

# Cornoid Lamella-Like Structures in HIV-Associated Epidermodysplasia Verruciformis: A Unique Histopathologic Finding

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**Abstract:** Epidermodysplasia verruciformis (EV) is an uncommon inherited skin condition with increased vulnerability to widespread infection by certain human papillomavirus types, resulting in extensive verruca plana-like papules coalescing to large confluent plaques. Since the AIDS epidemic starting in the 1980s, an acquired type of EV has been described in patients infected with human immunodeficiency virus. The histopathologic features of EV consist of papillated epidermal hyperplasia with hypergranulosis and a distinct bluish-gray color in the large human papillomavirus-infected keratinocytes in the stratum granulosum. The authors present a case of HIV-associated EV with a unique histopathologic finding of multiple cornoid lamella-like structures. To the authors' knowledge, this finding has not been previously described in the literature.

**Key Words:** epidermodysplasia verruciformis, human immunodeficiency virus, human papillomavirus, acquired epidermodysplasia verruciformis, cornoid lamella

(*Am J Dermatopathol* 2015;37:929–932)

## INTRODUCTION

Epidermodysplasia verruciformis (EV) is a rare autosomal recessive genodermatosis with increased susceptibility to widespread infection by the  $\beta$ -subtype of human papillomaviruses (HPV).<sup>1</sup> It is frequently caused by loss of function mutations in the EVER1/TMC6 or EVER2/TMC8 genes located on chromosome 17q25.3.<sup>2</sup> Patients with inherited EV are usually infected with multiple types of HPV. There are more than 20 known EV-specific HPV types, which include HPV 3, 5, 8, 9, 10, 12, 14, 15, 17, 19–25, 28, 29, 36, 46, 47, 49, and 50.<sup>1</sup> Development into squamous cell carcinomas (SCCs) occurs in 30%–60% of patients,<sup>3</sup> most often in sun-exposed skin in the fourth or fifth decades of life.<sup>1</sup> HPV-5 and HPV-8 are most commonly associated with SCC, accounting for 90% of cases.<sup>2</sup>

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The authors declare no conflicts of interest.

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Individual lesions of EV are essentially thin flat warts, but because of widespread cutaneous involvement, patients may seem to have hypopigmented, hyperpigmented, or lichenified patches and plaques mimicking pityriasis versicolor, ichthyosis, or lichenified eczema when pruritus is prominent. Typical histopathologic findings in EV include hyperkeratosis, hypergranulosis, papillated acanthosis, and large keratinocytes with pale blue-gray cytoplasm and perinuclear halos (koilocytes) found within the spinous and granular layers.<sup>3–6</sup>

An “acquired form” of EV occurs in the setting of immunosuppression. The term acquired epidermodysplasia verruciformis (AEV) was introduced by Rogers et al in 2009.<sup>1</sup> Several cases of AEV have been reported in patients with defects in cell-mediated immunity, including those with HIV/AIDS, solid organ transplants, Hodgkin disease, and systemic lupus erythematosus.<sup>1,7–9</sup> Patients with AEV are susceptible to the same EV-specific HPV subtypes as those with the inherited form and have similar clinical and histopathologic findings.<sup>10,11</sup> To our knowledge, a cornoid lamella-like pattern of tiered parakeratosis overlying dyskeratotic keratinocytes in the spinous layer has not been previously reported in EV. We present a case of HIV-associated AEV with a unique histopathologic finding of multiple cornoid lamella-like structures juxtaposed with the typical histopathologic features of EV.

## CASE REPORT

A 36-year-old HIV-positive woman presented to our outpatient dermatology clinic for evaluation of pruritic scaly skin that had been worsening over the past 12 months. Her symptoms included pruritic, scaly papules, and plaques on her bilateral upper and lower extremities and trunk. The most severe areas of involvement were her legs, arms, and back, with only mild facial involvement. She had previously been treated with topical triamcinolone 0.1% cream, emollients, cetirizine, and NB-UVB, none of which improved the condition of her skin.

The patient's medical history was remarkable for a 15-year history of HIV infection progressing to AIDS, molluscum contagiosum, and cervical dysplasia from high-risk HPV infection. She was a nonsmoker, had no allergies, and had no personal or family history of skin cancer. Her medications included abacavir/lamivudine, norvir, darunavir, valacyclovir, trimethoprim–sulfamethoxazole, amitriptyline, metoclopramide, and hydroxyzine.

Physical examination revealed diffuse, hypopigmented, scaly papules coalescing to plaques on the legs, abdomen, arms, and back (Figs. 1, 2). Hyperpigmented patches were also present on the back, face, and scalp. The clinical differential diagnosis included lichen



**FIGURE 1.** Lower extremity showing white/tan scaly papules coalescing into plaques.

simplex chronicus or a lichenified eczematous dermatitis, psoriasis, widespread pityriasis versicolor, and acquired ichthyosis. Atypical presentations of secondary syphilis, cutaneous T-cell lymphoma, or a nonspecific HIV-related dermatitis were also considered.

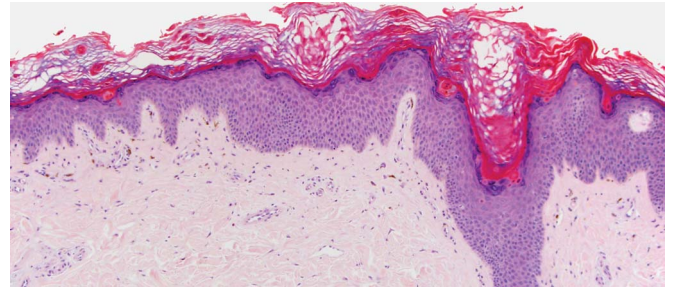
Laboratory tests revealed an HIV-1 viral load:  $>5,000,000$  and CD4 count of 0, with a negative rapid plasma reagin (RPR). Complete blood cell count showed leukopenia (WBC  $1.6 \times 10^3/\text{mL}$ ), anemia (Hgb 8.4 g/dL, Hct 25.9%), neutropenia (30%), eosinophilia (22%), and elevated bands (6%).

Three biopsies were performed, and all showed similar histopathologic findings. There was papillated epidermal hyperplasia with hyperkeratosis, areas of enlarged keratinocytes with abundant blue-gray cytoplasm beneath a variably thickened granular layer, and multiple tiers of parakeratosis present over columns of dyskeratotic keratinocytes with variable hypogranulosis (Figs. 3, 4, 5).

A diagnosis of HIV-associated AEV was made. PCR testing for HPV typing was positive for HPV-5, HPV-111, HPV-120, HPV-124, HPV isolate FA-88, and a new HPV isolate with closest homology to HPV-96. Treatment was initiated with cimetidine 400



**FIGURE 2.** Closer view of the thin scaly papules on the legs, arms, abdomen, and back.



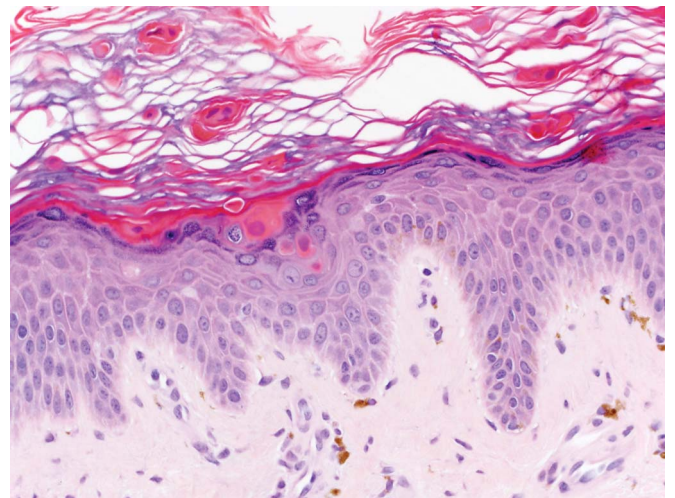
**FIGURE 3.** Biopsy from the right lower extremity showing papillated epidermal hyperplasia with hyperkeratosis and multiple narrow columns of parakeratosis over dyskeratotic keratinocytes in the spinous layer (H&E  $\times 100$ ).

mg 3 times a day orally, amlactin 12% topical cream bid, and hydroxyzine for the pruritus. The patient was noncompliant with these medications and her anti-HIV therapy.

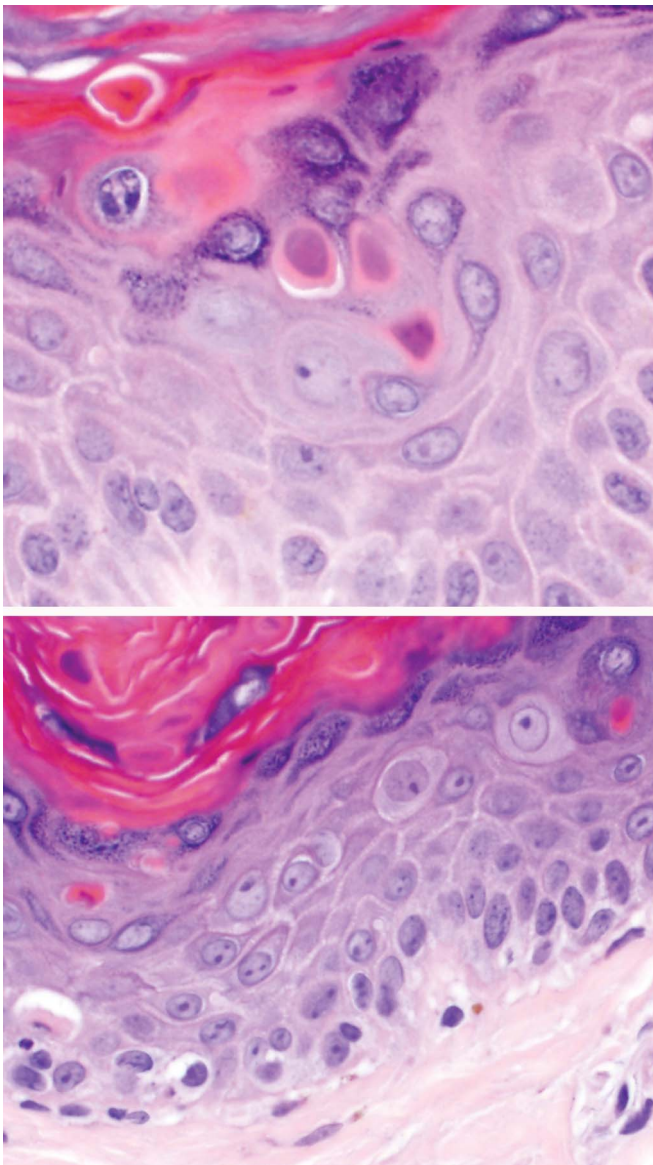
## DISCUSSION

We describe a case of AEV in an HIV-positive patient presenting with diffuse, pruritic, hypopigmented, and hyperpigmented scaly papules and plaques with a unique histopathologic finding of cornoid lamella-like structures. Only approximately 30 previous cases of HIV-associated EV have been reported in the literature.

The finding of cornoid lamella in the setting of EV has not been previously reported to our knowledge. Previous reports have described both focal parakeratosis<sup>4</sup> and generalized parakeratosis,<sup>3</sup> but nothing resembling cornoid lamella, which is typically seen in porokeratosis, could be found. We considered the possibility of an incidental cornoid lamella or concurrent porokeratosis coincidentally biopsied in our patient with EV. However, the pattern in which large HPV-infected keratinocytes were intimately associated with these cornoid lamella-like areas (Fig. 4, 5) suggests a direct relationship.



**FIGURE 4.** High-power view of cornoid lamella-like structures intimately associated with large keratinocytes in the upper spinous layer with blue-gray cytoplasm (H&E  $\times 400$ ).



**FIGURE 5.** High-power view of cytopathologic effects seen in EV with large keratinocytes in the upper spinous layer with blue-gray cytoplasm (H&E  $\times 600$ ).

Furthermore, the presence of cornoid lamella-like structures in 2 subsequent biopsies from different sites provides additional evidence that this is a histopathologic manifestation of the patient's EV and not an incidental finding.

These cornoid lamella-like structures are very similar to the pattern of "columnar dyskeratosis" reported in 2 patients with an acquired dermatosis with widespread verrucous plaques covering the majority of their bodies.<sup>12</sup> One patient was a solid organ transplant patient, and the other had no known immunosuppression. The authors of this report note a resemblance of their biopsies to cutaneous HPV infection and performed PCR, which was negative for HPV. The clinical pictures of these 2 patients, particularly the transplant patient, bear striking resemblance to patients with EV. Perhaps,

columnar dyskeratosis is a manifestation of HPV infection, and the PCR assay used did not detect the variant of HPV underlying this condition.

HPV types 5, 111, 120, 124, and FA-88 were isolated in our patient along with a new HPV strain with closest homology to HPV-96. HPV-5 is one of the most common subtypes found in hereditary and acquired EV, and its detection confirms the diagnosis of EV. HPV types 111, 120, 124, and FA-88 have not previously been reported in association with HIV-associated EV to our knowledge. The unusual finding of cornoid lamella-like structures may be related to infection by one of these additional HPV strains found in our patient.

EV is frequently caused by loss of function mutations in the EVER1/TMC6 or EVER2/TMC8 genes located on chromosome 17q25.3, which encode integral transmembrane proteins in the endoplasmic reticulum involved in zinc homeostasis in cells.<sup>2,7</sup> It has been suggested that the mutation downregulates cell-mediated immunity by decreasing the ability to present certain HPV antigens to T lymphocytes<sup>1</sup> and disrupts control of the apoptosis/survival balance in keratinocytes.<sup>13</sup> It is also hypothesized that the mutation alters zinc levels in the cell, leading to increased activity of transcription factors necessary for HPV replication.<sup>2</sup>

In hereditary EV, there is an increased risk for cutaneous SCC, most commonly associated with HPV-5 and HPV-8.<sup>2</sup> The E6 and E7 oncoproteins are essential for transformation of infected cells, as they prevent apoptosis, sustain proliferation, and create genomic instability. Although the E6 protein from HPV-5 and HPV-8 does not effectively degrade p53 like its counterpart in high-risk HPV types, it does reduce levels of several p53 modifying enzymes, interferes with differentiation of keratinocytes, and disrupts cell cycle regulation. The E7 protein in HPV-8 suppresses a critical regulator of Langerhans cell chemoattractant protein.<sup>13</sup> UVB from sunlight also plays a role causing additional mutations in p53 and contributing to EV tumor progression, and HPV oncoproteins prevent apoptosis of UV-damaged cells.<sup>13</sup>

In contrast to hereditary EV, the development of dysplasia in HIV-associated EV is infrequently reported in the literature, with no reports of invasive skin cancer to date.<sup>1</sup> This discrepancy could be secondary to the delayed acquisition of the EV phenotype in AEV, the different pathogenic pathway leading to the EV phenotype in the inherited and acquired forms, or to lack of sufficient follow-up surveillance in these AEV patients.<sup>10</sup> Vuillier et al<sup>14</sup> investigated the molecular processes underlying the cancer progression associated with  $\beta$ -HPV infection in EV by assessing the impact of EVER2 loss on the NF- $\kappa$ B and JNK activation pathways. They found that EVER2 loss induced JNK activation, which in turn promoted HPV-5 long-control region activation and subsequent inflammatory responses. This has not been studied in AEV patients, but perhaps, there is a difference in this cascade of events, which could also explain why cutaneous malignancy has not been reported in this subset of patients.<sup>14</sup>

In the HIV population, there is an increased prevalence and decreased clearance of HPV infection resulting in cutaneous HPV infections including verrucae, condylomata, and anogenital SCCs.<sup>10</sup> However, AEV occurs only in small

minority of individuals with HIV.<sup>15</sup> Although the weakened cell-mediated immunity in HIV-infected individuals clearly plays a large role in AEV, an underlying genetic predisposition seems necessary for AEV to develop. Hereditary EV is caused by mutations in EVER1/TMC6 or EVER2/TMC8 genes in 75% of cases.<sup>2</sup> Although neither homozygous nor compound heterozygous mutations in those genes have been found in patients with acquired EV, single nucleotide polymorphisms have been identified, suggesting a potential modulator function.<sup>2</sup> In addition, certain HLA DR-DQ haplotypes have been associated with EV, including HLA-DRB1\*11, DQA1\*0501, and DQB1\*0301. These HLA types are found much more frequently in patients with EV than in the general population, including patients with HIV-associated EV.<sup>16</sup> Thus, these specific HLA class II haplotypes could represent susceptibility alleles predisposing to the development of AEV.<sup>3</sup>

Treatment for EV is difficult. Topical 5-fluorouracil, imiquimod, cimetidine, systemic interferon, and oral retinoids are often used as monotherapy or combination treatments in patients with EV.<sup>1,7,17</sup> Different regimens have been tried with varying, and sometimes conflicting, results. Randomized clinical trials are lacking, and treatment decisions are often made on a clinical basis, with combined therapies tending to show better results.<sup>7</sup> Unfortunately in HIV-associated AEV, control of HIV infection with antiretroviral therapy may not lead to clinical improvement in the EV.<sup>18</sup> Additionally, although malignant transformation seems rare for acquired EV, patient education about daily sun protection, regular full-body skin examinations, and biopsy of suspicious or changing lesions remains important for treatment.<sup>1</sup>

## CONCLUSIONS

HIV-associated AEV is a relatively rare condition that clinically and histopathologically mirrors the inherited form of EV. Although the immunologic abnormalities of an HIV-infected individual clearly play a large role, there must also be a certain genetic predisposition that increases the chance of acquiring EV in this setting. Skin biopsy is helpful in establishing the diagnosis of EV. We report an additional case of HIV-associated EV and describe a unique histopathologic finding of cornoid lamella-like structures in biopsies of AEV.

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