

Epidermodysplasia Verruciformis Occurring in a Patient With Human Immunodeficiency Virus: A Case Report

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GOAL

To understand epidermodysplasia verruciformis (EV) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the 2 forms of EV.
2. Discuss the link between immunodeficiency and EV.
3. Identify therapies for EV.

CME Test on page 306.

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Epidermodysplasia verruciformis (EV) is an uncommon dermatosis associated with human papillomavirus (HPV) infection in association

with defects in cell-mediated immunity. Malignant transformation to squamous cell carcinoma has been associated with lesions caused by HPV-5, HPV-8, and HPV-14. Clinically, the disease may be confused with verruca plana, seborrheic keratosis, and pityriasis versicolor. We present an unusual case of EV occurring in a human immunodeficiency virus (HIV)-positive man and discuss the clinical and histologic findings. Clinically, the patient had 1- to 3-mm hypopigmented smooth macules covering the entire body. Histopathologic examination of the skin biopsy results demonstrated enlarged keratinocytes with prominent

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blue-gray cytoplasm and clumping of keratohyalin granules within the granular layer of the epidermis. Although EV typically is viewed as a disease of childhood, sometimes presenting in patients with a family history of the disease, it rarely may be seen in immunocompromised adults.

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Epidermodysplasia verruciformis (EV) is a rare dermatosis associated with an increased susceptibility to infection by human papillomaviruses (HPVs). The disease may present as disseminated flat warts, reddish brown macules, or pityriasis versicolor-like lesions. Two forms of the disease are recognized.¹ One form is characterized by multiple plane warts and is associated with HPV-3 and HPV-10.^{2,3} This variant has no tendency for malignant transformation. The second form often occurs in patients with a family history of the disease. Malignant transformation occurs in 30% to 60% of patients with this variant and is associated with HPV-5, HPV-8, and HPV-14.^{2,3} Malignant transformation is related to the oncogenic potential of the virus. Patients with defects in cell-mediated immunity are more susceptible to EV and EV has been reported in association with renal transplant, Hodgkin disease, systemic lupus erythematosus, and, most recently, human immunodeficiency virus (HIV) infection.^{4,9} We report a case of EV occurring in an HIV-positive patient.

Case Report

A 41-year-old African American man of Zimbabwean descent presented with a diffuse hypopigmented rash extending over most of his body. The eruption had been present for more than 20 years but had recently worsened. He denied pain, pruritus, and bleeding from the site. He previously was diagnosed with pityriasis versicolor and had been treated with urea cream 20% and ketoconazole, with no relief of symptoms. The patient tested positive for HIV in 1999 and was placed on a therapeutic regimen of efavirenz and lamivudine/zidovudine. Laboratory test results showed a CD4 cell count of 726/mm³ (reference range, 233–2555/mm³) and an undetectable viral load. Physical examination results revealed 1- to 3-mm smooth macules covering the entire body but more prominent on the back, with more than 100 macules present in this area (Figures 1 and 2). The macules were hypopigmented with a small amount of scale present.

Results of a shave biopsy demonstrated a lesion with mild basket-weave orthokeratosis (Figures 3 and 4). The underlying keratinocytes were enlarged and had prominent blue-gray cytoplasm. There was clumping of keratohyalin granules within the

granular layer of the epidermis. The individual keratinocytes had no significant cytologic atypia. There were no apoptotic keratinocytes or mitotic figures above the basal layer. Within the papillary dermis, there was a mild perivascular mononuclear cell inflammatory infiltrate. These findings were consistent with EV. Results of an additional biopsy with electron microscopy demonstrated the presence of numerous intranuclear viral particles consistent with HPV. The patient declined HPV testing but agreed to follow-up assessments every 6 months to monitor



Figure 1. Flat hypopigmented macules and papules on the upper back.



Figure 2. Hypopigmented lesions resembling pityriasis versicolor.

progression of the lesions to carcinoma. He was treated with acitretin 25 mg/d but discontinued therapy after 2 weeks due to lack of immediate improvement of the skin lesions and financial constraints.

Comment

EV often presents in childhood with flat wartlike lesions and/or reddish brown macules and plaques on the distal extremities and face.^{10,11} The lesions may be hypopigmented, such as in our case, and mistaken for pityriasis versicolor. The clinical differential diagnosis includes verruca plana, seborrheic keratosis, and pityriasis versicolor.

Two forms of the disease are recognized (Table). The first form is associated with HPV-3 and, to a lesser extent, HPV-10.¹ Both of these virus types also are associated with verruca plana, which makes it difficult to distinguish between EV and verruca plana. EV, however, has a wider distribution and is more chronic in nature than verruca plana.¹ Some patients with this variant have a family history of the disease, and there may be some defect in cell-mediated immunity.¹²

The second variant of EV most commonly is associated with HPV-5.¹³ There often is a family history. The disease is considered autosomal recessive, though autosomal dominant and X-linked recessive modes of inheritance have been reported in one family each, indicating possible genetic heterogeneity.¹³ In one study, 2 susceptibility loci were mapped to regions 17q25 and 2p21–24 in 5 consanguineous families, providing further evidence for nonallelic heterogeneity in EV.¹³ Numerous HPV strains have been reported in this group of patients, with only HPV-5, HPV-8, and HPV-14 associated with malignant transformation to squamous cell carcinoma.^{2,3} UV radiation likely plays a role in the progression of EV to cancer because malignancy most often occurs on sun-exposed areas such as the face and hands.¹¹ In addition, skin pigmentation seems to be protective; black individuals with EV rarely develop skin cancer. In a series of 12 Nigerians with EV, Jacyk and Subbuswamy¹⁴ reported no incidence of malignant transformation.

Patients with EV are known to have defects in cell-mediated immunity, such as anergy to cutaneously applied dinitrochlorobenzene and decreased responsiveness of peripheral T lymphocytes to the nonspecific T-cell mitogen.¹⁵ The link between immunodeficiency and EV is strengthened further by reports of disease in association with renal transplant, Hodgkin disease, systemic lupus erythematosus, and HIV infection.^{4,9} Majewski et al¹⁶ demonstrated decreased lysis of EV keratinocytes despite normal cell-mediated immunity against

K562 erythroleukemic cells. These findings suggest that patients with EV have depressed cell-mediated immunity to disease-specific keratinocytes. Additionally, an increase in CD8⁺ and CD57⁺ T cells (the T cells inhibit cell-mediated cytotoxicity) has been reported in 3 HIV-infected patients with EV.⁷ Boxman et al¹⁷ demonstrated the presence of EV-HPV types in plucked hairs of renal transplant patients and in 45% of healthy volunteers, suggesting that EV-HPV types may be present in the skin of the general population and that immunosuppression may lead to viral activation. Malignant transformation is linked to the oncogenic potential of the HPV type. Results of biopsies of EV lesions in patients

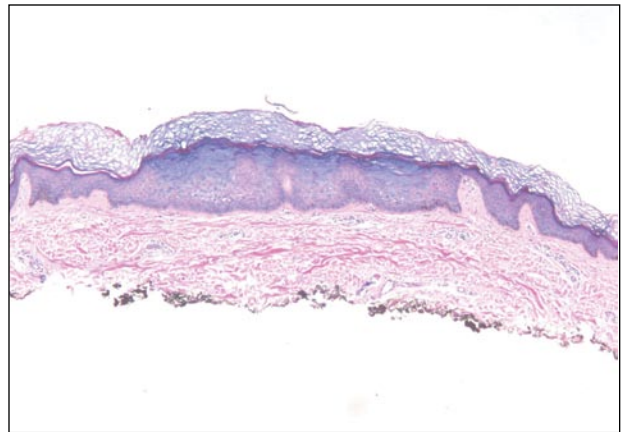


Figure 3. Mild basket-weave orthokeratosis and acanthosis of the central squamous lesion. Keratinocytes within the upper half of the epidermis had prominent blue-gray cytoplasm. The adjacent epidermis was unremarkable (H&E, original magnification $\times 40$).

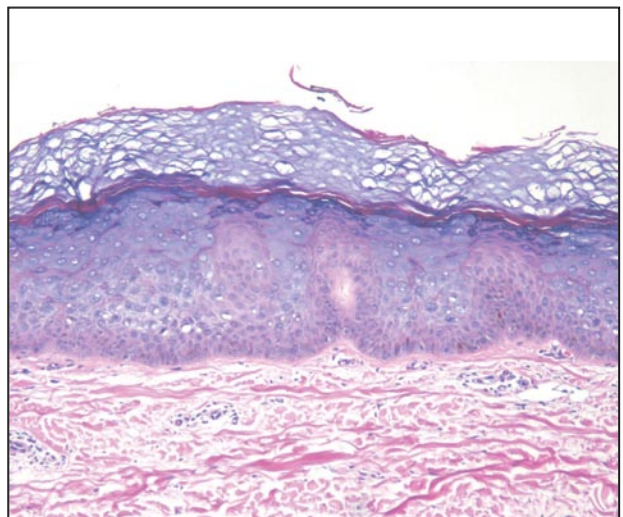


Figure 4. Thickening of the granular layer of the lesion and prominent blue-gray cytoplasm of the keratinocytes within the upper half of the epidermis (H&E, original magnification $\times 100$).

Epidermodysplasia Verruciformis*

	Form 1	Form 2
Age of onset	Typically early childhood	Typically early childhood
HPV types	3, 10	5, 8, 14
Clinical appearance of lesions	Flat-topped papules resembling verruca plana	Red, brown, or white slightly scaly macules that may coalesce into large patches with polycyclic borders resembling pityriasis versicolor; lesions resembling verruca plana and seborrheic keratosis also are present
Location of lesions	Predominately the trunk and limbs	Disseminated over the body
Malignant transformation	No	Yes; 30%–60% of patients; usually in lesions on UV-exposed areas of the body; after 30 years of age
Family history	Occasionally	Often; predominately autosomal recessive, with susceptibility loci at regions 17q25 and 2p21–24
Pathology	Resembles verruca plana, with hyperkeratosis, acanthosis, and vacuolation of cells in granular layer	Some lesions may resemble verruca plana; some lesions only will have enlarged keratinocytes with prominent blue-gray cytoplasm and clumping of keratohyalin granules within the granular layer of the epidermis

*HPV indicates human papillomavirus.

with HIV report higher rates of dysplasia (63%) compared with patients with EV without immunosuppression (20%).¹⁰

To date, 15 cases of HIV-associated EV have been reported. Patients have presented with similar symptoms, mainly hypopigmented pityriasis versicolor-like papules on the chest, upper extremities, trunk, or face.⁶⁻⁸ Trauner et al⁸ reported a case of EV in an HIV-positive patient who presented with scaly erythematous papules and plaques in the groin region that resembled psoriasis. In several cases, the patients' symptoms were present for more than 2 years before a diagnosis of EV was made.^{7,8} Patients often were previously treated with antifungal medications, with no improvement of symptoms. Biopsy results of lesions in patients with HIV have demonstrated the presence of HPV-5, HPV-8, and HPV-20.⁶⁻⁸

Therapy for EV has consisted of systemic and intralesional retinoids and interferon alfa, with

incomplete or temporary improvement reported.^{18,19} Because of increased malignancy rates, patients must have adequate protection from UV light and frequent skin surveillance.¹¹ The diagnosis of EV should be considered in patients with HIV who present with disseminated hypopigmented lesions resistant to treatment with antifungal medications.

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