

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.<sup>8</sup> However, the combined expression of various of these markers in a lymphoproliferative disease is highly specific to an origin in neoplastic  $T_{FH}$  lymphocytes.<sup>8</sup> 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<sup>+</sup> B-cell infiltrates typically found in SMPTCL,<sup>3,5</sup> as occurred in our case.

The prognosis of these lymphomas is excellent, particularly in cases with isolated lesions.<sup>1,6</sup> In localized lesions, surgical excision or local radiotherapy are the preferred alternatives.<sup>1</sup> Only 2 cases of spontaneous regression of untreated SMPTCL have been reported.<sup>9,10</sup> 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 to determine the benign or malignant nature of the disease, and thus avoid forcing a diagnosis to be made.<sup>3,9</sup>

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.

## References

1. 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.
2. Baum CI, Link BK, Neppalli VT, Swick BL, Liu V. Reappraisal of the provisional entity primary cutaneous CD4<sup>+</sup> small/medium

3. pleomorphic T-cell lymphoma: A series of 10 adult and pediatric patients and review of the literature. *J AM Acad Dermatol*. 2011;65:739–48.
3. Beltraminelli H, Leinweber B, Kerl H, Cerroni L. Primary cutaneous CD4<sup>+</sup> 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;4:317–22.
4. Ally MS, Prasad Hunasehally RY, Rodríguez-Justo M, Martín B, Verdolini R, Attard N, Child F, et al. Evaluation of follicular T-helper cells in primary cutaneous CD4<sup>+</sup> small/medium pleomorphic T-cell lymphoma and dermatitis. *J Cutan Pathol*. 2013;40:1006–13.
5. 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.
6. García-Herrera A, Colomo L, Camos M, Carreras J, Balague O, Martínez A, et al. Primary cutaneous small/medium CD4<sup>+</sup> T-cell lymphomas: A heterogeneous group of tumors with different clinicopathologic features and outcome. *J Clin Oncol*. 2008;26:3364–71.
7. Laurent C, Fazilleau N, Brousset P. A novel subset of T-helper cells: follicular T-helper cells and their markers. *Haematologica*. 2010;95:356–8.
8. Battistella M, Beylot-Barry M, Bachelez H, Rivet J, Vergier B, Bagot M. Primary cutaneous follicular helper T-cell lymphoma. A new subtype of cutaneous T-cell lymphoma reported in a series of 5 cases. *Arch Dermatol*. 2012;148:832–9.
9. Messegueur F, Gimeno E, Agustí-Mejías A, San Juan J. Primary cutaneous CD4<sup>+</sup> small-to medium-sized pleomorphic T-cell lymphoma: Report of a case with spontaneous resolution. *Actas Dermosifiliogr*. 2011;102:636–8.
10. Grogg KI, Jung S, Erickson LA, McClure RF, Dogan A. Primary cutaneous CD-4 positive small/medium-sized pleomorphic T-cell lymphoma: A clonal T-cell lymphoproliferative disorder with indolent behavior. *Mod Pathol*. 2008;21:708–15.

D. Ayala,<sup>a,\*</sup> M.D. Ramón,<sup>a</sup> M. Cabezas,<sup>b</sup> E. Jordá<sup>a</sup>

<sup>a</sup> Servicio de Dermatología, Hospital Clínico Universitario de Valencia, Valencia, Spain

<sup>b</sup> 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<sup>☆</sup>



### 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.<sup>1,2</sup>

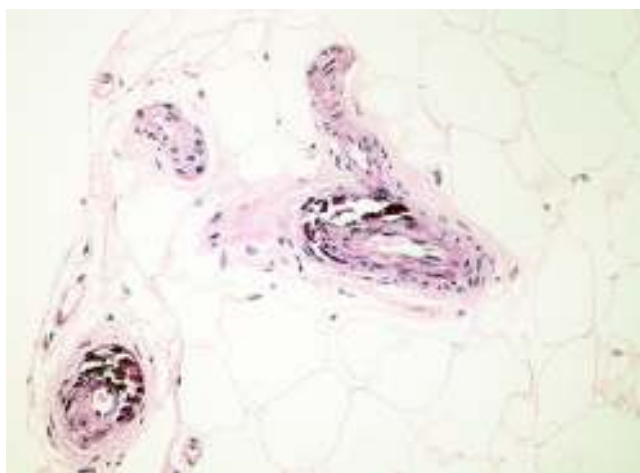
A 45-year-old woman with end-stage renal disease (ESRD) secondary to glomerulonephritis and on hemodialysis since 2008, consulted for a 10-month history of multiple, intensely painful ulcers on both lower limbs; the pain was resistant to opioids. She had previously undergone kidney transplant with subsequent 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

<sup>☆</sup> Please cite this article as: Ossorio-García L, Jiménez-Gallo D, Arjona-Aguilera C, Linares-Barrios M. Calcifilaxis tratada con tiosulfato sódico intralesional. *Actas Dermosifiliogr*. 2016;107:360–363.



**Figure 1** A and B, Skin ulcers with necrotic slough on a background of livedo racemosa and retiform purpura secondary to calciphylaxis. C and D, Healing of the calciphylaxis-induced ulcers after treatment with intralesional sodium thiosulfate.

(normal range, 2.7-4.5 mg/dL). Other additional tests, including complete blood count, general biochemistry, coagulation, serology for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, hypercoagulability study, autoimmunity, microbiology culture, and echocardiography were normal or negative. Skin biopsy was compatible with calciphylaxis (Fig. 2).



**Figure 2** Biopsy showing calcification of the media of blood vessels in the subcutaneous cellular tissue. Hematoxylin and eosin, original magnification  $\times 200$ .

After signing the informed consent, the patient started off-label treatment with intralesional sodium thiosulfate 1/6 molar, injecting 10 mL of the solution around the borders of the ulcers. The only adverse effect was pain during the injection; this improved when oral transmucosal fentanyl was administered prior to the injections. After the first treatment, the patient reported rapid pain relief that enabled the opioids to be withdrawn. The treatment was repeated each month for 6 months, achieving

**Table 1** Risk Factors for the Onset of Calciphylaxis in Patients With End-Stage Renal Disease.

Hyperparathyroidism
Calcium-phosphate product > 70
Vitamin D treatment
Diabetes mellitus
Systemic hypertension
Female
Obesity
Treatment with warfarin
Protein S or C deficiency
Immunosuppression
Liver disease
Hypoalbuminemia/weight loss/malnutrition
Congestive heart failure
Arteriovenous fistula

**Table 2** Investigation and Differential Diagnosis of Patients With Suspected Calciphylaxis.

Disease	Additional Tests	Comment
Antiphospholipid syndrome	IgG and/or IgM phospholipid antibodies	Arterial or venous thrombosis
	IgG and/or IgM $\beta$ 2 glycoprotein antibodies	Recurrent abortions
Type I cryoglobulinemia	Lupus anticoagulant Monoclonal peak and/or markedly elevated cryoglobulins in serum	B-cell lymphoproliferative disease. Predominant manifestations are of occlusive vascular disease (livedo racemosa/retiform purpura) vs vasculitis (palpable purpura) Diagnostic criteria of the autoimmune disease
Autoimmune diseases with vasculitis (PAN, MPA, SLE, rheumatoid arthritis, Churg-Strauss syndrome, Wegener granulomatosis). Thrombophilias	ANA Anti-DNA Anti-ENA ANCA Thrombophilia studies	
Disseminated intravascular coagulation	Thrombocytopenia  Prolonged coagulation times Peripheral blood smear (schistocytes) Elevation of fibrinogen degradation products and D-dimer	Purpura fulminans usually secondary to sepsis. May also be associated with trauma or obstetric complications
Atrial myxoma	Echocardiography	Benign tumor arising in the endothelial cells and frequently localized in the left atrium
Pharmacological (propylthiouracil, cocaine, levamisole)	Detection of atypical ANCA in the standard ANCA assay	Medical history. Consumption of cocaine adulterated with levamisole is associated with the presence of purpura especially in the earlobes and elastase-type atypical ANCA
Sickle cell anemia	Peripheral blood smear	Homozygous S hemoglobinopathy
Coumarin-induced skin necrosis	Protein S and C deficiency	Warfarin consumption in the previous 3 to 10 days. Predominance in obese women in body areas with more subcutaneous cellular tissue
Livedoid vascular disease	Skin biopsy	Hyalinization on histology Predominantly affects the malleolar area. Atrophic scars with telangiectasias and marginal pigmentation (white atrophy)
Sneddon syndrome	Skin biopsy	Neurologic disturbances, livedo reticularis, and thrombotic phenomena
Cholesterol emboli	Skin biopsy	Cholesterol crystals on histology History of catheterization, angioplasty, or angioradiology, or after starting anticoagulant or thrombolytic treatment
Primary hyperoxaluria	Skin biopsy	Birefringent crystals on histology Autosomal recessive hereditary disease that produces an increase in the body concentration of calcium oxalate, with the consequent precipitation of calcium oxalate crystals in the joints, kidneys (nephrolithiasis), heart, eyes, and skin
Lucio phenomenon	Suspected leprosy	Reactive form of untreated diffuse lepromatous leprosy

Abbreviations: ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; ENA, extractable nuclear antigen; MPA, microscopic polyangiitis; PAN, polyarteritis nodosum; SLE, systemic lupus erythematosus.

complete remission of all the skin ulcers (Fig. 1C and D). Maintenance therapy was then administered with an intravenous sodium thiosulfate regimen after each hemodialysis session. At 6 months the patient returned to outpatients

with new lesions. A further 3 monthly injections of sodium thiosulfate were therefore administered, and remission of the lesions was once again achieved. The patient now receives injections intermittently, whenever new

symptoms develop, and overall control of the disease is good.

Calciphylaxis is characterized by the appearance of very painful skin ulcers and necrosis, mainly affecting patients with ESRD on hemodialysis, with an estimated prevalence between 1% and 4% in these patients.<sup>1-3</sup> Mortality is high and is most commonly due to sepsis.<sup>4</sup> Cases of ischemia of internal organs have been reported.<sup>2</sup>

Risk factors for the onset of calciphylaxis in patients with ESRD are summarized in Table 1.<sup>1</sup> Calciphylaxis has been described in patients without uremia. These cases are associated with primary hyperparathyroidism, malignancy, alcoholic liver disease, and connective tissue diseases, and are grouped under the name calcific nonuremic arteriopathy.<sup>5</sup>

Clinically, calciphylaxis manifests as a livedo racemosa syndrome that progresses to retiform purpura and skin necrosis with the formation of very painful ulcers.<sup>6-8</sup> In Table 2 we describe the differential diagnosis and workup of this syndrome.

Diagnosis is mainly clinical. Skin biopsy is the gold-standard test for the diagnosis of calciphylaxis, although systematically performing biopsies when this disease is suspected is not recommended because of the risk of infection or poor wound healing. Histopathology findings include calcification of the media of small arteries and arterioles, intimal proliferation, small-vessel thrombosis and endovascular fibrosis, necrosis of the subcutaneous cellular tissue, and panniculitis.<sup>2</sup> No laboratory alterations specific to this disease have been detected. However, the presence of an elevated calcium-phosphate product increases the sensitivity for its detection.<sup>7</sup>

Among the imaging studies, ultrasound may show hyper-echoic foci with a posterior acoustic shadow suggestive of calcifications. Modified mammography can facilitate early diagnosis of calciphylaxis. A bone scan can be useful to detect calcium deposits in the subcutaneous cellular tissue and thus help to define the extent of the disease and evaluate the response to treatment.<sup>9</sup>

Treatment protocols have not been standardized. Treatment is based mainly on the use of bisphosphonates and intravenous sodium thiosulfate. Sodium thiosulfate acts as an antioxidant and vasodilator, producing rapid pain relief, and as an intravascular and intraparenchymal chelator of calcium salts.<sup>3</sup> Intravenous sodium thiosulfate is used at a dose of 25 mg immediately after each hemodialysis session. This treatment is considered innocuous and is inexpensive. The most common side effects are nausea and vomiting, rhinorrhea, and headache. The most serious adverse effect is metabolic acidosis.<sup>10</sup>

In the scientific literature, only Strazzula et al.<sup>11</sup> have described the use of intralesional sodium thiosulfate in 4 patients with calciphylaxis.

Although further studies are necessary to evaluate the therapeutic effect of intralesional sodium thiosulfate, we

would like to draw attention to certain aspects. Intralesional treatment was very successful and led to rapid relief of the ischemic pain caused by calciphylaxis. In our patient, this intralesional treatment led to complete healing of the calciphylaxis-induced skin lesions, an objective not achieved with intravenous administration. We therefore consider that for cases that do not respond to standard intravenous treatment, the adjuvant role of intralesional sodium thiosulfate should be evaluated. The tolerance of the combined treatments was good, and although pain was the main limitation, it could be reduced by the previous administration of analgesia.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## References

1. Yerram P, Chaudhary K. Calcific uremic arteriopathy in end stage renal disease: Pathophysiology and management. *Ochsner J.* 2014;14:380-5.
2. Hayashi M. Calciphylaxis: Diagnosis and clinical features. *Clin Exp Nephrol.* 2013;17:498-503.
3. Vedyas C, Winterfield LS, Vleugels RA. Calciphylaxis: A systematic review of existing and emerging therapies. *J Am Acad Dermatol.* 2012;67:e253-60.
4. Garcia CP, Roson E, Peon G, Abalde MT, De La Torre C. Calciphylaxis treated with sodium thiosulfate: report of two cases. *Dermatol Online J.* 2013;19:19616.
5. Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from nonuremic causes: A systematic review. *Clin J Am Soc Nephrol.* 2008;3:1139-43.
6. Herrero C, Guilbert A, Mascaró-Galy JM. *Livedo reticularis de las piernas: metodología de diagnóstico y tratamiento.* *Actas Dermosifiliogr.* 2008;99:598-607.
7. Markova A, Lester J, Wang J, Robinson-Bostom L. Diagnosis of common dermatopathies in dialysis patients: A review and update. *Semin Dial.* 2012;25:408-18.
8. Wilmer WA, Magro CM. Calciphylaxis: Emerging concepts in prevention, diagnosis, and treatment. *Semin Dial.* 2002;15:172-86.
9. Ng AT, Peng DH. Calciphylaxis. *Dermatol Ther.* 2011;24:256-62.
10. Ross EA. Evolution of treatment strategies for calciphylaxis. *Am J Nephrol.* 2011;34:460-7.
11. Strazzula L, Nigwekar SU, Steele D, Tsiaras W, Sise M, Bis S, et al. Intralesional sodium thiosulfate for the treatment of calciphylaxis. *JAMA Dermatol.* 2013;149:946-9.

L. Ossorio-García,\* D. Jiménez-Gallo, C. Arjona-Aguilera, M. Linares-Barrios

*Unidad de Gestión Clínica de Dermatología Médico-Quirúrgica y Venereología, Hospital Universitario Puerta del Mar, Cádiz, Spain*

\* Corresponding author.

E-mail addresses: [lidia.osga@gmail.com](mailto:lidia.osga@gmail.com), [lidia.ossoriogarcia@gmail.com](mailto:lidia.ossoriogarcia@gmail.com) (L. Ossorio-García).