Merkel Cell Carcinoma of the Breast

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To the Editor:
Merkel cell carcinoma (MCC) is a rare malignant skin tumor of neuroendocrine origin first described by Toker in 1972. Prognosis is poor and progression rapid. It usually presents as a rapidly-growing erythematous nodular lesion in individuals aged over 65 years.1 Atypical forms of presentation have also been described, such as minimal ulceration in the nasal tip, subcutaneous nodules in the inguinal region, granulation tissue on a toe, and an extensive wine-colored plaque in the frontal region.2 We could find only 4 cases of primary MCC of the breast reported in the literature.3-6 We describe a new case of MCC of the breast in a woman attended recently in our department.

The patient was 77 years old and had a history of hypertension and type 2 diabetes mellitus. She was referred to the dermatology department for asymptomatic lesions in the left mammary region that had first appeared 15 days earlier and that were growing rapidly. Examination revealed diffuse induration of the right breast on which multiple, violaceous, dome-shaped nodules could be seen (Figure 1). In view of the suspected diagnosis of breast cancer en cuirasse, a biopsy was taken of 1 of the lesions. The results showed tumoral infiltration of the dermis and subcutaneous cellular tissue by small round monomorphic cells with scant cytoplasm, a round nucleus, and small nucleoli. The cells were arranged in large nests, masses, and strands. The mitotic index was high. The formation of glandular lumens was not observed. The immunohistochemical study was positive for cytokeratin 20, neuronal specific enolase (NSE), and chromogranin A. Immunoreactivity for protein S100, leukocyte common antigen, thyroid transcription factor-1 (TTF-1), and estrogen and progesterone receptors was not observed. No pathological findings were reported on the plain chest X-ray. The patient attended 2 weeks later for follow-up. Rapid growth of the breast tumor could be observed, with necrotic and ulcerated areas on the surface, enlarged lymph nodes in the right axilla, and lymphedema of the right arm associated with disseminated cutaneous nodules (Figure 2). On the basis of the histopathological and immunohistochemical studies, she was diagnosed with MCC and referred to the oncology department.

MCC is an uncommon tumor with an annual incidence of approximately 0.4 cases per 100 000 inhabitants. It is most common on sun-exposed areas such as the head (mainly the eyelids and cheeks) and neck, followed by the limbs, buttocks, and trunk. Cases have also been described in the mucosas, including the bottom lip, oral and genital mucosas, and the anal region.7 Lesions localized to the breast are even less frequent; we have found several cases of metastasis of MCC to that site,8 but only 4 primary cases,3-6 1 of which was in a man.3
In this case, the differential histopathological diagnosis should be made with:

1. Skin metastases of internal neuroendocrine tumors such as small-cell lung cancer. In our case, the positive assay for cytokeratin 20 and the negative one for TTF-1 ruled out this tumor, an exclusion that was also supported by the lack of pathological findings on the plain chest X-ray.7
2. Primary neuroendocrine adenocarcinoma of the breast. This term is reserved for uncommon breast tumors in which more than half the cells express neuroendocrine markers (NSE, chromogranin A, or synaptophysin) and which present mainly in elderly women. This would perhaps be the main tumor to rule out here given that the site of the tumor in our patient was the breast, particularly as some reports indicate that superficial biopsies have led to initial misdiagnosis.8,9

Conflicts of Interest
The authors declare no conflicts of interest.

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References

Molluscum Contagiosum Over a Tattoo

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To the Editor:
In our daily practice, consultations for tattoos and associated dermatological complications are increasingly common. This ancient practice is currently becoming more widespread among the general population, and there are an increasing number of reports of dermatological processes associated with tattoos in the literature; these complications include contact dermatitis, local and systemic infections, transmission of hepatitis C and B virus (HCV and HCB), human immunodeficiency virus (HIV), syphilis, warts, and cutaneous tuberculosis.1,2

We report here our experience with this type of problem. A 36-year-old man consulted for several umbilicated papules measuring 1 to 3 mm in diameter on a black-ink tattoo on the right arm (Figures 1 and 2). Since he first had the tattoo several years earlier, no other associated problems had occurred. In view of progressive loss of pigment, however, he decided on a recoloring procedure and lesions appeared a few weeks later. These were completely asymptomatic and extended progressively but remained confined to the tattooed skin. The patient did not have any drug allergies or report any medical or surgical history of interest. A biopsy was taken of one of the lesions, and large intracytoplasmatic inclusion bodies or “molluscum bodies” were observed inside the epidermal cells while a deposit of blackish pigment was apparent in the dermis. The laboratory tests included serology for HIV, HCV, and HBV, and were normal. Once diagnosis of molluscum contagiosum was confirmed, treatment included curettage of the lesions. No recurrence was reported.
We found this case of interest because of the atypical presentation of molluscum contagiosum. Although this disease is very common, only 6 cases of molluscum contagiosum on tattoos have been reported in the literature. It is thought that the molluscum contagiosum virus might have been transmitted by the instruments that are used for tattooing or that the ink might have been contaminated with the virus. It has also been suggested that the black pigment might cause a localized weakening of cellular and humoral immunity (Table).

In any case, it is clearly the Koebner phenomenon that was occurring, as molluscum contagiosum only appeared on the area of skin covered by the tattoo and onset occurred weeks after the tattoo had been done or manipulated. Such a phenomenon has also been reported at times with the appearance of lupus or sarcoid lesions on tattoos.

**Table.** Characteristics of Cases of Molluscum Contagiosum on Tattoos Described Until Present

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Age/Sex</th>
<th>Immunosuppression</th>
<th>Time Until Onset</th>
<th>Site</th>
<th>Color</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Bergh R 1903'</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
</tr>
<tr>
<td>2 Salmaso F et al 2001'</td>
<td>20/F</td>
<td>No</td>
<td>3 weeks</td>
<td>Left forearm</td>
<td>Black ink</td>
<td>No treatment</td>
</tr>
<tr>
<td>3 Foulds H 1982'</td>
<td>No</td>
<td>3 months</td>
<td>Left arm</td>
<td>Black ink/ red ink and copper pigment</td>
<td>Spontaneous resolution after 6 months</td>
<td>Desaparición espontánea en 6 meses</td>
</tr>
<tr>
<td>4 Pérez-Gala S et al 2006'</td>
<td>20/M</td>
<td>No</td>
<td>5 months</td>
<td>Left calf</td>
<td>Brown-gray/ black/others</td>
<td>NK</td>
</tr>
<tr>
<td>5 Kiang SH et al 2006'</td>
<td>NK</td>
<td>NK</td>
<td>Recent tattoo</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
</tr>
<tr>
<td>6 Kluger N et al 2007'</td>
<td>59/M</td>
<td>No</td>
<td>3 months</td>
<td>Chest</td>
<td>Monochromatic</td>
<td>No treatment</td>
</tr>
<tr>
<td>7 Pérez-Barrio S et al 2008'</td>
<td>36/M</td>
<td>No</td>
<td>3 weeks</td>
<td>Right arm</td>
<td>Black ink</td>
<td>Curettage without subsequent relapse</td>
</tr>
</tbody>
</table>

*Color of the tattoo on which the molluscum appeared
Abbreviations: F, female; M, male; NK, not known.

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**Conflicts of Interest**
The authors declare no conflicts of interest.
To the Editor:

Burning mouth syndrome (BMS) is a painful, chronic, idiopathic complaint characterized by a sensation of burning, pain, itching, or scalding of the oral mucosa in the absence of clinically evident lesions. It is a common condition that usually affects postmenopausal women and that is often associated with anxiety, depression, or cancerophobia. There are currently no effective treatments available and, among others, anticandida agents, drugs for ulcers, hormone replacement therapy, benzodiazepines, tricyclic antidepressants, selective serotonin uptake inhibitors, and psychotherapy are used.

α-Lipoic acid (thioctic acid) is a potent antioxidant able to neutralize free radicals formed in the organism. It is a molecule that acts in aqueous and fatty media and that is active in both its reduced and oxidized state. In addition, it is able to regenerate other antioxidants such as glutathione, vitamin E, vitamin C, and coenzyme Q, and plays an important role in cell metabolism in that it acts as a cofactor in mitochondrial dehydrogenase-mediated reactions. Different clinical studies have demonstrated the neuroprotective effect and efficacy of this agent in the treatment of peripheral neuropathies caused by conduction disorders and neurotrophism. At the recommended dose of 600 mg/d, no relevant adverse effects have been reported, even over long treatment periods. Its usefulness in BMS was proposed by Fermiano et al., who suggested that the disorder behaves as a peripheral neuropathy influenced by stressful psychological events.

To test this hypothesis, we treated 10 patients who were suffering from BMS with α lipoic acid. A full medical history was taken, and the patients underwent a detailed examination of the oral mucosa; cultures for Candida species; and blood tests for vitamin B12, iron profile, and antinuclear, anti-Ro, and anti-La antibodies to rule out other localized or systemic diseases that might cause similar symptoms. The severity of the BMS was assessed using a visual analogue scale (0, no pain/burning; 1, mild pain/burning; 2, moderate pain/burning; 3, severe pain/burning).

Oral treatment with α-lipoic acid (600 mg/d) and γ-linoleic acid (360 mg/d) was administered over 8 weeks. Therapeutic efficacy was assessed after 2 months using another visual analogue scale (0, no improvement; 1 slight improvement; 2, moderate improvement; 3, strong improvement).

All our patients were postmenopausal women and the mean age of the series was 63.7 years (range, 55–74 years). Items of note in the personal history included anxiety and depression (3 patients). The mean duration of BMS was 35.5 months (range, 2–96 months). The symptoms were severe in 4 patients, moderate in 5, and mild in 1. Among the prior medication, of note were topical measures (antiseptic mouthwashes, corticosteroids, antifungals) (10 patients), oral antifungals (1 patient), tricyclic antidepressants (3 patients), serotonin reuptake inhibitors (1 patient), and antipsychotics related to olanzapine (3 patients). One patient had a positive culture for Candida species and was treated with oral antifungals.
without any improvement in symptoms. Two patients tested positive for antinuclear antibodies and 1 of these, diagnosed with systemic lupus, also tested positive for anti-Ro antibodies.

Of all the patients treated, only 3 showed a mild improvement. The remaining patients showed no response to treatment.

In the case series presented here, response was limited, as only 3 out of 10 patients reported a mild improvement in symptoms. Although this study cannot provide definitive conclusions, the results would seem to reject the hypothesis of the usefulness of α-lipoic acid in the treatment of BMS, as indicated in the systematic review published by the Cochrane library in 2005.² Rigorous clinical trials would therefore be needed to demonstrate whether or not this treatment is effective.

References


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The authors declare no conflicts of interest.

Blaschkoid, Zosteriform Linear Lichen Sclerosus et Atrophicus

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To the Editor:

Lichen sclerosus et atrophicus is a chronic inflammatory disease that can affect the genital and perineal area, occurring less frequently in extragenital locations. Blaschkoid or zosteriform linear forms of this dermatosis have rarely been described in the literature. We present a case of lichen sclerosus et atrophicus forming linear lesions of 2 different patterns in the same patient: the first along the Blaschko lines, and the others on top of previous scarring from herpes zoster as the manifestation of an isotopic response.

A 47-year-old man was referred to us for a clinical condition with onset 4 years previously. This consisted of the appearance of slightly pruritic, whitish lesions on an area of atrophic scars on the right-hand side of the abdomen where the patient had suffered an episode of herpes zoster 7 years previously. Over the last 2 years he had also noted the appearance of similar lesions extending from the right scapular region to the shoulder and the right pectoral zone. He reported no history of previous trauma, autoimmune disease or other relevant issues. Laboratory tests, including autoimmunity screening (antinuclear, anti-DNA, anti-SS-A, anti-SS-B, anti-RNP and anti-Scl-70 antibodies) were normal.

Physical examination revealed the presence of whitish plaques with an atrophic surface, follicular plugs, and erythematous edges in linear formations along the upper right-hand side of the back (Figure 1), as well as more isolated lesions in the area under the clavicle on the right.
Lichen sclerosus et atrophicus is a chronic inflammatory disease that usually affects the genital area although extragenital involvement is reported in 15% to 20% of cases. It is most common in adult women, although it can occasionally affect children too. In our review of the literature we have found 7 cases of lichen sclerosus et atrophicus with a blaschkoid distribution, predominantly among women (5:2), with lesions on the trunk, the lower limbs, the face, and the upper limbs. The blaschkoid linear pattern of inflammatory dermatosis seems to be the consequence of a genetic mosaicism where an abnormal keratinocyte clone remains inactive until an environmental factor stimulates growth leading to segmental clinical manifestations. The existence of mosaicism-related phenomena has been described in more than 15 monogenic skin diseases to date, and in various inflammatory cutaneous diseases.

The term "isotopic response," as defined by Wolf et al in 1995, describes the appearance of a new dermatitis in a location previously affected by an unrelated and healed skin disease, mainly on scarring from herpes zoster. Although various forms of dermatitis have been described in this context (granuloma annulare, pseudolymphoma, granulomatous folliculitis, Rosai-Dorfman disease, etc), only 3 such cases of lichen sclerosus et atrophicus have been reported. It has been suggested that the viral particles of herpes zoster remaining in the skin lesion could favor the development of a second dermatosis, but viral DNA has not been isolated in tissue from the lesion in most cases. Alternatively, postinflammatory changes in skin affected by herpes zoster could precipitate the appearance of a second dermatosis, in action similar to the Koebner response.

In conclusion, the association of blaschkoid and zosteriform lichen sclerosus et atrophicus in our patient could be a matter of chance, but the rarity of both processes

Hypopigmented and indurate plaques were also present on the right-hand side on a depressed area with postinflammatory hyperpigmentation in dermatomes D9-D10—an area where the patient had suffered an episode of herpes zoster 7 years previously (Figure 2). Histopathology of a biopsy extracted from the lesions on the shoulder showed thinning of the epidermis with the loss of the epidermal crests, marked edema in the papillary dermis, more homogenous collagen, and a lymphocytic infiltrate in the middle dermis (Figure 3). Once a diagnosis of lichen sclerosus et atrophicus was confirmed by histopathology, topical treatment with clobetasol propionate 0.05% was prescribed, with a moderate improvement seen in the lesions after a month of treatment.
suggests the existence of a link between the 2. We think the connection could lie in the existence of an individual genetic predisposition to lichen sclerosus et atrophicus, where greater vulnerability to certain keratinocyte clones and the presence of environmental factors like viral herpes infections, could be responsible for the unusual clinical presentation of the lesions in our patient.

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References

Hyperkeratosis Lenticularis Perstans, or Flegel Disease, With Palmoplantar Involvement

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To the Editor:
Hyperkeratosis lenticularis perstans (HLP) is an autosomal dominant or sporadic keratinization disorder that occurs equally in men and women from 40-50 years old.1 HLP has been described in association with endocrinal changes, and digestive and cutaneous tumors,2,3 and is characterized by the presence of small, asymptomatic erythematous papules that leave characteristic punctate bleeding when they become detached. The lesions generally occur symmetrically along the top of the foot and on the legs, appearing more rarely on the arms, forearms, palms, and soles, and even on the oral mucosa.4,5 Agreement has yet to be reached on the role of ultraviolet light in pathogenesis.6

Histologically, HLP is characterized by orthokeratotic, eosinophilic, and compact hyperkeratosis, hypogranulosis, thinning of the Malpighian layer, vascular dilation, and band-like lymphocytic infiltrate in the papillary dermis. Immunohistochemical study shows a predominance of CD4+ T cells that is more evident in the early stages of the illness. Many treatment options have been described, although none has proved effective.7,8

We present the case of a 64-year-old man with diabetes who consulted for asymptomatic, brown, hyperkeratotic papules that appeared progressively over the years with no relation to sun exposure. These were mainly located on the top of the feet, legs, arms, and forearms, leaving hemorrhagic pits on detachment (Figure 1). Pits or dimples could be seen on the palms and soles, reminiscent of the ungual pits of psoriasis (Figure 2). There was no family history of the disorder and tests including general biochemistry and thyroid profiling produced normal results. Biopsy of a papule from the top of the foot...
The condition is clinically characterized by asymptomatic erythematous or brown papules of 1 to 5 mm in diameter, which leave a characteristic punctate bleeding when removed. The lesions are generally located on the top of the feet and legs and, more rarely, on the arms, forearms, and the oral mucosa. Unilateral and localized forms have been described, as has possible palmoplantar involvement resulting in pitting—as was seen in our patient.

In 1994, De Argila et al. published a series of 10 cases of HLP in patients aged from 41-80 years old. Of these, 3 were hereditary cases, 9 presented involvement of the lower limbs, and 5 of the upper limbs. Only 2 experienced any endocrine disorder (hyperthyroidism and type 2 diabetes) and none of them had the palmoplantar lesions. Our patient had suffered from diabetes for several years, but given the high prevalence of diabetes in the adult population and the lack of controlled studies we cannot rule out a causal association.

Histologically, HLP is characterized by compact orthokeratotic hyperkeratosis, sometimes associated with parakeratosis, hypogranulosis, thinning of the Malpighian layer, and lichenoid lymphocytic infiltrate in the papillary dermis. The immunohistochemical study showed a predominance of CD4+ T cells, which is more marked in the early stages of the disease. Ultrastructural abnormalities were observed in the number and shape of the Odland bodies or keratinosomes.

In 2006, Ando et al. provided more detailed descriptions of the histological, immunohistochemical, and ultrastructural differences between early and late HLP, concluding that the characteristics of the early stage were compact hyperkeratosis with focal parakeratosis, hypogranulosis, epidermal atrophy, marked mononuclear infiltrate of a lichenoid type with a predominance of CD4+ T cells and superficial vascular dilation. Electron microscopy reveals the presence of lymphocytes with cerebriform nuclei, clusters of filaments and amorphous substance in corneocytes, and changes in the morphology displayed slight epidermal atrophy, compact orthokeratotic eosinophilic hyperkeratosis, and mild, predominantly leukocytic, lichenoid inflammatory infiltrate of the papillary dermis. Immunohistochemical studies for lymphoid markers did not establish a predominance of CD4+ over CD8+ T cells (Figure 3). The application of 30% urea every 12 hours, followed by topical calcipotriol, 2 times a day, led to a partial improvement of the lesions.

HLP, described by Flegel in 1958, is considered to be an autosomal dominant inherited keratinization disorder, although most cases are sporadic, affecting patients aged 40-50 years with no noted predominance in either sex. The condition has been described in association with endocrine abnormalities including diabetes and hyperthyroidism, while a possible relationship with digestive and cutaneous tumors is more open to debate. There is controversy over the pathogenic role of ultraviolet light, with some authors differentiating between a classic, hereditary form of HLP and another sporadic or acquired form, related to chronic sun exposure.

Figure 1. Multiple erythematous and hyperkeratotic papules and characteristic punctate bleeding on the top of each foot.

Figure 2. Punctate plantar pits.

and number of Odland bodies. They suggested that the absence or less marked presence of these characteristics in the later stages was due to the lesions reaching a more advanced stage of development.11

Differential diagnosis should include disseminated superficial actinic porokeratosis, Kyrle disease, stucco keratosis, acrokeratosis verruciformis of Hopf, and lichen nitidus.

Many treatment options have been discussed including topical and systemic retinoids, 5-fluorouracil, vitamin D derivatives, psoralen UV-A therapy, excision, and dermabrasion of the lesions. At present all of these are considered unsatisfactory due to high rates of recurrence.7,8

We draw attention to the uncommon presence of punctate palmoplantar pits in HLP and in our case the controversial association with diabetes and sun exposure.

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References

Figure 3. Papule on the top of the foot (hematoxylin-eosin, ×10) A. Compact orthokeratotic hyperkeratosis, slight epidermal atrophy, flattening of the interpapillary ridges, and scant lichenoid lymphocytic inflammatory infiltrate in the papillary dermis. B. Immunostaining for CD4 (PAP, ×20). C. Immunostaining for CD8 (PAP, ×20).
Verrucous Carcinoma of the Face: A Report of 2 Cases

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To the Editor:

Verrucous carcinoma is a clinicopathologic variant of squamous cell carcinoma, low-grade malignancy that may affect the skin, the anal and genital mucosa, and mucosas of the oral and pharyngeal region. We describe 2 cases of facial verrucous carcinoma: an exceptional location for this type of tumor.1-2

Case 1 was a 45-year-old man with no relevant medical or surgical history, who consulted in 1996 because of an asymptomatic tumor of 2 cm in diameter in the region of the left cheek that had grown progressively over the last 6 months (Figure 1). Two biopsies were taken with inconclusive results, and the tumor was finally removed. In the histological studies of the surgically removed tissue, findings characteristic of verrucous carcinoma were reported (Figure 2). Polymerase chain reaction (PCR) assay for the identification of the human papilloma virus (HPV) type 6, 11, 18, 31, and 33 was negative. There was no recurrence of the tumor 2 years after surgical removal.

Case 2 was a 74-year-old man who attended in 2001 for a verrucous lesion 4 cm across at the widest point in the right temporal region that had been present for more than 2 years (Figure 3). Two biopsies were taken but the histological findings were inconsistent with the clinical appearance of the lesion. In view of the delicate condition of the patient and the inconclusive microscopic results, the tumor was removed by electro surgery followed by curettage and electrocoagulation of the base of the lesion. Pathologic study of the tissue revealed histological changes indicative of verrucous carcinoma (Figure 4). PCR testing for HPV 6, 11, 16, 18, 31, and 33 was negative. The patient was monitored regularly over the following 3 years with no signs of local recurrence.

In 1948, Ackerman coined the term “verrucous carcinoma” and established the clinical and histological criteria for diagnosis on the basis of 31 cases affecting the oral cavity. Previously, in 1896, Buschke and Löwenstein observed 2 patients with similar lesions in the genital region; with Aird et al describing plantar cuniculatum epithelioma in 1954.1-2 Verrucous carcinoma generally presents in the palmoplantar region, or on the oral, anal, and genital mucosa, and facial involvement is in fact exceptionally rare.1-7

Histologically, verrucous carcinomas display microscopic similarities independent of location, showing a characteristic association of exophytic and endophytic components within the same lesion. The former consist of acanthosis and papillomatosis that generally display massive hyperkeratosis and frequent parakeratosis. The endophytic component is made up of a well-differentiated squamous epithelium, forming "bulbous" projections or processes, lumps that increase in size “pushing” the dermis. These extend to the reticular dermis and even the subcutaneous tissue, with no pattern of invasive growth. Other characteristics...
include the formation of keratin cysts and the presence of a variable inflammatory infiltrate. Clinical and histological differential diagnosis should mainly include other variants of squamous carcinoma, common warts, keratoacanthomas, and reactive epidermal hyperplasias. Less commonly, they can be confused with certain benign adnexal tumors, giant seborrheic keratoses, verrucous melanomas, verruciform xanthomas, and even with iododerma and bromoderma. Wherever diagnostic doubt exists, the complete removal of the tumor is required in order to reach a correct diagnosis as biopsies alone cannot show the 'exo-endophytic' growth characteristic of verrucous carcinoma. In the 2 cases presented, biopsies were taken from the lesions on several occasions giving contradictory results. Diagnosis of 1 of the cases was further complicated by the keratoacanthomatous clinical appearance of the lesion. In both cases complete excision of the tumor was required for definitive diagnosis.

The pathogenesis of the disease has classically involved chemical factors like chewing tobacco—in the case of Ackerman tumor—and various others including chronic inflammation. More recently, the identification of HPV by in situ hybridization or PCR in some of these tumors—mainly on the mucosa—has prompted consideration of the virus as another pathogenic agent. Both low risk (HPV 6 and 11) and high risk (HPV 16 and 18) genotypes have been implicated here. In fact, HPV 6 and 11 are characteristically related to Buschke-Löwenstein carcinoma, while other forms (HPV 16, 18, and 33) have also been demonstrated in verrucous carcinomas in other locations. In our 2 patients PCR did not identify HPV. This is in agreement with the findings of many other authors who confirm that it is rare to find these viruses in verrucous carcinomas in zones outside those traditionally affected.

In summary, we have described 2 cases of verrucous carcinoma of the facial area—a very rare location considering there are only 5 cases previously published. PCR for the identification of HPV was not undertaken in any of those 5 cases. PCR did not reveal presence of HPV in either of our patients, a fact that suggests the appearance of verrucous carcinomas in such light-exposed locations is the outcome of different pathogenic factors—mainly ultraviolet radiation—as is the case in other cutaneous squamous cell carcinomas.

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