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Epidermodysplasia verruciform-like Lesions in an HIV patient

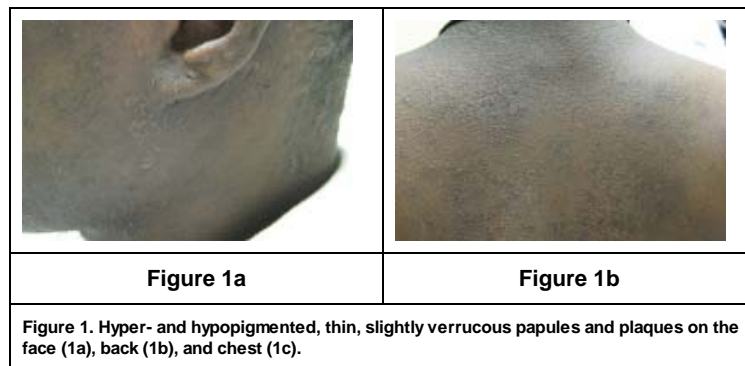
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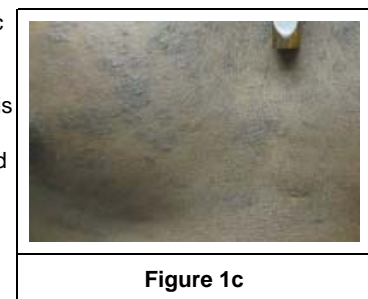
Abstract

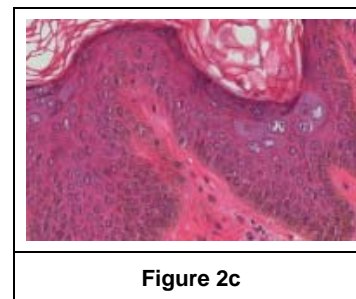
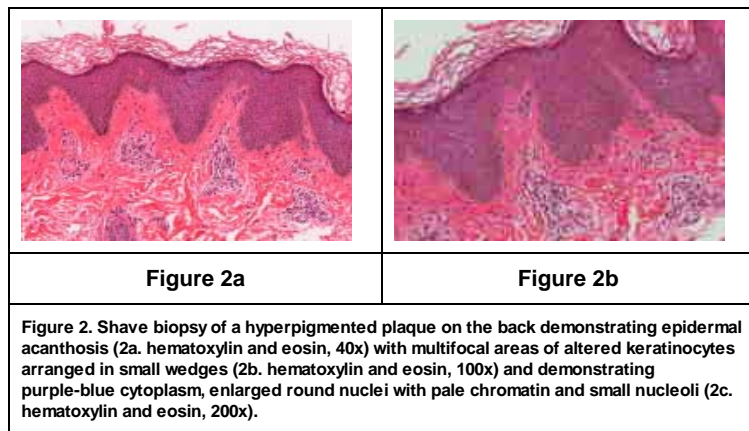
Epidermodysplasia verruciformis (EV) is a rare disorder involving widespread infection with specific human papillomavirus types and characteristic clinical lesions that may resemble verruca plana, tinea versicolor, psoriasis, or seborrheic keratoses. The most common HPV types found in EV are 5, 8, 17, 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 one or multiple 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

ages, (2) seroreactivity to EV-associated HPV is increased in non-EV patients with SCC [28, 29], and (3) transcriptionally active EV-associated HPV can often be detected in SCC in non-EV patients [30, 31], especially in immunosuppressed [32] and xeroderma pigmentosum patients [33], and particularly during the early stages of lesions (EV-associated HPV is more commonly found in actinic keratoses than SCCs) [34, 35]. However, EV-associated HPV has also been isolated from lesions of psoriasis [36], seborrheic keratoses [37], nevus sebaceous [38], epidermal inclusion cysts [39], HPV vulvitis [40], melanoma [41], and normal skin [42]. Interestingly, in immunocompetent individuals, sun exposure directly correlates with both EV-associated HPV positivity in clinically normal skin and EV-associated HPV seropositivity [43]. Nevertheless, it remains unclear whether EV-associated HPV directly causes SCC, serves as a co-factor (to ultraviolet radiation) in SCC development, only plays a role in early stages of SCC development, or is simply a bystander in actinic keratoses and SCC. In a recent case-control study, EVER2 polymorphisms were associated with SCC development [44]. Recent studies have also highlighted the potential transforming properties of several proteins coded by EV-associated HPV, such as HPV-8 E2 [45] and HPV-5 E6 [46]. The concept of the EV acanthoma (incidental EV-associated HPV in skin of non-EV patients) has been proposed [47], and may represent "field cancerization" (skin altered by EV-associated HPV, sunlight, and/or immunosuppression such that there is increased risk for tumor development) [48].

Epidermodysplasia verruciformis has been reported in various immunosuppressed states (sometimes referred to as "EV-like lesions") including HIV [9, 49-57], common variable immunodeficiency [58], graft versus host disease [59], renal transplantation [60], systemic lupus erythematosus [61], Hodgkin disease [62], WILD syndrome (warts, immunodeficiency, lymphedema, anogenital dysplasia) [63], and IgM deficiency [20, 64]. Of these conditions, HIV-associated EV has been most frequently described, although a recent case report and review [55] identified only 15 reported cases of HIV-associated EV and the largest series [49, 50, 51] of HIV-associated EV have included only 3 patients. The authors of that review noted that most patients with HIV-associated EV presented with typical hypopigmented tinea versicolor-like lesions on the upper trunk and face, and had previously received antifungal therapy. Unusual presentations of EV-like lesions or EV-associated HPV in HIV patients have included scaly, erythematous, flat papules and plaques in the groin [56] and associated cervical intraepithelial during immune restoration [65]. Because EV only rarely occurs in HIV patients, some authors have hypothesized that EV only arises in those HIV patients with as yet undefined genetic susceptibilities [52, 53, 54]. A report of EV in HIV-infected half-siblings supports this notion [9].

Our patient did not follow-up for treatment after his biopsy. Treatment is usually less successful in HIV-associated EV than in classical EV. In the largest series of HIV patients with EV, multiple modalities were attempted and found to be either ineffective or limited by recurrence after treatment [49, 50, 51]. Highly active antiretroviral therapy does not seem to significantly impact the course of disease [51, 53], although one case report highlighted improvement [57]. Finally, the rate of SCC in HIV-associated EV seems to be much less than in classical EV. We are not aware of a reported case of HIV-associated EV with malignant transformation [56].

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