2. Segal RJ, Watson W. Kaposi's varicelliform eruption in mycosis fungoides. Arch Dermatol. 1978; 114:1067-9.
3. Brion N, Guillaume JC, Dubertret L, Touraine R. Herpes cutane dissemine de l'adulte et syndrome de Sezary. Ann Dermatol Venereol. 1981;108:517-21.
4. Hayashi S, Yamada Y, Dekio S, Jidoi J. Kaposi's varicelliform eruption in a patient with mycosis fungoides. Clin Exp Dermatol. 1997;22:41-3.
5. Masessa JM, Grossman ME, Knobler EH, Bank DE. Kaposi's varicelliform eruption in cutaneous T cell Lymphoma. J Am Acad Dermatol. 1989;21:133-5.
6. Taulbee KS, Jhonson SC. Disseminated cutaneous herpes simplex infection in cutaneous T-cell lymphoma. Arch Dermatol. 1981;117:114-5.
7. Axelrod PI, Lorber B, Vonderheid EC. Infections complicating mycosis fungoides and Sezary syndrome. JAMA. 1992;267:1354-8.
8. Epstein EH Jr, Levin DL, Croft JD Jr. Mycosis fungoides: survival, prognostic, features, response to therapy and autopsy findings. Medicine. 1972;15:61-72.
9. Posner LE, Fossieck BE, LE Joyce, Bunn PA. Septicemic complications of the cutaneous T-cell Lymphomas. The American Journal of Medicine. 1981;71:210-6.
10. Donai P, Geokas M, Worsley G. Mycosis Fungoides. Hematologic findings and terminal course. Arch Dermatology. 1966;94:558-73.

Verrucous Carcinoma of the Foot Associated with Human Papillomavirus Type 18

M.U. Floristán,[a] R.A. Feltes,[a] J.C. Sáenz,[b] and P. Herranz[a]

[a]Servicio de Dermatología and [b]Departamento de Anatomía Patológica, Hospital Universitario La Paz, Madrid, Spain

To the Editor:

Verrucous carcinoma (VC) is an uncommon and well-differentiated variant of squamous cell carcinoma of the skin and mucosas. The clinical and pathological concept was first described by L.V. Ackerman in 1948.[1]

In the past, VC has been called according to its anatomical location.[2] When found on the oral mucosa, the term florid oral papillomatosis is used whereas, in the anogenital region, it receives the name giant condyloma of Buschke and Löwenstein. VC of the sole of the foot, the most common site, is known as epithelioma cuniculatum. Clinically it resembles a plantar wart, and has an endophytic appearance, with multiple orifices on its surface that correspond histologically to crypts full of keratin and interconnected tunnels. This gives it a certain similarity to a rabbit warren, justifying the use of the term cuniculatum (in Latin, cuniculus means rabbit or tunnel). Less commonly, VC may be situated on other areas of the skin and is then known simply as cutaneous VC.

Although the etiology of VC has not been fully explained, a number of factors have been implicated in its development, including infection by human papillomavirus (HPV).[3,4]

The patient was a 61-year-old white man with no past history of interest, who was seen for a progressively enlarging lesion on the sole of the left foot; it had been present approximately 1 year. Previously, the lesion had been diagnosed as a plantar wart and was treated with a number of cycles of cryotherapy, with no improvement.

Physical examination revealed a hyperkeratotic plaque of 2 by 2 cm, of verrucous appearance, with well-defined margins, and a macerated central tissue with orifices full of purulent material (Figure 1).

There were a number of possibilities in the differential diagnosis, including squamous cell carcinoma, superinfected plantar wart, and amelanotic melanoma.

Biopsy of the lesion revealed a bulbous proliferation of keratinocytes forming nests of different shapes and sizes in the superficial half of the dermis. Some of these nests presented central keratin pearls (Figure 2).

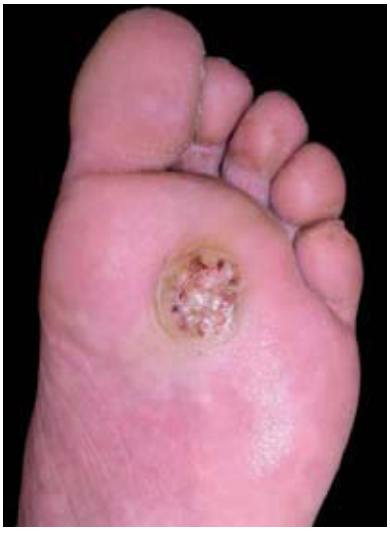

Figure 1. Plaque with a verrucous appearance.

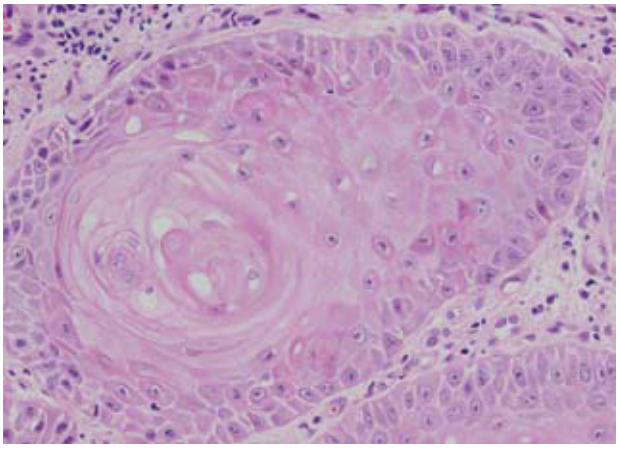

Figure 2. The nests of the lesion showed grouped keratinocytes in the periphery, many of them triangular with a small degree of nuclear atypia; a corny pearl is visible in the centre (hematoxylin-eosin, ×10).

A diagnosis of VC was made based on the verrucous appearance of the lesion and the histopathology of well-differentiated squamous cell carcinoma; it was excised surgically.

Later, using the polymerase chain reaction, a study was performed to detect the presence of any type of HPV. Typification was performed after DNA amplification and digestion with the RsaI restriction enzyme; HPV type 18 was identified.

We present the case of an immunocompetent patient with VC on the sole of the foot in which the DNA of HPV-18 was identified.

The etiology of VC is not fully understood. A number of factors have been implicated in its development, including chemical carcinogens, trauma, chronic inflammation, immunosuppression, and HPV infection.

The papillomavirus is highly specific. Its life cycle can only be completed in well-differentiated squamous epithelia. HPV is classified into different types according to whether it infects the skin or mucosas (HPV-muc),[3,5] and these latter types are subclassified according to their oncogenic potential into high-risk HPV (subtypes 16 and 18), intermediate-risk (subtypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82, and 83), and low-risk (subtypes 6, 11, 26, 30, 32, 40, 42 to 44, 53 to 55, 62, 66, 70, 72, and 81). There is a considerable volume of clinical and experimental evidence that supports the association between HPV and the appearance of benign and malignant neoplasms. The oncogenic mechanisms of HPV-muc have been described in cancers of the anogenital region.[6] The DNA of HPV is randomly integrated into the keratinocyte genome. HPV proteins E6 and E7 play a fundamental role, as they produce alterations of genes p53 and Rb, respectively, giving rise to cell immortality and tumor progression.[7]

Mucous type (HPV-muc) HPV-18 is a high-risk subtype. The relationship between HPV-18 and malignant genital neoplasms such as carcinoma of the cervix, bowenoid papulosis, genital squamous cell carcinoma, and genital (Buschke-Löwenstein) VC is well documented in the literature.

In contrast, isolation of HPV-muc in extramucosal neoplastic lesions is very rare. The cases of isolation of HPV-muc of intermediate-high risk in extramucosal VC can be listed individually: 1 case of HPV-33 on the scalp,[8] 2 cases of HPV-16 on the sole of the foot,[9] and only 1 case on the leg, with isolation of HPV-11 in combination with HPV-18.[10] We present the first case of VC of the foot in which HPV-18 DNA has been identified.

The implication of HPV in the oncogenesis of VC, a variant of squamous cell carcinoma, could have important repercussions on dermatological practice,[3] in terms both of prophylaxis (role of new vaccines against HPV-muc or the use of topical imiquimod to treat condyloma acuminatum), and of therapeutic management (some authors maintain that isolation of HPV is associated with a poorer prognosis).

Correspondence:
María Uxúa Floristán Muruzábal
Servicio de Dermatología
Hospital Universitario La Paz
Paseo de la Castellana, 261
28046 Madrid, Spain
uxuafloristan@hotmail.com

Conflicts of Interest
The authors declare no conflicts of interest.

References

1. Ackerman LV. Verrucous carcinoma of the oral cavity. Surgery. 1948;23:670.
2. Assaf C, Steinhoff M, Petrov, Geilen CC, de Villiers EM, Schutz-Ehrenburg U, et al. Verrucous carcinoma of the axilla: case report and review. J Cutan Pathol. 2004;31:199-204.
3. Corbalán-Vélez R, Ruiz-Maciá JA, Brufau C, Carapeto FJ. Carcinoma espinocelular cutáneo y papilomavirus (VPH). Actas Dermosifiliogr. 2007;98:583-93.
4. Melton JL, Rasmussen JE. Clinical manifestations of human papillomavirus infection in nongenital sites. Dermatol Clin.1991;9:219-33.
5. De Villiers EM. Taxonomic classification of papillomaviruses. Papillomavirus Report. 2001;12:57-63.
6. Bjorge T, Engeland A, Luostarinen T, Mork J, Gislefoss RE, Jellum E, et al. Human papillomavirus infection as a risk factor for anal and perianal skin cancer in a prospective study. Br J Cancer. 2002;87:61-4.
7. Crook T, Wrede D, Tidy J, Scholefield J, Crawford L, Vousden KH. Status of c-myc, p53, and retinoblastoma genes in human papillomavirus positive and negative squamous cell carcinomas of the anus. Oncogene. 1991;6:873-5.

8. Murao K, Kubo Y, Fukumoto D, Matsumoto K, Arase S. Verrucous carcinoma of the scalp associated with human papillomavirus type 33. Dermatol Surg. 2005;31:1363-5.
9. Schell BJ, Rosen T, Rády P, Arany I. Verrucous carcinoma of the foot associated with human papillomavirus type 16. J Am Acad Dermatol. 2001;45:49-55.
10. Garven TC, Thelmo WL, Victor J, Pertschuk L. Verrucous carcinoma of the leg positive for human papillomavirus DNA 11 and 18: a case report. Hum Pathol. 1991;22:1170-3.

Cold Urticaria Associated With Epstein-Barr Virus Mononucleosis

S.A. Arias-Santiago, F.M. Almazán-Fernández, P. Burkhardt-Pérez, and R. Naranjo-Sintes
Servicio de Dermatología, Hospital Clínico Universitario San Cecilio, Granada, Spain

To the Editor:

Physical urticarias are characterized by the appearance of wheals or angioedema after exposure to different physical stimuli. In cold urticaria, symptoms develop with cold. In the majority of these patients, no triggering agent is found, though in some cases it has been associated with viral or bacterial infections, autoimmune, hematologic, or thyroid diseases, or drug ingestion.[1]

We present the case of a 14-year-old girl with no past history of interest, who was seen in June 2007 for episodes of facial wheals and pruritus after bathing in the sea wearing a neoprene suit. Cold drinks, ice creams, and cold air did not trigger the condition, nor did water at other temperatures. The urticaria appeared a few minutes after contact with cold water and disappeared spontaneously within 20 to 30 minutes. There was no angioedema, syncope, hypotension, Raynaud phenomenon, or purpura, and no other cardiovascular, respiratory, or gastrointestinal symptoms. At the time of consultation, the patient was asymptomatic. To confirm the diagnosis of cold urticaria, a provocation test was performed with an ice cube; a wheal of 3 by 2 cm appeared on the forearm after 5 minutes.

Two weeks before the first episode, the patient had suffered an episode of exudative pharyngitis with fever and submandibular lymphadenopathies. Suspecting cold urticaria secondary to infectious mononucleosis, serological tests were performed for Epstein-Barr virus (EBV), cytomegalovirus (CMV), and other viruses related with cold urticaria, such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). A complete blood count and basic biochemistry were performed, together with the levels of total immunoglobulin (Ig) E, complement, cryoglobulins, cryoagglutinins, and cryofibrinogen. This study revealed the presence of IgM to EBV, with negative or normal results of the other parameters. Subsequent follow-up showed a clinical improvement of the cold urticaria, coinciding with seroconversion to anti-EBV IgG; the patient was asymptomatic 2 months after the onset of the condition (negative ice cube test). Until resolution of the disorder, she was advised to avoid contact with cold water, the principal trigger, and was given treatment with cetirizine at a dose of 10 mg/24 h.

Cold urticaria accounts for 2% to 3% of physical urticarias[2] and was first described in 1866 by Bourdon.[3] It can be associated with other forms of physical urticaria such as dermographism (21%), heat urticaria (10%), and cholinergic urticaria (8%).[4] Wanderer[5] classified these conditions into 3 groups according to the severity of the clinical manifestations: type I (localized lesions), type II (systemic phenomenon without symptoms of hypotension), and type III (with hypotension or shock), which can be life-threatening.

No etiological agent is detected in more than 95% of patients with cold urticaria, and the condition is classified as primary or idiopathic.[2] A small percentage of cases are secondary to various viral or bacterial infections, such as *Mycoplasma*, *Treponema pallidum*, *Helicobacter pylori*, *Toxoplasma gondii*, rubella virus, EBV, CMV, HBV, HCV, and HIV.[1]

The most common skin manifestation in patients with infectious mononucleosis is the generalized rash associated with treatment with β-lactam antibiotics[6]; in addition, 5% of patients present urticaria during the course of the disease.[7] However, Doeglas et al,[8] in a series of 39 patients with cold urticaria, found no significant differences with the control group with respect to EBV infection. In contrast, they found that other infections, such as those due to *Mycoplasma*, CMV, or herpes simplex virus, were more common in patients with cold urticaria.

In our patient, we observed a clear relationship between EBV infection and the cold urticaria: the clinical signs of urticaria and the positive IgM serology of the infectious episode coincided in time, and the cold urticaria resolved as seroconversion developed. In addition, attention is drawn to the short duration of the condition—8 to 9