

**A REVIEW ON EPIDERMODYSPLASIA VERRUCIFORMIS (EV)**

**D. Lakshman Chaturvedhi\*, B. Prasanna Kumar, U. Sai Prasad, K. Chandra Sekhar,  
A. Rajasekhar, S. K. Abdul Rakeeb and P. Lakshmi Deepak**

Nalanda Institute of Pharmaceutical Sciences, Kantepudi, Sattenapalli, Guntur District.

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**\*Corresponding Author****D. Lakshman Chaturvedhi**

Nalanda Institute of  
Pharmaceutical Sciences,  
Kantepudi, Sattenapalli,  
Guntur District.

**ABSTRACT**

Epidermodysplasia verruciformis (EV), also known as Tree man syndrome, is extremely a rare autosomal recessive hereditary skin disorder. It is associated with high risk of cancer. It is a rare Genodermatosis characterized by a unique susceptibility to cutaneous infection by a group of phylogenetically related human papilloma virus (HPVs). These patients show a defect in cell mediated immunity towards HPVs leads to lifelong disease. The resulting uncontrolled HPV infections result in the growth of scaly macules and papules, with plane warts, pityriasis versicolor like lesions and reddish verrucous plaques mainly on hand and feet.

**KEYWORDS:** Epidermodysplasia verruciformis, Pityriasis versicolor, Genodermatosis, Verrucous plaques.

**INTRODUCTION**

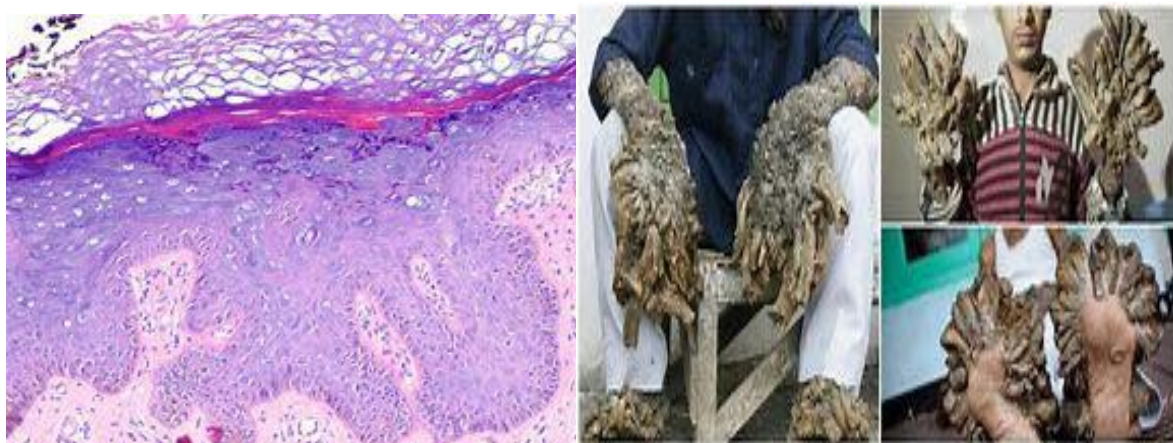
Epidermodysplasia verruciformis (EV) was first introduced by Lewandowski and lutz in 1922.<sup>[1]</sup> It is characterized by an extreme susceptibility to certain human papilloma virus.<sup>[2]</sup> It is typically associated with HPV types 5 and 8 (among- 4, 5a, 5b, 8, 9, 12, 14, 17, 19-25, 36-38, 47).

Mutations in family of genes called EVER genes.<sup>[3]</sup> Due to mutations in the EVER genes which is caused due to HPVs there is an abnormal deposition of zinc and abnormalities in growth of the tissues such as macules and papules like structures generally seen on face, mainly on forelimbs and hindlimbs.

Research has shown genetically deficiencies in cutaneous immunity leave patients vulnerable to HPV infection. It is typically associated with HPV types 5 and 8, which are found in about

80% of the normal people as asymptomatic infections. The condition usually has an onset of age between 1 and 20 but can occasionally present in middle age. The condition is known as Lewandowsky-Lutz<sup>[1]</sup> dysplasia named after the physicians who first diagnosed.

The other type of genes has also rarely been associated with this condition. These include the ras homolog gene family member H (Human RHOH deficiency causes T cell defects and susceptibility to EV-HPV infection).<sup>[4]</sup>



## EPIDEMIOLOGY

The prevalence of Epidermodysplasia verruciformis (EV) is not known. A total of **501** patients have been described worldwide, most cases are sporadic, but there are several reports of family cases.

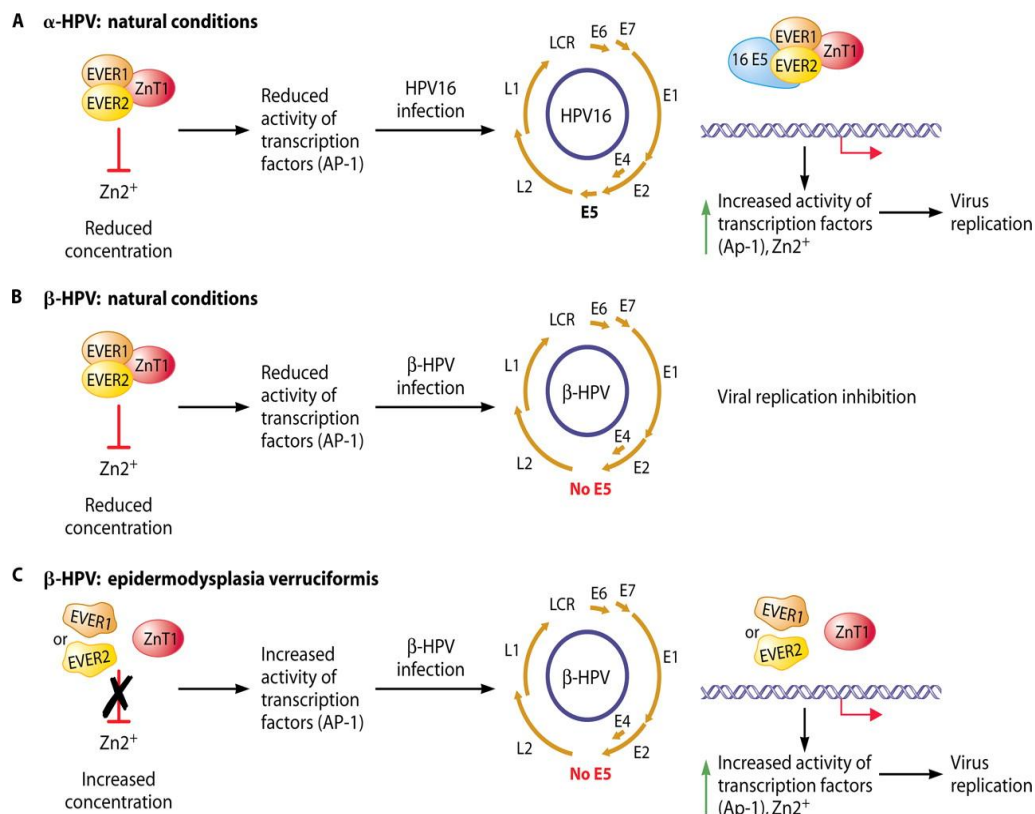
## ETIOLOGY

- Congenital.
- Abnormal susceptibility to clinical HPV infection, which only causes asymptomatic infection in 80% of normal population.
- Congenital cases are usually autosomal dominant, autosomal recessive, rarely X linked recessive.
- Usually HPV 5 or 8, less commonly 3, 4, 51.
- Congenital cases are due to mutation that inactivates EVER1 and EVER2 which are located adjacent to chromosome 17.<sup>[5]</sup>
- Ultra violet radiation (UVR) is associated with an increased risk of squamous cell carcinoma.

## PATHOPHYSIOLOGY

Mutations in the EVER1 or EVER2 genes, probably also known as TMC6 and TMC8 genes respectively....

- Under Normal conditions, these two genes code for membrane proteins which interacts with a zinc transporter protein (**ZnT-1**) in Endoplasmic reticulum<sup>[6]</sup> of skin cells known as Keratinocytes which are susceptible to HPV infection.<sup>[6]</sup>
- The exact mechanism of mutations of the EVER1 and EVER2 genes are unknown.
- The most acceptable hypothesis was that intracellular equilibrium in Zn levels catalyzed by EVER + Zn proteins complexes may inhibit HPV expression (or) that they may play a direct role in immune response to HPV infection.
- Mutations in other genes (RHOH, MST1 and LCK) lead to abnormalities in receptors and cells of T-lymphocytes.<sup>[4]</sup>



▪ The genetic mutations may be as follows

- a) Autosomal dominant.
- b) Autosomal recessive.
- c) X-linked inheritance.

**a) Autosomal dominant**

- These traits or disorders that are present only one copy of mutation on Non-sex chromosome.
- Under these conditions, the individual has one normal copy and one mutant copy of genes.<sup>[7]</sup>
- The abnormal genes dominate the effect of normal functioning gene.
- The chance of passing the abnormal genes to their offspring's is 50%.
- Children's who do not get their parents genes, they act as a carrier to their offspring's. Generally, these conditions are known as SKIP GENERATION INHERITANCE.

**b) Autosomal recessive**

- These traits or disorders that occurs when two copies of an abnormal gene have been inherited on a non-sex chromosome.<sup>[7]</sup>
- If both the parents have an autosomal recessive condition, there is a 100% chance of passing the mutated gene to their children, but only one mutated copy of the gene is inherited, the individual will be a carrier of the condition, but with no symptoms.
- Children's who born to two carries, have 25% chance of being to be homozygous dominant (unaffected), a 50% chance of being heterozygous (carrier), and a 25% chance of being homozygous recessive (affected).

**c) X-linked inheritance**

- These traits or disorders that occur when two copies of an abnormal gene are inherited on sex chromosome (X and Y chromosomes).<sup>[7]</sup>
- All the X-linked recessive traits are fully evident in males, because they have only one copy of X chromosome.
- All males who are affected will pass the mutated gene to their female offspring's because they must inherit one copy of X chromosome from each parent.
- This means that they will be unaffected carriers.
- Females are rarely affected by X-linked recessive disorder because they have two copies of X chromosomes.

**SIGNS AND SYMPTOMS**

\* The common signs and symptoms include

\*Formation of wart like lesions, in the form of **papules** (small raised, tender bumps on skin) and **macules** (an area of skin discoloration).

\*The formation of lesions on several parts of body include

- Arms and legs.
- Hands and feet.
- Head and neck region may also include chin, earlobes.
- Palms and soles.<sup>[8]</sup>
- Trunk region like chest, back, abdomen.
- External genitals.

\*These all lesions are formed together an unorganized, asymmetrical and rough appearance of skin<sup>[8]</sup>, thus earning Epidermodysplasia verruciformis.

### **RISK FACTORS (predisposing factors)**

- Family history.
- HIV infection.
- Usage of IMMUNO SUPPRESSANT drugs.
- Lymphoma (lymphatic cancer).
- Risk for development of cutaneous malignancies.<sup>[9]</sup>

NOTE- Having the one of the following risk factors doesn't mean that u will definitely affect with EV but, these risk factors may increase the chance of effecting with EV.

### **COMPLICATIONS**

The main possible complications include,

- Transformation of skin lesions to cancer especially **squamous cell carcinoma**<sup>[10]</sup> (or) **intra epidermal carcinoma**, which have a chance of approximately 30-60% of every effected individual.
- The transformation mainly seen in individual having an age group of 30-50 years.
- In advanced stages **metastatic carcinoma** may occurs but it is generally rare, if in case metastatic condition occurs that condition may be worse and turns to fatal.
- **Subungual Bowen disease**<sup>[11]</sup> (often with benign lesions such as fungal infection, onychomycosis).
- Rare **palmar pit**<sup>[12]</sup>-like lesions (pit like lesions shows Hyperkeratosis, acanthosis with prominent vacuolar degradation in granular layer and scattered large atypical nuclei).
- Sometimes epidermodysplasia verruciformis may be misdiagnosed as **Pityriasis versicolor**.<sup>[13]</sup>

## DIAGNOSIS

- Physical examination.
- By evaluating family medical history.
- **BIOPSY** of the lesions to check
  - Acanthosis (Dark patches).
  - Hyperkeratosis (Thickening of the outer skin layer).
  - Hypergranulosis (Granular cells of the skin).
- **IN-SITU HYBRADIZATION** to check for HPV viral particles. This can be done by using a probe to identify the nucleic acid material of HPV in skin sample.<sup>[14]</sup>
- **IMMUNO HISTOCHEMICAL ANALYSIS** – This is a process in which an anti HPV antibody is used to bind the virus in the sample, which is then finally visualized with a microscope.
- Many other tests can be performed to rule out the other clinical conditions to arrive at a definitive diagnosis.

## TREATMENT

The treatment of EV include

### 1. Oral (systemic) and topical rotenoids, such as ALDARA and ZYCLARA.

- For **EXTERNAL GENITAL WARTS**

**ZYCLARA 3.75%** -Apply as thin film

**ALDARA 5%** - Apply three times a week for maximum of 16 weeks.<sup>[15]</sup>

- For **SUPERFICIAL BASAL CELL CARCINOMA**

**ALDARA 5%** - Apply 5 times a week used for several weeks.<sup>[16]</sup>

- For **ACTINIC KERATOSIS**

**ZYCLARA 2.5% or 3.75%**- Apply directly on affected area.

**ALDARA 5%** - Apply two times a week for several weeks.<sup>[17]</sup>

### 2. 5-FLUORO URACIL

- **ADRACIL – 50mg in 1ml.**

Dosage form- injection or cream.

- **CARAX – 5mg in 1ml.**

Dosage form- Cream.

- **EFUDEX**
- **EFUDIX**

### **3. SYSTEMIC RETEINIDS**

- First Generation Drugs.

#### **RETINOL**

**ISOTRETINOIN-** 1-2mg/kg/day.<sup>[18]</sup>

- Second Generation Drugs.

#### **ETRETINATE**

**ACITRETIN-**10mg, 1705mg, 25mg per month.

- Third Generation Drugs.

**ADAPALANE-** Topical gel 0.1% or 0.3% (OTC).

Topical lotion 0.1% (RX).

Topical cream 0.1% (RX).<sup>[19]</sup>

#### **BEXAROTENE**

#### **TARAZOROTENE**

### **4. INTERFERON ALPHA (2b)**

Injectables →6 million IU/ml (3.8ml vial).

Powder for injection →10 million units/vial.<sup>[20]</sup>

### **5. AMINO LEVULINIC ACID**

Lyophilized powder for oral solution-30mg/ml (after reconstitution).<sup>[21]</sup>

- 6. CRYOSURGERY** – This is the technique of removing the undesirable growth by using highly cold liquid nitrogen.<sup>[22]</sup>

- 7. LASER ABLATION** -- Technique of vaporizing the unwanted tissue by using laser.



**PREVENTION**

- In case any family history, then counselling them before planning for children.
- Individual with EV must avoid exposing to sunlight which leads to radiation of (UVA and UVB) may worsen the condition by transforming the lesions to cancers.
- Regular medical screening tests with in a periodic interval are strongly recommended.

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