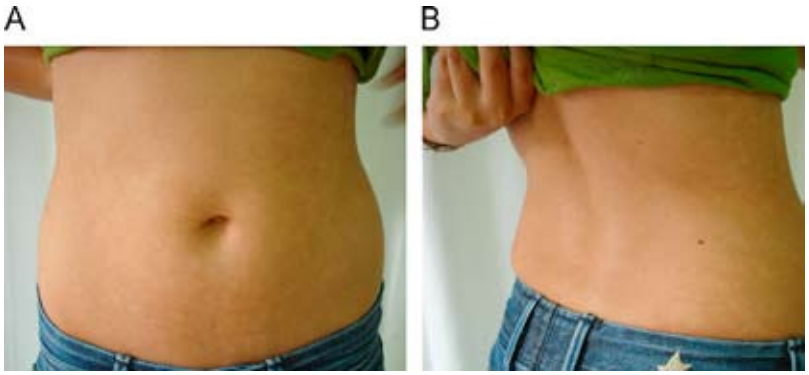

Figure 3 Hypopigmented lesions in the second patient. A, on the abdomen. B, on the flanks and in the lumbar region.

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Mixed Intraepithelial Lesion of the Vulva

Lesión intraepitelial combinada de vulva

To the Editor:

The vulva, as a site of contact with viral agents such as the human papilloma virus, may develop intraepithelial neoplasms such as Bowen disease (BD).[1] It can also be affected by extramammary Paget disease (EPD), given the high density of apocrine glands in the anogenital region.[2] There is also the possibility of a melanotic lesion developing on the vulva, or, more rarely, an intraepidermal adnexal tumor.

A mixed intraepithelial BD and EPD lesion of the vulva,[3-7] as in the case we describe below, is rare.

We report the case of an 89-year-old woman, with an indurated lesion of the vulva affecting the left labia majora and labia minora. The patient had no past history of relevance. A left hemivulvectomy was performed and our laboratory received a surgical specimen measuring 10 cm by 9 cm, with a maximum depth of 3 cm. A hardening of the tissue was evident in the area of the left labia majora and labia minora, occupying an area measuring 5 cm by 3.5 cm. On section, the lesion was found to be up to 9 mm in depth.

Microscopically, there were 2 clearly distinct epidermal areas. One area showed a marked distortion of the epidermal architecture, it not being possible to identify any of the normal epidermal layers because they had been replaced by clearly atypical cells with dense eosinophilic cytoplasm and a number of intercellular bridges (Figure 1). The lesion did not infiltrate the dermis at any point. The other area had a completely different appearance; maturation of the epithelium was unaltered, but there were scattered atypical cells with clear vacuolated cytoplasm (with mucin) and very prominent nucleoli (Figure 2).

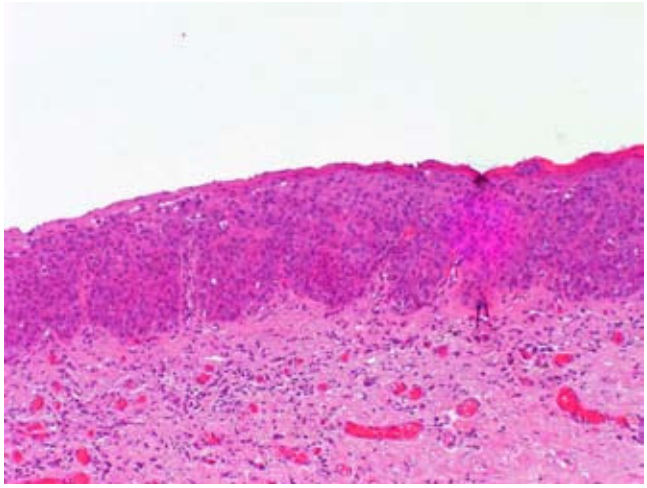

Figure 1 Marked atypia affecting the full thickness of the epidermis (hematoxylin-eosin, original magnification ×100).

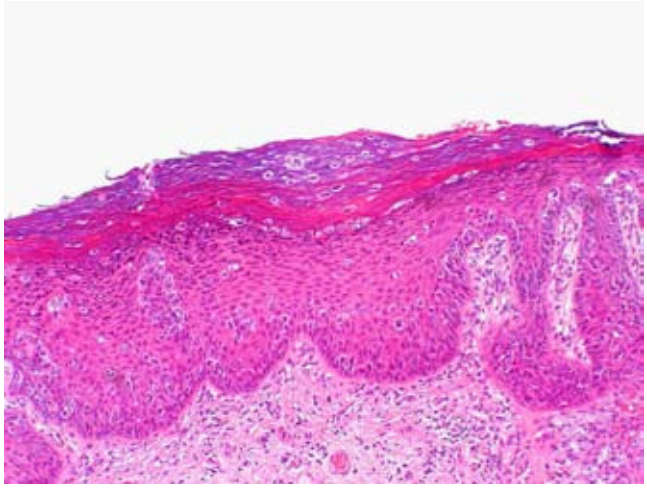

Figure 2 Abundant atypical cells with a clear cytoplasm distributed throughout the full thickness of the epidermis (hematoxylin-eosin, original magnification ×100).

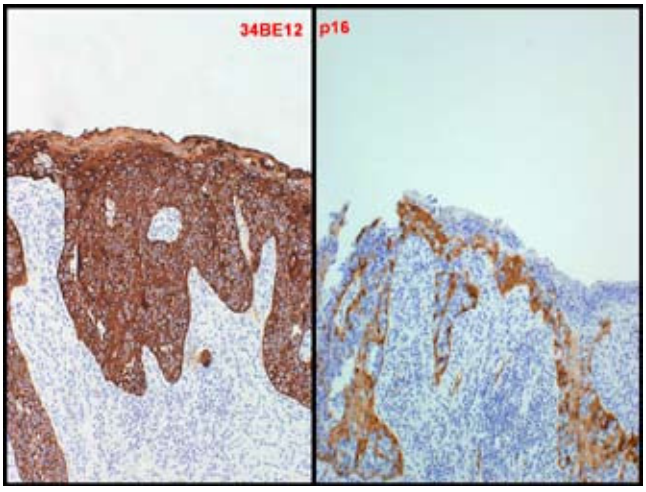

Figure 3 Staining for CK34bE12 and p16 in the bowenoid areas (original magnification ×100).

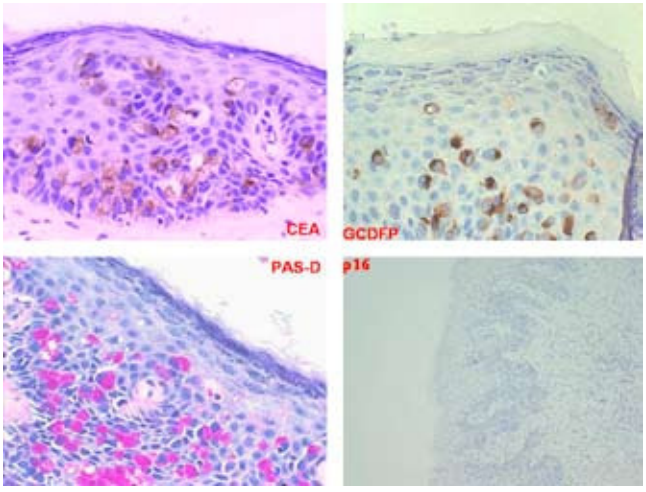

Figure 4 Staining for carcinoembryonic antigen, gross cystic disease fluid protein, and p16, and staining with digested periodic acid-Schiff in the pagetoid areas (original magnification ×400).

A broad panel of immunohistochemical markers was evaluated: S100, Melan-A and HMB-45 (melanocytic markers); cytokeratins (AE1/AE3, CK7, CK20, CK8, CK-34βE12); carcinoembryonic antigen (CEA); the gross cystic disease fluid protein (GCDFP); and the p16 and p53 proteins.

In managing a vulvar intraepithelial lesion such as that described in our patient, the first step is to rule out a melanocytic lesion (ie, a nevus or melanoma) rather than an epithelial lesion; the fact that the melanocytic markers S100, HMB-45 and Melan-A were negative excluded this possibility in our patient. A malignant intraepidermal poroma was ruled out for morphological reasons, given the absence of intraepidermal ductal differentiation and of poroid features at the cellular level. Seborrheic keratosis was also ruled out, given that this consists of squamous cells with no atypia. The differential diagnosis was thus reduced to 3 possibilities: EPD with bowenoid features, BD with pagetoid features, or a mixed BD and EPD lesion.

In EPD with bowenoid features, the entire lesion (both the bowenoid and pagetoid areas) expresses CEA and CK8, but not high molecular weight cytokeratins such as CK-34βE12. In our patient, however, dual staining was evident, with areas of BD that expressed high molecular weight keratins, but not CK8, CEA or GCDFP, and areas of EPD that expressed CEA and GCDFP, but not high molecular weight keratins such as CK-34βE12. Furthermore, the digested periodic acid-Schiff (PAS-D) stain revealed intracytoplasmic mucin that is typical of Paget cells (Figures 3 and 4).

Expression in BD with pagetoid features is the reverse of expression in EPD with bowenoid features; the entire lesion, both in areas of intraepithelial squamous cell carcinoma and in areas with pagetoid features, expresses

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]

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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