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Title

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Journal

Dermatology Online Journal, 25(3)

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Publication Date

2019

DOI

10.5070/D3253043340

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Peer reviewed

Multiple flat-topped scaly violaceous papules

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Abstract

Epidermodysplasia verruciformis (EV) is an autosomal recessive genodermatosis characterized by susceptibility to beta-genus human papillomavirus (HPV) infection. Owing to *TMC6/EVER1* and *TMC8/EVER2* mutations that lead to abnormal transmembrane channels in the endoplasmic reticulum involved in immunological pathways, keratinocytes cannot combat infection from non-pathogenic HPV strains. Mutations involving *RHOH*, *MST-1*, *CORO1A*, and *IL-7* have also been associated with EV in patients without *TMC6* or *TMC8* mutations. We highlight a 27-year-old man with multiple violaceous flat-topped papules with scale and irregular borders distributed on his chest, extremities, abdomen, and back. The striking physical examination and the subsequent biopsy findings of enlarged nests of cells in the granular and spinous layers with blue-gray cytoplasm and keratohyaline granules confirmed the diagnosis. We conclude with a brief discussion on the differential diagnosis, which includes confluent and reticulated papillomatosis, Darier disease, and disseminated superficial actinic porokeratosis.

Keywords: epidermodysplasia verruciformis, Darier disease, disseminated superficial porokeratosis, confluent and reticulated papillomatosis

Introduction

Epidermodysplasia verruciformis (EV) is a rare and predominantly autosomal recessive genodermatosis characterized by susceptibility to beta-genus human papillomavirus (HPV) infection; autosomal dominant and X-linked inheritance patterns have been noted as well [1]. First described by Lewandowsky and Lutz in 1922, the condition most often presents in

childhood with pityriasis versicolor-like macules or verruca plana-like papules [2]. Herein, we report a striking example of a young man presenting with EV and discuss the pertinent conditions in the differential diagnosis that clinicians should consider in such cases.

Case Synopsis

A 27-year-old man presented for evaluation of disseminated flat-topped papules on his entire body. The asymptomatic lesions had been present since he was eight years old and had previously been evaluated with skin biopsies by a dermatologist, but he did not recall the results. His condition had been recalcitrant to treatment with topical tretinoin but had moderate response to systemic isotretinoin, which he used from ages nine to twelve. He currently denied pain, bleeding, or pruritus and had been attempting management with over-the-counter lotions to no avail.



Figure 1: Generalized, discrete, flat-topped violaceous papules with irregular borders coalescing into plaques on the chest, upper extremities, and abdomen.

Physical examination demonstrated multiple violaceous flat-topped papules with scale and irregular borders as well as hypopigmented macules, distributed on his chest, extremities, abdomen, and back (**Figure 1**). A 4mm punch biopsy specimen of a characteristic lesion from the right anterior shoulder demonstrated epidermal changes consistent with epidermodysplasia verruciformis (**Figure 2**). This diagnosis aligned with the clinical history of the early onset, the extended duration, and the asymptomatic and treatment-resistant nature of the lesions in our patient. Owing to the risk of malignant transformation of existing lesions, our patient was advised on sun protection measures and scheduled for routine follow-up.

Case Discussion

Epidermodysplasia verruciformis (EV) has classically been believed to arise from homozygous inactivating mutations in *TMC6/EVER1* and *TMC8/EVER2*, transmembrane channels in the endoplasmic reticulum involved in immunological pathways that mitigate viral infection. As a result, keratinocytes lose the ability to combat infection from non-pathogenic HPV strains [1]. More recently, it has been elucidated that *TMC6* and *TMC8* mutations account for about 75% of EV patients [3]. The remaining cases, in which *TMC6* and *TMC8*

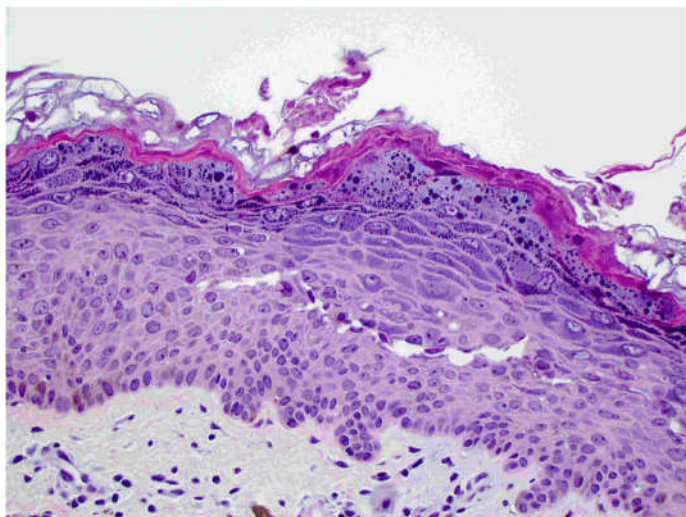


Figure 2: Histopathological analysis of a 4mm punch biopsy sample from the abdomen displaying enlarged nests of cells in the granular and spinous layers with blue-gray cytoplasm and keratohyaline granules. H&E, 40x.

mutations have been excluded, have been associated with a growing list of mutations affecting *RHOH*, *MST1*, *CORO1A*, and *IL7* [3]. Specifically, *RHOH* functions as an intracellular switch, conducting signals between T and B cell membrane receptors [3]. *CORO1A* is an actin-binding protein responsible for microtubule formation and phagocytosis [3]. Finally, *MST1* is a negative growth regulator and *IL7* stimulates hematopoietic stem cell differentiation [3]. Currently, the downstream effect of these mutations and how they result in EV-like phenotypes has yet to be clarified. Nevertheless, it is relevant to note that an understanding of the underlying pathogenesis will continue to evolve with further research.

The clinical manifestations often present before age ten and include polymorphic, disseminated, flat-topped hypo- or hyper-pigmented papules or plaques, verrucous keratotic lesions on sun-exposed surfaces, seborrheic keratosis-like lesions, or hypopigmented macules. These lesions have the potential to undergo malignant transformation into non-melanoma cancer (most often squamous cell carcinoma), especially in cases of HPV-5, HPV-8, and HPV-14 infection [1, 2].

Epidermodysplasia verruciformis lesions can be mimicked by clinical entities such as disseminated superficial porokeratosis, confluent and reticulated papillomatosis, and Darier disease, often requiring histopathological analysis to elucidate the diagnosis. The most frequent histological findings include mild to moderate acanthosis and hyperkeratosis, keratinocyte enlargement with blue-gray pallor in the stratum granulosum and spinosum, and keratohyaline granules. Less commonly, a basket-weave pattern in the stratum corneum and perinuclear halos can be evident [1].

Disseminated superficial porokeratosis presents with pink-brown hyperkeratotic papules and plaques with a peripheral keratotic ridge [4]. Unlike EV, lesions tend to be annular and expand centrifugally, with subsequent central atrophy. Notably, lesions are primarily confined to sun-exposed areas [4]. Furthermore, the clinical picture is different, with patients presenting in their third-to-fourth decades [4]. Histologically, parakeratotic cells arranged in a

thin column (also known as the cornoid lamella) are evident and the granular layer is reduced or absent, in contrast with EV [4].

Confluent and reticulated papillomatosis demonstrates small, 1mm to 2mm, erythematous hyperkeratotic papules to shiny atrophic macules in a reticulated pattern, most often presenting in the inframammary region and subsequently extending to the chest, abdomen, and back [5]. Unlike EV, coalesced lesions adopt a reticulated pattern, are negative on HPV testing, and often first present in young adults [5]. Histological hallmarks include epidermal undulation, squat papillomatosis, and acanthosis projections between papillomatous regions [5]. Notably, clinical resolution is observed when treated with azithromycin or minocycline treatment [5].

Darier disease presents with brown keratotic papules in seborrheic areas such as the central chest and back, regions also affected by EV; however, lesions also tend to be pruritic and malodorous [6]. Notably, cases presenting with acrokeratosis verruciformis of Hopf, flat-topped skin-colored keratotic lesions on the dorsum of the hands and feet, can be clinically

indistinguishable from EV [6]. In such patients, histological findings of dyskeratosis, evidenced by corps ronds or grains, and acantholysis resulting in suprabasal cleavage help differentiate this clinical entity from EV [6].

Owing to the known risk of cutaneous oncogenesis in EV patients, routine physical examinations are critical. In addition, patients should be advised on sun protection measures [1, 2]. Attempted treatment modalities for skin lesions include systemic and topical retinoids, cryotherapy, imiquimod, acitretin, and electrodesiccation [1].

Conclusion

We present a 27-year-old man with epidermodysplasia verruciformis. This case serves to highlight an extraordinary presentation of a rare condition, comparing and contrasting it with conditions that can clinically appear similarly.

Potential conflicts of interest

The authors declare no conflicts of interests.

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