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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Emi Dika, Martina Lambertini, Giulia Veronesi, Cosimo Misciali and Costantino Ricci have given substantial contributions to study conception and validation, manuscript writing, revision and editing, Caterina Longo to study conception, validation and supervision, manuscript writing, revision and editing. All authors read and approved the final version of the manuscript.

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Acquired *epidermodysplasia verruciformis*: a therapeutic challenge

Epidermodysplasia verruciformis (EV) is a life-long genetic disease associated with potentially oncogenic human papillomavirus (HPV) types (mostly 5 and 8). An acquired form of EV (AEV) occurs in immunocompromised individuals, including HIV-positive patients; therapeutic management is particularly challenging, because no therapy produces a complete clearing of the lesions.[1]

A 65-year-old man, HIV-positive since 2004, presented for a diffused cutaneous eruption on the posterior site of his scalp, upper back, and arms. He was under antiretroviral therapy: indeed, his viral load was undetectable and his CD4 count was 560. He had been suffering from the eruption for the last three years. At first consultation, we observed multiple hyperkeratotic papules and plaques, with thick, adherent, and lamellate surfaces resembling guttate psoriasis. He had been diagnosed in 2012 for psoriatic oligoarthritis by the rheumatologists and was being treated with systemic salazopyrine and methylprednisolone. He had also been taking tenofovir, maraviroc and darunavir/cobicistat for his HIV infection.- A 5-mm punch biopsy from a skin lesion was performed, showing epidermal hypergranulosis, orthokeratosis, acanthosis, and focal keratinocytes with bluish-gray cytoplasm. These clinical and histological features led to the diagnosis of AEV. A treatment with topical keratolytic ointment (salicylic acid, retinoic acid, and Vaseline) for a month was initiated. No significant improvement was visible, so we then added a systemic acitretin-based therapy at the dosage of 30mg/day for a month. Because no improvement was seen, we decided to reinforce the therapeutic system by increasing the daily dosage of acitretin up to 50mg/day, five times a week. We also changed the topical therapy with the application of 5-fluorouracil cream (4%) in combination with a vitamin D3 analogue ointment (tacalcitol). After 6 months, a certain improvement was visible, with the flattening and clearing of the warty lesions, although we were still far from a complete clearance (Figure 1).

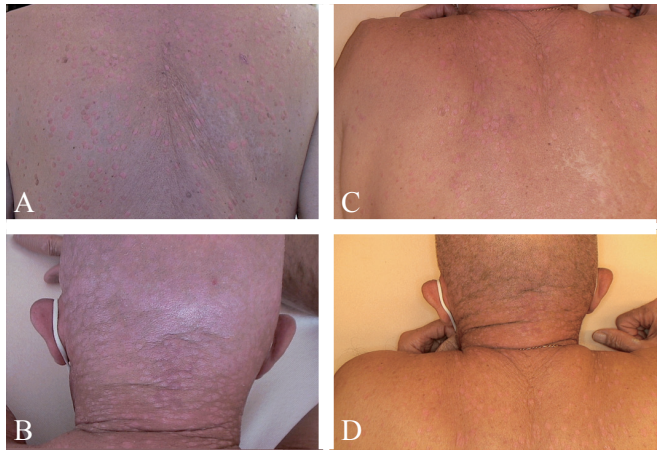

Figure 1.—A, B) Patient before the treatment, showing multiple hyperkeratotic papules and plaques, with thick, adherent, and lamellate surfaces on the limbs, back (A), head and neck (B). C-D: Relative improvement, with the flattening and clearing of the warty lesions, after 6-month-therapy with systemic acitretin, and topical tacalcitol with 4% 5-fluorouracil cream, from the back (A) and head and neck (B).

EV is a rare genodermatosis associated with an increased skin cancer susceptibility due to defective cell-mediated immunity. It shows no preference for a specific sex, race, or geographic area. A novel classification divides EV into three categories based on suspected cause: classic genetic EV, non-classic genetic EV and acquired EV (AEV). AEV is an EV-like syndrome found secondarily in immunocompromised states, such as HIV and iatrogenic immunosuppression contexts such as organ transplant medication. The first clinical signs in EV patients often develop during infancy as scaly reddish skin lesions resembling flat warts, red-brown plaques and pityriasis versicolor-like elements on the chest and abdomen. Due to koebnerization, the areas most involved often appear to be those more easily exposed to trauma. Patients subsequently develop precancerous lesions on sun-exposed areas which, if left untreated, often undergo malignant transformation, and become invasive squamous cell carcinoma. No therapy has proven to be equally effective and multiple trials show differences in the ways patients may respond to treatments.[1] Classically, EV therapy

is structured in first line choices, including UV avoidance, surgical destruction of lesions, and topical retinoids; whenever topical treatments are not effective, it is necessary to rely upon second line therapies, including intralesional interferon alpha, oral retinoids (*i.e.*, acitretin), topical vitamin D3 analogs (*i.e.*, tacalcitol), imiquimod and photodynamic therapy.[2-4] Finally, skin autografts could be used to replace skin areas majorly affected by EV.[5]

In conclusion, we presented a rare case of AEV with partial benefit achieved after systemic and topical treatment with acitretin and fluorouracil+tacalcitol, respectively.

However, we must remember here that our patient was affected by a severe form of AEV, and topical treatments had been demonstrated ineffective.

Although we were far from achieving a complete clinical success, we believe that a second-line treatment at high dosages of acitretin in combination with topical agents should be considered for most severe EV-cases.

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