

Acquired epidermodysplasia verruciformis in setting of tumor necrosis factor- α inhibitor therapy



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Key words: acquired epidermodysplasia verruciformis; human papillomavirus; immunosuppression; tumor necrosis factor- α inhibitor therapy.

INTRODUCTION

Epidermodysplasia verruciformis (EV) is a rare dermatologic condition in which patients have recalcitrant lesions associated with specific human papillomavirus (HPV) types. More than 20 types of HPV are associated with EV (termed *EV-HPV types*) and most commonly include HPV 5 and 8.¹⁻³ First described as a genodermatosis, it has more recently been reported as an acquired form in patients with an underlying source of immunosuppression, namely, HIV.² It has not been reported in patients on tumor necrosis factor (TNF)- α inhibitors. Here we present 2 cases of acquired EV (AEV) occurring in 2 patients on adalimumab.

CASE REPORTS

Case 1

A 70-year-old man with rheumatoid arthritis on adalimumab for more than 8 years presented with a 5-year history of a pruritic lesion on his abdomen, unresponsive to topical corticosteroids. Examination of the left side of the abdomen found a 3-cm light brown papillated plaque (Fig 1, A). Given persistence of the lesion, a punch biopsy was performed, and changes were consistent with EV (Fig 1, B). Polymerase chain reaction analysis was positive for HPV 73 DNA using methods detailed in Argyris et al,⁴ but confirmatory DNA sequencing was unable to be performed. HIV results were negative and complete blood count was normal. The patient was sexually monogamous with his wife. Neither had a history of genital warts, and his wife had no history of cervical

Abbreviations used:

AEV: acquired epidermodysplasia verruciformis
EV: epidermodysplasia verruciformis
HPV: human papillomavirus
TNF: tumor necrosis factor

dysplasia. Topical imiquimod and discontinuation of adalimumab were unsuccessful in the treatment of the lesion. He ultimately underwent excision without recurrence to date.

Case 2

A 68-year-old man with psoriasis and taking adalimumab presented with multiple verrucous lesions. Shave removal was performed. Two lesions demonstrated verruca vulgaris, but the third lesion on the left dorsal forearm showed changes consistent with EV, similar to findings shown in Fig 1, B. HPV typing was not completed. HIV testing was negative, but further medical history is unknown, as the patient was lost to follow-up.

DISCUSSION

Epidermodysplasia verruciformis is a genodermatosis in which patients have HPV-associated lesions beginning in childhood, with 30% to 70% of lesions progressing to squamous cell carcinoma by the fourth decade of life, particularly if lesions are located on sun-exposed areas.³ AEV is a newer entity in which immunosuppressed patients have similar propensity for HPV-associated lesion development.

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Case 1 was previously presented on May 12, 2017 at a Minnesota Dermatological Society Meeting for interest. Case 2 has never previously been presented.

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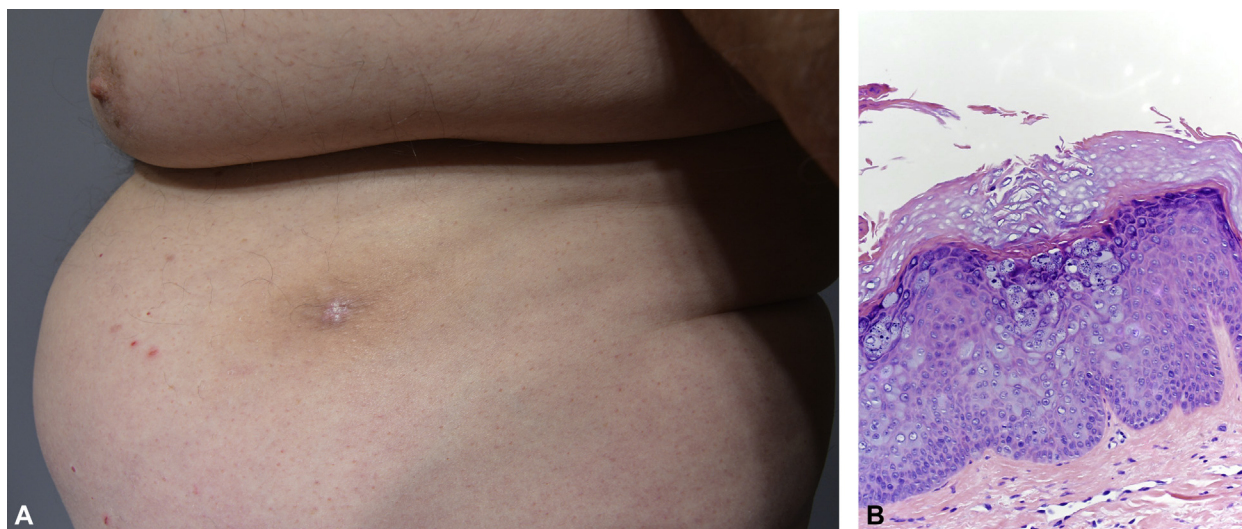


Fig 1. Case 1. **A**, Clinical photograph of 3-cm light brown papillated plaque on left abdomen with prior punch biopsy site in center. **B**, Punch biopsy from left abdomen. Histopathology shows an acanthotic epidermis that focally contains large, swollen-appearing cells within granular and spinous layers. The cells exhibited nuclear clearing, gray cytoplasm, and coarse keratohyalin granules. (Original magnification: $\times 100$.)

It has been observed in association with HIV, renal transplant, hematologic malignancy, autoimmune diseases, and medications including bendamustine and cyclosporine.¹⁻³ The risk of cutaneous malignancy in AEV is unknown. There is a report of bowenoid dysplasia occurring in an EV lesion in a patient with HIV,⁵ but there have been no reported cases of invasive skin cancer developing in patients with AEV. Nevertheless, risk for malignant transformation is thought to be higher than that reported in the literature given baseline immunosuppression, lack of long-term follow-up, and small number of described cases.²

EV is most often associated with HPV types 5 and 8, although many others have been reported including 3, 4, 8 through 10, 12, 14, 15, 17, 19 through 25, 28, 29, 36 through 38, 46, 47, 49, and 50.¹⁻³ Similar findings are also found in AEV, with most common associations being HPV types 5 and 8 followed by 14 and 19.² Most of these genotypes belong to the Betapapillomavirus genus, although several belong to the Alphapapillomavirus genus. In prior studies, cutaneous squamous cell carcinoma has been found to be strongly associated with β -HPV serotypes; no similar association was found with α -HPV serotypes.⁶ This is in accordance with the HPV serotypes that have been associated with malignant transformation in congenital EV lesions (5, 8, 17, 20, 47)³ as well as the case of bowenoid dysplasia in an AEV lesion (5, 8, 14, 37 present within 1 specimen),⁵ all of which belong to the β -genus. HPV 73 is an Alphapapillomavirus that has not previously been

reported as an EV-HPV type, although DNA sequencing was unable to be performed to confirm.

AEV has not previously been reported in patients on TNF- α inhibitors, although HPV and molluscum contagiosum lesions have been reported in patients on etanercept and infliximab.⁷ An increased susceptibility to viral infections in patients on anti-TNF- α therapy is suspected to be caused in part by inhibition of TNF- α , which normally acts to induce apoptosis in virus-infected cells. Paradoxically, lesions of EV have been found to have increased levels of TNF- α compared with healthy individuals, with the highest levels of expression in patients with EV with cutaneous malignancies.⁸ The reason for the increased levels of TNF- α in lesional EV skin is unclear. One possibility is that elevated levels of TNF- α reflect the internal cytokine milieu of a virally infected cell; however, in one small study, there was no difference in TNF- α expression between verruca from immunocompetent individuals and skin from healthy individuals.⁹ In contrast, patients with verrucae were found to have elevated levels of circulating soluble TNF receptors, whereas these levels were normal in patients with widespread EV.¹⁰ The implications of these findings for our patients are unclear but do suggest an interplay between TNF- α and EV. Furthermore, the development of EV lesions in the setting of anti-TNF- α therapy supports the theory that patients with impaired cell-mediated immunity are susceptible to cutaneous HPV infections.³

In contrast to congenital EV, AEV is an entity occurring in the context of immunosuppression but has similar clinical manifestations and associated HPV genotypes. It has not previously been reported in patients on TNF- α inhibitors. With increasing use of biologic therapy, the incidence of AEV may continue to increase. The risk of malignant transformation in AEV is unknown but is hypothesized to be higher than that reported in the literature. The relationship between TNF- α and EV lesions is unclear, but further investigation may provide clues to the development of lesions in our patients. We present these novel cases to highlight the possibility of AEV occurring in patients on biologic therapy, particularly TNF- α inhibitors, and to discuss the potential role of TNF- α in EV. As in many of other immunosuppressed patients, careful clinical monitoring is warranted.

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