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Autosomal dominant epidermodysplasia verruciformis lacking a known EVER1 or EVER2 mutation

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Abstract

Epidermodysplasia verruciformis (EV) is a rare genodermatosis characterized by abnormal susceptibility to infection with specific human papillomavirus (HPV) serotypes. EV is a genetically heterogeneous disease, and autosomal recessive and X-linked inheritance patterns have been reported. Nonsense mutations in the genes EVER1 and EVER2 have been identified in over 75% of cases. We present EV in a father and son with typical histologic and clinical findings that occur in the absence of mutations in EVER1 or EVER2. EV in this father/son pair in a non-consanguinous pedigree is consistent with autosomal dominant inheritance. This is the first report of autosomal dominant transmission of EV, providing further evidence of the genetic heterogeneity of EV.

Introduction

Epidermodysplasia verruciformis (EV; OMIM #226400) is a rare genodermatosis characterized by abnormal susceptibility to infection with specific serotypes of human papillomavirus (HPV). EV HPVs are thought to be ubiquitous and non-pathogenic in the normal population, while EV patients develop disseminated cutaneous lesions early in childhood. Lesions are heterogeneous and may resemble verruca plana, or be macular and either hyper- or hypopigmented resembling the lesions of pityriasis versicolor (1). Mucous membranes are spared. These lesions are most often initially asymptomatic although non-melanoma skin cancer may develop in the third, fourth, and fifth decades of life in sun-exposed skin. Classic histologic findings include enlarged keratinocytes present in the spinous layer of the epidermis with abundant, vacuolated pale blue cytoplasm (2, 3). Other, less specific, histologic findings include abundant coarse keratohyaline granules in the granular layer, and a thickened cornified layer with parakeratosis.

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Case Report

We present two cases of EV in a father and son. Patient 1 is a 34 year-old white male with a history of macular warts on the dorsa of his hands since age 12. Additional warts developed on the shoulders and scalp during the patient's teenage years. The warts were resistant to multiple rounds of cryotherapy. The patient lived in Florida and received extensive UV exposure during childhood and adolescence. Eight years prior to presentation, the patient was found to have numerous superficial and invasive squamous cell carcinoma and basal cell carcinoma lesions present on the scalp that were subsequently treated by excision. Other scalp lesions responded to topical application of 5% imiquimod cream. No new lesions had developed in the several year period prior to presentation. The patient had no genital or plantar warts and denied significant past sinopulmonary, dental, skin, mucosal or CNS infections. The patient's parents were not consanguineous, and only patient 1's son is known to be similarly affected.

Lesions on the dorsal hands were hypopigmented flat-topped or verrucous papules ranging from 1-5 mm in size. Lesions on the scalp, forehead, chest, shoulders and back were 1-2 cm in diameter, round, slightly hypopigmented macules with telangiectasias. A few lesions (of similar appearance to the trunk lesions) were present on the bilateral lower extremities and localized around the knees. Round, coalescent hypopigmented macules with scattered telangiectasias were present on the left shoulder (Fig. 1a), while scattered pink verrucous papules ranging from 3-6 mm in size with slight scale were present on the left dorsal hand (Fig. 1b).

Patient 2, the eight year-old son of patient 1, presented with history of asymptomatic scalp verrucae since age three that were associated with significant alopecia in lesional areas. The patient met all growth and development milestones and had no history of significant sinopulmonary, dental, skin, mucosal or CNS infections. Skin exam revealed numerous discrete (as well as confluent) monomorphic, round, slightly elevated, flat-topped hypopigmented papules on the scalp and forehead (Fig. 1c). Lesions with similar appearance were scattered over the extensor surfaces of both hands (Fig. 1d), trunk, shoulders and legs. Two café au lait patches (2 cm in size) were present on the abdomen. The patient had bilateral peritemporal thinning of scalp (Fig. 1c), corresponding to areas of confluent papules.

Histologic examination of biopsies from each patient revealed typical features of EV, including epidermal koilocytosis, acanthosis, and hypergranulosis (Fig. 2a, patient 1). Enlarged keratinocytes with abundant blue-gray cytoplasm in the upper spinous level were also present (Fig. 2b, patient 2). Histologic examination of grossly normal skin from patient 2 revealed none of the findings common to the two lesional biopsies (not shown). HPV typing by established methods (4) of biopsies from our patients revealed the presence of EV HPV subtype HPV17 from lesional skin of patient 1 and HPV36, HPV5c and HPV15b at lower copy numbers in tissue from patient 2.

We searched for EVER1 and EVER2 mutations by automated fluorescent bidirectional sequencing of multiple amplicons from each coding exon using a method similar to that described in Sun et al. (5) (primers and conditions available upon request). No non-synonymous open reading frame mutations were found in either patient. EVER1 and EVER2 mRNA expression in lymphoblastoid cell lines derived from the patients and healthy volunteers determined by RT-PCR were similar. This suggested that potential mutations affecting transcription had not altered the expression of the EVER1/2 genes in our patients. Taken together, these results suggested that EVER1/2 mutations were not involved in the susceptibility of this father/son pair to HPV infection.

Discussion

The natural history of disease in our patients is consistent with previous reports in EV patients. As illustrated by our cases, EV lesions do not regress and are generally refractory to standard treatments, including alpha-interferon and retinoids (6-8). Imiquimod has been reported to be ineffective (9), but patient 1 appeared to have at least partially responded to topical imiquimod. Successful treatment has been reported with a combination of acitretin and interferon alfa-2a (10). An important clinical consideration in patients with EV is their increased susceptibility to non-melanoma skin cancers (NMSC). In one survey of 147 EV cases, one third of patients developed NMSC, with an average interval of 24 years from development of the benign lesion to development of NMSC (11). Interestingly, not all EV HPV types are associated with a development of NMSC. HPV5 is most often implicated, while types 8, 14, 17, 20 and 47 are occasionally associated with cancer development. Irrespective of HPV serotype, cancers appear on sun-exposed areas, most often on the forehead, and are usually squamous cell carcinomas (SCC). Patients should be educated on sun protection given their increased risk of development of NMSC.

Recent studies have advanced our understanding of the genetic defects carried by EV patients. Genome-wide linkage studies of two consanguineous populations revealed two susceptibility loci at chromosome regions 2p21-p24 and 17q25 (12). Subsequently, Ramoz *et al.* linked genotype and phenotype when they identified two relevant genes, EVER1 and EVER2 in the17q25 region, by finding homozygous nonsense mutations in these two genes that correlated with disease (13). A number of different mutations resulting in truncated proteins have subsequently been elucidated in additional pedigrees (5, 13, 14). However, genetic heterogenity has been suggested by finding an X-linked recessive inheritance pattern in a family affected by the disease (15). Furthermore, an international collaborative study revealed that only 75% of EV patients carry homozygous nonsense mutations in either EVER1 or EVER2 (1).

The functions of the proteins encoded by EVER1 and EVER2 have not been established, but EVER1 and EVER2 show extensive homology to members of the transmembrane channel-like (TMC) gene family. EVER1 and EVER 2 are predicted to possess 10 (EVER1) and 6 (EVER2) transmembrane domains and to localize to the endoplasmic reticulum (13). The function of proteins encoded by the TMC family genes is unclear, but their structure is highly conserved across species, supporting the idea that they play an important cellular role. Mutations of TMC1 have been shown to cause sensorineural hearing loss in murine models (16, 17). These findings suggest that TMC proteins are ion channels or transporters that are important in signal transduction. All identified mutations of EVER1 and EVER2 result in truncation that eliminates the conserved TMC motif common to members of this family.

The two described cases fall into the 25% of EV patients without detectable mutations in the EVER1/2 genes. Furthermore, there is no history of consanguinity in the pedigree, nor is there a history of abnormal susceptibility to HPV in the other members of the family. The susceptibility to HPV was passed from father to son, supporting the idea that this is an autosomal dominant mutation. X-linked and autosomal recessive patterns of inheritance have previously been described for EV, but at the time of manuscript submission, autosomal dominant transmission of EV has yet to be reported, providing further evidence of the genetic heterogeneity of the disease.

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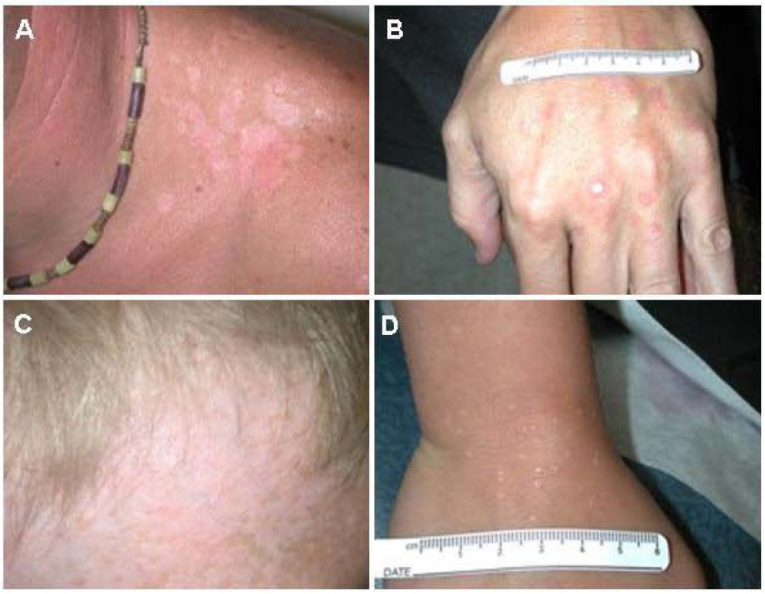

Fig. 1a-d.

(a) Left suprascapular region of patient showing numerous round hypopigmented macules with some coalescing into patches. Telangiectasias are apparent within the lesions. (b) Left dorsal hand of patient 1 showing 3-6 mm round, pink, papular lesions with scant scale. A distinct, hyperkeratotic, verrucous papule is apparent over the dorsal surface of the second metacarpophalangeal joint. (c) Right temporal and frontal region of patient 2 shows numerous flat-topped polyangular hypopigmented papules with confluence over the right temple and extending into the hairline. Alopecia is evident in the confluent region. (d) Right dorsal wrist of patient 2 shows scattered round, pink 1-2 mm flat-topped papules without scale.

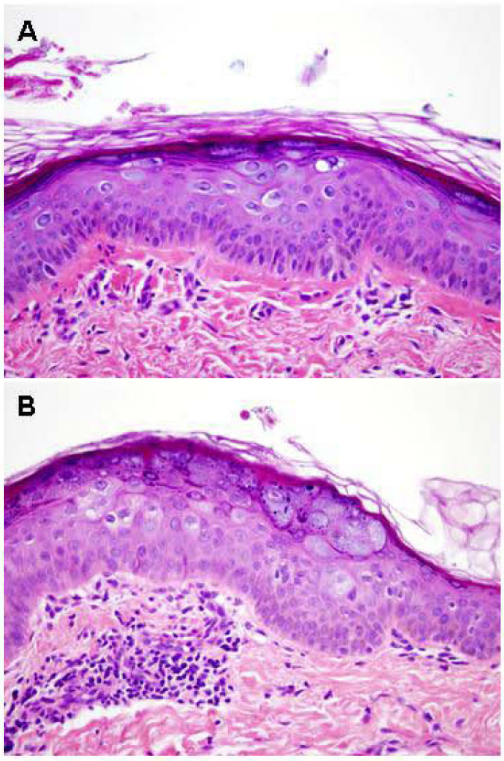

Fig. 2a,b.
Hematoxylin and eosin staining (40x) of representative skin lesions from patient 1 (Fig. 2a) and patient 2 (Fig. 2b), depicting characteristic features of EV, including hyperkeratosis, mild acanthosis, an enlarged granular layer, and keratinocytes with abundant clear or blue-gray cytoplasm in the spinous layers.