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## CASE AND RESEARCH LETTERS

### Cutaneous Infiltration due to Waldenström Macroglobulinemia<sup>☆</sup>



### Infiltración cutánea por macroglobulinemia de Waldenström

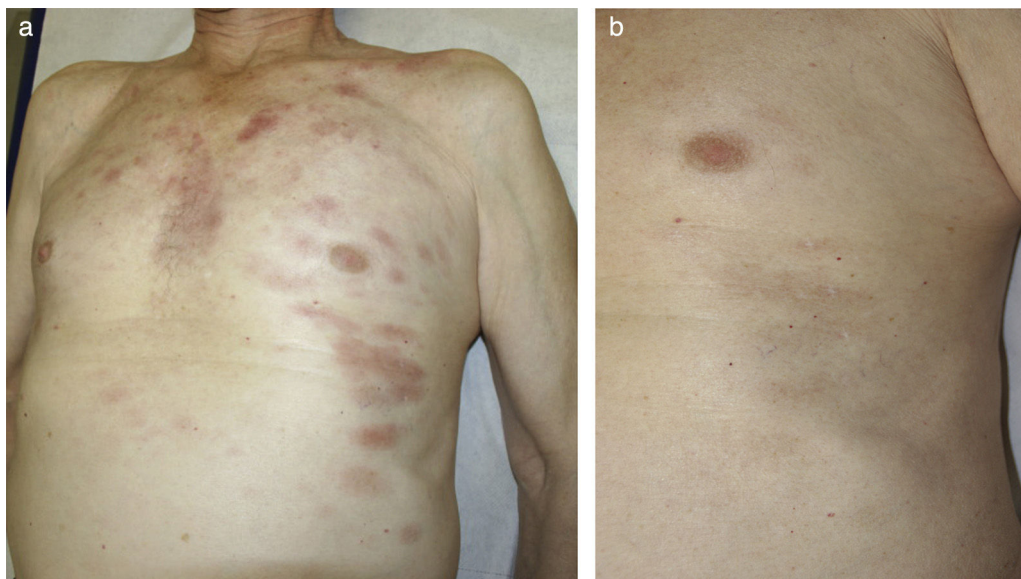
To the Editor:

Infiltration of the skin by lymphoplasmacytic cells is very rare in Waldenström macroglobulinemia (WM).<sup>1</sup>

A 73-year-old man was diagnosed with WM in 2011 after investigation for anemia and monocytosis detected in a routine blood test. At the time of diagnosis, he presented massive bone marrow infiltration by lymphoplasmacytic cells, accounting for more than 45% of the total cell count, with  $\lambda/\kappa$  light chain restriction and a monoclonal immunoglobulin (Ig) M component in blood of 3.84 g/dL (normal value < 2.7 g/dL). Study of the L265P mutation in exon 5 of gene *MYD88* (3p22.2) was positive.

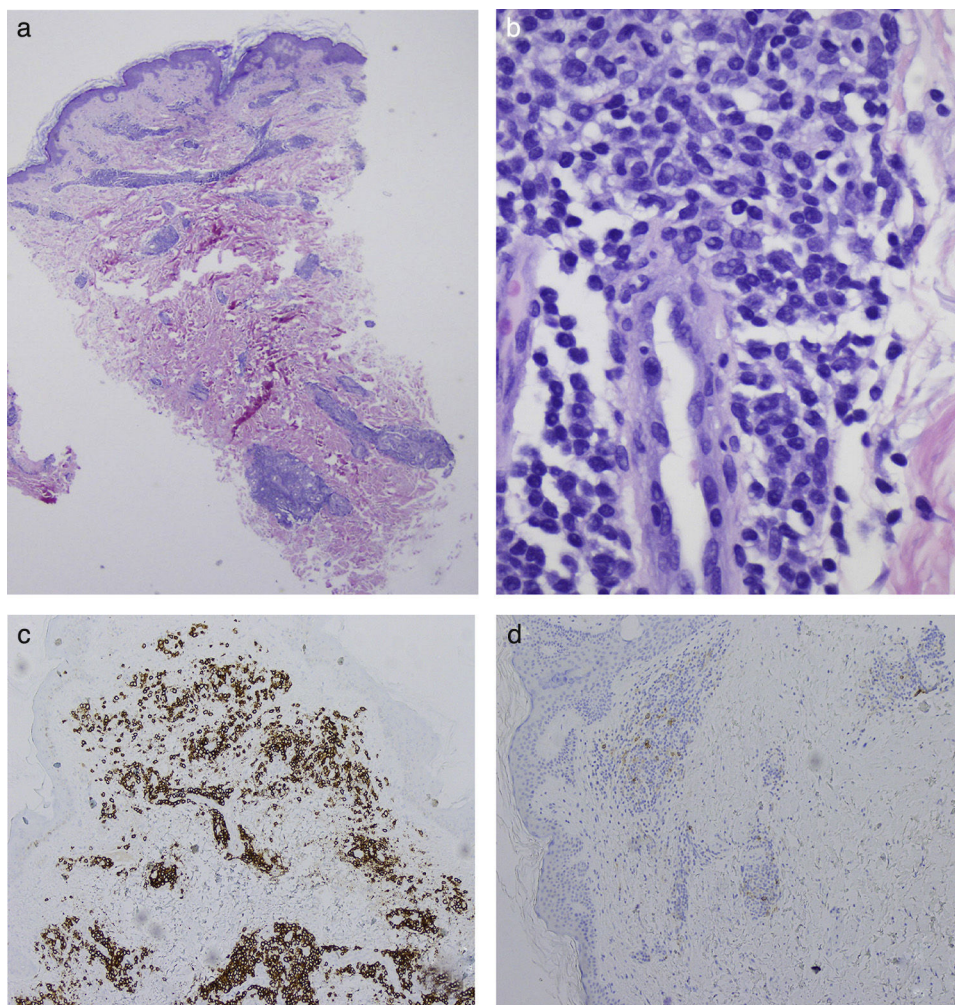
The metastatic work-up showed axillary, retroperitoneal, iliac, and inguinal lymphadenopathies and hepatosplenomegaly. The patient did not report symptoms suggestive of hyperviscosity, and adipose tissue biopsy was negative for amyloid. It was therefore decided to adopt a wait-and-see approach.

In September 2014, the patient was seen in dermatology for the appearance of asymptomatic erythematous plaques with mild desquamation on his upper trunk, back, and face (Fig. 1A). Histology revealed a lymphoplasmacytic infiltrate suggestive of B-cell lymphoma (Fig. 2, A and B), predominantly positive for CD20 (with a 2:1 ratio with CD3) and negative for CD38 and CD138 (Fig. 2, C and D). The few associated plasma cells did not show  $\lambda/\kappa$  light chain restriction. Genetic analysis identified positive monoclonal IgH (FR1 region) and biclonal IgH (FR3 region) rearrangements, confirming the diagnosis as cutaneous infiltration by lymphoplasmacytic lymphoma/WM. Immunohistochemistry for IgM was not performed on the skin biopsy because that study is not available at our hospital.



**Figure 1** A, Initial presentation: desquamating erythematous plaques on the chest and flanks. B, Healing of the skin lesions a month after completing chemotherapy treatment.

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**Figure 2** A, Perivascular lymphoplasmacytic infiltrates around the superficial and deep plexuses. Hematoxylin and eosin (H&E), original magnification  $\times 2$ . B, Periglandular lymphoplasmacytic infiltrates. H&E, original magnification  $\times 40$ . C, Positivity for CD20 in the lymphoplasmacytic infiltrate. CD20 immunohistochemical stain, original magnification  $\times 10$ . D, Negativity for CD38 in the neoplastic infiltrate. The few plasma cells that are present are not monoclonal cells and are positive for CD38. CD38 immunohistochemical stain, original magnification  $\times 10$ .

Clinical progression (asthenia, joint pain, weight loss, sweating) was observed during 2015, with progressive anemia (hemoglobin  $< 10$  g/dL) and an increase in the size of the previously present lymph nodes. It was therefore decided to start systemic treatment with 6 cycles of rituximab plus bendamustine at standard doses. In addition, topical methylprednisolone was prescribed for the skin lesions. A month after completing the chemotherapy regimen, the skin lesions had disappeared. The patient reported an improvement in his general wellbeing, and blood test results (hemoglobin  $> 12$  g/dL) and radiological findings had improved. At the time of writing, the patient has no general or cutaneous symptoms and continues on follow-up by the hematology department (Fig. 1B).

WM is a rare B-cell lymphoproliferative disorder of unknown etiology. It is characterized by a proliferation of lymphoplasmacytic cells in the bone marrow and a monoclonal IgM peak in peripheral blood.<sup>2</sup>

Skin involvement occurs in 5% of patients with WM. According to the classification by Libow et al., 2 types of skin lesion can develop<sup>1,3</sup>: neoplastic lesions due to direct infiltration of the skin by the lymphoplasmacytic cells; and nonneoplastic lesions, secondary to the paraproteinemia. The nonneoplastic lesions are more common and are divided into 3 subtypes: those caused by a hyperviscosity syndrome (acral purpura, mucosal bleeding, peripheral edema); those associated with cryoglobulinemia (acral cyanosis, Raynaud phenomenon, cold hypersensitivity, livedo reticularis, leukocytoclastic vasculitis); and those related to the specific paraproteins (IgM bullous dermatosis, macroglobulinemia cutis, and erythematous papules associated with WM).

The neoplastic skin lesions, due to direct infiltration of the skin by the lymphoplasmacytic cells, are less common. Only around 20 cases have been reported in the literature, (Table 1)<sup>3-8</sup> and their diagnosis in daily practice is very rare. They present clinically as mildly desquamating,



Table 1 Summary of Cases of Skin Involvement by Waldenström Macroglobulinemia Reported in the Literature (See Additional Material).

No. of Cases	Mean Age, y	Sex, M/F	Cutaneous Manifestations	Cutaneous Histology <sup>a</sup>	Bone Marrow <sup>b</sup>	Treatments	L265P Mutation in Gene MYD88
20	71.31	8/12	Sites of desquamating erythematous-violaceous plaques: Face and auricles of the ears: 13/20 Trunk: 7/20 Lower limbs: 4/20 Upper limbs: 2/20	Lymphoplasmacytic infiltrate in the reticular dermis and hypodermis.  IgM + : 12/20 IgM- or NP: 8/20	Positive: 15/20 Negative or NR: 5/20	Clorambucil: 9/20 Cyclophosphamide: 3/20 Vincristine: 3/20 Radiotherapy: 2/20 CHOP: 2/20 Lomustine: 1/20 Plasmapheresis: 1/20 Rituximab + bendamustine: 1/20	NR: 19/20 Positive: 1/20 (Oscoz-Jaime et al)

Abbreviations: CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; F, female; M, male; NP, not performed; NR, not recorded or not performed.

<sup>a</sup> Cutaneous histology: IgM in cutaneous histology measured by direct immunofluorescence.

<sup>b</sup> Bone marrow biopsy: Positive indicates consistent with lymphoplasmacytic lymphoma.

slightly infiltrated erythematous plaques localized mainly symmetrically on the face and ears and also on the chest, flanks, and back.<sup>3-8</sup> They can arise early in the course of the disease, but it should be stressed that their presence does not worsen the prognosis. Cells found in these skin lesions are from the lymphoplasmacytic cell line. They are positive for B-cell markers (CD19, CD20, CD22) and negative for plasma cell markers (CD38 and CD138).

The distinction between cases of lymphoplasmacytic lymphoma/WM and marginal zone lymphoma (MZL) with intense plasmacytic differentiation can be difficult in some cases because of the degree of clinical-pathologic overlap. Investigation of cyclin D1 (positive in MZL and negative in skin involvement by WM) and of *MYD88* gene mutation (somatic mutation L265P is present in the majority of cases of WM<sup>9</sup>) and t11;18 translocation (present in MZL) can be used to make a definitive diagnosis.<sup>10</sup>

In multiple myeloma, the lesions analogous to the neoplastic lesions of WM are plasmacytomas. These present clinically as erythematous-violaceous or erythematous-yellowish plaques or nodules, and are the result of direct infiltration of the skin from underlying bony foci. Histology reveals a deep dermal and hypodermal infiltrate of plasma cells that are positive for CD38 and CD138 and negative for B-cell markers. In contrast to lesions due to infiltration by WM, the presence of plasmacytomas worsens the prognosis of multiple myeloma.

We draw attention to the peculiarities of our case because direct cutaneous infiltration by the lymphoproliferative disease is relatively rare, based on the literature, and does not lead to a worsening of the prognosis despite being a manifestation of disease progression.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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## Lupus Erythematosus Affecting the Genitalia: An Unusual Site<sup>☆</sup>



### Lupus eritematoso con afectación genital: una localización inusual

To the Editor:

Lupus erythematosus (LE) rarely affects the genitalia, and few cases have been reported in the literature.<sup>1–6</sup> In all types of LE, the skin lesions typically appear in sun-exposed areas. However, involvement of nonexposed areas, such as the scalp, the oral mucosa, or the palms and soles, is common and has been extensively described.<sup>1</sup> Genital involvement, on the other hand, is rare and reports in the literature are sparse, for which reason we consider it interesting to report the different genital manifestations observed in 2 patients with LE.

#### Case 1

A 65-year-old woman with a past history of depressive syndrome on treatment with venlafaxine, alprazolam, and lorazepam, was referred from gynecology for asymptomatic skin lesions that had arisen a year earlier on her external genitalia. Whitish, atrophic, alopecic plaques with hyperpigmented borders were observed on the labia majora (Fig. 1A). In addition, examination revealed erythematous edematous plaques on her arms and scarring alopecic on her scalp. A biopsy taken from the genital region showed hyperkeratosis, a lichenoid infiltrate, vacuolar degeneration of the basal layer, and mucin deposits (Fig. 1B). In the blood tests, the antinuclear antibody titer was 1:160, and antiribonucleoprotein antibodies were positive. With a diagnosis of discoid LE (DLE), treatment was started with topical clobetasol for 2 months plus hydroxychloroquine, 400 mg/d, for 5 months, leading to an improvement in the edematous plaques on the arms and in the erythema of the alopecia on the scalp, while

the genital lesions remained stable. At the time of writing, the patient was taking hydroxychloroquine, 200 mg/d, and had no active DLE lesions.

#### Case 2

A woman aged 35 years, diagnosed with systemic LE (SLE) 10 years earlier, had presented numerous distinct cutaneous manifestations of SLE and DLE, for which she had received treatment with chloroquine, hydroxychloroquine, methotrexate, thalidomide, and immunoglobulins. She was seen for a 3-month history of painful genital ulcers that appeared to be related to menstruation and lasted for about 10 days. Examination revealed bilateral erosions at the introitus (Fig. 2A), labia minora, and perianal region. Herpesvirus culture was negative and biopsy showed parakeratosis, focal ulceration, and vacuolar degeneration of the basal layer, with apoptotic keratinocytes in the epidermis and a chronic inflammatory infiltrate in the superficial dermis (Fig. 2B), consistent with LE. Topical clobetasol was prescribed for the outbreaks of genital lesions, leading to an improvement in the pain and duration of the ulcers, though they continued to appear intermittently.

The genital manifestations of LE have been described on few occasions in the literature. In 1989, Burge et al.<sup>2</sup> estimated a prevalence of 5% in patients with chronic DLE, whereas Fresko et al.,<sup>7</sup> in 1993, found no genital lesions in a series of 48 women with SLE.

We have found only 8 published cases (Table 1),<sup>1–6</sup> of which 7 were women. Five of those patients had DLE and 3 SLE. Clinically the lesions include ulcers and erosions,<sup>1–4</sup> as well as erythematous atrophic plaques with scarring alopecia characteristic of DLE.<sup>1,2,5,6</sup> Both the ulcers and the plaques typical of DLE can appear in patients with SLE or DLE. Although they are usually asymptomatic, 2 women reported dyspareunia<sup>3,5</sup> and one described pruritus and discomfort on passing urine or defecating.<sup>4</sup> The histology is typical of LE, with hyperkeratosis, a perivascular and periadnexal inflammatory infiltrate, vacuolar degeneration of the basal layer, apoptotic keratinocytes, and mucin deposits, although not all findings are always present.<sup>1–6</sup>

A recent publication from 2015 described a series of 22 patients with bullous LE, in which 2 of the patients presented genital lesions. However, the morphology, site, duration,

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