

5. González-Sixto B, Conde A, Mayo E, Pardavila R, De la Torre C, Cruces M. Sarcoma de Kaposi asociado a corticoterapia sistémica. *Actas Dermosifiliogr.* 2007;98:553-5.
6. Antón E. Kaposi's sarcoma in an immunocompetent patient following corticosteroid therapy. *Eur J Intern Med.* 2008; 19:226.
7. Rady PL, Hodak E, Yen A, Memar O, Trattner A, Feinmesser M, et al. Detection of human herpesvirus-8 DNA in Kaposi's sarcomas from iatrogenically immunosuppressed patients. *J Am Acad Dermatol.* 1998;38:429-37.
8. Cohen CD, Horster S, Sander CA, Bogner JR. Kaposi's sarcoma associated with tumour necrosis factor alpha neutralising therapy. *Ann Rheum Dis.* 2003;62:684.
9. Sánchez-Salas MP, Oncins Torres R, López Franco I. Sarcoma de Kaposi iatrogénico en una paciente en tratamiento con fármaco anti-TNF α . Poster presented at the 37th National Conference of

the Spanish Academy of Dermatology and Venereology, June 2009.

M.L. Martínez-Martínez,^{a,*} L.J. Pérez-García,^a
E. Escario-Travesedo,^a and P.A. Ribera-Vaquerizo^b

^a*Servicio de Dermatología, Complejo Hospitalario Universitario de Albacete, Albacete, Spain*

^b*Servicio de Digestivo, Complejo Hospitalario Universitario de Albacete, Albacete, Spain*

*Corresponding author.

E-mail address: mlmartinezm@sescam.jccm.es, marialuisamx2@hotmail.com (M.L. Martínez-Martínez).

Angioendotheliomatosis Associated With Chronic Venous Insufficiency

Angioendoteliomatosis reactiva asociada a insuficiencia venosa crónica

To the Editor:

Reactive angioendotheliomatosis (RAE) is the name introduced by Tappeiner and Pflieger in 1963 to refer to a rare condition characterized by a benign proliferation of endothelial cells. It has been observed in patients with concurrent systemic diseases, in whom vascular occlusion or underlying vascular disease favors a reactive proliferation of endothelial cells. Presentation varies from multiple foci of erythematous macules, ecchymoses, or purpuric plaques to ulcerated plaques affecting the trunk, limbs, or face.¹ Histology shows vascular proliferation with obliteration of the lumina secondary to endothelial cell hyperplasia and noninflammatory microthrombosis. The differential diagnosis must include benign and malignant vascular tumors, particularly Kaposi sarcoma and angiosarcoma. RAE has no specific treatment; it tends to be self-limiting and resolves spontaneously or after treatment of the underlying disorder.

We present the case of a 68-year-old woman who consulted for the progressive appearance of violaceous plaques on the skin of the left leg. The plaques were completely asymptomatic and had gradually enlarged over several months. Examination revealed multiple erythematous-purpuric macules and plaques on the left leg. The lesions had an irregular outline with an atrophic center that was more yellow in color and on palpation they had an infiltrated, fibrous texture. The clinical findings were suggestive of Kaposi sarcoma (Figure 1). The patient's history included chronic venous insufficiency treated surgically 30 years earlier by varicose vein stripping in the left leg and sclerotherapy in the same leg 20 years later. Based on this history, we also considered a diagnosis of stasis dermatitis. Hematoxylin-eosin staining of a histology specimen showed a vascular proliferation of capillaries lined by prominent

endothelial cells, with microthrombi that occluded the vascular lumen; there was no pleomorphism or nuclear atypia and there were few mitoses. The findings were suggestive of reactive angioendotheliomatosis (Figure 2A). Immunohistochemistry was positive for CD31, confirming the vascular origin of the proliferative cells (Figure 2B), and was negative for CD68. Additional studies, including complete blood count, biochemistry, coagulation, antiphospholipid antibodies, hepatitis serology, rheumatoid factor, protein electrophoresis, and immunoelectrophoresis, were normal or negative. The patient was diagnosed with RAE associated with chronic venous insufficiency; the injection of varicose vein sclerosant could have played an additional pathogenic role. The clinical course during follow-up was favorable, with stability, spontaneous regression, and persistence of discrete brownish macules at revision after 1 year.

RAE is a rare disorder characterized by the presence of



Figure 1 Clinical appearance of reactive angioendoteliomatosis: poorly delimited, infiltrated plaques and macules on the leg, with atrophic central areas, clinically consistent with a malignant vascular tumor.

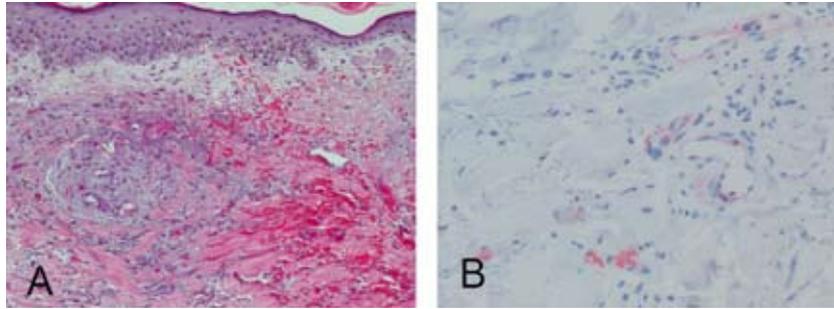


Figure 2 A, Proliferation of endothelial cells and intravascular thrombosis that block the vessel lumen, with intraluminal hyaline microthrombosis (hematoxylin-eosin, original magnification $\times 100$). B, Immunohistochemistry positive for CD31, an endothelial cell marker.

cutaneous vascular lesions that appear in the context of various types of systemic diseases.²⁻⁴ It is a benign, self-limiting vascular disorder that only affects the skin.

Presentation is variable and nonspecific, which hinders diagnosis.⁷ It usually manifests as multiple, poorly delimited purpuric macules or plaques with irregular borders. The plaques develop slowly but progressively and may resemble Kaposi sarcoma. Other forms of presentation are RAE in ulcerated plaques, ecchymoses, or cellulitis-like plaques. The condition is typically asymptomatic, but there have been occasional reports of fever, shivers, general malaise, and weight loss. It often affects the trunk, limbs, or face. The mean age of presentation is between 50 and 60 years, with similar prevalence in both sexes. According to most authors, the histologic differential diagnosis includes Kaposi sarcoma, angiosarcoma, plaque morphea, calciphylaxis, and other benign and malignant vascular tumors.⁵⁻⁸ In the case of RAE associated with chronic venous insufficiency we describe, it was essential to rule out the diagnosis of stasis dermatitis, which has similar clinical and histopathologic traits to RAE but is characterized by the proliferation of capillaries running perpendicular to the skin and lined with fine endothelial cells and surrounded by variable degrees of dermal fibrosis containing hemosiderin deposits. The definitive diagnosis of RAE requires histologic study showing dense proliferation of small capillary vessels and hyaline microthrombi that obliterate the lumen of pre-existing dermal vessels,⁸ with the occasional presence of a mild inflammatory infiltrate. Nuclear atypia and cellular pleomorphism are not observed, and there are few mitoses. Immunohistochemistry is positive for endothelial cell markers CD31 and CD34, and negative for other markers such as CD68 and podoplanin,^{9,10} which would stain histiocytic cells and lymphatic endothelium, respectively. RAE has been associated with numerous concomitant diseases and disorders able to cause total or subtotal vascular occlusion, leading to tissue hypoxia with the subsequent increase in circulating angiogenic factors. In decreasing frequency, the conditions with which RAE has been associated include renal disease, antiphospholipid syndrome, acute bacterial endocarditis, valve disease,

renal transplantation, atherosclerosis, cryoglobulinemia, myelodysplastic syndrome, and leukocytoclastic vasculitis.¹ In the literature there are no reports of RAE associated with chronic venous insufficiency, although the persistent hypoxia in these cases could act as a trigger for RAE, as in the other diseases. There is no specific treatment, and the disease is managed by treating the underlying systemic disorder. Lesions tend to improve or disappear spontaneously, but recurrences are common.

References

1. Kirke S, Angus B, Kesteven PJ, Calonje E, Simpson N. Localized reactive angioendotheliomatosis. *Clin Exp Dermatol.* 2007;32:45-7.
2. Shyong EQ, Gorevic P, Lebowitz M, Phelps RG. Reactive angioendotheliomatosis and sarcoidosis. *Int J Dermatol.* 2002;41:894-7.
3. Ortonne N, Vignon-Pennamen MD, Majdalani G, Pinquier L, Janin A. Reactive angioendotheliomatosis secondary to dermal amyloid angiopathy. *Am J Dermatopathol.* 2001;23:315-9.
4. Creamer D, Black MM, Calonje E. Reactive angioendotheliomatosis in association with the antiphospholipid syndrome. *J Am Acad Dermatol.* 2000;42(5 Pt 2):903-6.
5. Rongioletti F, Rebora A. Cutaneous reactive angiomatosis: patterns and classification of reactive vascular proliferation. *J Am Acad Dermatol.* 2003;49:887-96.
6. McMenamin ME, Fletcher CD. Reactive angioendotheliomatosis: a study of 15 cases demonstrating a wide clinicopathologic spectrum. *Am J Surg Pathol.* 2002;26:685-97.
7. Aguayo-Leiva I, Vano-Galván S, Salguero I, Carrillo-Gijón R, Vallés A, Herrera P, et al. Reactive angioendotheliomatosis in a patient with myelodysplastic syndrome presenting as a cellulitis-like plaque. *Eur J Dermatol.* 2009;19:182-3.
8. Requena L, Fariña MC, Renedo G, Alvarez A, Yús ES, Sanguenza OP. Intravascular and diffuse dermal reactive angioendotheliomatosis secondary to iatrogenic arteriovenous fistulas. *J Cutan Pathol.* 1999;26:159-64.
9. Requena L, El-Shabrawi-Caelen L, Walsh SN, Segura S, Ziemer M, Hurt MA, et al. Intralymphatic histiocytosis. A clinicopathologic study of 16 cases. *Am J Dermatopathol.* 2009;31:140-51.
10. Mensing CH, Krenzel S, Tronnier M, Wolff HH. Reactive

angioendotheliomatosis: is it 'intravascular histiocytosis'?
J Eur Acad Dermatol Venereol. 2005;19:216-9.

A. Agusti,* P. Hernández, V. Oliver, R. García,
 and V. Alegre de Miquel

Servicio de Dermatología, Consorcio Hospital General

Universitario, Valencia, Spain

*Corresponding author.

E-mail address: annaagusti@comv.es (A. Agusti).

Blepharoconjunctivitis Due to Phenylephrine

Blefarconjuntivitis alérgica por fenilefrina

To the Editor:

Phenylephrine is an α -adrenergic receptor agonist used in topical preparations such as eye drops, ear drops, and skin creams.

We present the case of a 60-year-old man who had suffered acute myocardial infarction and a cerebrovascular accident in 1980. In April 2009 he attended the Ophthalmology Emergency Department of our hospital with a bilateral mucopurulent conjunctival secretion that had developed 3 days earlier. In the preparation for the ophthalmological examination, various eye drops (Colircusi Atropine 1%, Colircusi Anesthetic, Colircusi Tropicamide, Colircusi Cycloplegic, and Colircusi Phenylephrine) were used. These had been administered to the patient on 2 previous occasions for similar examinations. After the examination he was diagnosed with acute bacterial conjunctivitis, for

which various eye drops (Azydop [azithromycin dihydrate] Acuolens [sodium chloride and hypromellose] and Lipolac [topical carbomer]) were prescribed, but not used.

Two hours after discharge from the emergency department, the patient began to experience increased reddening of the eye and progressive edema of both eyelids (Figure 1). The marked worsening of the patient's condition, with involvement of the skin of the eyelids and the appearance of vesicles on an erythematous plaque on the neck, led to a suspicion of contact dermatitis. The patient was told not to use the eye drops that had been prescribed and treatment was started with methylprednisolone aceponate cream, applied once daily for 4 days. The initial conjunctivitis resolved spontaneously, as the eye drops were never applied, and the lesions on the eyelids improved, with complete resolution of the symptoms in 10 days.

Due to the suspicion of contact dermatitis caused by a component of the eye drops used to prepare the patient for ophthalmologic examination in the emergency department, we performed patch tests. The standard batteries of the Spanish Contact Dermatitis and Skin Allergy Research Group (GEIDAC) (Thin-layer Rapid Use Epicutaneous [TRUE] Test, Mekos Laboratories, ApS, Denmark, and additional allergens of Chemotechniques Diagnostics, Sweden), the Martí Tor ophthalmic tray (atropine sulfate 1%, chlorhexidine digluconate 0.5%, disodium edetate 1%, phenylmercuric acetate 0.5%, phenylmercuric nitrate 0.01%, idoxuridine, papain 1%, pilocarpine chloride,



Figure 1 Edema of the eyelids following the application of eye drops in the emergency department.



Figure 2 Patch tests. Positive (+++) on day 7 for Colircusi Phenylephrine. It can be seen that the results were negative for the entire standard battery, including thimerosal, and for the other eye drops used.