

Acquired epidermodysplasia verruciformis in an HIV-positive patient

Fatima Amaaoune, Asma Lahrougui, Chaima Fikri, Abderrachid Hamdaoui, Meriam Aboudouraib, Ouafa Hocar, Said Amal

¹Department of Dermatology-Venerology, CHU Med VI, Marrakech - Laboratory of Bioscience and Health-FMPM-University Quadi Ayyad, Marrakech, Morocco, ²Zohor El Hadika El Kobra Laboratory, Marrakech, Morocco

Corresponding author: Fatima Amaaoune, MD, E-mail: fati.amaaoun@gmail.com

ABSTRACT

Epidermodysplasia verruciformis, or Lutz–Lewandowsky disease, is a rare genodermatosis, usually autosomal recessive, characterized by abnormal susceptibility to infection by certain types of human papillomavirus. There are hereditary and acquired forms. Immunocompromised people, such as HIV-positive patients and kidney transplant recipients, are at risk for acquired epidermodysplasia verruciformis. This pathology poses management problems, and variable responses are observed in different individuals. The prognosis of epidermodysplasia verruciformis is related to the oncogenic potential of certain types of human papillomavirus, inducing carcinomas in sun-exposed areas in 30% to 60% of cases. Tumors grow slowly or sometimes rapidly and are locally destructive. Lesions of epidermodysplasia verruciformis are refractory to conventional wart treatments, yet preventive treatments for complications and symptomatic treatments for lesions may be offered with regular follow-up. Herein, we report a case of acquired epidermodysplasia verruciformis in an HIV-positive patient.

Key words: Epidermodysplasia verruciformis, Human papillomavirus, Human immunodeficiency virus, Immunosuppression, Genodermatosis

INTRODUCTION

Epidermodysplasia verruciformis (EV) is a rare, autosomal recessive genodermatosis described in 1922 by Lewandowsky and Lutz and characterized by abnormal susceptibility to cutaneous infection by certain types of human papillomavirus (HPV) [1]. It results in the appearance of scaly macules and disseminated verrucous papules of chronic evolution. The recent discovery of acquired EV phenotypes in immunocompromised subjects such as HIV positives and organ transplant recipients suggests the role of an acquired immune deficiency [2]. Herein, we report a case of acquired epidermodysplasia verruciformis in an HIV-positive patient.

CASE REPORT

This was a 64-year-old patient followed for retroviral infection for six months under treatment presented

with diffuse painless and non-itchy skin lesions on the trunk and back evolving for four years in a context of unquantified weight loss and apyrexia.

A general examination revealed a patient hemodynamically and respiratory stable and afebrile. A dermatological examination found flat, erythematous, yellowish, millimetric papules with regular edges, well-defined, with a smooth and shiny surface, painless, confluent in places in patches, and diffuse on the thorax, abdomen, and back (Figs. 1a – 1d). A histopathological study of the flat papules confirmed the diagnosis of epidermodysplasia verruciformis evoked by showing an intraepithelial lesion delimited on both sides by a healthy lining. She showed acanthosis with strong orthokeratotic hyperkeratosis. Cells from the corpus mucosa revealed koilocyte lesions with a perinuclear halo and rare, binucleate or dyskeratotic cells. Deep cells showed hyperchromatic,

How to cite this article: Amaaoune F, Lahrougui A, Fikri C, Aboudouraib M, Hocar O, Hamdaoui A, Amal S. Acquired epidermodysplasia verruciformis in an HIV-positive patient. *Our Dermatol Online*. 2024;15(3):278-281.

Submission: 31.01.2023; **Acceptance:** 28.07.2023

DOI: 10.7241/ourd.20243.14

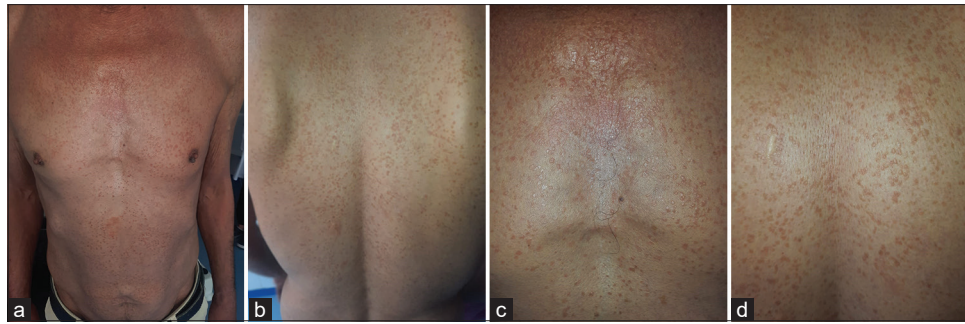


Figure 1: (a-d) Flat papules of diffuse, acquired epidermodysplasia verruciformis on the trunk and back in an HIV-positive patient.

bulky nuclei with a high cytonuclear ratio. At the level of the superficial layers, there were large cells with bluish-gray cytoplasm, sometimes vascular. The dermis was fibrous (Figs. 2a and 2b). The patient was put on an oral retinoid (isotretinoin 20 mg/day), by default of acitretin, after a normal liver and lipid balance sheet associated with the adjuvant treatment with a possible clinical and biological control in one month.

DISCUSSION

Epidermodysplasia verruciformis (EV), or Lutz-Lewandowsky disease [3,4], is a rare genodermatosis, usually autosomal recessive, characterized by abnormal susceptibility to infection by certain types of HPV. The infection is disseminated and of chronic evolution. EV is considered by some to be a multifactorial disease involving specific viruses and genetic, immunological, and environmental factors, with no preference for sex, race, or geographic area [5]. The condition is familial in around 25% of cases and consanguinity is found in 10% of the patients, yet in our case, there was no family history of the disease.

Genome screening of consanguineous families has identified two loci of susceptibility to EV and shown the non-allelic genetic heterogeneity of the disease. The first locus (EV1) was identified on chromosome 17q25. Disease-associated mutations affect two adjacent genes at this locus *EVER1/TMC6* and *EVER2/TMC8*, which are expressed by T and B lymphocytes, NK cells, endothelial cells, myeloid cells, and dendritic cells [6-8].

The *EVER* genes code for transmembrane proteins that play an important role in zinc homeostasis, the loss of which increases the expression of the pro-oncogenic viral genes E6 and E7 [9]. Interestingly, EV1 is located within a familial psoriasis susceptibility locus; and DNA from HPV 5 and other EV HPVs has been detected in psoriasis lesions, suggesting that the same gene may

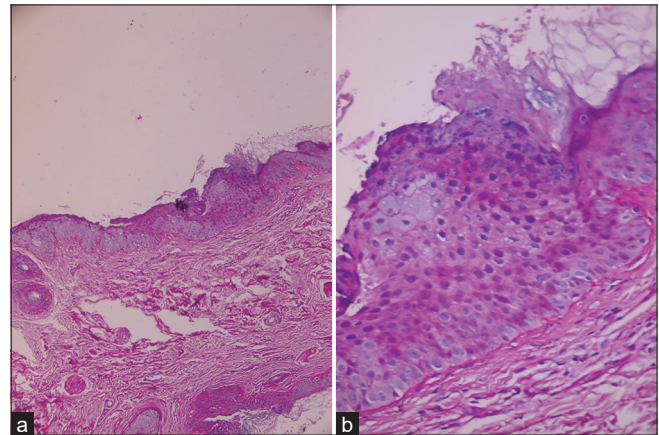


Figure 2: (a) Intraepithelial lesion bounded on either side by a healthy lining (H&E; 40 \times). (b) Acanthosis and severe orthokeratotic hyperkeratosis (H&E; 400 \times).

predispose to EV or psoriasis [10]. The second locus (EV2) at 2p21-p24 has been identified in a French family [11]. Patients are selectively infected with certain types of HPV. There are more than thirty β -types of HPV isolated from these patients in the world at present, including HPV5, HPV8, HPV12, HPV14, HPV15, HPV17, HPV19-HPV25, HPV36, HPV38, HPV47, and HPV50 [12], yet the prognosis is related to the oncogenic potential of some of them found with greater frequency. HPV 5 and 8 are responsible for 90% of carcinomas in EV. EV-specific HPV types are only rarely isolated from the general population, apart from HPV 3 and HPV 10, which are responsible for common flat warts. Most patients have a deficiency in cellular immunity, leading to a lack of recognition of EV-specific HPVs and the inability to eradicate the induced lesions. This immune deficiency, genetic or acquired, is characterized by the inhibition of the natural killer activity and the cytotoxic activity of the T cells. UV light may play a role in the development of this immune deficiency [13].

Only several cases of acquired EV have been described in the literature, most of which were case reports,

especially in immunocompromised subjects, such as HIV positives, as was the case in our patient, organ transplant recipients, and cases of Hodgkin's disease and systemic lupus erythematosus [14]. The development of EV lesions in HIV-positive patients does not seem to be related to the CD4 count and viral load, since in these patients the CD4 count ranges generally from 2 to 767 and the viral load <50 to 623 000⁵. Moreover, the increase in the CD4 count after the introduction of highly active antiretroviral therapy (HAART) often has not caused the skin lesions of EV to disappear [15]. In an observational study, ten patients developed early EV lesions after the diagnosis of HIV and the initiation of HAART. Only one patient in this study developed these lesions before the diagnosis, as was the case in our patient. However, HAART did not affect skin lesions in eleven patients [16]. In other case reports, EV has also been described after the initiation of HAART and has been considered a manifestation of immune reconstitution inflammatory syndrome (IRIS) [17,18]. Once the viral load decreases with HAART, it is often accompanied by an increase in CD4 counts and improved CD4 T-cell function. Increasing the CD4 count and possibly improving antigen recognition increases the risk of patients developing HPV-associated disease [19].

EV is manifested by two types of skin lesions, which are highly characteristic of the disease and allow an early diagnosis before the appearance of skin cancers. It is, on the one hand, a persistent eruption of slightly scaly or keratotic papules, such as flat, isolated warts, sometimes confluent in more or less psoriasiform plaques and, on the other, erythematous macules, sometimes atrophic, pigmented, or achromic, finely scaly, resembling pityriasis versicolor. These lesions sit electively on the back of the hands, forearms, face (in particular, the forehead), legs, and trunk, ranging in rare cases to generalized forms; usually, the mucous membranes are respected [20]. The diagnosis is based on clinical data and the histopathological and anatomopathological aspects, which show mild hyperkeratosis, hypergranulosis, and acanthosis of the epidermis, while the keratinocytes of the upper layer of the epidermis are enlarged and show a vacuolated nucleus [21,22]. Viral sequence detection, not routinely practiced, and the typing of viral sequences by sequencing from lesion scrapings or biopsies, allow the identification of group B HPV [21].

The prognosis of EV is linked to the oncogenic potential of certain HPVs, inducing carcinomas in light-exposed

areas in 30% to 60% of cases [23]. The tumors grow slowly or sometimes rapidly and are locally destructive. Lesions of EV are refractory to conventional wart treatments, yet preventive treatments for complications and symptomatic treatments for the lesions may be proposed. Viral eradication is impossible because the virus is ubiquitous, and the risk of skin carcinomas requires early, permanent, and rigorous photoprotection and regular dermatological monitoring. It should be noted that zinc has been used to treat EV, with a response rate of 20% to 40%, with no recurrence after six months [24]. Pharmacological treatments include cidofovir 1%, topical tretinoin 0.05%, topical glycolic acid, alpha and beta interferons, and imiquimod, yet efficacy is inconsistent and temporary. Cosmetically troublesome, benign lesions are treated with oral retinoids (0.5 mg/kg), yet the results are inconsistent with relapses when the doses are reduced or when the treatment is stopped. Dynamic phototherapy and cryotherapy seem effective in viral lesions. The combination of acitretin 0.5–1 mg/day and interferon alfa-2a has been used successfully, making it possible to obtain a prolonged remission of benign lesions. The treatment of cutaneous carcinomas, diagnosed early, does not present any particularity. However, therapeutic irradiations are strictly contraindicated [13,25-27].

CONCLUSION

Acquired EV is an entity that deserves special attention in immunocompromised subjects, such as HIV positives. The risk of skin cancer is high. It is important to make an early diagnosis and to recommend optimal photoprotection and regular follow-up.

Consent

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

REFERENCES

1. Zerguine R. Epidermodysplasie verruciforme compliquée d'un carcinome spinocellulaire. *Batna J Med Sci.* 2014;1:130-2.
2. Olivier C, Robert PD, Daihung D. What is the evidence for effective treatments of acquired epidermodysplasia verruciformis in HIV-infected patients? *Arch Dermatol.* 2010;146:903-5.

3. Gueye AM, Dioussé P, Bammo M, Dial C, Diallo TAA, Dione H, et al. [Kaposi's disease due to HIV/viral hepatitis B co-infection associated with a Lutz-Lewandowski epidermodysplasia verruciformis in a child in Thiès (Senegal)]. *Our Dermatol Online*. 2020;11(Supp. 1):28-31.
4. Orth G. Genetics of epidermodysplasia verruciformis: Insights into host defense against papillomaviruses. *Semin Immunol*. 2006;18:362-74.
5. Shruti S, Siraj F, Singh A, Ramesh V. Epidermodysplasia verruciformis: trois rapports de cas et une brève revue. *Acta Dermatovenerol Alp Pannonica Adriat*. 2017;26:59-61.
6. Vohra S, Sharma NL, Shanker V, Mahajan VK, Jindal N. Epidermodysplasie verruciforme autosomique dominante: une expérience clinico-thérapeutique dans deux cas. *Indien J Dermatol Venereol Leprol*. 2010;76:557-61.
7. Rodríguez L, Contreras R, Di Martino Ortiz B, de Lezcano LB. Acquired epidermodysplasia verruciformis in an HIV positive child. Report of a case. *Our Dermatol Online*. 2015;6:32-5.
8. Ramoz N, Rueda L. A, Bouadjar B, Montoya L. S, Orth G, Favre M. Mutations in two adjacent novel genes are associated with epidermodysplasia verruciformis. *Nat. Genet*. 2002;32:579-81.
10. Favre M, Orth G, Majewski S, Pura A, Jablonska S, Baloul S. Psoriasis: A possible reservoir for human papillomavirus type 5, the virus associated with skin carcinomas of epidermodysplasia verruciformis. *J Invest Dermatol*. 1998;110:311-7.
11. Ramoz N, Taieb A, Rueda L. A, Montoya L. S, Bouadjar B, Favre M. Evidence for a nonallelic heterogeneity of epidermodysplasia verruciformis with two susceptibility loci mapped to chromosome regions 2p21-p24 and 17q25. *J Invest Dermatol*. 2000;114:1148-53.
12. Alshammari R, Al-Issa A, Ghobara YA. Epidermodysplasia verruciformis: A rare case report. *Curéus*. 2020;12:e9046.
13. Moore S, Rady P, Tying S. Acquired epidermodysplasia verruciformis: Clinical presentation and treatment update. *Int J Dermatol*. 2021.
14. Gül Ü, Kılıç A, Gönül M, Çakmak SK, Bayis SS. Aspects cliniques de l'épidermodysplasie verruciforme et revue de la littérature. *Int J Dermatol*. 2007;46:1069-72.
15. Jacobelli S, Laude H, Carlotti A, Rozenberg F. Epidermodysplasia verruciformis in human immunodeficiency virus-infected patients: A marker of human papillomavirus-related disorders not affected by antiretroviral therapy. *Arch Dermatol*. 2011;147:590-6.
16. Lau C, Acharya S, Arumainayagam JT, Kasparis C, Dhesi I. Acquired epidermodysplasia verruciformis in an HIV-positive patient. *Int J STD AIDS*. 2016;27:1023-5.
17. Mermet I, Guerrini JS, Cairey-Remonnay S, Drobacheff C. Cervical intraepithelial neoplasia associated with epidermodysplasia verruciformis HPV in an HIV-infected patient: A manifestation of immune restoration syndrome. *Eur J Dermatol*. 2007;17:149-52.
18. Iarikov D, Duke W, Skiest D. Extensive development of flat warts as a cutaneous manifestation of immune reconstitution syndrome. *AIDS Read*. 2008;18:524-7.
19. King MD, Reznik DA, O'Daniels CM, Larsen NM. Human papillomavirus-associated oral warts among human immunodeficiency virus-seropositive patients in the era of highly active antiretroviral therapy: An emerging infection. *Clin Infect Dis*. 2002;34:641-8.
20. de Jong SJ, Imahorn E, Itin P, Uitto J, Orth G, Jouanguy E, et al. Epidermodysplasia verruciformis: Inborn errors of immunity to human beta-papillomaviruses. *Front Microbiol*. 2018;9:1222.
21. De Oliveira WR, Festa Neto C, Rady PL, Tying SK. Clinical aspects of epidermodysplasia verruciformis. *J Eur Acad Dermatol Venereol*. 2003;17:394-8.
22. Agrawal P, Mahajan S, Khopkar U, Kharkar V. Epidermodysplasia verruciformis: An unusual malignant transformation, *Indian J Dermatol Venereol Leprol*. 2013;79:97-9.
23. Meziou TJ, Dammak A, Chaabéne H, ZAZ T. Epidermodysplasie verruciforme associée à une dysplasie osseuse congénitale. *Rev Tun Infectiol*. 2008;2:37-9.
24. Sharma S, Barman KD, Sarkar R, Manjhi M, Garg VK. Efficacité de la thérapie orale au zinc dans l'épidermodysplasie verruciforme avec carcinome épidermoïde. *Indian Dermatol Online J*. 2014;5:55.
25. Darwich E, Darwich L, Canadas MP, Klaustermeier J. New human papillomavirus (HPV) types involved in epidermodysplasia verruciformis (EV) in 3 HIV-infected patients: Response to topical cidofovir. *J Am Acad Dermatol*. 2011;65:e43-5.
26. Nijhawan RI, Osei-Tutu A, Hugh JM. Sustained clinical resolution of acquired epidermodysplasia verruciformis in an immunocompromised patient after discontinuation of oral acitretin with topical imiquimod. *J Drugs Dermatol*. 2013;12:348-9.
27. Rallis E, Papatheodorou G, Bimpakis E. Systemic low dose isotretinoin maintains remission status in epidermodysplasia verruciformis. *J Eur Acad Dermatol Venereol*. 2008;22:523-5.

Copyright by Fatima Amaaoune, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Source of Support: This article has no funding source,

Conflict of Interest: The authors have no conflict of interest to declare.