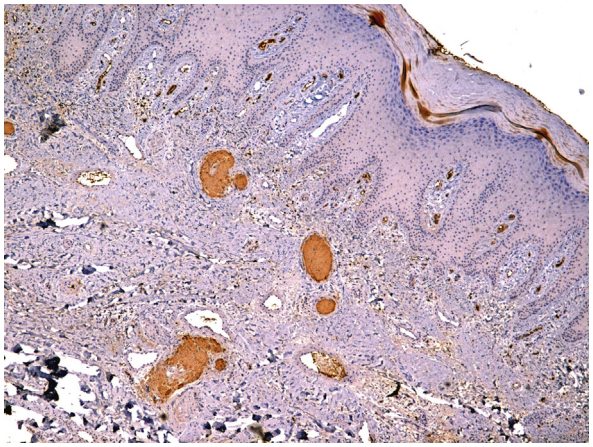

Fig 4. Cutaneous macroglobulinosis. Material proved IgM positive using immunohistochemical stains.

reaction to this substance is associated with anti-IgM. In addition to these cutaneous manifestations, the clinical case described here shows a CM characterized by the accumulation of the amorphous material in the dermis, with an interesting clinical presentation that makes it worthy of being reported.

To our knowledge, the location is atypical because plantar involvement has never reported in the literature. Furthermore, extremely painful nodules surmounted by hyperkeratosis do not fall into the classic presentation of the CM that is usually characterized by the appearance of translucent papules. Importantly, the patient had no chemotherapy and the lesions were initially diagnosed as plantar viral warts. Only after the diagnosis of CM, and in light of the intense pain associated, the hematologist considered starting a specific treatment. Previously, the patient was considered to be suffering from a monoclonal gammopathy of undetermined significance, which needs only periodic checks and not therapy. Thus, in our patient, the skin involvement associated with severe pain may justify the initiation of a specific therapy in WM otherwise asymptomatic. We are not able to give a plausible explanation of the pain at the plantar nodules, although peripheral neuropathy is reported in patients with WM and could be taken into account.[3] Our conclusion is that this clinical case is a sporadic cutaneous manifestation of CM, but it has to be considered a new manifestation of this pathological condition.

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