Re-evaluation of epidermodysplasia verruciformis: Reconciling more than 90 years of debate

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Epidermodysplasia verruciformis (EV) is a rare genodermatosis characterized by abnormal susceptibility to cutaneous human beta-papillomavirus infections causing persistent flat warts or pityriasis versicolor–like lesions. This generalized verrucous skin disorder resembles generalized verrucosis, but these 2 conditions are distinguished by differences in clinical manifestation and the human papillomavirus types involved. A breakthrough in our understanding of EV was the discovery that homozygous inactivating mutations in *TMC6* (*EVER1*) and *TMC8* (*EVER2*) determine susceptibility to this disorder; however, they have not solved all EV cases fully. These deficiencies account for 75% of affected individuals, leaving a substantial number of patients without an underlying genetic cause. Recently, it has been revealed that mutations in additional genes (*RHOH*, *MST-1*, *CORO1A*, and *IL-7*) result in extensive human beta-papillomavirus replication and therefore manifest with an EV-like phenotype. The term "acquired EV" is used to describe an EV-like phenotype that develops in immunocompromised hosts, and the introduction of this entity further aggravates the confusion. Reevaluation of these entities is warranted. Here, we review the available data on this issue, provide up to date information on the major characteristics that differentiate between these seemingly clinically similar disorders, and highlight the different mechanisms involved in each disorder. (J Am Acad Dermatol 2017;76:1161-75.)

Key words: epidermodysplasia verruciformis; EVER1; EVER2; general verrucosis; genetics; genodermatoses; human papillomavirus; immunodeficiency; SCID; squamous cell carcinoma.

Epidermodysplasia verruciformis (EV) is a rare but well-known genodermatosis that is characterized by abnormal susceptibility to infection with β-genotype human papillomavirus (HPV).[1-5] EV-HPV serotypes are ubiquitous and nonpathogenic in the normal population.[6] However, in patients with specific genetic susceptibility that determines defective cell-mediated immunity, they are the cause of disseminated cutaneous lesions that commence in childhood or early adolescence and are highly resistant to treatment.[7] HPVs-5 and -8 have been reported to be the main causative agents in EV, and therefore have been called "EV-associated" HPV types.[8,9] However, many other HPV subtypes (eg, 3, 9, 10, 12, 14, 15, 17, 19-25, 29, 36, 38, 46, 47, 49, and 50)[7,9,10] and recently also Merkel cell polyomaviruses[11,12] have been isolated from EV lesions. EV patients are susceptible to the development of nonmelanoma skin cancers within HPV-infected warts,[13] predominantly squamous cell carcinoma (SCC),[14,15] which affects between 30% to 70% of patients.[16-18] These cancers usually appear in areas exposed to sunlight

Abbreviations used:

AEV:	acquired epidermodysplasia verruciformis
cART:	combination antiretroviral therapy
EV:	epidermodysplasia verruciformis
GV:	generalized verrucosis
HPV:	human papillomavirus
NMSC:	nonmelanoma skin cancer
SCC:	squamous cell carcinoma
TMC:	transmembrane channel

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Supported in part by the Israel Cancer Association (20150020) and the Hadassah–Hebrew University Joint Research Fund (6070803).
Conflicts of interest: None declared.
Accepted for publication December 21, 2016.
Reprints not available from the authors.

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Published online February 10, 2017.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2016.12.035

and in the fourth decade of life,[19] usually 10 to 30 years after the initial manifestation of the disease.[20-22] Malignant transformations have been associated with HPV subtypes 5, 8, 17, 20, and 47.[23,24]

The most common manifestations of EV are flat, scaly, reddish hypo- and hyperpigmented macules, verruca-like papillomatous lesions, seborrheic keratosis–like lesions, and pink-red pityriasis versicolor–like lesions (Fig 1).[16,18,25,26] Mucous membranes are spared. The cutaneous lesions have a tendency to be disseminated over the body, but a few cases with a limitation to 1 extremity have also been described in the literature.[26] EV is prevalent worldwide and is present in many races.[27-29]

While EV is regarded as an individual entity, there are conditions that can mimic its characteristic clinical phenotype. For example, recently, several inherited immunodeficiency conditions have been discovered, manifesting with an EV-like phenotype. Generalized verrucosis (GV) is a general term for a clinical entity that because of widespread HPV infections can sometimes resemble EV. Acquired EV (AEV) is another clinical entity that bears resemblance to EV but differs in its pathogenesis, not being a hereditary condition.

The aim of this review is to provide up to date information on the major characteristics that differentiate between these seemingly clinically similar disorders and highlight the different mechanisms involved in each disorder. We first summarize the current knowledge regarding the common pathogenesis of EV with a special emphasis on all known current genetic mutations that contribute to the development of this disorder and the other genetic conditions that manifest with an EV-like phenotype. We then briefly elaborate on AEV especially in context of newly discovered EV susceptibility loci. Distinguishing factors of EV and AEV, such as clinical manifestations, histopathology, malignant potential, and available treatments will be addressed. We summarize by providing information on open questions and key research gaps that still exist in this entity.

CAPSULE SUMMARY

- Mutations in several genes leading to epidermodysplasia verruciformis–like syndromes have been revealed.
- Acquired epidermodysplasia verruciformis and generalized verrucosis share several common features with primary epidermodysplasia verruciformis.
- Further research evaluating the relationship between these disorders can provide better genetic counselling and understanding of host response to human papillomavirus.

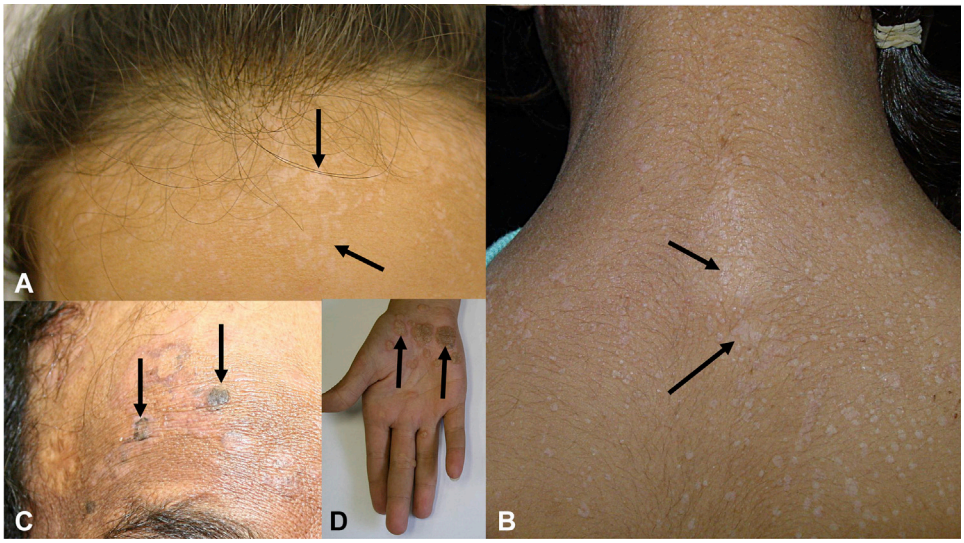

Fig 1. Characteristic clinical features of epidermodysplasia verruciformis. Flat, scaly reddish hypopigmented macules, resembling pityriasis versicolor, located on the (**A**) forehead and (**B**) upper aspect of the back (arrows). **C**, Seborrheic keratosis–like lesions on the forehead (arrows). **D**, Thick papillomatous lesions on the hand (arrows).