2009

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Epidermodysplasia verruciform-like Lesions in an HIV patient

David R Berk MD, Anna L Bruckner MD, Dongsi Lu MD PhD

Abstract

Epidermodysplasia verruciformis (EV) is a rare disorder involving widespread infection with specific human papillomavirus types and characteristic clinical lesions that may resemble verruca plana, tinea versicolor, psoriasis, or seborrheic keratoses. The most common HPV types found in EV are 5, 8, 17, and 20. Histopathologically, lesions demonstrate stereotypical enlarged keratinocytes in the upper epidermis with gray-blue cytoplasm, enlarged round nuclei with pale chromatin, and one or multiple nucleoli. Epidermodysplasia verruciformis may occur in either a classical form (often familial, early onset, and complicated by squamous cell carcinoma) or in association with various hereditary or acquired immunodeficiencies, particularly HIV. Fewer than 20 cases of HIV-associated epidermodysplasia verruciformis have been reported. We describe a 42-year-old HIV-positive man who presented with hypo- and hyperpigmented papules and plaques on the upper trunk, head, and neck, with histopathologic findings of epidermodysplasia verruciformis.

Case report

A 42 year-old HIV-positive African-American man presented with a 1-year history of asymptomatic hyper- and hypopigmented lesions, refractory to ketoconazole cream. He was on atazanavir, ritonavir, emtricitabine, and tenofovir and his CD4 count was 7 cells/mm³. Physical examination demonstrated thin, scaly, slightly verrucous hypo- and hyperpigmented papules and plaques on his head, neck, and upper trunk (Fig. 1). His hands were largely spared. Shave biopsy of a hyperpigmented plaque on his back revealed epidermal acanthosis with multifocal areas of altered keratinocytes arranged in small wedges in the granular and upper spinous layers. The altered keratinocytes have purple-blue cytoplasm, variable sized keratohyaline granules, enlarged round nuclei with pale chromatin, and one or multiple small nucleoli (Figure 2). A diagnosis of HIV-associated epidermodysplasia verruciform (EV) was made.
Discussion

Epidermodysplasia verruciformis may occur in either a classical, often hereditary form or in association with various hereditary or acquired immunodeficiencies. Patients with EV demonstrate infection with specific human papillomavirus (HPV) types and develop characteristic verrucous, premalignant clinical lesions. In classical EV, patients usually present in childhood with verruca plana-like lesions (often red-brown) on the extremities (especially dorsal hands), face, and neck [1, 2, 3]. A subset of patients may present as young adults [3]. Patients also often develop tinea versicolor-like lesions on the trunk, psoriasis-like lesions on the elbows, and/or seborrheic keratosis-like lesions on the forehead, neck, and trunk [4]. Lesions of EV have a stereotypical histopathologic appearance characterized by distinctive keratinocytes in the upper epidermis with gray-blue cytoplasm, enlarged round nuclei with pale chromatin and small nucleoli. Epidermodysplasia verruciformis-associated HPV types include 3 and 10 (both typical of verruca plana in non-EV patients) as well as types more unique to EV such as 5, 8, 9, 12, 14, 15, 17, 19-25, 36-38, 47, and 50 (beta-HPVs). Individual EV patients often demonstrate multiple HPV types in their lesions and the most commonly identified HPV types depend on the molecular techniques used. Overall, HPV types 5, 8, 17, and 20 have most commonly been identified but the significance of more recently discovered HPV types remains poorly characterized [5]. Human papillomavirus types 5 and 8 are closely associated with malignant EV lesions. Classical hereditary EV may be caused by autosomal recessive defects in EVER1/TCM6 or EVER2/TCM8, both of which are located on chromosome 17 (near a psoriasis susceptibility locus) and encode integral membrane proteins of unknown function in the endoplasmic reticulum [6]. A second susceptibility locus has been mapped to chromosome 2 (near another psoriasis susceptibility locus), although the specific gene defect is still undiscovered [7]. Finally, several pedigrees with classical EV have suggested the existence of an X-linked recessive form of transmission [8, 9].

Squamous cell carcinoma (SCC) develops in 30-60 percent of EV patients on sun-exposed surfaces usually beginning between 20-40 years of age. Darkly pigmented EV patients are highly protected from SCC [10]. The vast majority of EV-associated SCCs are associated with HPV types 5 and 8, although HPV types 14 and 47 may also be important. Epidermodysplasia verruciformis patients who have lower production of interleukin-10 genotypes are predisposed to develop SCC [11]. Epidermodysplasia verruciformis-associated SCCs may be quite locally destructive but infrequently metastasize. Actinic keratoses, Bowen disease, and basal cell carcinomas are other possible complications. Rarely, extracutaneous malignancies have been associated with EV [12, 13, 14]. Epidermodysplasia verruciformis patients have impaired cell-mediated immunity and cannot be sensitized to topical immunosensitizers [15, 16, 17].

Management of EV includes strict photoprotection and regular clinical surveillance for SCC. When possible, SCC should be surgically excised. Radiation therapy is contraindicated [3, 18]. If skin grafts are required, they should be taken from photoprotected areas. Other approaches include topical and oral retinoids, topical calcipotriol, photodynamic therapy, cidofovir, cimetidine, interferon alpha-2a, 5-fluorouracil, cryotherapy, and imiquimod. However, in general, responses to these treatments have been either unsuccessful, inconsistent, or associated with rapid recurrence after treatment. The most commonly reported non-surgical treatments include systemic retinoids [2, 3, 19, 20, 21] or interferon [2, 3]. More recently, multiple patients have been treated with imiquimod with variable responses [3, 9, 22, 23, 24]. Although not studied systematically, the most effective non-surgical treatments which have reported may be combinational approaches with systemic or topical agents, such as acitretin and interferon [2, 3, 25, 26] and, more recently, interferon and imiquimod [23].

Although the importance of HPV in cervical SCC is well-documented, the role of HPV in cutaneous SCC is controversial [2]. Epidermodysplasia verruciformis may offer a model for cutaneous SCC [27] because (1) EV patients develop frequent SCC at early...
Epidermodysplasia verruciformis (EV) is a rare genetic disorder characterized by an increased risk of cutaneous and mucosal squamous cell carcinoma (SCC) in patients with a history of HPV infection. EV is associated with familial and sporadic cases, and it is caused by a subset of HPV types, which are usually diarrhoeal type (d-polyomaviridae) HPV 25. The association between EV-associated HPV and SCC development is well documented, and the incidence of SCC in EV patients is significantly higher than in the general population. EV is considered to be a precursor lesion for SCC, and the risk of developing SCC is estimated to be between 10% and 15% in EV patients. However, the long-term outcomes of EV patients are still controversial, with some studies reporting a higher incidence of SCC in HIV-associated EV compared to classical EV. The development of SCC in EV patients is thought to be influenced by multiple factors, including HPV type, immunosuppression, and genetic susceptibility. The treatment of EV is usually less successful in HIV-associated EV than in classical EV due to the immune suppression associated with HIV. However, recent studies have shown that antiretroviral therapy can improve the clinical course of EV in HIV patients. The underlying genetic mechanisms responsible for the increased risk of SCC in EV patients are not fully understood, but evidence suggests that certain genetic polymorphisms, such as EVER2, may contribute to the development of SCC in EV patients. Overall, EV remains a rare and complex disorder, and more research is needed to better understand its clinical presentation and management.


57. Haas N, Fuchs BS, Hornes B, Hanz BM: Remission of epidermodysplasia verruciformis-like skin eruption after highly...


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