Epidermodysplasia verruciformis: report of two patients with autosomal dominant inheritance

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Abstract

Epidermodysplasia verruciformis is a rare genodermatosis associated with mutations in the *EVER1/TMC6* and *EVER2/TMC8* genes. The inheritance is considered to be autosomal recessive, but reports suggesting an autosomal dominant inheritance indicate disease genetic heterogeneity. Its onset occurs in early childhood and presents as a combination of pityriasis versicolor-like, flat wart-like and seborrheic keratosis-like lesions, with a potential for malignant transformation, mainly squamous cell carcinoma.

Keywords: epidermodysplasia verruciformis, genodermatosis, HPV, cutaneous oncology, squamous cell carcinoma

Introduction

Epidermodysplasia verruciformis (EV) is characterized by disseminated infection caused by specific types of human papillomavirus (HPV), [1]. About 500 cases have been reported worldwide and it has no preference to gender or race [1,2]. Parental consanguinity is observed in most cases and the inheritance is considered to be autosomal recessive in its classic form [3]. Epidermodysplasia verruciformis presents clinically as a combination of pityriasis versicolor-like lesions and reddish verruca-like and seborrheic keratosis-like plaques with a potential for malignant transformation. Our aim is to report two cases of EV in a mother and son with a possible autosomal dominant inheritance.

Case Synopsis

Case 1

A 45-year old woman with no history of parental consanguinity and a mild cognitive impairment presented with multiple reddish verruca-like lesions and brown waxy papules on her face, trunk, and limbs, that had been increasing in number and size since childhood (**Figure 1A)**. Her examination also revealed an asymptomatic erythematous infiltrated plaque on her back, which had grown for a few months. Her parents and all four siblings were normal, but her 20 year old only son had similar cutaneous lesions. Histopathology of a brown waxy papule was compatible with seborrheic keratosis associated with EV. Biopsies of two reddish verruca-like lesions showed features of plane warts associated with viral cytopathic effect (**Figure 2**). The infiltrated plaque on her back was compatible with invasive well-differentiated squamous cell carcinoma (SCC).

Case 2

The 20-year-old male son of the first patient was born of non-consanguineous parents and presented with multiple pityriasis versicolor-like and flat wart-like lesions on his face, trunk, and limbs, which had been growing since the age of three years (**Figure 1B**, **C)**. He also had a diagnosis of autism controlled with risperidone, quetiapine, and biperiden. Histopathological examination confirmed the diagnosis of flat warts associated with viral cytopathic effect in the upper layers of the epithelium, compatible with EV.

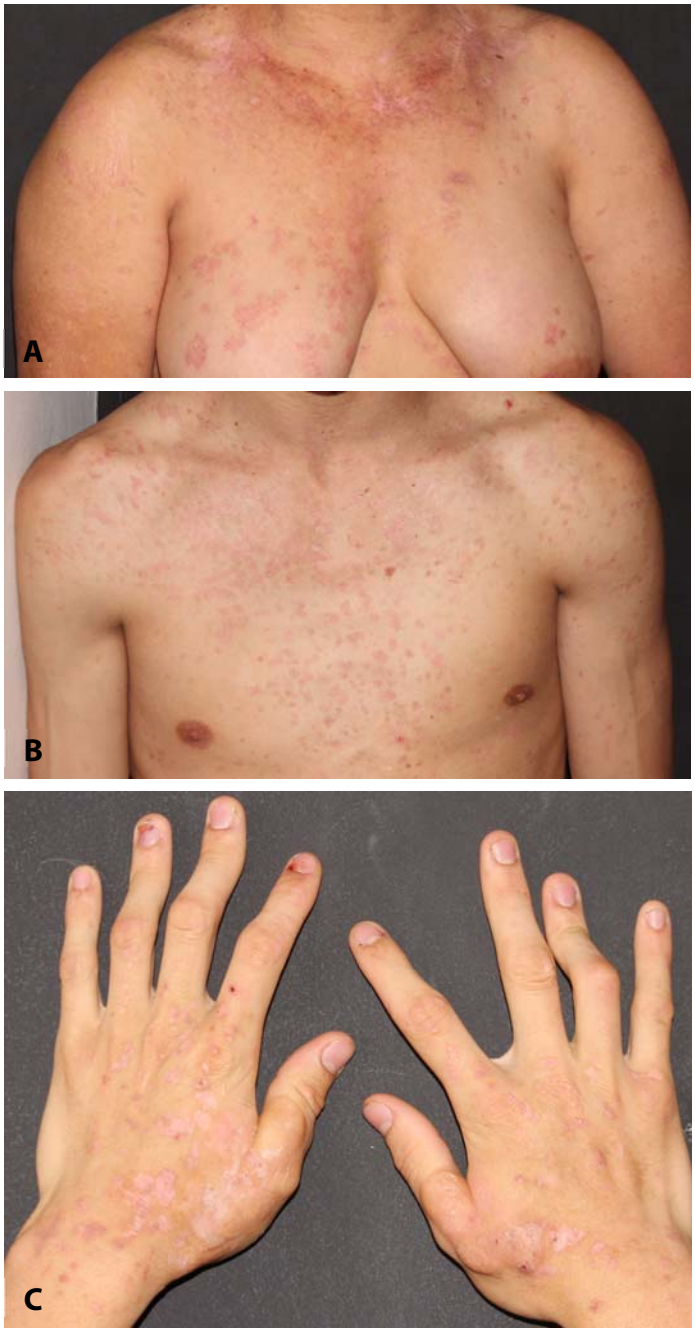

Figure 1. *Clinical features of epidermodysplasia verruciformis.* ***A)*** *Multiple flat wart-like lesions on the trunk and upper limbs of patient 1.* ***B)*** *Multiple pityriasis versicolor-like and flat wart-like lesions on the trunk of patient 2.* ***C)*** *Multiple flat wart-like lesions on the hands of patient 2.*

Case Discussion

Epidermodysplasia verruciformis was the first disease to correlate skin cancer and viral infection [1,4]. It is regarded as a model of cutaneous HPV oncogenesis owing to a specific defect in cell-mediated immunity toward a group of beta-HPV genotypes (EV-HPV) with a tropism for keratinocytes and cell proliferation induction [1-6]. To date, over a hundred HPV types have been identified and HPV 3, 5, 8, 9, 10, 12, 14, 15, 17, 19–25, 28, 29, 36, 46, 47, 49, and 50 have been related to EV [3,6]. The EV-HPV have a tropism for keratinocytes, induce cell proliferation, and can cause atypia, dysplasia, and cancer [1,7,8]. In contrast to other oncogenic HPVs, these do not seem to need integration into the host's genome [4].An autosomal recessive inheritance model was initially proposed by Cockayne in 1933, confirmed by Rajagopalan in 1974 and mapped in two susceptibility loci in chromosomes 17q25 (EV1) and 2p21-p24 (EV2) by Ramoz in 1999. Shortly after, bi-allelic loss-of-function mutations of *EVER1* and *EVER2* genes located within the EV1 locus were identified by Ramoz in 2002. To date, eight mutations of *EVER1*/*TMC6* and eleven mutations of *EVER2*/*TMC8* genes have been described [9,10].

More recently, several other genes have been implicated in EV, including *RHOH*, *MST-1*, *CORO1A*, and *ECM*. Considering this, the disease can be classified in two categories: classic EV, associated with *EVER1*/*TMC6* and *EVER2*/*TMC8* mutations, and nonclassic EV, associated with mutations other than the *EVER* genes [3]. Furthermore, reports suggesting an autosomal dominant or recessive X-linked inheritance indicate disease genetic heterogeneity [1,6,7,10]. More than 40% of familial cases reported have no mutations of the genes known to be associated with EV [9]. In our cases, no other family

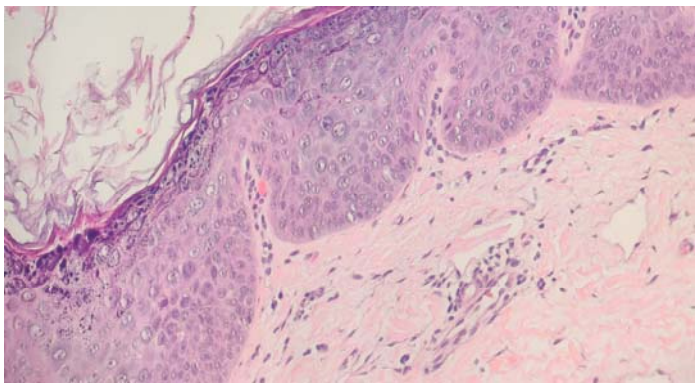

Figure 2. *Histologic findings of epidermodysplasia verruciformis. Basket-weave hyperkeratosis, mild acanthosis and vacuolated cells in the upper epidermis, with a pale blue cytoplasm. H&E, 200×.*

members were affected in the three generations studied. There was no evidence of parental consanguinity and the pattern of inheritance appears to be autosomal dominant (**Figure 3**). The absence of the disorder in the parents of case 1 may be explained by lack of penetrance or a "de novo" mutation.

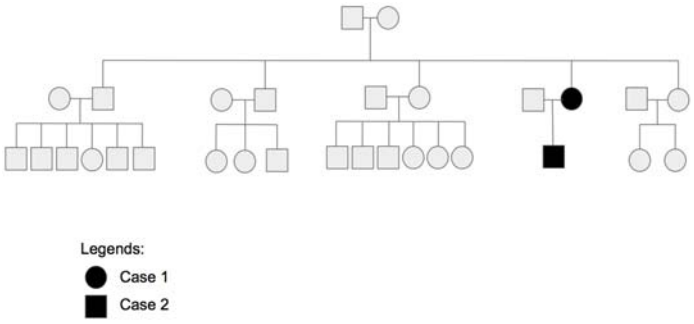

Figure 3. *Pedigree chart of epidermodysplasia verruciformis patients in this study.*

Epidermodysplasia verruciformis onset occurs in early childhood and presents as a combination of pityriasis versicolor-like, flat wart-like, and seborrheic keratosis-like lesions; it usually does not affect mucous membranes [1]. Skin lesions are generally located on sun-exposed areas and up to 50% of EV patients develop nonmelanoma skin cancer, mainly SCC [1,6,9]. Tumors are frequently reported to have a low potential to invasive growth and low metastatic potential. A more aggressive course may occur in association with other risk factors, such as ultraviolet radiation [5,10]. Mental disorders, such as cognitive impairment, can be seen in about 10% of the cases [1,3,7,8].

All clinical lesions of EV share the same histopathological features, which include stratum corneum in "basketball weave pattern", parakeratosis, acanthosis, and cytopathic changes, such as keratohyalin granules. One also observes large cells with perinuclear halos and pale, blue-gray cytoplasm ("bird eyes" aspect). The cytopathic effect is similar in all EV-HPV infections, independent of the virus genotype [1]. In malignant lesions, atypical cells show viral particles in the nuclei, identifiable by electron microscopy [1].

The diagnosis of EV is based on the presence of typical skin lesions, outset in childhood, slow progression through years, anatomical-pathological correspondence and identification of HPV-EV [1,2]. To date, there is no effective treatment for EV and patients should be periodically examined for early detection of malignant changes [1,6,9,10].

Conclusion

As a rare genodermatosis, EV needs further studies to understand the patterns of inheritance, additional genetic loci, and individual susceptibility. Novel mutations were mapped in the past few decades and the disease is becoming better understood but a unifying genetic theory for EV is still lacking.

Potential conflicts of interest

The authors declare no conflicts of interest.

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