

Verrucous lesions in an HIV-positive man



Freidrich Anselmo, BS,^a Umer Ansari, MD,^a J. Michael Gagnier, MD,^a
Stephen K. Tying, MD, PhD, MBA,^b Peter Rady, MD, PhD,^b and Marcia S. Driscoll, MD, PharmD^a
Baltimore, Maryland and Houston, Texas

Key words: acquired epidermodysplasia verruciformis; β -human papilloma virus; epidermodysplasia verruciformis; HIV; verrucous lesion.

INTRODUCTION

Epidermodysplasia verruciformis (EV) is a rare autosomal recessive, dominant, or X-linked genodermatosis characterized by abnormal susceptibility to cutaneous human β -papillomavirus (β -HPV) infections.¹⁻³ Classic genetic EV manifests most commonly as flat, scaly, reddish hypo- and hyperpigmented macules, verruca-like papillomatous papules, seborrheic keratosis-like lesions, and pink-red pityriasis versicolor-like macules.¹⁻³ Lesions develop in childhood and are highly resistant to treatment.² EV is associated with mutations in the *EVER1/TMC6* and *EVER2/TMC8* genes.¹ Both genes are thought to play a role in cell-mediated immunity against human papillomavirus (HPV) and are expressed in keratinocytes, immune cells such as B and T lymphocytes, and dendritic cells.¹ Nonclassic genetic EV describes EV lesions associated with recent discoveries of mutations in genes such as *RHOH*, *MST-1*, and *CORO1A*.¹

The term *acquired epidermodysplasia verruciformis* (AEV) describes an EV-like syndrome that develops in immunocompromised individuals due to iatrogenic or infectious causes.^{1,2} Both genetic and acquired EV are associated with certain specific β -HPV subtypes (3, 5, 8, 9, 10, 12, 14, 15, 17, 19–25, 28, 29, 36, 46, 47, 49, and 50), most commonly 5 and 8.^{1,3} There are few descriptions of AEV occurring in HIV-infected individuals, with approximately 35 cases published in the medical literature.³⁻⁵ We present a case of a 37-year-old man with a history of well-controlled HIV infection who presented with AEV.

Abbreviations used:

AEV: acquired epidermodysplasia verruciformis
EV: epidermodysplasia verruciformis
HAART: highly active antiretroviral therapy
HPV: human papilloma virus

CASE REPORT

A 37-year-old man with history of well-controlled HIV infection (undetectable viral load, CD4⁺ >500) and atopic dermatitis was referred for a rash on his face, arms, and neck present for the last 12 years. The eruption showed hypopigmented and hyperpigmented verrucous papules scattered on the bilateral upper and lower extremities, neck, and preauricular cheeks. A conspicuous group of lesions occurred overlying a tattoo on the upper back. About 3 years after receiving the tattoo on his upper back, he stated that lesions seemed to move down to the tattoo from his posterior neck, suggestive of pseudo-Koebnerization (Fig 1).

The appearance of the lesions coincided with his diagnosis of HIV, which was treated promptly and continuously with highly active antiretroviral therapy (HAART). He denied any change in quality or quantity of lesions. There was no family or close contacts with similar lesions.

A punch biopsy from a lesion on the right arm found histopathology consistent with EDV (Fig 2), and HPV-typing from a paraffin-embedded skin biopsy was positive for HPV-5. He was counseled on sun protection to reduce risk for cutaneous carcinoma and started on a trial of tretinoin 0.025% nightly to his face and neck.

From the Department of Dermatology, University of Maryland School of Medicine^a and the Department of Dermatology, McGovern Medical School at UTHealth.^b

Funding sources: None.

Conflicts of interest: None disclosed.

Correspondence to: Freidrich Anselmo, BS, 419 W Redwood Street, Suite 235, Baltimore, MD 21201. E-mail: freidrich.anselmo@som.umaryland.edu.

JAAD Case Reports 2019;5:825-7.

2352-5126

© 2019 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jidcr.2019.06.036>



Fig 1. **A**, Right preauricular face. **B**, Left posterior neck. Numerous hypopigmented and hyperpigmented verrucous papules were noted, scattered on the bilateral upper and lower extremities, neck, and preauricular cheeks. There was an increased prominence of lesions noted along the patient's tattoo.

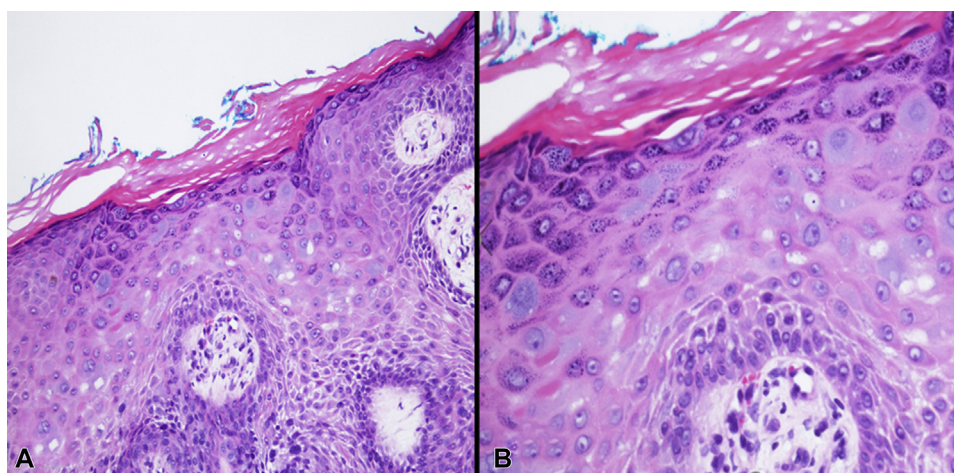


Fig 2. Punch biopsy of the right arm. Mild acanthosis with disordered maturation of keratinocytes containing abundant blue grey cytoplasm and enlarged nuclei, some with nuclear clearing, were noted. A fairly prominent granular layer was also noted, without increased mitotic activity. Given the clinical history, this finding was consistent with epidermodysplasia verruciformis. (Original magnifications: **A**, $\times 200$; **B**, $\times 400$.)

DISCUSSION

AEV typically presents in immunocompromised individuals without family history, affecting any age group or sex.^{2,3} The lesions are identical to genetic EV, both clinically and histologically.¹ The pathogenesis is unknown and in HIV patients is unrelated to the CD4⁺ count and viral load.¹

The EVER1/TMC6 and EVER2/TMC8 proteins form a complex with zinc transporter ZnT1, which decreases intracellular zinc concentration resulting in inhibition of zinc-dependent transcription factors

and suppression of HPV in keratinocytes.^{1,2,6} The α -papillomaviruses express the E5 gene that inhibits the zinc transporter complex to promote replication.⁶ In contrast, the β -papillomavirus genome lacks the E5 gene; therefore, it primarily infects individuals with defective zinc transporter complex as is seen in classic genetic EV.⁶ The mechanism of EV is hypothesized to also be related to impaired cell-mediated immunity given the similar pathogenesis of AEV in immunocompromised and HIV patients.¹ There is possibly an interplay between genetic susceptibility

and immunosuppression, as only a small subset of HIV-infected or otherwise immunocompromised patients go on to have EV.²

EV is considered a virus-associated premalignant condition, eventually leading to nonmelanoma skin cancer in 30% to 70% patients—most commonly Bowenoid dysplasia or squamous cell carcinoma in the fourth and fifth decades of life.^{2,3} HPV-5 and HPV-8 are the types most frequently associated with development of nonmelanoma skin cancers, accounting for more than 90% of classical EV-associated cutaneous malignancies.³ Despite the incidence of all squamous cell carcinomas in HIV-infected patients being 5 times higher than the normal population, reports in HIV-associated AEV cases are rare.^{3,7} Histologically, immunocompromised individuals with AEV show a higher rate of HPV-related dysplasia than those with congenital EV.⁸ Furthermore, there is an increased prevalence of common HPV infection in HIV-infected patients and decreased clearance of the virus.⁷

An interesting manifestation of AEV was noted in our patient, who reported that after receiving a tattoo on his neck, pre-existing lesions spread along the distribution of the tattoo, suggesting autoinoculation. However, it is also possible that the infection may have been a result of contamination from the instruments, inks, or tattooist's saliva.⁹ Interestingly, β 1-HPV-type infection in cutaneous lesions of verrucae planae near a tattoo have also been reported in healthy, immunocompetent individuals.⁹ Additionally, our patient has atopic dermatitis, which has only been reported once in association with AEV in a patient who had AEV lesions after cyclosporine therapy for atopic dermatitis.¹⁰

There is no consensus on treatment. Systemic retinoids, topical imiquimod, interferon- α , oral retinoids, cimetidine, and other immunomodulating drugs have resulted in variable clinical outcomes in both genetic and acquired EV.^{1,8} In HIV-associated AEV, HAART therapy has shown mixed results with some patients improving after initiation and some patients, as our case shows, showing no improvement.^{2,7,8} Of note, some AEV lesions develop as an

immune reconstitution inflammatory syndrome after initiation of HAART.⁷

It is difficult to draw conclusions regarding treatment because of limited case reports and an incomplete understanding of the underlying mechanisms.^{2,7,8} This report adds another case of HIV-associated AEV, with positive HPV-5 and characteristic histopathology, to further characterize the history of this rare cutaneous manifestation; in this case the AEV arose concurrently with diagnosis of HIV infection, but his AEV had no response to HAART.

REFERENCES

1. Huang S, Wu JH, Lewis DJ, Rady PL, Tyring SK. A novel approach to the classification of epidermodysplasia verruciformis. *Int J Dermatol*. 2018;57(11):1344-1350.
2. Przybyszewska J, Zlotogorski A, Ramot Y. Re-evaluation of epidermodysplasia verruciformis: reconciling more than 90 years of debate. *J Am Acad Dermatol*. 2017;76(6):1161-1175.
3. Kaushal A, Silver S, Kasper K, Severini A, Hamza S, Keynan Y. Epidermodysplasia verruciformis in an HIV-infected man: a case report and review of the literature. *Top Antivir Med*. 2012;20(5):173-179.
4. Ashida A, Shimizu A, Okuyama R. Acquired epidermodysplasia verruciformis associated with human papillomavirus type 47 in a HIV-infected patient. *J Dermatol*. 2016;43(6):717-718.
5. Rogers HD, MacGregor JL, Nord KM, et al. Acquired epidermodysplasia verruciformis. *J Am Acad Dermatol*. 2009;60(2):315-320.
6. Lazarczyk M, Cassonnet P, Pons C, Jacob Y, Favre M. The EVER proteins as a natural barrier against papillomaviruses: a new insight into the pathogenesis of human papillomavirus infections. *Microbiol Mol Biol Rev*. 2009;73(2):348-370.
7. Jacobelli S, Laude H, Carlotti A, et al. Epidermodysplasia verruciformis in human immunodeficiency virus-infected patients: a marker of human papillomavirus-related disorders not affected by antiretroviral therapy. *Arch Dermatol*. 2011;147(5):590-596.
8. Lee KC, Risser J, Bercovitch L. What is the evidence for effective treatments of acquired epidermodysplasia verruciformis in HIV-infected patients? *Arch Dermatol*. 2010;146(8):903-905.
9. Krecké N, Smola S, Vogt T, Müller CSL. HPV-47-induced and tattoo-associated verrucae planae: report of a case and review of the literature. *Dermatol Ther (Heidelb)*. 2017;7(4):549-554.
10. Fernandez KH, Rady P, Tyring S, Stone MS. Acquired epidermodysplasia verruciformis in a child with atopic dermatitis. *Pediatr Dermatol*. 2014;31(3):400-402.