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Epidermodysplasia verruciformis: revision of a model of carcinogenic disease

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Abstract

Background: This review addresses current issues regarding epidermodysplasia verruciformis (EV), which are relevant in clinical practice and to comprehend the mechanisms by which human papillomavirus (HPV) acts in cutaneous carcinogenesis.

Main body: EV is an unusual genodermatosis, related to beta-HPV, with high risk for developing skin cancer. Clinical manifestations begin in childhood and they are characterized by flat warts, pityriasis versicolor-like macules and seborrheic keratoses lesions. Up to 50% of EV patients develop nonmelanoma skin cancer in sun exposed areas, mainly squamous cell carcinomas (SCC). Unlike genital carcinomas associated to alpha-HPV, in which transcriptionally active viral genomes invariably occurs, the EV-HPV seems to act by interaction with the host cell, the ultraviolet radiation and immunosuppression to result in carcinogenesis. The EV diagnosis is clinical and it can be confirmed by characteristic histopathological findings and EV-HPV identification. Until now, there is no effective treatment for EV. EV patients need regular clinical follow-up for early detection and treatment of cutaneous carcinomas.

Conclusion: Despite the rarity of EV, the study of this genodermatosis is important to better understand the process of beta-HPV carcinogenesis.

Keywords: Epidermodysplasia verruciformis, Human papillomavirus, Cutaneous squamous cell carcinoma, Carcinogenesis

Introduction

Until the identification of human papillomavirus 5 (HPV-5) genome in skin cancer from epidermodysplasia verruciformis (EV) patients, there was not any evidence of HPV involvement in human carcinomas. Since then, EV has been considered a model of study of viral oncogenesis in humans (Majewski and Jablonska 1995).

EV is a rare genodermatosis, with multifactorial etiopathogenesis, that results in abnormal susceptibility to a specific group of beta-HPV genotypes (EV-HPV) (Oliveira et al. 2006; Jablonska and Majewski 1994). EV patients develop skin lesions throughout life and they may undergo malignant transformation in up to 50% of cases, mainly in sun exposed areas (Oliveira et al. 2006; Jablonska and Majewski 1994; Gül et al. 2007).

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The EV oncogenesis has not been fully elucidated yet. Unlike genital carcinomas induced by alpha-HPV, there is no integration of beta-HPV DNA into the human genome (Majewski and Jablonska 1995). It is believed that beta-HPV acts in the initial process of cutaneous carcinogenesis, through the destabilization of the host genome (Howley and Pfister 2015). Besides, the presence of beta-HPV is probably not enough for EV carcinogenesis, since not all cutaneous lesions of EV, even those related to oncogenic HPV, undergo malignant transformation. The long period of latency (5–20 years) between infection and development of carcinomas suggests the need of participation of cofactors in this process, in which ultraviolet (UV) radiation is the most implicated (Majewski and Jablonska 1995).

The beta-HPV presents tropism to keratinocytes, where it causes cell proliferation and can induce cellular atypia, epithelial dysplasia and cancer. In epithelial carcinogenesis, tissue architecture disappears, with intercellular disorganization and loss of cell-matrix adhesion (Lourenço et al. 2010). The knowledge of structural

changes that occur in malignant transformation is important for better understanding of viral oncogenesis.

This article reviews the main findings of EV, including its clinical manifestation, disease course, histopathologic findings, its etiology and pathogenesis, as well as EV diagnosis and therapeutic options.

Historic

Epidermodysplasia verruciformis (EV), also known as "Lutz-Lewandowsky disease", is a rare genodermatosis, which was initially described by Lewandowsky and Lutz in 1922 as a congenital anomaly of the epidermis (Lewandowsky 1922). Its nosological entity was discussed for decades. The virus' involvement as an etiological agent was only confirmed after auto and heteroinocculation experiments, performed by Lutz and Jablonska (Jablonska and Milewski 1957) in benign lesions of EV, associated with observation of viral particles with a morphology similar to human wart virus (Jablonska et al. 1966).

The viral involvement in skin cancers associated with EV was only demonstrated decades later, when HPV-5 genome was detected in EV carcinomas (Orth et al. 1979). Since then, EV has been considered a model of study of viral oncogenesis in humans (Orth 2006).

Epidemiology

Despite its rarity, EV is a universal disease, with no predisposition to gender, race or geographic distribution (Gül et al. 2007; de Oliveira et al. 2003; Vohra et al. 2010). Approximately 501 patients have been described in the whole world (de Jong et al. 2018), but its incidence is uncertain due to sporadic cases worldwide. It is estimated a frequency of 11% in Europe and in United States of America (USA), reaching 40% among Japanese (Sehgal et al. 2002).

Clinical manifestations

The disease begins in childhood, between 5 and 11 years old, although there are reports of early (at birth) or late onset (between the third and fourth decades of life) (Gül et al. 2007; de Oliveira et al. 2003; Majewski et al. 1997; Lutzner 1978). The clinical presentation is polymorphic and characterized by flat warts, pityriasis versicolor-like macules and seborrheic keratoses lesions (Gül et al. 2007; de Oliveira et al. 2003) (Fig. 1).

The flat warts are the most common initial lesions and they are mainly located on face and dorsal aspect of hands (de Oliveira et al. 2003; Majewski and Jablonska 1997a). They are flat papules or plaques, with skin color or rosy and discreetly scaly. A pseudo Koebner phenomenon is often seen, with multiple flat warts lesions in areas of excoriation, resulting from HPV infection (de Oliveira et al. 2003; Berthelot et al. 2007). Common warts may occasionally be present but the occurrence of anogenital warts is exceptional (Orth 2006).

The EV macules are erythematous, discretely scaly, similar to pityriasis versicolor lesions (Orth et al. 1979; de Oliveira et al. 2003). They develop in face, neck and trunk, and may change their appearance and color over the years, becoming hypochromic (Orth 2006; de Oliveira et al. 2003). They usually appear after the flat warts, but they may begin along with them in up to 46% of the cases (de Oliveira et al. 2003; Lutzner 1978).

Seborrheic keratosis (SK) lesions are brown papules and plaques, well-circumscribed and hyperkeratotic,

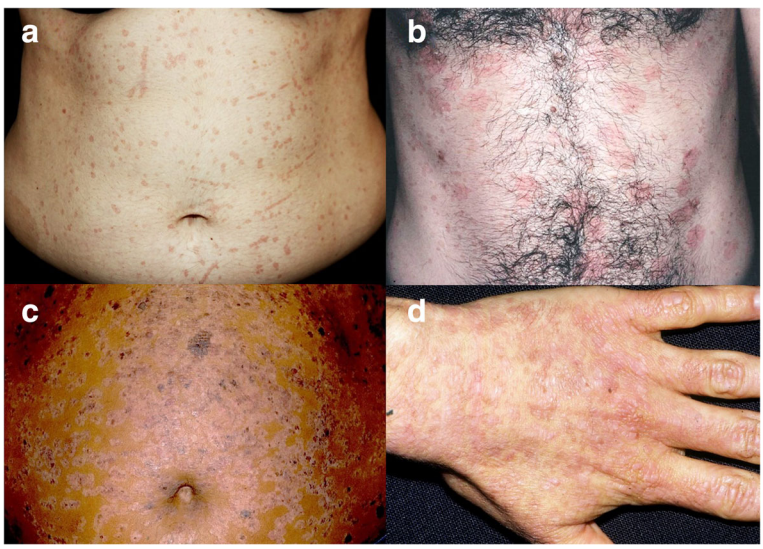

Fig. 1 Examples of clinical presentation of epidermodysplasia verruciform **a** Multiple flat warts lesions on trunk (note pseudo Koebner). **b** Pityriasis versicolor-like macules on trunk. **c** Multiple seborrheic keratoses associated with pityriasis versicolor-like lesions. **d** Flat warts on the dorsal aspect of the hand

located in sun exposed areas, such as forehead, cervical region and upper back (Roncalli de Oliveira et al. 2003). They are usually multiple and associated with other EV clinical findings. They are more common in black individuals and are possibly associated with the malignant phenotype of EV (Majewski and Jablonska 1997a). Although SK lesions are considered benign, there is a report of its transformation into Bowen's disease (Bloch 1978). Oliveira et al. (Roncalli de Oliveira et al. 2003) observed SK lesions in 20 patients with EV over 8 years, but they did not notice malignant transformation. According to the authors, this possibility cannot be excluded, since the mean time elapsed between the onset of benign lesions and cancer is approximately 25 years in patients with EV (Roncalli de Oliveira et al. 2003).

EV usually does not affect mucous membranes (Orth 2006; de Oliveira et al. 2003). In addition to cutaneous alterations, mental retardation has been described in 10–14.2% of the patients (Gül et al. 2007; Lutzner 1978). Subjective symptoms are infrequent and irrelevant (de Oliveira et al. 2003).

EV can be classified as benign or malignant forms, according to the type of HPV involved and its clinical presentation. When the clinical manifestation is limited to flat warts, EV is classified as a "benign form" and it is usually associated with non-oncogenic HPV-3 and/or -10 (de Oliveira et al. 2003). The "malignant form" is characterized by polymorphic lesions, with a tendency to malignant transformation and it is usually associated with multiple EV-HPV (some oncogenic), such as – 5, – 8 and -14 (de Oliveira et al. 2003).

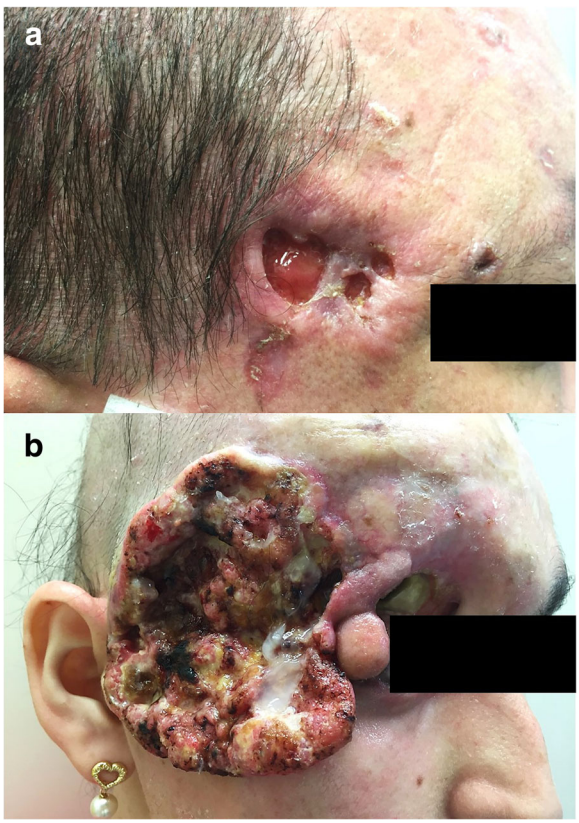

Fig. 2 Examples of malignant skin lesions in epidermodysplasia verruciform **a** Ulcerated squamous cell carcinoma in the temporal region. **b** Invasive squamous cell carcinoma of fast growing after adjuvant radiotherapy

Disease course

EV has a chronic and progressive course. HPV-EV lesions do not present spontaneous regression (Orth 2006). However, there is a report about skin lesions regression after two pregnancies in a patient with EV due to HPV type 3 (Jablonska et al. 1982). Approximately 30–50% of EV patients develop nonmelanoma skin cancer, mainly squamous cell carcinomas (SCC) (Fig. 2a), and these lesions usually appear between the second and fourth decade of life (Orth 2006; de Oliveira et al. 2003; Majewski and Jablonska 1997b). Oliveira et al. (de Oliveira et al. 2003) described a malignancy index of 62% in their patients, with development of cutaneous tumors in 100% of the patients with the malignant form of EV.

The lesions which undergo malignant transformation are usually located in sun exposed areas and correspond to actinic keratoses (AK) (de Oliveira et al. 2003; Majewski and Jablonska 1997b). Despite the large sun exposure in nasal and malar region, premalignant changes are rare in these regions (Majewski and Jablonska 1997b). Cutaneous tumors are located mainly on the forehead (50%) and temporal region. The high incidence of cancer in these regions could be explained as consequence of chronic sun exposure, by the presence of stem cells in the hair follicles, as probable reservoirs of EV-HPV, in addition to the synergistic action of chemical carcinogens, such as squalene and tallow fatty acids (de Oliveira et al. 2003; Majewski and Jablonska 1997b).

Skin cancers develop slowly but are locally destructive. Deep invasion and metastasis are rare, but they have been observed in some patients, especially when exposed to local radiotherapy (Lutzner et al. 1984; de Oliveira et al. 2015) (Fig. 2b).

Histopathological and ultrastructural findings

All clinical lesions of EV share the same histopathological features, with stratum corneum in "basketball net", parakeratosis and acanthosis (Kirnbauer and Lenz 2013). In the Malpighian hyperplastic stratum, the characteristic cytopathic changes are observed: large cells, with perinuclear halos and pale, blue-gray cytoplasm, giving the appearance of "cells in bird eyes", besides kerato-hyaline granules of varying sizes and shapes (Majewski and Jablonska 1995; de Oliveira et al. 2003;

Kirnbauer and Lenz 2013) (Fig. 3). This cytopathic effect is characteristic for all EV-HPV infections, independent of the virus genotype (Jablonska and Majewski 1994).

In flat warts lesions from malignant form of EV, the viral cytopathic effect is observed from the suprabasal layer to the upper layers of the epidermis, which is characteristic of the lesions caused by HPV-EV, mainly HPV-5 and -8 (Jablonska and Majewski 1994). In lesions from benign form of EV, viral cytopathic effect is observed only in the upper layers of the epithelium (Majewski and Jablonska 1995) (Fig. 3a).

Seborrheic keratosis lesions present the viral cytopathic effect of EV associated with the histopathological findings' characteristic of this type of lesion: hyperkeratosis, basaloid acanthosis, papillomatosis and corneal pseudocysts, with melanin widely distributed in the keratinocyte cytoplasm (de Oliveira et al. 2003) (Fig. 3b). In all EV lesions, the dermis does not present significant changes, and may exhibit mild perivascular mononuclear inflammatory infiltrate (Ouban and Ahmed 2010).

Malignant transformation begins as a proliferation of the epidermal crests with numerous dyskeratotic cells (Majewski et al. 1997). The pattern of epithelial dysplasia and loss of epidermal polarity is similar to those observed in actinic keratosis and even Bowen's disease, with hyperkeratosis and parakeratosis, containing a large amount of HPV's DNA (Majewski et al. 1997). Atypical mitoses may be present in all layers of the epithelium. The characteristic viral cytopathic effect disappears or is observed only in the adjacent epidermis, where there are no signs of malignant transformation (Majewski et al. 1997). Often, malignant transformation begins around hair follicles (Majewski et al. 1997).

Bowen's disease and cutaneous SCC are the most frequent tumors of EV. They are characterized by Bowenoid atypia, with monstrous dyskeratotic cells -

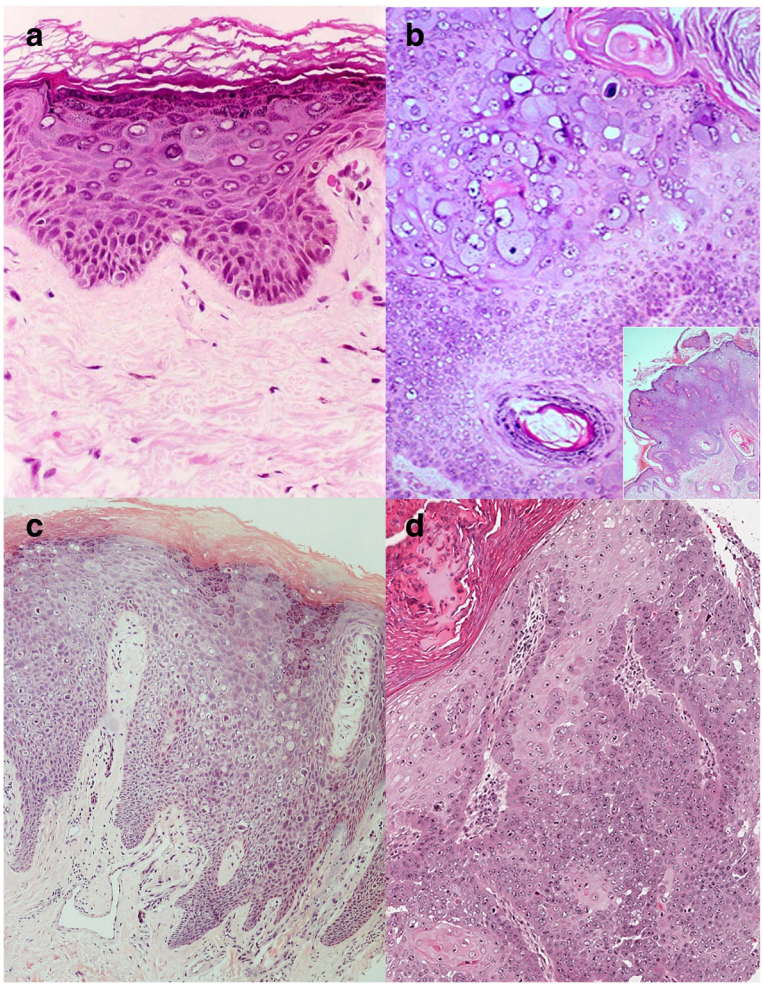

Fig. 3 Examples of cytopathic effect in epidermodysplasia verruciform (EV) in different skin lesions. **a** Flat wart (Hematoxylin-eosin- HE, × 400). **b** Seborrheic keratosis (HE, × 400). **c** In situ squamous cell carcinoma (HE, × 200). **d** Invasive squamous cell carcinoma (HE, × 200)

multinucleated and dyskeratotic cells with irregular, large, hyperchromatic and pleomorphic nuclei associated with atypical mitoses (Jablonska and Majewski 1994; Majewski et al. 1997) (Fig. 3c).

Invasive cancers preserve the main ultrastructural feature of Bowenoid atypia (dyskeratosis and apoptosis) (Fig. 3d). The apoptotic bodies, usually encompassed by neighboring keratinocytes, are composed of compact beams of tonofilaments interspersed with remnants of mitochondria and endoplasmic reticulum (Majewski et al. 1997). They are involved by a single or double membrane and they are degraded by lysosomal proteolytic enzymes (Majewski et al. 1997).

In electron microscopy, atypical cells are characteristic and show viral particles in the nuclei of the upper layers, disorganized nucleoplasm, with marginalization of the chromatin (Majewski et al. 1997; Yoshida et al. 2014) (Fig. 4). The cytoplasm is poor in organelles, except ribosomes (Majewski et al. 1997). The kerato-hyaline granules are prominent, irregular and they are not associated with tonofilaments (Majewski et al. 1997).

Etiology and pathogenesis

EV is a multifactorial disease, with involvement of infectious agent (HPV), genetic factors, environmental and immunological changes (Jablonska and Majewski 1994; Majewski et al. 1997).

Infectious agent: HPV infection

Structural characteristics and phylogenetic classification of HPV Human papillomaviruses (HPV) are small DNA viruses (50-55 nm), which present an icosahedral capsid, without a peripheral lipoprotein envelope (Orth 2006; de Villiers et al. 2004; Tyring 2002). Over 200 HPV types are already described (de Villiers et al. 2004).

Papillomaviruses share the same genetic organization. The HPV genome consists of a circular double stranded DNA molecule, with 7500–8000 base pairs of DNA, COULD containing UNTIL 10 gene coding sequences (Orth 2006; Tyring 2002). Its genome can be divided into three regions: the "E" ("early"), the "L" ("late") regions and a non-coding region "LCR" ("long control region") (Tyring 2002; Accardi and Gheit 2014) (Fig. 5).

The "E" proteins encode six non-structural proteins and they are, in general, responsible for the regulation of viral function (Tyring 2002). The E1 and E2 proteins are required for the replication of viral DNA. The E4 protein binds epithelial keratins, facilitating the production of virions, by disrupting normal cell differentiation (Majewski et al. 1997). The E5 protein also exhibits growth-promoting properties (Orth 2006). The E6 and E7 proteins are required for the promotion of the "S" phase and for inhibiting apoptosis and in differentiated terminal keratinocytes (Orth 2006). They also cooperate to maintain latent intracellular infection (Tyring 2002) and they can induce genetic and chromosomal instability in potentially oncogenic HPV genotypes (Orth 2006).

The late region (L) encodes two structural proteins known as L1 and L2, which are required for the formation of HPV capsids and virus-like particles (VLP) (Munger et al. 2004; Tungteakkhun and Duerksen-Hughes 2008). In addition, the L1 protein contains neutralizing antibody-inducing epitopes and the L2 epitopes are responsible for the group-specific reactivity of antisera (Majewski et al. 1997).

The LCR portion contains control elements for viral transcription and replication (Tyring 2002). These elements bind to various transcription factors involved in DNA regulation and viral gene expression (Majewski et al. 1997).

The HPV belongs to the *Papillomaviridae* family (Simmonds and Storey 2008). The various types of HPV

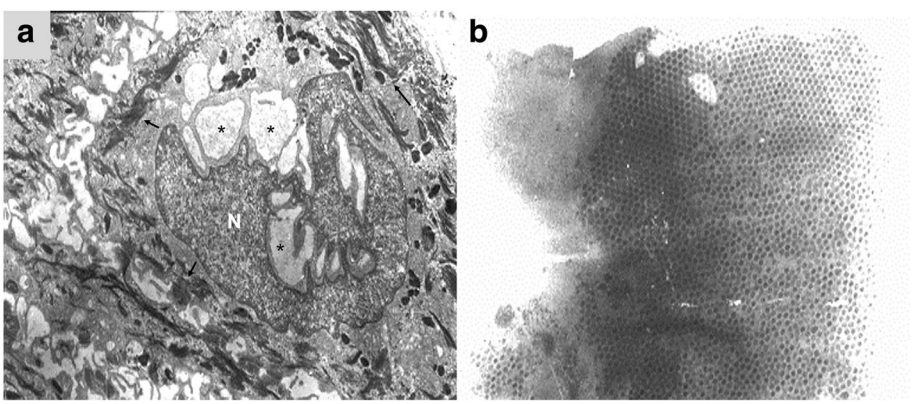

Fig. 4 Transmission electron microscopy of epidermodysplasia verruciform lesion. **a** Keratinocyte with irregular-shaped nucleus (N), dilated endoplasmic reticulum cisternae (*) and tonofilaments grouped (arrows) at cytoplasm periphery (original magnification 10,000x) **b** Typical viral particles with crystalline arrangement (original magnification 27,000x)

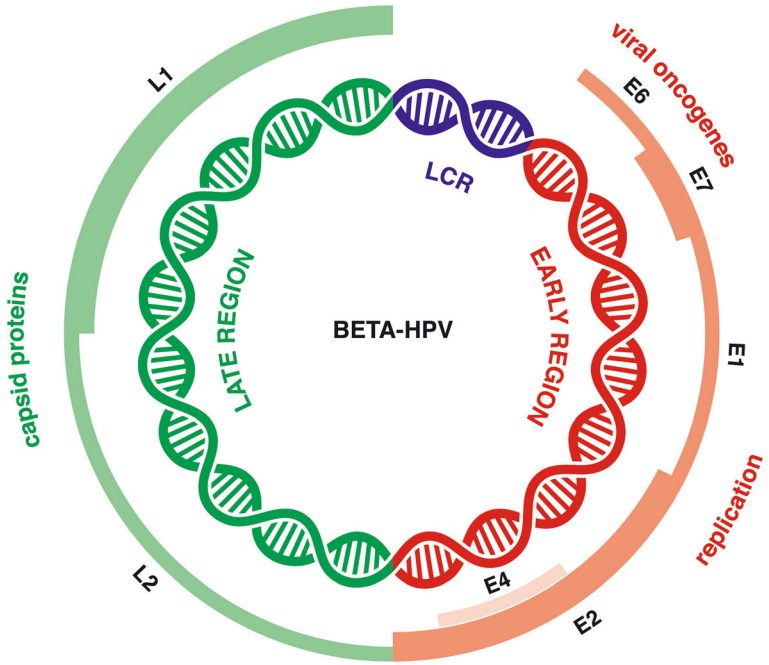

Fig. 5 Schematic representation of beta-HPV genome, showing its three regions: early ("E") and late ("L") regions, and a non-coding region "LCR" ("long control region")

are distributed in five phylogenetic genera: alpha, beta, gamma, mu and nu-papillomavirus (de Villiers et al. 2004). The genera are subdivided into species and types, based on the comparison of the nucleotide sequence (Orth 2006). Members of the same species have similar biological and pathological properties (de Villiers et al. 2004). A new type of HPV is defined when it has a homology in the nucleotide sequence of its L1 gene (the most conserved region of the viral genome) lower than 90%, when compared to the most closely related HPV known (de Villiers et al. 2004; Tyring 2002). Differences between 2 and 10% define a subtype and less than 2% define a variant (de Villiers et al. 2004; Egawa et al. 2015).

All genotypes of genital HPV belong to alpha-papillomavirus genus. Cutaneous HPV present greater heterogeneity and belong to the alpha, beta, gamma, mu, or nu-papillomavirus genera (de Villiers et al. 2004).

EV-related HPV (EV-HPV) Patients with EV are prone to infection by specific HPV strains, called EV-HPV. Although initially described only in patients with EV, it is now known that EV-HPV may be present in the normal skin of healthy individuals, indicating that the normal (asymptomatic) population can serve as a reservoir for EV-HPV (Kirnbauer and Lenz 2013; Nunes et al. 2018).

Mostly EV-HPV genotypes belong to the genus beta-papillomavirus. More than 100 types of HPV have already been identified, but mainly HPV-3, − 5, − 8, − 9, − 10, − 12, − 14, − 17, − 19 to − 25, − 28, and − 29 are related to EV (Vohra et al. 2010; Gewirtzman et al. 2008).

Several types of EV-HPV may be present in benign lesions of EV, as well as more than one type of HPV may be present in the same patient. The malignant transformation depends on the oncogenic potential of the infecting virus, with HPV-5 and -8 being the main associated types (Vohra et al. 2010; Gewirtzman et al. 2008). In Brazil, Oliveira et al. (de Oliveira et al. 2004) found high prevalence of EV-HPV-25 and -14 in EV carcinomas.

Pathogenesis and carcinogenesis of HPV infection

The HPV life cycle is directly related to cell differentiation of the host cell. In the skin, HPV infection begins with breakdown of the cutaneous barrier (Levinson 2014). The *papillomavirus* initially infects the cells of basal layer by heparan sulfate binding, on the surface of these cells (Giroglou et al. 2001). Then, it reaches the nucleus, where it remains in a latent phase as extrachromosomal plasmids, which replicate concomitantly with the chromosomes' cells, but there is no virus production by these cells (Levinson 2014; Arron et al. 2011) (Fig. 6a).

The replicative phase, the protein synthesis, as well as the assembly of new viruses occur in differentiated keratinocytes from the suprabasal layers (Alberts et al. 2002). As keratinocytes differentiate and ascend to more superficial layers of the epidermis, infectious viral particles replicate (Fig. 6a). Normally, before reaching the corneal

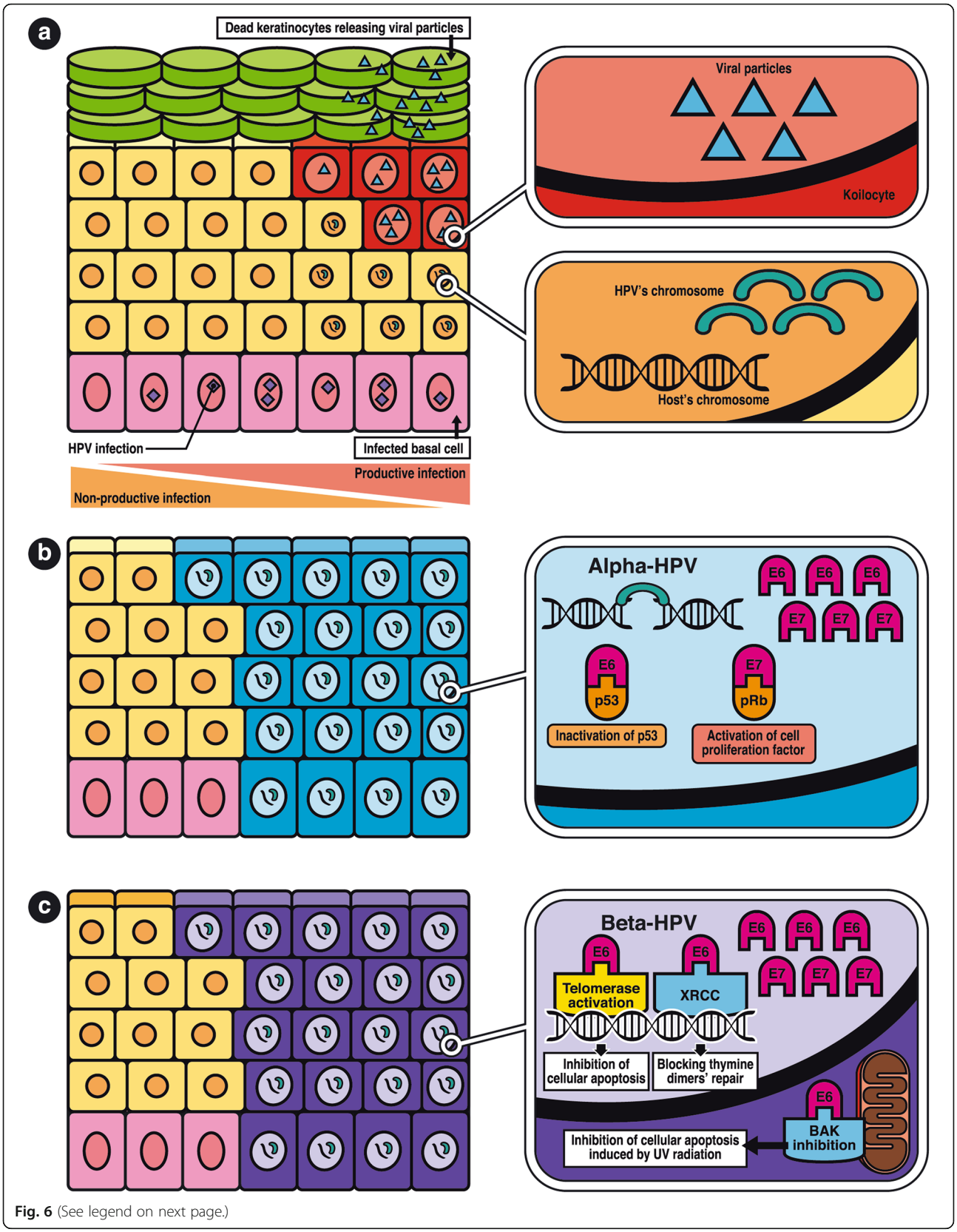

Fig. 6 (See legend on next page.)

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Fig. 6 Schematic representation of HPV infection and its carcinogenesis. **a** After breakdown the cutaneous barrier, occurs the basal cell layer infection, where the HPV remains in a latent phase as extrachromosomal plasmids. The infectious viral particles replicate in differentiated keratinocytes from the suprabasal layers. **b** Epithelial carcinogenesis by alpha-HPV, with integration of the viral genome into the host cell chromosomes, as observed in cervical uterine carcinogenesis. **c** Mechanisms on cutaneous carcinogenesis by beta-HPV, which includes telomerase activation by E6 protein, block of pro-apoptotic protein BAK and binding the XRCC1 protein, with blocks the DNA repair mechanism

layer, keratinocytes interrupt the cell division, but the presence of virus interferes with cell cycle interruption, allowing the replication of its genome, which histologically translates as acanthosis associated with papillomatosis, observed in these lesions (Alberts et al. 2002).

The integration of the viral genome into the host cell chromosomes is the main event in cervical uterine carcinogenesis, which is association with "high-risk" alpha-HPV (HPV-16 and -18) (Arron et al. 2011). Integration of viral DNA may result in the breakdown of the E2 viral regulatory gene, leading to dysregulated expression of E6 and E7 viral genes. In high risk HPV, viral proteins E6 and E7 produced by HPV leads to the degradation of retinoblastoma proteins (pRb) and p53 of the host cells, resulting in chromosomal instability, with proliferation, malignant transformation and immortalization of infected cells (Arron et al. 2011) (Fig. 6b).

The involvement of HPV in the development of cutaneous carcinoma in the general population is still controversial. Detection of HPV in the lesions of extragenital Bowen's disease, located mainly in the hands, suggests autoinoculation from genital lesions, where the role of HPV is already well documented (Leto et al. 2011).

However, not all SCC are infected by HPV and the prevalence described vary depending on the detection method used (Arron et al. 2011). In addition, detection of HPV in cutaneous SCC samples does not imply causality (Wang et al. 2014). It is not known whether the virus has a supporting role in some subgroups of cutaneous SCC, if its presence is merely expectant, or if current HPV detection techniques are limited, failing on demonstrating the presence of HPV in all studied samples (Arron et al. 2011) . Currently, only HPV-5 and -8 are classified as possible carcinogens (group 2B) by the International Agency for Research on Cancer (IARC), in the context of EV (Arron et al. 2011; Bouvard et al. 2009).

The molecular mechanism by which beta-HPV facilitates the progression of skin cancer in EV differs from the proposed mechanism for alpha-HPV. Beta-HPV probably act early in the process of carcinogenesis and is not essential to the maintenance of this process (Nunes et al. 2018). It is believed that beta-HPV infections destabilize the host genome, allowing the development of tumors even in the absence of the viral genome (Howley and Pfister 2015).

Three acting mechanisms on cutaneous carcinogenesis have already been elucidated (Fig. 6c). Production of the E6 protein of beta- HPV activates telomerase, prolonging the life cycle of infected keratinocytes, which would die with natural senescence. This allows these cells to transmit the UV-mutated DNA to their progeny, a relevant fact when it affects stem cells, since keratinocytes have a short life cycle (Arron et al. 2011). In addition, beta-HPV can abrogate the pro- apoptotic protein BAK ("BCL2-antagonist/ killer"), which is expressed after DNA damage induced by UV radiation, increasing the probability of the mutated cell to survive (Arron et al. 2011). Finally, beta-HPV blocks the DNA repair mechanism by binding directly to XRCC1 ("X- ray repair cross complementing protein-1"), preventing the repair of the thymine dimers induced by UV radiation, leading to an increase in mutations (Arron et al. 2011).

However, studies have shown that different beta-HPV work in different ways. Beta-HPV-38 appears to be the most versatile, acting through several pathways. Its E6 protein attenuates phosphorylation of p53 protein and ubiquitination in response to exposure to UV rays, resulting in less repair of damaged cellular DNA (Accardi and Gheit 2014). The E6 protein also changes the ability to activate p53 proteins involved in apoptosis, inducing the accumulation of delta Np73, an isoform and p53 antagonist (Accardi and Gheit 2014). Beta-HPV-38 also induces telomerase by an E6-associated protein-dependent mechanism (E6-AP) (Caldeira et al. 2003).

As alpha-HPV, E6 protein of some beta-HPV induces BAK degradation via interaction with E6-AP, thereby avoiding the release of mitochondrial pro-apoptotic factors (Simmonds and Storey 2008). The interaction of E6 with E6-AP is also required for the induction of hTERT (human telomerase transcriptase) (Bedard et al. 2008). It was also observed that in human keratinocytes transduced with E6 and E7 proteins of HPV-38 and -39, the induced transcription factor E2F family protein increases, since these viral proteins induce hyperphosphorylation of pRb (Nunes et al. 2018; Caldeira et al. 2003).

Genetic factors

EV can be a genetic or sporadic transmitted disease (de Oliveira et al. 2003). Most authors consider an autosomal recessive disease due to high familial incidence, with more than 30% of affected siblings, but with infrequent involvement of successive generations (de Oliveira et al. 2003; Sehgal et al. 2002). In addition, 10 to 92% of patients with EV are the result of inbreeding marriages

(de Oliveira et al. 2003; Orth 2008). Cases of inheritance linked to X-chromosome and autosomal dominant inheritance have been reported, indicating great genetic heterogeneity in EV (Vohra et al. 2010; Aochi et al. 2007; Androphy et al. 1985).

Sporadic cases are defined when there are no reported cases in family. The term "acquired EV" has been used to describe immunocompromised individuals who develop EV phenotype, such as solid organ transplanted patients and patients with AIDS (Shruti et al. 2017; Przybyszewska et al. 2017; Huang et al. 2018).

About 75% of affected individuals have homozygous mutations, inactivating the genes *EVER1* and *EVER2* ("Epidermodysplasia Verruciformis Enhancing Region"), which belong to a large family of proteins transmembrane channels-like (TMC), also known as TMC6 and TMC8 respectively (Orth 2006; Gewirtzman et al. 2008; Shruti et al. 2017; Przybyszewska et al. 2017). Seven mutations have been identified in *TMC6* gene and five mutations in the *TMC8* gene in EV (Kalińska-Bienias et al. 2016).

Both genes are located on chromosome 17q25 and they are expressed in keratinocytes and in immune system cells, such as T and B lymphocytes, "natural killer" (NK) cells, endothelial cells, myeloid bone marrow cells and dendritic cells (Kalińska-Bienias et al. 2016). The *TMC6* and *TMC8* genes encode proteins that inhibit the transcription factors critical for HPV gene expression and negatively regulate cell-mediated immunity, impairing the ability to present peptides derived from HPV to subpopulations of T lymphocytes (Przybyszewska et al. 2017). These transmembrane channel proteins are expressed in the endoplasmic reticulum and form a complex with transporter-1 of zinc (ZnT-1), which regulates the distribution of intracellular zinc (Egawa et al. 2015). ZnT-1 is involved in efflux and resistance to zinc toxicity, leading to the possibility of unbalanced intracellular levels affecting the viral life cycle (Lazarczyk et al. 2008).

Keratinocytes from patients with TMC deficiency present a change in zinc homeostasis and an increase in proliferative activity (Przybyszewska et al. 2017). As a result, it was observed persistence of EV-HPV, uncontrolled proliferation of stem cells and transitory amplification of infected cells with HPV-5 and HPV-8, which can lead to malignant transformation of some lesions (Kalińska-Bienias et al. 2016). Patel et al. (Patel et al. 2010) showed a connection between *TMC8* gene *(EVER2)* and skin SCC, with HPV- 5 and HPV – 8 as causative agents in 90% of cases.

Recently, it has been described EV patients with homozygotes for null mutations of the gene *CIB1,* which encodes calcium binding protein-1 and integrin ("calcium - and integrin-binding protein-1") (de Jong et al. 2018). The CIB1 protein forms a complex with EVER1 and EVER2, however its functions are independent. In EV patients, the absence of CIB1-EVER1-EVER2 complex allows the transcription of beta-HPV minichromosome, which leads to the development of EV lesions in the skin. These patients have the same phenotypes as those with mutations in *EVER1* and *EVER2* (de Jong et al. 2018) and they are clinically indistinguishable.

Mutations in other genes (*RHOH, MST-1*, *CORO1A* and *IL-7*) have also been described in patients with susceptibility to beta-HPV infections, in which mutations of *TMC6* and *TMC8* were previously excluded (Przybyszewska et al. 2017). These mutations were related to phenotypic cutaneous manifestations similar to EV, however, these patients have a greater predisposition to several infections, depending on the affected gene and the nature of the deficient T cell (de Jong et al. 2018). Huang et al. (Huang et al. 2018) suggest classifying these individuals with mutations in genes other than *EVER* as "non-classical EV".

Environmental factors

Ultraviolet (UV) radiation is an important skin carcinogen in general population, formed by three different wavelengths: UVC (ranging from 190 to 280 nm), UVB (280 to 320 nm) and UVA (320 to 400 nm) (Nindl et al. 2007). UV radiation acts synergistically with beta-HPV, being the main environmental factor involved in the pathogenesis of EV. The mechanisms by which UV radiation induces carcinogenesis involves direct damage of DNA and immunomodulatory mechanisms.

UVA radiation induces photooxidative stress and, secondarily, characteristic genomic mutations (Patel et al. 2010). UVB radiation causes direct damage to the DNA of keratinocytes, with formation of thymine dimers, capable of carrying mutations in the genes that control cell cycle, DNA repair pathways and apoptosis (Nindl et al. 2007). UVB radiation can also lead to local (cutaneous) and systemic immunosuppression by several mechanisms. During UV-mediated immunosuppression, Langerhans cells leave the epidermis, which is then repopulated with precursor Langerhans cells, by the Langerhans cells chemoattractant protein CCL20 ("chemokine CC motif 20 ligand") (Sperling et al. 2012). EV lesions that lack Langerhans cells express little or no CCL20 protein. Keratinocytes expressing the E7-HPV-8 protein produce low amounts of the chemokine CCL20 and exhibit reduced chemotactic activity compared to Langerhans cells (Sperling et al. 2012). Thus, Langerhans cells can not properly replenish the EV injuries due to UV exposure (McLaughlin-Drubin 2015).

UVB radiation also leads to formation of the *cis* isomer of urocanic acid, the main absorber of this radiation in the stratum corneum, with consequent suppression of the reactions of delayed hypersensitivity, stimulation of suppressor T lymphocytes and alteration in the antigens-presenting cells (Jablonska and Majewski 1994;

Arron et al. 2011). The increase of *cis* isomer of urocanic acid results in local production of cytokines immunomodulatory agents, inhibiting the antigenic presentation. There is an increase of tumor necrosis factor alpha (TNF-α) and beta-1 transforming growth factor (TGF-β), with consequent reduction on migration of Langerhans cells to regional lymph nodes that hinders recognition of cutaneous tumor antigens by the immune system (Arron et al. 2011). It is noteworthy that increased levels of *cis* isomer of urocanic acid were observed in the epidermis of sun exposed areas of EV patients, as well as levels of TNF-α and TGF-β biologically active in cutaneous lesions in these patients (Majewski et al. 1997).

Several authors have emphasized radiotherapy (RT) as a co-carcinogen in lesions induced by beta-HPV (Gül et al. 2007; de Oliveira et al. 2015; Rajabi et al. 2014). RT seems to increase tumor growth, invasion and metastasis formation (Majewski and Jablonska 1995; Jablonska and Majewski 1994; Gül et al. 2007; de Oliveira et al. 2003; Rajabi et al. 2014). Radiation therapy is believed to act synergistically with sunlight to induce mutations in the tumor suppressor gene *p53* (de Oliveira et al. 2015*)*. Radiation therapy causes both local and systemic immunosuppression, by releasing large amounts of cytokines such as TNF-α and TGF-β (de Oliveira et al. 2003; de Oliveira et al. 2015). Thus, radiotherapy is contraindicated in patients with EV, even as adjunctive therapy (de Oliveira et al. 2015).

Immunological changes

Patients with EV do not present changes in humoral immunity, with normal antibody production (Jablonska and Majewski 1994). Their Langerhans cells have a normal alloantigen presentation capacity, as well as NK cell activity (Jablonska and Majewski 1994).

Due to the rarity of this disease, immunological evaluations in patients with EV are poorly available and often inconsistent (de Jong et al. 2018). Deficiencies in cellular immunity have been reported, including low T cell ratios of CD4+/CD8+, unresponsiveness to mitogen T-cell, anergy to skin antigens and sensitization to dinitrochlorobenzene (de Oliveira et al. 2003; Majewski and Jablonska 1997a; Glinski et al. 1976; Prawer et al. 1977).

The presence of mutation in genes *TMC6/EVER1* and*TMC8/EVER2* seems not to reduce its expression in lymphocytes and in skin (Lazarczyk et al. 2008). Its role is probably related to intrinsic immunity of the skin, restricting viral replication and genetic expression of beta-HPV in keratinocytes (de Jong et al. 2018). The EVER1 and EVER2 proteins interact with ZnT-1 zinc transporter, influencing the concentration of intracellular Zn2C and thus the activity of transcription factors, such as AP-1, a key activator in the HPV life cycle and cellular proliferation (de Jong et al. 2018; Lazarczyk et al. 2008). There is a hypothesis that EVER2 influences response to TNF-α promoting apoptosis, rather than NF-kB activation (nuclear factor kappa B) and pro-survival signaling pathways (Vuillier et al. 2014; Gaud et al. 2013).

Diagnosis

According to Majewski et al. (Majewski et al. 1997), the diagnosis of EV is based on the association of the following findings: presence of characteristic skin changes (flat warts on the dorsal aspect of hands and limbs, lesions similar to pityriasis versicolor and seborrheic keratoses on trunk); beginning of injuries in early childhood; and in some cases, family occurrence and consanguinity of the parents; the presence of cutaneous lesions and their slow progression; the absence involvement of mucosa and lymph nodes, good general condition and absences of subjective complaints; transformation of some malignant lesions, generally in the third and fourth decade of life, especially in sun-exposed areas of face and areas of trauma; and anatomopathological examination confirming the clinical findings, besides the identification of HPV-EV.

Treatment

There is no specific treatment for EV and the lesions are resistant to the therapies employed, limiting their use (Jablonska and Majewski 1994; Majewski et al. 1997). Due to the widespread distribution of lesions and the progressive development of multiple skin cancers, the treatment of this disease becomes a real challenge.

Surgical removal is indicated for localized skin tumors. Some authors have suggested the use of systemic and topical retinoids, interferon, 5-fluorouracil (5-FU), 5-aminolevulinic acid (ALA) and imiquimod as therapeutic options (Majewski et al. 1997; Gewirtzman et al. 2008).

HPV infection is characterized by epithelial hyperplasia and retinoids have an antiproliferative effect, by controlling the differentiation of epithelial cells (Anadolu et al. 2001). This beneficial effect of retinoids may result from modification of terminal differentiation, direct antiviral action or enhancement of NK cells (Craven and Griffiths 1996; Lippman et al. 1988). Despite good results, the effects of retinoids are reversible after their discontinuation (Majewski et al. 1997; Anadolu et al. 2001).

Interferons are glycoproteins produced by the immune system in response to viral infections (Anadolu et al. 2001). In addition to the antiviral effect, interferon can inhibit the growth of neoplastic cells, promote cell differentiation and stimulate NK cells (Majewski and Jablonska 1995; Anadolu et al. 2001). Some authors suggest that its efficiency in the treatment of EV depends on an intact immune system (Weber et al. 1994). Its combined use with retinoids presented better results when compared to monotherapy (Anadolu et al. 2001; Weber et al. 1994).

The 5-FU acts by inhibiting DNA synthesis. Its effectiveness is associated with the inflammatory activity it causes. The application of 5-FU ointment may be useful in the treatment of actinic keratoses effects of EV but does not prevent the appearance of malignant lesions (Majewski and Jablonska 1997b).

Topical photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) has shown good results for the treatment of superficial skin tumors, such as basal cell carcinoma, actinic keratosis and Bowen's disease, and proliferative skin diseases such as psoriasis and condyloma acuminatum (Kennedy et al. 1990; Szeimies et al. 1996; Boehncke et al. 1994; Frank and Bos 1996). The use of PDT in HPV infections is due to its anti-inflammatory and anti-proliferative abilities (Rossi et al. 2009), however, it is known that PDT is not able to reduce viral load in normal tissues (Karrer et al. 1999). The use of ALA leads to a photosensitization of the proliferating tissue. The subsequent application of radiation, using a light which wavelength corresponds to the absorption bands of the synthesized porphyrins, results in cell death through the generation of reactive oxygen species, in particular, oxygen "singlet" (Kennedy et al. 1990; Szeimies et al. 1996). Although some authors describe good results of ALA-PDT in EV, their use is still considered experimental (Karrer et al. 1999; Sunohara et al. 2012).

Imiquimod is a synthetic agonist of "toll-like" 7 receptor, with a low molecular weight, which allows its topical use (Alessi et al. 2009). It acts by stimulating both innate and cellular immunity, through the production of cytokines and stimulates the development of a cellular immune response mediated by Th1 lymphocytes (Alessi et al. 2009). Its use in 5% cream has already been approved for the treatment of anogenital warts, actinic keratoses and superficial basal cell carcinoma (Alessi et al. 2009; Schulze et al. 2005). Imiquimod also has proven effective in the treatment of "in situ" SCC, but its use with EV patients have shown variable results (Berthelot et al. 2007; Glinski et al. 1976; Alessi et al. 2009; Heratizadeh et al. 2010). Some authors suggest its use in cutaneous field cancerization, which represented by extensive area of actinic damage and epidermal dysplasia, which occurs mainly in the forehead of patients with EV (Heratizadeh et al. 2010).

Despite the various treatment options, no therapy in EV is definitive (Shruti et al. 2017). The sun protection is still the preventive measure with greater effectiveness and should be started at a young age for the prevention of cancers associated with EV (Majewski and Jablonska 1995; Berthelot et al. 2007).

Conclusion

EV was the first disease to correlate skin cancer and viral infection, being a model of study of viral oncogenesis. Although the role of beta-HPV in SCC in EV patients is well established, much remains unknown about the biological mechanisms by which the virus induces cutaneous oncogenesis. Beta-HPV infection appears to play a role at an early phase of carcinogenesis, which requires a synergistic action of UV radiation for development of skin tumors. Further research about this molecular pathway is still needed and could provide the foundation for preventive actions to reduce the impact of carcinogenesis related to beta-HPV infection in the population at risk.

Abbreviations

5-FU: 5-fluorouracil; AIDS: Acquired immunodeficiency syndrome; AK: Actinic keratoses; ALA: 5-aminolevulinic acid; BAK: BCL2-antagonist/ killer; CCL20: Chemokine CC motif 20 ligand; CIB1: Calcium - and integrin-binding protein-1; DNA: Deoxyribonucleic acid; E6-AP: E6-associated protein-dependent; EV: Epidermodysplasia verruciformis; *EVER*: Epidermodysplasia verruciformis enhancing region; HPV: Human papillomavirus; hTERT: Human telomerase transcriptase; IARC: International Agency for Research on Cancer; LCR: Long control region; NF-kB: Nuclear factor kappa B; NK: Natural killer; ORF: Open read frames; PDT: Photodynamic therapy; pRb: Retinoblastoma proteins; RT: Radiotherapy; SCC: Squamous cell carcinoma; SK: Seborrheic keratosis; TGF-β: Beta-1 transforming growth factor; TMC: Transmembrane channels-like; TNF- α: Tumor necrosis factor alpha; USA: United States of America; UV: Ultraviolet; VLP: Virus-like particles; XRCC1: X- ray repair cross complementing protein-1; ZnT-1: Transporter-1 of zinc

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Authors' contributions

LLCS drafted the manuscript. WRPO and MNS revised it critically for important intellectual content. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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