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A COMPREHENSIVE STUDY ON EPIDERMODYSPLASIA VERRUCIFORMIS

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Abstract

Epidermodysplasia verruciformis (EV) is a rare genodermatosis that predisposes certain individuals to developing cutaneous malignancies caused by infectious agents. Mutations in the transmem brane channel gene TMC6 or TMC8 create patient susceptibility to infections by human papilloma virus (HPV) and the development of EV-typical plane warts. Mainly in the UV-exposed regions, af fected individuals have a lifelong increased risk for the development of cutaneous malignancy, especially squamous cell carcinoma (SCC). EV is the first disease to correlate cancer and viral infection, therefore EV now serves as the cornerstone to our understanding of viral oncogenesis. The EV mod el of cutaneous SCC may be applied to the general population; it is suggested that the TMC mutations impair the immunity of the patients, supporting the amplification of specific HPV types. Despite sev eral advances in our comprehension of EV, the pathogenesis of the disease is not well understood.

Introduction

A rare skin condition known as epidermodysplasia verruciformis (EV) that develops during childhood or infancy is permanent. It is brought on by a variety of distinct human papillomavirus (HPV) strains, occasionally even those linked to flat warts in the general public. Refractory, disseminated skin lesions that resemble flat warts or manifest as multicolored macules are the hallmark of EV. A significant percentage of people develop cutaneous carcinomas in situ or invasive carcinomas, typically of the Bowen's type, frequently at a young age. In most cases, HPV type 5 DNA sequences are found in EV carcinomas. In addition to certain HPVs, EV is a complex illness involving immune, genetic, and extrinsic factors. Parental consanguinity and the involvement of siblings in certain cases, as well as the majority of patients' reported paired cell-mediated immunity and the typical location of skin malignancies in places exposed to light, have all suggested this.

Lewandowsky and Lutz first identified EV as a congenital epidermal defect in 1922, but over the next forty years, there was debate regarding the nosological entity of EV. According to some writers, EV is an acquired defect of epidermal division (Geno dermatosis), causing the epidermis to vacuolate and making it more prone to skin cancer growth (Maschkilleisson, 1931; Waisman and Montgomery, 1942; Midana, 1949; Lazzaro et al., 1966; Oehlschlaegel et ai., 1966; Relias et al., 1967). Others considered EV as a particular form of generalized

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verrucosis (Hoffmann, 1926; Kogoj, 1926; Sullivan and Ellis, 1939; Jablonska and Milewski, 1957).

Patients are more vulnerable to HPV infections and the development of EV-typical plane warts if they have mutations in the transmembrane channel genes TMC6 or TMC8. Those who are affected, primarily in areas exposed to UV radiation, are at a lifelong higher risk of developing cutaneous cancer, particularly squamous cell carcinoma (SCC). Since EV was the first illness to link viral infection to cancer, it is now the basis for our knowledge of viral oncogenesis. The EV modality of cutaneous SCC may be used to the general population; it is hypothesized that patients' immunity is compromised by TMC mutations, which encourages the amplification of particular HPV strains. Even though our understanding of EV has advanced significantly, the disease's pathophysiology is still poorly understood.

Clinical Manifestations

The first symptoms of EV typically develop on the patient's skin during infancy or childhood. These symptoms usually present as squamous reddish skin lesions similar to verrucae planae on the extremities and red or red brownish plaques and pityriasis versicolor-like lesions mostly distributed on the trunk (fig. 1).

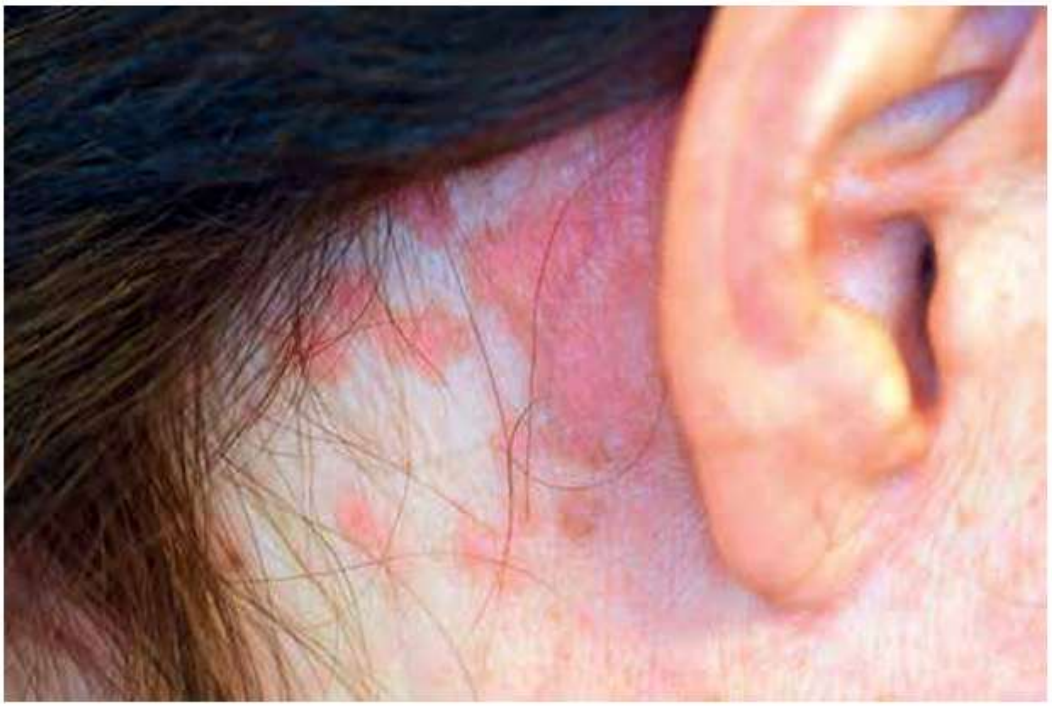

Fig. 1 . Typical pityriasis versicolor-like lesions behind the ear of an EV patient

The histopathology of EV plane warts typically demonstrates mild acanthosis and hyperkeratosis but still the typical blue cells (fig. 2). The disease is associated with an increased risk of non melanoma skin cancer (NMSC), mainly SCC. Particularly in the UV-exposed regions, EV patients develop precancerous lesions (actinic keratoses) which later un dergo malignant transformation and become invasive NMSC. This trans formation from healthy skin to malignancy could take approximately 20 years.

HPV infections are detectable in all EV patients; almost all infections are due to members of the genus β.

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EV-typical HPVs are also detectable in EV skin lesions and hair bulbs; consequently patients demon strate a significantly increased serum antibody reactivity against β-HPVs. This correlation between HPV and the occurrence of NMSC in sun-exposed areas has led to the assumption of their synergistic role in the development of NMSC. Al though an association between EV HPV and NMSC is also seen in the general pop ulation, initiation and mechanisms of HPV influence remain to be elucidated.

Plane Warts

Analysis of specific epidermal markers (KRT1, 10, 14, 16, 4, involucrin, filaggrin, and E-cadherin) demonstrated a disturbed expression of single markers in EV lesions. The K1/10 expression is diminished and substituted by K14, reflecting immatu rity and lack of differentiation in the abnormal epidermis. Also K16 and K4, normal ly not found in the epidermis, as well as involucrin were overexpressed in the spinous layer suggesting a disturbed proliferation and differentiation of the epidermal cells. Such alterations could be induced by the E7 gene of some HPV types. HPV infec tion seems to alter the keratinocytes' differentiation in a way that predisposes them to SCC.

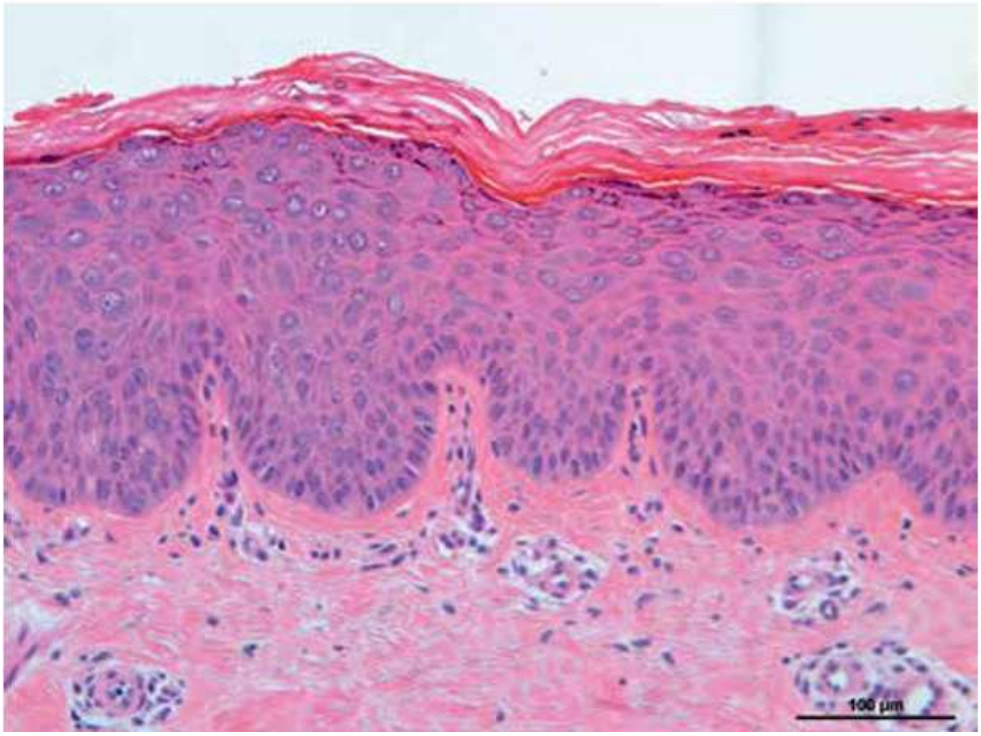

Fig. 2 . Histopathology of EV lesions only showed a mild acanthosis but the Typical blue cells with pallor (by courtsey of P . Häusermann, Basel).

Genetics and Pathogenesis

After the identification of 2 susceptibility loci on chromosome 17 (EV1) [22] and chromosome 2 (EV2), 2 genes (TMC6 and TMC8 also named EVER1 and EVER2) were identified as being mutated in approximately 75% of EV patients. A consid erable number of clinically diagnosed EV patients reveal no mutation in either of these genes indicating a nonallelic heterogeneity of the disease. Since the discovery of these genes, which are

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homozygously or compound hetero zygously mutated in some EV patients, 22 patients from 14 families were de scribed to carry a mutation (table 1). All mutations are loss-of-function mutations caused by a nonsense, a splice site, a frameshift mutation or an exon deletion and re sult in a lack of protein production.

TMC6 and TMC8 are normally expressed in several tissues including the skin, but recently it was shown that they are highly expressed in lymphocytes. Expression of these genes results in a protein complex with ZnT1 within the membrane of the endoplasmic reticulum which is involved in the Zn2+ homeostasis of the cell. The pathogenic consequence of the TMC mutations in EV patients is unknown. EV pa tients are susceptible to skin infections by particular types of HPVs that are considered to be innocuous for the general population. It is assumed that they are not able to reject the EV HPV-harboring keratinocytes due to impaired Zn2+ homeostasis. This disability only seems to affect EV-specific HPVs and has no influence on the sus ceptibility to the remaining HPV types.

Table 1 . Range of HPV types identified in EV noncancerous lesions

No.	Genus	Reference
3	α	Glinski et al. Kaminski et al. Majewski and Jablonska
5	β	Dell'Oste et al. Kaminski et al.
8	β	Dell'Oste et al.
9	β	Kaminski et al.
10	α	Dell'Oste et al.
12	β	Kaminski et al.
14	β	Majewski and Jablonska
15	β	Kaminski et al. Dell'Oste et al.
17	β	Majewski and Jablonska
19	β	Kaminski et al.

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20	β	Kaminski et al.
	β	Dell'Oste et al.
21	β	
	β	Dell'Oste et al. Kaminski et al.
22		
	β	Majewski and Jablonska
23		
		Majewski and Jablonska
24		
25	β	Majewski and Jablonska
	α	
26		De Oliveira et al.
	β	
36	β	De Oliveira et al.
38		De Oliveira et al.

TMC6 and TMC8 belong to a larger gene family, named as transmembrane chan nel-like gene family, which comprises a group of highly conserved transmembrane proteins. TMC6 and TMC8 form a trimeric complex with ZnT1 and influence the zinc homeostasis in cells. It is suggested that the complex is located in the en doplasmic reticulum. The authors hypothesized that the Zn2+ level controlled by the TMC/ZnT1 complex leads to a reduced activity of transcription factors which are essential for the replication of EV HPVs. Due to the mutated and missing TMC/ZnT1 complex, the levels of the transcription factors increase and enable the EV HPVs to replicate, leading to the EV phenotype. Indeed, an induced decrease in TMC ex pression in cell culture leads to an accumulation of free Zn2+ ions in lymphocytes which blocks naïve T cell activation and proliferation. Consistent with these results, the Zn2+ level in lymphoblastoid cells or primary T cells from EV patients is elevated.

Mouse models have elucidated additional possible proteins and mechanisms par ticipating in EV SCC development. For instance, the active form of the protooncogene Stat3 (signal transducer and activator of transcription) was shown to be increased in HPV8 transgenic mice and therefore boosted tumorigenesis in the epidermis. After UVB irradiation, Stat3-overexpressing keratinocytes were protected from apop tosis. The number of Stat3-positive cells in HPV8-positive papillomas was signifi cantly higher than in nonlesional skin leading to the suggestion of involvement of Stat3 in the HPV-8-induced hyperproliferation. Examinations of the epidermis of EV patients revealed an overexpression of trans forming growth factor β1 and tumor necrosis factor α (TNF-α) compared to samples of non-EV patients. Recent studies showed that TMC8 influences the TNF-α dependent apoptosis by interaction with TNF receptor-associated death domain pro tein, which again is involved in the activation of caspase 8 by Fas-associated pro tein with death domain leading to apoptosis.

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A defective Fas function was reported in a patient with the clinical diagnosis of EV but without a mutation in TMC6 or TMC8. Whether a genuine correlation exists between patient data and in vitro analysis has yet to be studied.

Immunological studies indicated an influence of an impaired immunity on the susceptibility to the specific HPV infections in EV patients. Recently it was shown that EV patients demonstrate a significant increase in memory CD4+ and ef fector memory CD8+ T cells as well as an increase in skin-homing CD4+ T cell subsets. T cell development and function seem not to be affected by this increase. Patients suffering from RHOH (ras homolog gene family member H) or MST1 (macrophage stimulating 1) disorder are reported to be susceptible to EV HPV infections and to develop EV-like lesions as well. However, in contrast to EV patients they reveal an impaired T cell function. The contribution of the T cells to the pathogenesis of EV has to be clarified in further studies.

Acquired EV

A few years ago, patients with a late developing form of EV were described. These patients mostly developed their first signs of disease during adulthood. Since all patients have an impaired immune system, this type of EV is termed ‘acquired EV’. Most patients are immunodeficient by the HIV; descriptions of acquired EV in patients with other types of immunosuppression are rare. Histological examinations of the acquired EV lesions revealed the typical blue cells with pallor and a mild acan thosis consistent with EV. Also the finding of β-HPV types 5 and 8 in the skin con firmed the diagnosis of EV in these patients. In contrast to the congenital form of EV and in conformance with acquired immunodeficiency, neither homozygous nor com pound heterozygous mutations in the TMC6 or TMC8 genes are present. It is worth noting that rare single-nucleotide polymorphism variations of both genes have been identified in patients suggesting a possible modulator function in the devel opment of acquired EV.

Treatment

EV is a rare genodermatosis, and no curative therapies are presently available. Current treatment is geared towards symptomatic management. Cryotherapy is considered first line in the management of precancerous lesions and minimally invasive skin can cers. Surgical excision is recommended for localized aggressive SCC. Several topical treatments have been described in the management of skin cancers in EV patients. Positive results were seen with imiquimod, and other topical therapies like 5-flu orouracil, interferon, tacalcitol or retinoids have been described. As in most genetic diseases, the lesions and cancer reappear as soon as the therapy is stopped.

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Conclusion

EV is a rare autosomal recessive genodermatosis with an increased risk for NMSC. The disease is caused by mutation in the TMC genes, making the patients susceptible to specific HPV types. Subsequently, the patients develop NMSC at the UV-exposed skin, mainly SCC. The curative treatment of the skin cancers is most commonly sur gical excision but in early lesions immunomodulators such as imiquimod or 5-fluo rouracil or cryotherapy and electrocauterization can be performed. However, the ge netic susceptibility to cancer cannot be influenced. Even though EV serves as a mod el disease for the development of SCC in the general population, the pathogenesis of EV remains unexplained and will be the topic of future studies.

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