Primary Cutaneous CD4+ Small/Medium-Sized Pleomorphic T-Cell Lymphoma With Expression of Follicular T-Helper Cell Markers and Spontaneous Remission☆

Linfoma cutáneo primario de células T pleomórficas de pequeño y mediano tamaño CD4+ con expresión de marcadores de linfocito T *helper* folicular y resolución espontánea

To the Editor:

The CD4+ small/medium-sized pleomorphic T-cell lymphoma (SMPTCL) is a type of primary cutaneous lymphoma included as a provisional entity in the World Health Organization-European Organization for Research and Treatment of Cancer classification of cutaneous lymphomas.[1] This lymphoma is characterized by a predominance of CD4+ small/medium-sized pleomorphic T cells and presents a favorable clinical course.

A 62-year-old man with no past medical history of interest presented an asymptomatic tumor that had appeared on his right cheek a month earlier and had shown rapid growth. Physical examination revealed a well-defined erythematous nodule measuring 2 × 1.5 cm. The nodule had a rubbery consistency and presented a central erosion (Fig. 1A).

The lesion was biopsied. On histology, a diffuse, dense infiltrate was seen to occupy the full thickness of the dermis, with extension into the subcutaneous cellular tissue; there was no evidence of epidermotropism (Fig. 2). This was a polymorphous infiltrate formed mainly of lymphocytes, histiocytes, and plasma cells. The predominant cells in the neoplastic infiltrate were small- and medium-sized lymphocytes with marked pleomorphism. Immunohistochemistry (Fig. 3) was intensely positive for CD3, CD4, and CD5, and was negative for CD8 and CD30. Poorly defined infiltrates rich in CD20+ cells without light chain restriction were also evident. The sample was also positive for PD1 and Bcl-6. Molecular biology study revealed a monoclonal rearrangement of the T-cell receptor (TCR) beta gene. The Ki67 cell proliferation index was below 20%. Epstein-Barr virus expression was negative. Further tests included an analysis of lymphocyte populations and immunoglobulin levels, computed tomography of the neck, chest, abdomen, and pelvis, and a bone-marrow biopsy. All the results were normal or negative.

After 4 weeks of follow-up, the tumor lesion underwent spontaneous regression until its complete disappearance, leaving only a scar at the site of biopsy (Fig. 1B). No changes were observed in pigmentation, and the area was not infiltrated or indurated to palpation. After a year of follow-up, the patient remained asymptomatic, with no evidence of tumor recurrence.

Since the description of SMPTCL as a provisional entity in 2005, the disease has been reported in adults and children,[2] but it accounts for only 2% of all primary cutaneous lymphomas.[1] Clinical presentation is usually as a solitary, fast-growing plaque or tumor, typically on the face, neck, or upper part of the trunk.[3]

Histologically there is a dense, nodular, or diffuse dermal infiltrate that extends into the subcutaneous cellular tissue. There is a predominance of small/medium-sized pleomorphic CD4+ T cells, although up to 30% of the population can be large pleomorphic cells.[4] A mixed inflammatory infiltrate of lymphocytes, plasma cells, eosinophils, and histiocytes can be observed in some cases.[3,5,6] By definition, these

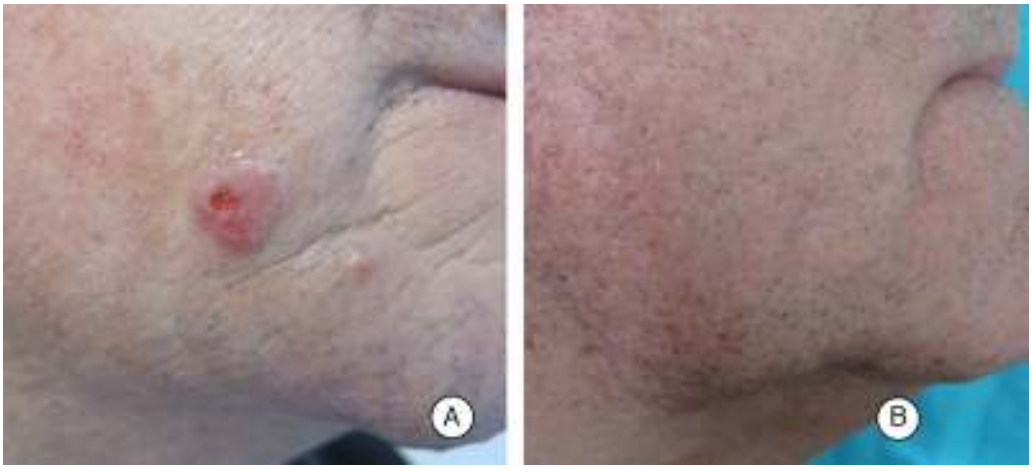

Figure 1 A, Well-defined erythematous nodular lesion on the right cheek, with an erosion affecting part of the surface. B, Complete resolution of the lesion after 4 weeks, with a scar corresponding to the site of biopsy.

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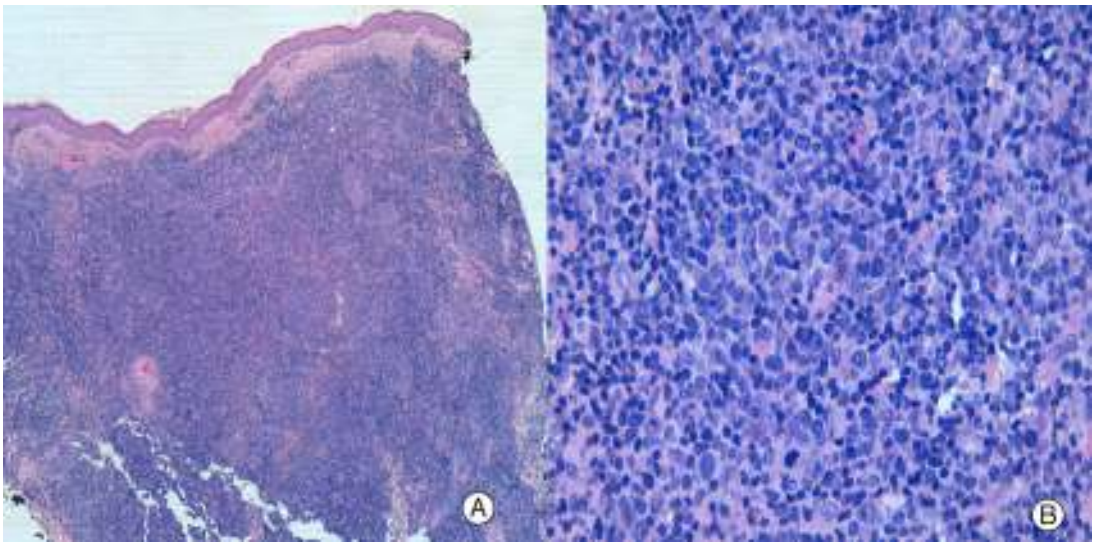

Figure 2 A, The low-power image shows a dense dermal infiltrate that extends into the subcutaneous cellular tissue but shows no epidermotropism. Hematoxylin and eosin, original magnification ×4. B, The infiltrate is formed mainly of small- and medium-sized pleomorphic lymphocytes. Hematoxylin and eosin, original magnification ×40.

lymphomas have a $CD3^+$, $CD4^+$, $CD8^-$, $CD30^-$ immunophenotype, sometimes with a loss of T-cell markers. A monoclonal rearrangement of the TCR gene is detected in the majority of cases.

Various studies have evaluated the expression of follicular helper T cells (T_{FH}) markers in this type of primary cutaneous lymphoma.[4,5] The T_{FH} cell is a specific subtype of $CD4^+$ T_H cell, usually found in the germinal center of lymphoid follicles.[7] The function of these particular lymphocytes is to regulate the immune response of B cells, favoring their differentiation into immunoglobulin-secreting plasma cells or memory B cells. A number of criteria exist

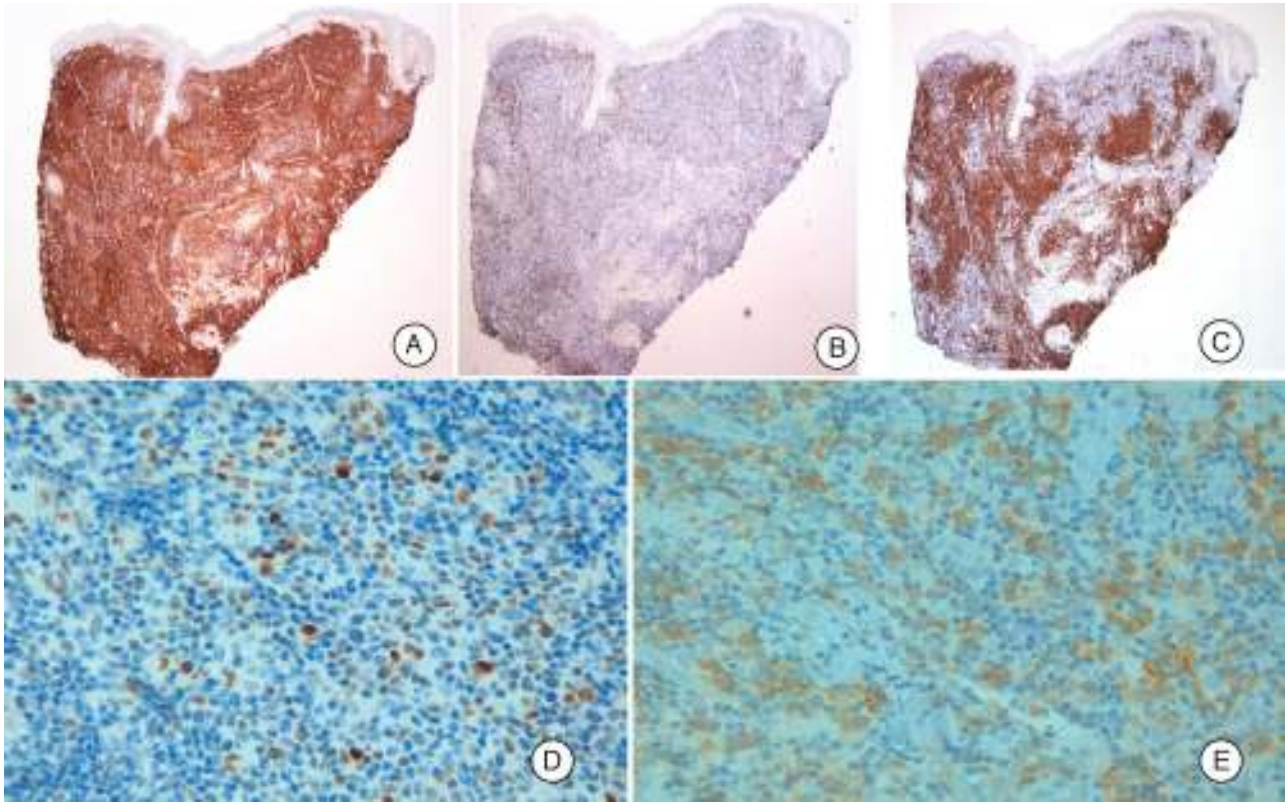

Figure 3 A and B, Immunohistochemistry stains show the cells to be strongly positive for CD4 and very weakly positive for CD8. CD4 and CD8 stains, original magnification ×4. C, Poorly defined infiltrates rich in $CD20^+$ cells. CD20 stain, original magnification ×4. D and E, Cell expression of Bcl-6 and PD1. Bcl-6 and PD1 stains, original magnification ×40.

to differentiate T_{FH} lymphocytes from other T_H cell subtypes, including the expression of a series of markers such as CXCL13, CD10, Bcl-6, ICOS, and PD1. None of these markers is wholly specific to T_{FH} cells, as some of them have occasionally been detected in cases of mycosis fungoides and Sezary syndrome, as well as in adult T-cell lymphomas and leukemias.[8] However, the combined expression of various of these markers in a lymphoproliferative disease is highly specific to an origin in neoplastic T_{FH} lymphocytes.[8] In our case, the cells were positive for the markers Bcl-6 and PD-1. This expression of T_{FH}-cell markers in the neoplastic lymphocytes may explain the foci of $CD20^+$ B-cell infiltrates typically found in SMPTCL,[3,5] as occurred in our case.

The prognosis of these lymphomas is excellent, particularly in cases with isolated lesions.[1,6] In localized lesions, surgical excision or local radiotherapy are the preferred alternatives.[1] Only 2 cases of spontaneous regression of untreated SMPTCL have been reported.[9,10] The heterogeneous nature of this entity has led some authors to propose the term *cutaneous proliferation of pleomorphic T lymphocytes of undetermined significance* to refer to cases in which it is impossible determine the benign or malignant nature of the disease, and thus avoid forcing a diagnosis to be made.[3,9]

Although it is sometimes difficult to distinguish this type of cutaneous T-cell lymphoma from reactive lymphoproliferative disorders, SMPTCL is a recognizable disease with characteristic expression of T_{FH}-cell markers. In conclusion, we have presented an atypical case of SMPTCL with rapid, spontaneous resolution, and with expression of the markers Bcl-6 and PD1, which suggests a T_{FH} cell origin of the neoplastic disease.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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D. Ayala,[a,*] M.D. Ramón,[a] M. Cabezas,[b] E. Jordá[a]

[a] *Servicio de Dermatología, Hospital Clínico Universitario de Valencia, Valencia, Spain*
[b] *Servicio de Anatomía Patológica, Hospital Clínico Universitario de Valencia, Valencia, Spain*

* Corresponding author.
E-mail address: dayalca83@hotmail.com (D. Ayala).

Intralesional Sodium Thiosulfate to Treat Calciphylaxis☆

Calcifilaxis tratada con tiosulfato sódico intralesional

To the Editor:

Calciphylaxis or calcifying uremic arteriopathy is characterized by calcification of the media of the small arteries and arterioles of the skin, provoking cutaneous ischemia.[1,2]

A 45-year-old woman with end-stage renal disease (ESRD) secondary to glomerulonephritis and on hemodialysis since 2008, consulted for a 10-month history of multiple, intensely painful ulcers on both lower limbs; the pain was resistant to opioids. She had previously undergone kidney transplant with subsequent rejection. Physical examination of the lower limbs revealed multiple skin ulcers, some with necrotic slough, on a background of livedo racemosa and retiform purpura. The largest ulcer measured approximately 6 cm in diameter (Fig. 1, A and B). Important findings on the blood tests were secondary hyperparathyroidism with parathormone levels of 911 pg/mL, calcium 10.1 mg/dL (normal range, 8.2-10.3 mg/dL), and phosphorus, 7.7 mg/dL

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