Multiple flat-topped scaly violaceous papules

Raghavendra L Girijala¹ BS, Domina Nyinawinyange² PA, Palak K Parekh² MD, Ronald E Grimwood² MD

Affiliations: ¹Texas A & M University College of Medicine, College Station, Texas, USA, ²Department of Dermatology, Baylor Scott and White Health, Temple, Texas, USA

Corresponding Author: Raghavendra L Girijala, 8447 Bryan Road, Bryan, TX 77807, Tel: 847-387-7519, Email: rairijala@gmail.com

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

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.

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 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 electrodessication [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.

---

**References**