high molecular weight keratins but not CEA, GCDFP, or low molecular weight keratins such as CK8.

A lesion with dual morphological and immunohistochemical differentiation is therefore only consistent with a diagnosis of a mixed BD and EPD lesion, with expression of high molecular weight keratins in the areas of BD, and of CEA, GCDFP, and CK8 in the areas of EPD.

Mixed vulvar lesions are infrequent, with only 6 cases described in the literature.[3-8]

There are 3 hypotheses regarding the origin of mixed BD and EPD vulvar lesions. The first is that the a part of the tumor dedifferentiates from another part, as occurs in liposarcomas or chordomas with focal divergent differentiation. This theory does not seem feasible in our case, however, as we have no morphological or immunohistochemical evidence of transition between 2 tumors. The second hypothesis is that the tumor is a collision tumor (an incidental lesion). The third possibility is that both parts of the tumor are derived from a stem cell. The latter hypothesis could be applied to our case, since—in addition to the fact that the plasticity of stem cells has been proven—this hypothesis fits with current and recognized theories of carcinogenesis. However, since our immunohistochemistry results for p16 were positive in the areas of BD, but negative in the areas of EPD—indicating that the BD, but not the EPD, was associated with the human papilloma virus—the only hypothesis we were unable to rule out was the second one, namely, a collision of 2 different tumors.

From the therapeutic point of view, the patient was diagnosed with an in situ carcinoma of the vulva, and aggressive treatment—vulvectomy, the treatment of choice for this type of lesion—was performed. Other treatments are currently being investigated, such as photodynamic therapy, which is already used in diseases such as psoriasis and basal cell carcinoma, with cure rates for BD ranging between 90% and 100% achieved after 2 sessions of therapy.[9] For EPD, surgery with wide margins (2 cm or more) is considered the treatment of choice by many authors. A better prognosis is obtained with more radical excision because Paget cells may be encountered beyond the macroscopic limits of the lesion, and, if not adequately removed, recurrence is possible. More recently the treatment of these lesions using Mohs micrographic surgery has been studied.[10]

References

1. McKee PH, Calonje E, Granter S. Pathology of the skin. London: Elsevier Mosby; 2005. p. 523.
2. Parker LP, Parker JR, Bodurka-Bevers D, Deavers M, Bevers MW, Shen-Gunther J, et-al. Paget's disease of the vulva: pathology, patterns of involvement and prognosis. Gynecol Oncol. 2000; 77:183-9.
3. Ohnishi T, Watanabe S. The use of cytokeratins 7 and 20 in the diagnosis of primary and secondary extramammary Paget disease. Br J Dermatol. 2000;142:243-7.
4. Brainard JA, Hart WR. Proliferative epidermal lesions associated with anogenital Paget's disease. Am J Surg. Pathol. 2000;24:543-52.
5. Bathia P, Ahuja A, Suri V. Vulval intraepithelial neoplasia with extramammary Paget's disease: a rare association. J Clin Pathol. 2007;60:110-2.
6. Matsumoto M, Ishiguro M, Ikeno F, Ikeda M, Kamijima R, Hirata Y, et al. Combined Bowen disease and extramammary Paget disease. J Cutan Pathol. 2007;34(Suppl 1):47-51.
7. Orlandi A, Piccione E, Sesti F, Spagnoli LG. Extramammary Paget's disease associated with intraepithelial neoplasia of the vulva. J Eur Acad Dermatol Venereol. 1999;12:183-5.
8. Orlandi A, Francesconi A, Spagnoli LG. Simultaneous vulvar intraepithelial neoplasia and Paget's disease. Report of two cases. Int J Gynecol Cancer. 2001;11:224-8.
9. Fernández-Guarino M, García-Morales I, Harto A, Montull C, Pérez-García B, Jaén P. Terapia fotodinámica: nuevas indicaciones. Actas Dermosifiliogr. 2007;98:377-95.
10. Gutiérrez-Pascual M, Gómez de la Fuente E, Vidente-Martín FJ, Pinedo-Moraleda F. Enfermedad de Paget extramamaria: descripción de dos casos tratados con cirugía micrográfica de Mohs. Actas Dermosifiliogr. 2009;100:239-40.

G. Muñoz,* C. Hörndler, P. Sota, and M.J. Ríos-Mitchell

Servicio de Anatomía Patológica, Hospital Universitario Miguel Servet, Zaragoza, Spain

*Corresponding author.
E-mail address: guillermomunoz7@hotmail.com
(G. Muñoz).

Sneddon Syndrome Associated with Urticarial Vasculitis and Factor V Leiden Mutation

Síndrome de Sneddon asociado a urticaria vasculitis y mutación del factor V Leiden

To the Editor:

Sneddon syndrome consists of the association of livedo reticularis with cerebrovascular ischemic attacks.[1] It is believed to be a thrombotic disorder, although its pathophysiology is not fully understood, particularly in patients with negative antiphospholipid antibodies (aPL).

A 36-year-old woman consulted with a 5-year history of asymptomatic lesions on the trunk and limbs. The lesions were initially transitory, but with time they had become stable. Over the previous 2 years, she had presented episodes of transitory focal neurological deficits (paresis of the left side of the face and of the left upper limb). She also reported frequent headaches that had started at the same time as the neurologic abnormalities. The patient had a 2-year history of high diastolic blood pressure and had been taking oral contraceptives for over 10 years. She did not drink or smoke and had no personal or family history of miscarriage or venous thrombosis.

Physical examination revealed reticulated, reddish-brown macules covering a large part of the body surface (Figure 1). She also presented a small necrotic ulcer on the

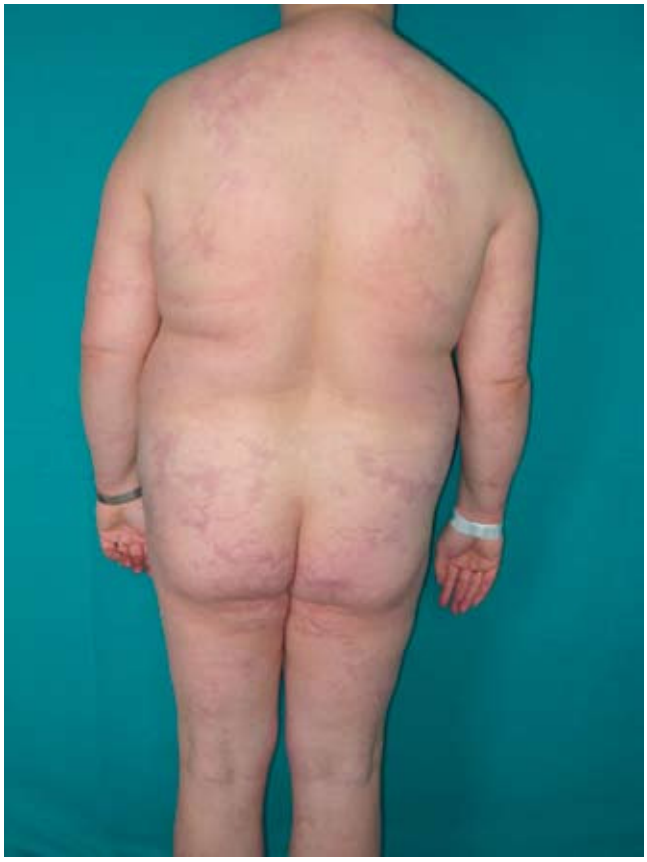

Figure 1 Livedo reticularis lesions affecting the trunk and limbs.

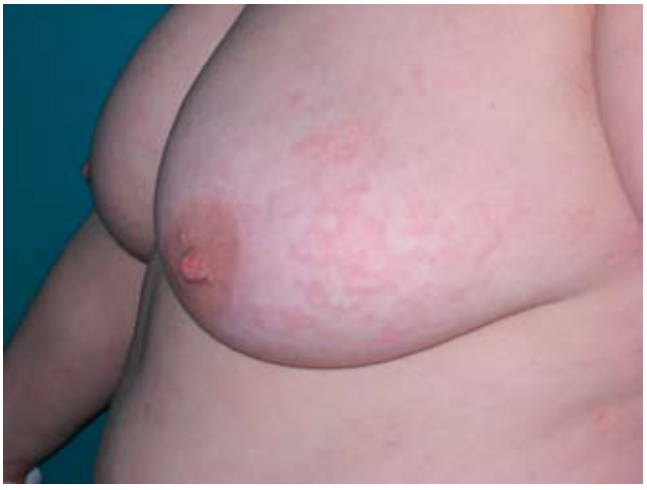

Figure 2 Urticarial plaques with a reticulated pattern on the breast.

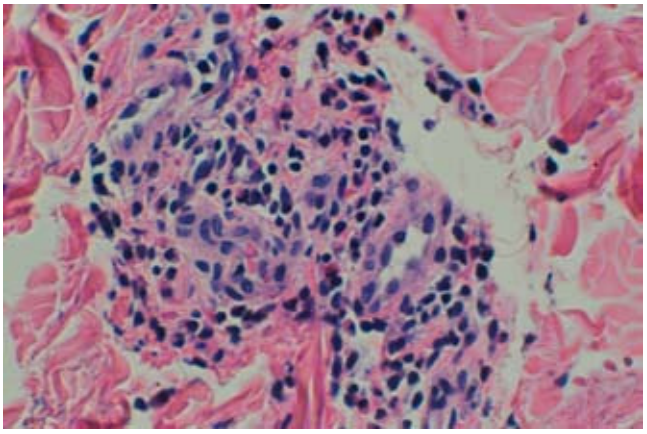

Figure 3 Histological image of the urticarial lesions showing a perivascular infiltrate of lymphocytes and neutrophils with leukocytoclasis. Hematoxylin-eosin, original magnification ×200.

fifth toe of the right foot and reticulated wheals on both breasts that persisted for more than 24 hours and resolved leaving no residual lesions (Figure 2).

Blood tests including complete blood count, biochemistry, calcium and phosphorus levels, antinuclear antibodies, anticardiolipin and antineutrophil cytoplasmic antibodies, lupus anticoagulant, complement, cryoglobulins, thyroid hormones, protein electrophoresis, erythrocyte sedimentation rate, and serology for syphilis, hepatitis B and C viruses, and human immunodeficiency virus, and urinary sediment, were all normal or negative. The coagulation study showed a heterozygous factor V Leiden mutation.

Abdominal ultrasound revealed no abnormalities. Cerebral magnetic resonance imaging showed hyperintense lesions in the subcortical white matter and in the optic radiations. Cerebral angiography and echocardiography were normal.

Histopathologic study of the livedo reticularis lesions revealed deep vessels with thickening and hyperplasia of the media, running vertically towards the mid dermis. Biopsy of the breast wheals showed a superficial perivascular infiltrate formed of lymphocytes and neutrophils with leukocytoclasis suggestive of urticarial vasculitis (Figure 3). Histopathology of the necrotic lesion on the foot showed it to be a skin ulcer covered by necrotic slough and associated with a thrombosed vessel in the deep dermis that had recanalized.

The pathogenesis of Sneddon syndrome is unknown. Histopathologic study of the skin lesions often shows occlusion of vascular lumina due to intimal proliferation and accumulations of mononuclear cells, erythrocytes, and fibrin.[2] It is debated whether this occlusion is due to a primary endothelial dysfunction, recurrent thrombotic phenomena in the context of a state of hypercoagulability, or a combination of the two mechanisms.

Various abnormalities of coagulation have been described in relation to Sneddon syndrome, such as familial antithrombin III deficiency, modification of tissue plasminogen activator/inhibitor ratio, and protein Z deficiency.[3,4] In recent years the possible involvement of factor V Leiden mutations in the pathogenesis of Sneddon syndrome has been suggested. This abnormality consists of

a factor V mutation that makes it resistant to the inhibitory action of protein C. It is a known risk factor for venous thrombosis and arterial phenomena such as cerebrovascular accidents.

Few cases of this mutation in Sneddon syndrome have been described to date. Homozygotic mutations or their association with aPL positivity is very rare.[5,6] Recently the prevalence of heterozygotic factor V Leiden was calculated to be between 15% and 19% in patients with aPL-negative Sneddon syndrome.[4,7] This prevalence is higher than that estimated for the general population.

In addition to livedo reticularis, patients with Sneddon syndrome present acrocyanosis, Raynaud phenomenon, and, more rarely, circumscribed skin necrosis.[8] The presence of vasculitic lesions is very uncommon and has been seen in association with systemic lupus erythematosus. In our review of the literature, we found no report of Sneddon syndrome in which the vasculitis presented as urticarial vasculitis. In a series of 78 patients with systemic lupus erythematosus, 15 presented moderate or severe livedo reticularis and 6 of these patients had associated vasculitic lesions in the form of palpable purpura, skin infarcts, and chilblains.[9,10] The livedo reticularis was related to high titers of anticardiolipin antibodies, renal disease, central nervous system alterations, and cutaneous vasculitis. There was no histological evidence of vasculitis in the livedo reticularis lesions but this was found in other concomitant lesions.[9,10] The clinical course in 2 of these patients was compatible with Sneddon syndrome and did not meet the criteria for systemic lupus erythematosus until 3 and 10 years later. Follow-up must therefore be performed in patients like ours who do not meet the criteria for systemic lupus erythematosus on diagnosis but who have anticardiolipin antibodies or vasculitic lesions, as Sneddon syndrome could be an initial developmental phase of systemic lupus erythematosus.

In conclusion, we report a case of Sneddon syndrome in association with vasculitic lesions in the form of urticarial vasculitis. This association has not been described previously and could be a marker of progression to systemic lupus erythematosus. The patient also presented a factor V Leiden mutation, which, in conjunction with the use of oral contraceptives, could be the cause of a state of hypercoagulability. Both vasculitic and thrombotic phenomena could be involved in the development of skin and cerebral lesions.

References

1. Herrero C, Guilabert A, Mascaró-Galy JM. Livedo reticularis de las piernas: Metodología de diagnóstico y tratamiento. Actas Dermosifiliogr. 2008;99:598-607.
2. González-Vilas D, García-Gavín J, Sánchez-Aguilar D, Toribio J. Valor de la biopsia cutánea en el síndrome de Sneddon. Med Clin (Barc). 2010;135:44.
3. Donnet A, Khalil R, Terrier G, Koeppel MC, Njee BT, Aillaud MF. Cerebral infarction, livedo reticularis and familial deficiency in antithrombin III. Stroke. 1992;23:611-2.
4. Ayoub N, Esposito G, Barete S, Soria C, Piette JC, Francès C. Protein Z deficiency in antiphospholipid-negative Sneddon's syndrome. Stroke. 2004;35:1329-32.
5. Gualtieri RJ, Walton GD. Activated protein C resistance and Sneddon's syndrome. Am J Med. 1999;107:293.
6. Finis A, Ssenyonjo H, Knopp U, Koch C, Seidel G, Arnold H, et al. Infarction of the right hemisphere in a patient with antiphospholipid antibody syndrome. Acta Neurochir (Wien). 2005;147:997-1002.
7. Besnier R, Francès C, Ankri A, Aiach M, Piette JC. Factor V Leiden mutation in Sneddon syndrome. Lupus. 2008;12:406-8.
8. Francés C, Papo T, Wechsler B, Laporte JL, Biousse V, Piette JC. Sneddon syndrome with or without antiphospholipid antibodies. A comparative study in 46 patients. Medicine (Baltimore). 1999;78:209-19.
9. Weinstein C, Miller MH, Axtens R, Buchanan R, Littlejohn GO. Livedo reticularis associated with increased titers of anticardiolipin antibodies in systemic lupus erythematosus. Arch Dermatol. 1987;123:596-600.
10. Francès C, Piette JC. The mystery of Sneddon syndrome: relationship with antiphospholipid syndrome and systemic lupus erythematosus. J Autoimmun. 2000;15:139-43.

L. Rodríguez-Pazos, S. Gómez-Bernal, D. Sánchez-Aguilar, M.T. Rodríguez-Granados, and J. Toribio*

Departamento de Dermatología, Complejo Hospitalario Universitario, Facultad de Medicina, Santiago de Compostela, Spain

*Corresponding author.
E-mail address: jaime.toribio@usc.es (J. Toribio).