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Lifelong widespread warts associated with human papillomavirus type 70/85: a new diagnostic entity?

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Abstract

We present a patient with HPV 70/85–positive widespread cutaneous warts characterized by clinical and histological features atypical for classic generalized verrucosis or epidermodysplasia verruciformis. The cutaneous HPV infection is characterized by verrucous papules or plaques variable in size, number, and distribution depending on the genotype of HPV involved and the immune status of the patient. Human papillomaviruses comprise five genera (alpha, beta, gamma, mu, and nu papillomavirus) with different life-cycle characteristics, epithelial tropisms, and disease associations. Epidermodysplasia verruciformis (EV) is a rare, lifelong, autosomal recessive skin disease characterized by persistent cutaneous human papillomavirus infection not necessarily associated with immune system defects. The disease results from an unusual genetic susceptibility to infections with various types of HPVs (especially β-HPV), some of which cause malignant transformation. Conversely, generalized verrucosis has been more typically associated with generalized warts, which are associated with immunocompromised conditions.

Keywords: generalized verrucosis, epidermodysplasia verruciformis, widespread warts, papillomavirus infection, cryosurgery

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Introduction

Cutaneous HPV infection is characterized by verrucous papules or plaques variable in size, number, and distribution depending on the genotype of HPV involved and the immune status of the patient. Its diagnosis is generally easy for dermatologists. There are, however, cases such as generalized forms that are a challenge to the clinician. The recent opinion is that generalized verrucosis (GV) and epidermodysplasia verruciformis (EV) should be considered as two separate entities that present similar clinical features. Thus epidermodysplasia verruciformis and other genetic or immunodeficiency disorders are described as a subset of generalized verrucosis (1, 2). We present the case of a patient with widespread warts characterized by clinical and histological features atypical for classic GV or EV.

Case report

In April 2013, a 38-year-old man came to our clinic for warty, grayish-white papules on the forehead, extensor surface of both arms, and neck. On the flexor surface of arms he presented isolated erythematous scaly papules and plaques (Figs. 1a, b). The first lesions appeared in 2001 and they increased gradually in both size and number over time. The patient did not mention pain or other symptoms. He denied any similar cases in his family members. His medical history showed that the patient had been suffering from Crohn's disease for about 18 months. Skin biopsy of two lesions, one localized on right arm and the other one localized on the neck, was performed. Histological examination showed an acanthotic epidermal pattern with a compact keratin layer, and enlarged clear cells with perinuclear vacuolization in the superficial squamous layer. Basophil granules around the cells were found. The lesion had a papillomatous growth; atypical cells and clusters of nuclei were not found. Inflammatory infiltration was not present in the papillary dermis. The small superficial vessels were occasionally ectatic (Fig. 2).

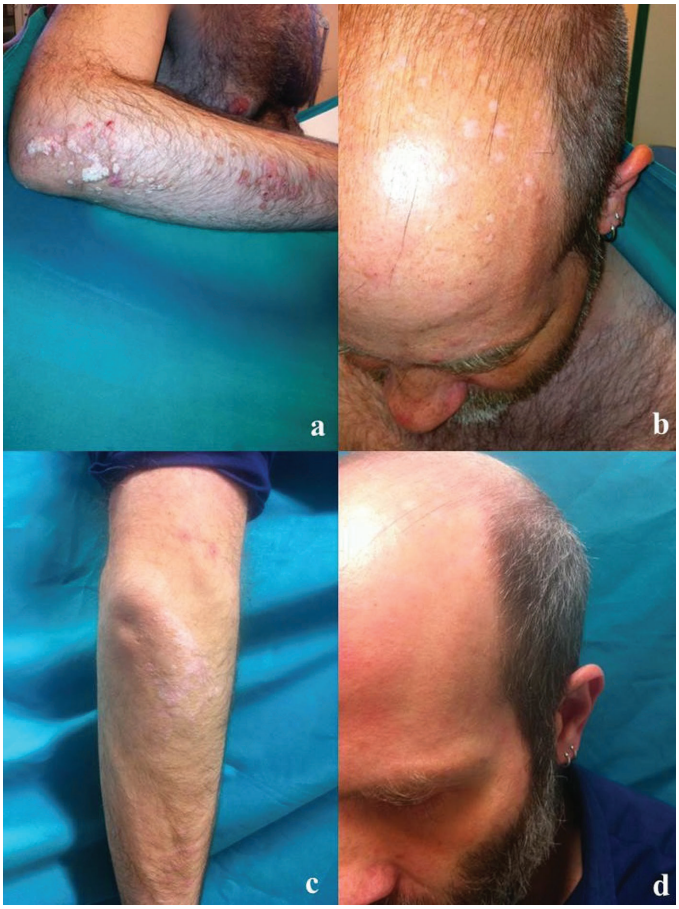

Figure 1 | Warty, grayish-white papules on the extensor surface of right arm and on the forehead before (a and b) and after (c and d) cryotherapy.

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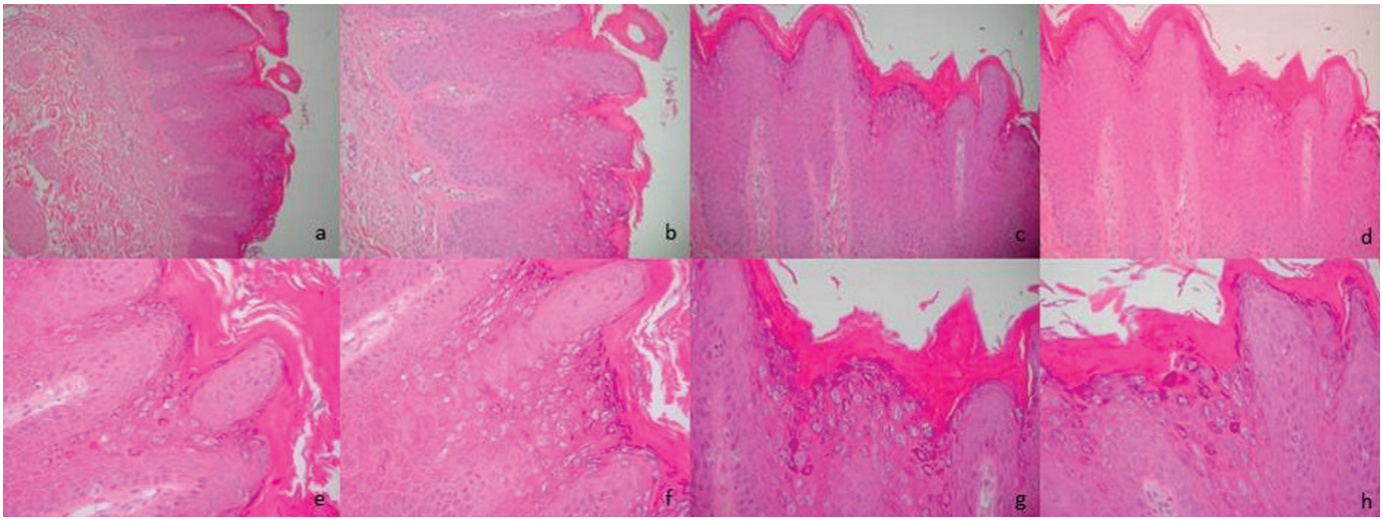

Figure 2 | Histological findings. Papillomatous growth of the lesion with an acanthotic epidermal layer. Vacuolization of the superficial squamous cell cytoplasm and basophil granules. Superficial blood vessels were dilated. Hematoxylin and eosin, original magnification (a) ×4; (b, c, d) ×10; (e, f) ×16; (g, h) ×20.

HPV DNA extraction from a biopsy (not paraffin embedded) was performed using a commercial kit (QIAamp DNA Mini Kit, QIAGEN®), following the commercial specifications for tissue. HPV detection was performed using a homemade PCR already described elsewhere (3); the combination of primers used has proved to be more sensitive and capable of amplifying over 100 HPV genotypes. The technique is based on the amplification of a 173-208 bp on the L1 open reading frame conserved region. Then 12 microliters of the amplified fragment (range 173–208 bp depending on HPV type) were used in two different restriction reactions with endonucleases *Rsa*I and *Tru*91, respectively, and analyzed using a capillary electrophoresis system. The sample results were HPV 10/27/39/67/70/85–positive.

For these HPV genotypes, the same number of fragments and the same length (a similar restriction pattern) are obtained by digestion. To resolve these cases, the amplified product was also digested with *Afl*III restriction endonuclease. However, even with this enzymatic digestion it is not possible to further distinguish HPV70 from HPV85. It would be possible to distinguish the two genotypes by sequencing the amplification product, but this was not considered clinically required.

Laboratory evaluation revealed slight lymphopenia and mild eosinophilia. Phenotypic study of peripheral blood lymphocytes showed no significant alterations in the T-cell population, with moderate increase of CD19 B-lymphocytes. A serological test for human immunodeficiency virus was negative. The patient started treatment with liquid nitrogen cryosurgery. Cryotherapy was performed every 2 weeks a total of eight times, and the patient showed significant clinical improvement (Figs. 1c, d) with the disappearance of all lesions.

Discussion

Generalized verrucosis has been defined as a diffuse cutaneous human papillomavirus infection characterized by more than 20 lesions located in more than one region of the body. Epidermodysplasia verruciformis and other widespread wart forms linked to genetic or immunodeficiency disorders may be classified as part of GV. Thus patients with diffuse warts have to be evaluated for underlying disease and for genetic and immunodeficiency syndromes that could play a role in increased susceptibility to HPV infection (4–7). Cases of GV caused by common warts occurring in patients with no detected immunodeficiency background have been described in the literature (1, 8). In our patient, verrucosis was also not associated with underlying syndromes: the patient had no family members with similar cutaneous lesions and no immunity defect was identified.

HPV DNA test screening revealed the presence of HPV 70/85, which, together with other phylogenetically related HPV types, including HPV 18, belongs to the papillomavirus alpha 7 species group, a high-mucosal oncogenic viral subset. In particular, HPV 70/85 belongs to IARC category 2 B, proposed for types that are possibly carcinogenic to humans because of their close phylogenetic relationship with the established carcinogenic types (9, 10). The chosen protocol did not make it possible to distinguish HPV type 70 from 85 because the two genotypes have the same restriction pattern for the enzymatic digestion used. All of these findings argued against a diagnosis of EV, but also excluded a diagnosis of classic GV. Generalized verrucosis is described as a chronic disease with marked resistance to localized and systemic therapies. This disease's clinical behavior differentiates GV from localized warts, where spontaneous resolution may occur in healthy individuals within 5 years (2). The rapid and complete response of cutaneous lesions to cryotherapy led us to consider a distinct diagnostic entity. The exact mechanism by which our patient presented widespread warts is unclear. It has been shown that many immunocompetent individuals experience persistent HPV infection lasting several years (10). Some HPV viruses (especially beta and gamma HPV types) are only responsible for chronic infections that are not visible, whereas alpha types in particular employ several mechanisms for evading the host's immune system and causing persistent visible warts. High-risk alpha types interfere with normal epithelial cell-cycle regulation, preventing keratinocyte apoptosis and amplifying their genome. Moreover, most nuclear viral proteins produced in HPV-infected cells do not activate the immune system because they are not released outside the cell and so they can not bind to cells capable of presenting viral antigens to immunocompetent effectors (9, 10).

Although high-risk HPV infection is common, the risk of developing cancer is low. Clearly, the genetic susceptibility of the host can play an important role (1, 11, 12).

In conclusion, our patient presented disseminated life-long cutaneous lesions resembling common warts without the combination of pityriasis versicolor–like lesions, reddish plaques, and eventually cutaneous carcinomas, which is typical of classic EV (11, 13). No EV-specific HPV was detected, no form of evident immunodeficiency or genetic underlying syndrome was found, and the warts disappeared after cryosurgery. All of these features led

us to exclude the diagnosis of both EV and GV. Thus we propose that our patient had an abnormal specific susceptibility to HPV, which led him to a diffuse and persistent skin infection by common warts. This could also explain the excellent response of the lesions to cryotherapy.

The detection of HPV70/85 in the lesions of our patient is not enough to prove the etiology of the disease and it is also possible that HPV 70/85 is a contaminant, but we did not choose to distinguish it using sequencing of HPV DNA because the patient had an excellent response to cryotherapy.

The best-studied HPV types are the types that cause cervical cancer, but the multiplicity of the HPV types and the diversity of the resulting infections are not all known. Further investigations are required to understand the unstable balance between viral replication and immune tolerance and to formulate a precise differential diagnosis of all types of diffuse and persistent HPV infections.

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