Acquired epidermodysplasia verruciformis secondary to methotrexate

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Key words: acquired; epidermodysplasia verruciformis; methotrexate.

INTRODUCTION

Epidermodysplasia verruciformis (EV) is a rare genodermatosis that is characterized by the presence of disseminated, tinea versicolor-like scaly hypo- and hyperpigmented macules and flat papules. The lesions usually appear during childhood and are typically distributed throughout the body, mainly over the trunk, arms, legs, face, and neck. Sometimes they coalesce to form wart-like papillomatous lesions.[1] Classically, EV was thought to be a purely genetic condition until Rogers et al[2] coined the term "acquired EV" reporting the development of EV in immunocompromised patients. This landmark publication led to an influx of reports of similar cases; more than two-thirds of the publications about acquired EV came after this report, as documented by Limmer et al.[3] Significant interest in understanding the etiology and pathogenesis of this condition stems not only from the psychosocial impact of EV on patients but also from patients' increased susceptibility to develop nonmelanoma skin cancers, especially squamous cell carcinoma.

CASE REPORT

A 23-year-old Yamani man not known to have any medical illness except his need to attend regular follow-ups at our dermatology clinic as a case of recalcitrant disseminated granuloma facial. He received various therapies, including intralesional corticosteroids, pulse dye laser, minocycline, and systemic corticosteroids without significant improvement. After that, he was started on methotrexate 20 mg and folic acid 5 mg per week as a sparing agent during the tapering phase of the systemic corticosteroids. After 2 months of the initiation of methotrexate treatment, at which he was weaned off systemic corticosteroids completely, he developed asymptomatic skin lesions over the cubital fossae and flexural surface of both his forearms. On examination, there were a few skin-colored to pink flat-topped papules ranging in size from 3 to 6 mm (Fig 1). Examination of other regions—skin, hair, nail, and mucous membrane—proved unremarkable. The rest of the systemic review was normal. Complete blood count, kidney function, and liver function tests were within normal range. A 4-mm punch biopsy sample was obtained from one of the representative lesions; the tissue was fixed in formalin and prepared with hematoxylin and eosin stain for assessment under light microscopy by an expert dermatopathologist. Histopathologic evaluation of the skin biopsy sample revealed hyperkeratosis and acanthosis with blue-gray cytoplasm, perinuclear halos, and mild dysplastic nuclear change (Figs 2 and 3). The clinical presentation coupled with the histopathologic findings was consistent with the diagnosis of acquired EV secondary to iatrogenic immunosuppression. Cessation of treatment with methotrexate resulted in complete clearance of EV skin lesions.

Abbreviation used:

EV: epidermodysplasia verruciformis

DISCUSSION

Lewandowsky and Lutz[4] first described EV in 1922; the genetic foundation of this disorder was

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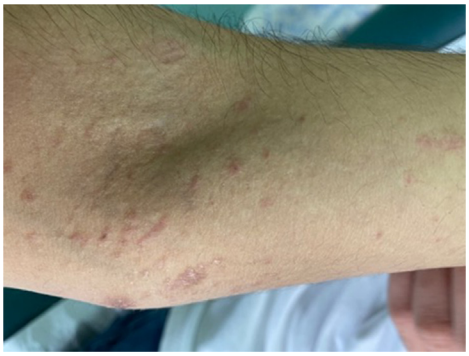

Fig 1. Multiple 3 to 5-mm pink to skin-color flat-topped papules over the cubital fossa (lesions at the bottom of the photograph represent the residue of regressed skin lesions of the patient's original dermatosis).

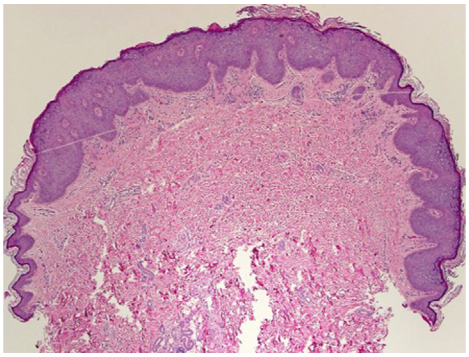

Fig 2. A photomicrograph of the skin biopsy sample shows hyperkeratosis and acanthosis. (Hematoxylin-eosin stain; original magnification: ×40)

established later.[5] Mutations in the EVER1/TMC6 and EVER2/TMC8 genes are the main culprits that cause the disease and are found in approximately 75.6% of cases. The EVER1 and EVER2 genes are transcribed in various immune cells and responsible for controlling the intracellular zinc level within the keratinocytes, which indicates that these genes have immune regulating roles. Therefore, dysfunction in these genes can make patients with EV more susceptible to a human papillomavirus infection.[6] Huang et al[7] proposed a classification system that divided EV into 2 broad categories: genetic and acquired. Genetic EV is subdivided on the basis of the type of genetic mutations into the following: (i) classic—EVER1/TMC6 and EVER2/TMC8 mutations—and (ii) nonclassic—less common genetic mutations, like RHOH, MST-1, CORO1A, and ECM1. Acquired EV is further subdivided on the basis of the cause of immunosuppression into the following: (i) secondary to infection, such as HIV and (ii) secondary to iatrogenic immunosuppression.[7] Both categories of EV have similar clinical presentation and histopathologic findings and identical susceptibility to certain

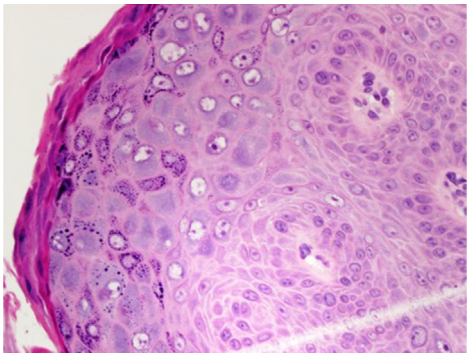

Fig 3. A higher power view showing blue-gray cytoplasm, perinuclear halos, and mild dysplastic nuclear changes. (Hematoxylin-eosin stain; original magnification: ×400)

types of human papillomavirus. A useful clue to differentiate between the 2 categories is the chronological evolution of symptoms. In genetic EV, patients present at an early age and usually have a family history of the condition, and since it is usually inherited as an autosomal recessive condition, a significant number of these patients are siblings of consanguineous families. On the other hand, acquired EV can present in adulthood or childhood but with a clear preceding exogenous cause of immune deficiency, such as HIV or iatrogenic immunosuppression, and usually patients lack a family history of the disease. Our patient presented as an adult at the age of 23 years and he does not have a family history of the condition. Furthermore, he developed the EV lesions directly after the initiation of methotrexate, and these lesions resolved after the cessation of the medication. All of these findings together suggested that he mostly suffered from acquired EV.

Acquired EV as a result of iatrogenic immunosuppression was first described in patients who had undergone renal transplants.[8] Development of EV has been linked with several medications—sirolimus, tacrolimus, bendamustine, cyclosporine, corticosteroids, azathioprine, and other immunomodulating drugs. Acquired EV as a result of iatrogenic immunosuppression has been reported in different clinical settings, including organ transplant, graft-versus-host disease, atopic dermatitis, tumor chemotherapy, and systemic lupus erythematosus.[7] Our 23-year-old patient developed EV lesions secondary to exposure to methotrexate over a 3-month period while being treated for another benign skin condition. The exact pathogenic mechanism by which these medications cause the development of EV lesions in these different clinical settings is still unclear, but it has been suggested that the wide immune modifying effect of these medications makes patients generally more prone to infections

not specific to EV—human papillomavirus only. On the other hand, the relationship between these immunosuppressive medications and EV is quite complex in the sense that clinical presentation of EV secondary to these immunosuppressive medications can be delayed, even after completion of immunosuppressive therapy, and cessation of these culprit medications does not always result in clearance of EV lesions.[7] In a recent review of acquired EV cases that reached a complete resolution, Limmer et al[3] found that only 9 of 100 patients with acquired EV lesions secondary to HIV achieved complete resolution after treatment with topical cidofovir, imiquimod, or tretinoin. Also, in their review, only 1 patient achieved complete resolution of acquired EV lesions secondary to iatrogenic immunosuppression after a 2-week course of tazarotene 0.5% cream twice weekly. The very rapid clearance of this patient after only 4 applications of tazarotene might be a spontaneous clearance despite the active treatment.[9] Overall, these findings indicate variability of response to the same type of therapy within the same subcategory of acquired EV.

Although it is difficult to treat EV, it is important that it is treated because of the psychosocial impact of the disease and the potential malignant transformation of the EV lesions. The treatment plan should start with patient counseling about the challenging nature of the disease; for one thing, there is no single treatment option that is considered to be superior in efficacy and for another, although treatment might result in complete or partial clearance of the EV lesions, relapse is likely if therapy is discontinued. Treatment options that have been described in the literature include topical tretinoin, imiquimod, cidofovir, and 5-fluorouracil; oral acitretin; or a combination of these.[3] Contrary to previously reported cases of acquired EV, our patient achieved gradual complete clearance of his EV lesions after withdrawal of the immunosuppressive medication.

Our case illustrates and adds to the accumulating medical evidence that EV can present as an acquired condition and can be secondary to a variety of immunosuppressive etiologies. Therefore, treating physicians should keep an open mind when any patient with an altered immune status presents with flat wart-like papules and proceed accordingly.

Conflicts of interest

None disclosed.

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