Primary Cutaneous CD4+ Small- to Medium-Sized Pleomorphic T-Cell Lymphoma: Report of a Case With Spontaneous Resolution☆

Linfoma cutáneo primario de células T pleomórficas de pequeño y mediano tamaño CD4+: a propósito de un caso con resolución espontánea

To the Editor:

Primary cutaneous CD4+ small- to medium-sized pleomorphic T-cell lymphoma is included as a provisional entity in the group of primary cutaneous peripheral T-cell lymphomas, both in the latest WHO classification of tumors of hematopoietic and lymphoid tissues and in the WHO-EORTC classification for cutaneous lymphomas.[1,2] This lymphoma is defined by a predominance of CD4+ small- to medium-sized pleomorphic T cells, with no prior history of macules or plaques that would suggest mycosis fungoides.[1,2]

A 35-year-old man visited our department with an asymptomatic lesion on his left cheek; the lesion had appeared 4 weeks earlier and had grown rapidly. The only relevant information in the patient's past history was that he had taken allopurinol for 3 months to treat asymptomatic hyperuricemia. He had interrupted this medication 3 days before visiting our department. Physical examination revealed an oval, dome-shaped erythematous tumor measuring 3 x 4 cm on the left cheek. The tumor had well-defined borders and a shiny surface and was indurated on palpation (Fig. 1A).

A biopsy of the lesion was taken for histopathology study. The low-magnification view showed that the epidermis was not involved and revealed a dense cellular infiltrate occupying the entire thickness of the dermis and reaching the subcutaneous tissue. The neoplastic infiltrate consisted predominantly of small- to medium-sized lymphocytes with moderate pleomorphism and mild atypia. Numerous histiocytes were also found among the lymphocytes (Fig. 2). Immunohistochemistry showed the cells to be strongly positive for CD3, CD4, and CD5. Furthermore, staining was focally positive for CD8, CD20, and CD68, but negative for CD7 and CD30. The analysis of T-cell clonality using PCR for the T-cell receptor gamma (TCRG) gene showed monoclonal rearrangement. On the basis of these data we established a diagnosis of primary cutaneous CD4+ small- to medium-sized pleomorphic T-cell lymphoma.

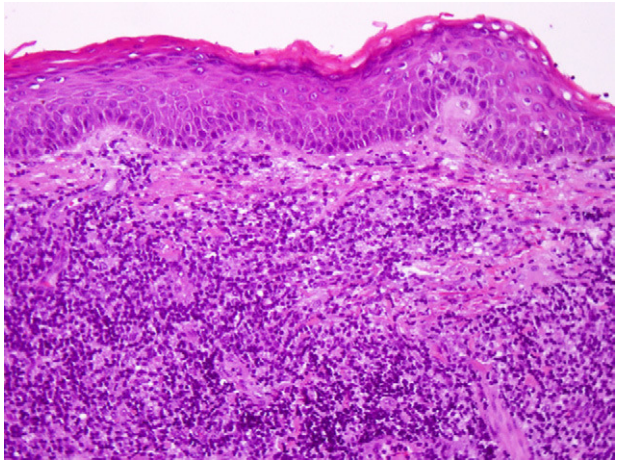

Figure 2 Dense dermal infiltrate consisting of small- and medium-sized pleomorphic lymphocytes and histiocytes (hematoxylin–eosin, original magnification x250).

Further tests included an analysis of lymphocyte populations and immunoglobulin levels, computed tomography of the neck, thorax, abdomen, and pelvis, and bone-marrow biopsy. All results were normal or negative. The lesion underwent a rapid spontaneous reduction in size and was completely flat after 6 weeks of follow-up (Fig. 1B). The area of residual hyperpigmentation was not infiltrated or hard to the touch. The patient subsequently underwent local radiation therapy using a 6-MeV electron beam, with a total dose of 4000 cGy administered at a dosage of 200 cGy per day. He remained asymptomatic at 7 months (Fig. 3).

Primary cutaneous CD4+ small- to medium-sized pleomorphic T-cell lymphoma is a rare disease and accounts for just 2% of all primary cutaneous lymphomas.[2] Clinical pre-

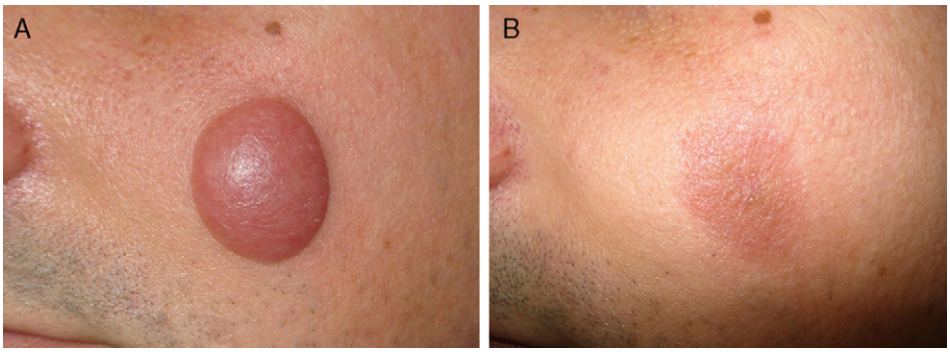

Figure 1 A, Brownish-red skin tumor on the left cheek, with a smooth, shiny surface. B, Complete remission of the lesion 6 weeks later, showing residual hyperpigmentation and a depressed central area corresponding to the biopsy site.

☆ Please cite this article as: Messeguer F, et al. Linfoma cutáneo primario de células T pleomórficas de pequeño y mediano CD4+: a propósito de un caso con resolución espontánea. Actas Dermosifiliogr.2011;102:636-8.

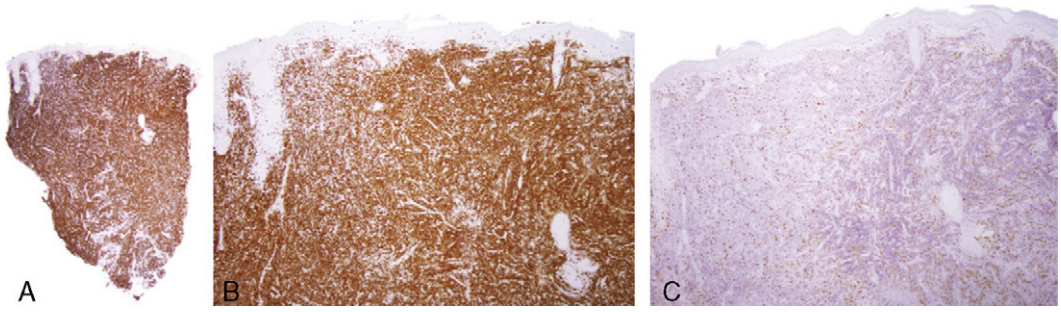

Figure 3 A and B, Strongly positive staining for CD4 in almost the entire sample (original magnifications x20 and x100). C, The histiocytes were positive for immune staining with CD68 (original magnification x100).

sentation is usually as a solitary plaque or tumor, typically located on the face, neck, or upper torso; it is asymptomatic and fast-growing.[3–6] Spontaneous total remission of the lesions, as occurred with our patient, has been previously reported in only 1 case.[3]

Histology reveals dense nodular or diffuse dermal infiltrates that tend to infiltrate the subcutaneous tissue. Focal epidermotropism is a possible finding and means that a diagnosis of mycosis fungoides should always be considered.[1,4,6,7] By definition, there is a predominance of CD4+ small- to medium-sized pleomorphic lymphocytes, although up to 30% of large pleomorphic lymphocytes may be found. Cases where a higher percentage of large cells is found should be classified as peripheral T-cell lymphoma, not otherwise specified. Mixed inflammatory infiltrates have also been reported, consisting of histiocytes, B cells, plasma cells, and, in some cases, CD8+ T cells and eosinophils.[5,8,9] TCRG analysis shows monoclonal rearrangement in 60% to 70% of cases.

The differential diagnosis should principally include benign lymphoid proliferations (T-cell pseudolymphoma, pseudolymphomatous folliculitis, papules, nodules, and solitary lymphoid tumors) and mycosis fungoides in its unilesional and granulomatous forms.[8] In our case, the rapid, self-limiting course, together with the fact that the patient had previously been treated with allopurinol, led to an initial diagnosis of T-cell pseudolymphoma. The subsequent pathology report made it possible to establish the diagnosis of primary cutaneous CD4+ small- to medium-sized pleomorphic T-cell lymphoma.

The prognosis in these lymphomas is generally very favorable, particularly in cases of solitary lesions, and 5-year survival is around 80%.[2,3,5] These cases of localized disease are usually treated with surgical excision or local radiation therapy, and more aggressive treatments such as chemotherapy are not required.[1–3,6,8] However, careful monitoring with regular follow-up visits is recommended.[8]

The usually painless course and the clinical and histologic similarity that this type of lymphoma may bear to other cutaneous lymphoid infiltrates has led some authors to suggest the term *lymphocyte proliferations of uncertain significance* to refer to cases, without forcing a diagnosis, where it is not possible to determine whether the process is benign or malignant.[8,10]

In conclusion, we present an unusual case of primary cutaneous CD4+ small- to medium-sized pleomorphic T-cell lymphoma with spontaneous remission. Because the clinical, histologic, and immunohistochemical characteristics of this type of lymphoma may coincide with those of other cutaneous lymphoid infiltrates, a careful study is required to reach a diagnosis. Dermatologists and pathologists should be aware of this entity in order to avoid unnecessary aggressive treatments.

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri S. Stein Hea. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2008. p. 312–6.
2. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105:3768–85.
3. Grogg KL, Jung S, Erickson LA, McClure RF, Dogan A. Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma: a clonal T-cell lymphoproliferative disorder with indolent behavior. Mod Pathol. 2008;21:708–15.
4. Bekkenk MW, Vermeer MH, Jansen PM, van Marion AM, Canninga-van Dijk MR, Kluin PM, et al. Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic factors in a group of 82 patients. Blood. 2003;102:2213–9.
5. García-Herrera A, Colomo L, Camos M, Carreras J, Balague O, Martínez A, et al. Primary cutaneous small/medium CD4+ T-cell lymphomas: a heterogeneous group of tumors with different clinicopathologic features and outcome. J Clin Oncol. 2008;26:3364–71.
6. Sterry W, Siebel A, Mielke V. HTLV-1-negative pleomorphic T-cell lymphoma of the skin: the clinicopathological correlations and natural history of 15 patients. Br J Dermatol. 1992;126:456–62.
7. Friedmann D, Wechsler J, Delfau MH, Esteve E, Farcet JP, de Muret A, et al. Primary cutaneous pleomorphic small T-cell lymphoma. A review of 11 cases. The French Study Group on Cutaneous Lymphomas. Arch Dermatol. 1995;131:1009–15.
8. Beltraminelli H, Leinweber B, Kerl H, Cerroni L. Primary cutaneous CD4+ small-/medium-sized pleomorphic T-cell lymphoma: a cutaneous nodular proliferation of pleomorphic T lymphocytes of undetermined significance? A study of 136 cases. Am J Dermatopathol. 2009;31:317–22.
9. Rodríguez Pinilla SM, Roncador G, Rodríguez-Peralto JL, Mollejo M, García JF, Montes-Moreno S, et al. Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma expresses follicular T-cell markers. Am J Surg Pathol. 2009;33:81–90.
10. Bachelez H. The uncertain status of cutaneous pseudolymphoma. Actas Dermosifiliogr. 2009;100 Suppl 1:33–7.

F. Messeguer,[a,*] E. Gimeno,[b] A. Agusti-Mejias,[c]
J. San Juan[d]

[a] *Servicio de Dermatología, Instituto Valenciano de Oncología, Valencia, Spain*
[b] *Servicio de Dermatología, Hospital Arnau de Vilanova, Valencia, Spain*
[c] *Servicio de Dermatología del Hospital General Universitario de Valencia*
[d] *Servicio de Anatomía Patológica, Hospital Arnau de Vilanova, Valencia, Spain*

* Corresponding author.
E-mail address: francescmb@comv.es (F. Messeguer).

doi:10.1016/j.adengl.2010.10.009

Esomeprazole-Induced Subacute Cutaneous Lupus Erythematosus☆

Lupus eritematoso cutáneo subagudo inducido por esomeprazol

To the Editor:

We report the case of a 74-year-old woman with a history of hypertension, diabetes mellitus, dyslipidemia, spondyloarthritis, and idiopathic thrombocytopenic purpura for which she had undergone splenectomy 5 years previously. She was being followed up by her rheumatologist for joint pain of inflammatory origin with low titers of rheumatoid factor and was taking lorazepam, ranitidine, domperidone, indapamide, AM3, and ursodeoxycholic acid. She attended our clinic with a pruritic disorder that had begun a week earlier and took the form of well-defined discretely desquamative erythematous papules on her back and, to a lesser extent, on her chest, thighs, and proximal upper arms. She had no blisters or mucosal lesions. These signs first appeared during winter, and the patient reported no previous sun exposure. Of interest, she reported starting esomeprazole and a vitamin complex (B_1, B_6, and B_{12}) 3 weeks before the lesions first appeared. A biopsy specimen of one of the lesions was obtained, and the patient was prescribed mometasone cream twice daily. Esomeprazole and the vitamin supplement were withdrawn.

At 3 weeks, the lesions had progressed to confluent annular erythematous-violaceous plaques on the above-mentioned sites (fig. 1). The biopsy revealed hyperkeratosis in the epidermis, epidermal atrophy, degeneration of the basal layer, lymphocytic exocytosis, spongiosis, and occasional necrotic keratinocytes. A superficial perivascular lymphohistiocytic inflammatory infiltrate was observed in the dermis (fig. 2). Based on clinical and microscopy findings, the patient was diagnosed with subacute cutaneous lupus erythematosus (SCLE).

The results of a complete blood count and routine biochemistry were unremarkable. The immunology workup revealed positive titers for antinuclear antibody (1/160), anti-SSA/Ro antibody, and anti-SSB/La antibody. These results had also been positive in laboratory studies performed 2 years previously in the rheumatology department.

Based on a suspected diagnosis of SCLE induced or exacerbated by esomeprazole, treatment with a topical corticosteroid was continued and the culprit medication was withdrawn. The lesions had completely resolved 8 weeks after the interruption of esomeprazole.

SCLE is a well-defined subtype of lupus erythematosus characterized by annular or psoriasiform lesions, limited systemic involvement, and the presence of circulating anti-SSA/Ro antibody.[1–3] An association has been described between SCLE and various drugs, including thiazides, statins, calcium channel antagonists, phenytoin, griseofulvin, tumor necrosis factor antagonists, terbinafine,[1–5] and, recently, proton pump inhibitors such as omeprazole, lansoprazole, and pantoprazole.[6–8] Esomeprazole is the S enantiomer of omeprazole and is used to treat gastroesophageal reflux disease. It came onto the market in Spain in 2002.[9]

Unlike drug-induced systemic lupus erythematosus, which usually involves positive antihistone antibody titers, drug-induced SCLE is generally associated with positive anti-SSA/Ro antibody titers, but not with positive antihistone antibody titers. In some cases, these titers become negative once the culprit agent is withdrawn.[7]

In the case we present, it is striking that anti-SSA/Ro and anti-SSB/La antibody titers were previously positive and that this finding was maintained after onset of the skin symptoms. Four of the 8 previously reported cases of SCLE induced by proton pump inhibitors presented positive antinuclear antibody titers before the onset of cutaneous symptoms; however, it is unknown whether anti-SSA/Ro or anti-SSB/La antibody titers were positive. No analytical results were available for the remaining 4 patients (Table 1).[6–8] These findings point to a predisposition to SCLE, which was triggered by proton pump inhibitors. The pathogenic mechanism responsible for the formation of antibodies is unknown. It has been postulated that binding of the drug to proteins could trigger the immune response through a hapten-type mechanism, leading to formation of antibodies.[3]

The suspect medication must be withdrawn in order to achieve resolution of the symptoms; topical or oral corticosteroids can be used as coadjuvant therapy to speed up recovery. Without withdrawal of the medication, cure is not possible, as shown in previous cases where lesions persisted despite treatment with oral corticosteroids or hydroxychloroquine.[6]

Our patient was taking a vitamin complex concomitantly with esomeprazole; however, this medication seems a highly unlikely culprit, since there have been no previous reports

☆ Please cite this article as: Alcántara-González J, et al. Lupues eritematoso cutáneo subagudo inducido por esomeprazol. Actas Dermosifiliogr. 2011;102:640-2.