

# Research in Pharmacy and Health Sciences

## Review Article

### Epidermodysplasia Verruciformis: A Dreadful Disease

Tarun Virmani\*, Virmani Reshu, Tanwar Rohit, Chhabra Vaishnavi

School of Pharmaceutical sciences, MVN university, Palwal, Haryana, India

#### ABSTRACT

Epidermodysplasia Verruciformis or tree man illness disease is extremely dreadful, rare and genetic hereditary skin disorder. Disease usually begins in infancy or early childhood, with the development of various types of flat, wart like lesions and confluent plaques on the skin. Various types of treatment were reported by various researchers for the treatment of Tree man illness disease, but very few were on the contra indicatory part. However, if the epidermodysplasia verruciformis has already progressed into a carcinoma that is invasive in nature, then a surgical excision may be necessary to prevent further problems.

**Received:** 13-1-2017

**Revised:** 29-1-2017

**Accepted:** 27-02-2017

**\*Correspondence to:**

**Tarun Virmani,**

**Email:**

*tarun.virmani@mvn.edu.in*

**Funding:** Nil

**Competing Interests:**

None

**Keywords:** Epidermodysplasia verruciformis (EV), Tree Man illness, carcinoma, HIV

#### INTRODUCTION:

Epidermodysplasia verruciformis is extremely rare in nature and it is an autosomal recessive genetic [1] hereditary skin disorder associated with a high risk of carcinoma of the skin. This is also known as Lutz-Lewandowsky Epidermodysplasia verruciformis or Lewandowsky – Lutz dysplasia (named after the physicians who first documented it [2], Felix Lewandowsky Lewandowsky Wilhelm Lutz de) or commonly as tree man illness. Tree man disease usually begins in infancy or early childhood, with the development of various types of flat, wart like lesions and confluent plaques on the skin. Patients may also

The resulting uncontrolled HPV infections result in the growth of scaly macules and papules, particularly on the hands and feet. It is typically associated with HPV types 5 and 8 [4], which are found in about 80% of the normal population as asymptomatic infections [5], although other types may also contribute. [6]

#### SIGNS AND SYMPTOMS

Common signs and symptoms are lesions that resemble the appearance of warts, extensive skin outbreak that are even to papillomatous in nature and reddish to brownish pigmented plaques located various parts of body. It is also isolated and localized in one area and has papule like wart appearance which resembles that of psoriasis. In other cases there

develop tinea versicolor \_like lesions on the trunk. These lesions may progress to form verrucous plaques and nodules, or they may transform into invasive squamous cell carcinomas, most commonly between the ages of 20 and 40 years. It is particularly an autosomal recessive genetic disorder and the patients who inherited the disease are products of marriages that are consanguineous. Other cases are sporadic, autosomal dominant and sex-linked transmission. The conditions is characterized by development of cutaneous squamous cell carcinomas and multiple types of Human papilloma virus or HPV – which will likely happen in ages 20 – 40 years old [3].

are white spots which resembles tinea and pityriasis versicolor (pale rash caused by a yeast like germ) in the trunk area. Patients present with flat, slightly scaly, red-brown macules on the face, neck, and body, recurring especially around the penial area, or verruca-like papillomatous lesions, seborrheic keratosis-like lesions, and pinkish-red plane papules on the hands, upper and lower extremities, and face in the early stages whereas the malignant form shows a higher rate of polymorphic skin lesions and development of multiple cutaneous tumors. [7, 8] Thus the extreme symptoms are

1. Thick visible warts all over the body as well as on the inside of the skin.
2. The skin becomes thick and hardened and as old skin dies new skin is created.

3. The hands and feet, the extremities, are enlarged and it is difficult to use them.  
4. Hands and feet have been described as looking like contorted, yellow-brown branches extending up to 3 feet. Skin looks like tree bark or tree roots, hence the name Tree-Man Disease or Tree-Man Syndrome (TMS).

### TYPES OF EPIDERMODYSPLASIA VERRUCIFORMIS LESIONS:

Generally epidermodysplasia verruciformis is of two types-

**a. Flat types:** The first type includes flat or even lesion with flat-topped papules, resembles like a wart and verruca plana with rough surfaces and hypo or hyper pigmented elongated patches. Small patches may fuse or come together to form prominent, large patches with irregular borders and reddish to brownish color.

**b. Seborrhic-like or verrucous types:** This type mostly resembles like as wart. The wounds usually form a linear column in sun exposed areas of the body, such as the upper and lower extremities, neck, face and even the earlobes. The lesions also appear in areas like the soles of the feet, the genital area as well as the axillae or the underarm area. Infrequent locations are the moist parts of the body such as the oral mucosa and conjunctivae.

### Causes

Epidermodysplasia verruciformis-associated HPV's can be divided into 2 groups.

- One group has more prone to oncogenic potential (HPV types 5, 8, 10, and 47). More than 90% of epidermodysplasia verruciformis-associated skin cancers contain these HPV virus types.
- The other group has low oncogenic potential (HPV types 14, 20, 21, and 25). These types are usually detected in benign skin lesions.

### Proposed mechanisms for the development of epidermodysplasia verruciformis include the following:

An highly autosomal recessive mode of genetic inheritance is supported by the way that few percentage usually about 10% of patients with epidermodysplasia verruciformis are offspring of consanguineous marriages. X-linked inheritance has

rarely been reported [9]. A clear mode of genetic inheritance is not evident in all cases.

- Pathogenic mutations in 2 adjacent position located in the genes, *EVER1* and *EVER2*, have been identified[10,11].
- Major histocompatibility complex (MHC) class II alleles (DR-DQ) have been found in a large series of patients with epidermodysplasia verruciformis from Europe, Africa, America and other parts of the country.
- Neither chromosomal abnormalities nor the relationship to any specific major histocompatibility class I antigens has been found in patients with epidermodysplasia verruciformis.
- The exact replicate method involved in the keratinocytic transformation within epidermodysplasia verruciformis skin lesions is not having much information about the same. Transcripts of the early region of viral genomes (E6 and E7 gene proteins) have been detected in epidermodysplasia verruciformis tumors. However, in most of the cases associated with cells involved in formation of cancer causing cells i.e carcinomas, viral sequences are not integrated into the host genome.
- Studies have shown that various interactions occur between oncogenic HPV's and the antioncogene products, p53 and pRb, in cell cycle regulation, DNA repair, and the execution of programmed cell death (apoptosis). A decrease in UV-induced DNA repair synthesis, coupled with antioncogenic viral infection, further enhances the disposition for somatic mutations and malignant transformation in patients with epidermodysplasia verruciformis.
- A specific defect of cell-mediated immunity, manifested by the inhibition of natural cytotoxicity and the proliferation of T lymphocytes against HPV-infected squamous cells in epidermodysplasia verruciformis skin lesions, is a characteristic feature of tree man illness.
- Sun-exposure coupled with immunologic defects in patients with the dreadful disease i.e epidermodysplasia verruciformis is likely to induce sudden change in the genetic makeup of the tumor suppressor gene protein (p53), leading to the development of malignant skin cancer in adult patients.
- UV-B-induced local immunosuppression on the skin of patients with epidermodysplasia verruciformis is known to be related to

overproduction of immunosuppressive cytokines, such as tumor necrosis factor-alpha (TNF-a), transforming growth factor-beta (TGF-b), interleukin 4, and interleukin 10, as well as excessive formation of *cis*-urocanic acid.

- The activity of beta islets of Langerhans cell antigen presentation appears normal in epidermodysplasia verruciformis, thus suggesting other cells cause immune tolerance to epidermodysplasia verruciformis-associated HPVs.
- Lesions of epidermodysplasia verruciformis have been associated with common variable immunodeficiency and graft versus host disease.[12]

### Differential Diagnosis and Tests:

*The diagnosis of epidermodysplasia verruciformis should be initiated upon the appearance of verrucous (rough, wart-like) lesions and when the condition is not relieved by the administration of a treatment regimen.*

### Treatment of EV Disease:

The warts can be surgically removed; however, they do grow back. Direct radiation therapy to control the growth has led to cancer in one patient, Ivan. The symptoms can be alleviated by taking vitamins and anti-viral medication. Scientists and doctors such as Dr. Anthony Gaspari, an American dermatologist from the University of Maryland, are currently studying three cases of Tree-Man Disease in the hope of finding a genetic link that will lead to a cure of this disease. No specific treatment against Tree man illness has been found yet. Several treatments have been suggested, however, most importantly, education of the patient, early diagnosis, and excision of the tumoral lesions take preference to prevent the development of cutaneous tumors. Once this type of growth of cells is detected, treatment is mainly designed based on the rate and extent of disease. Localized cells growth of carcinoma can be removed surgically, but the extensive, nonmalignant lesions need a more practical therapy. Review of literature suggest various treatment approaches against the dreadful disease-

- Anadolu et al reported that retinoids is used for their endogenous antiproliferative effect through the better control of epithelial cell differentiation. A case was presented by author that was treated with a combination of acitretin and interferon alfa2a for ninety days with marked improvement. Though the wounds appeared again after discontinuation of

treatment, the patient restarted combination therapy for 4 months, followed by acitretin alone for 3 months [13].

- A 25 year old woman with a daily dose of 0.5–1 mg/kg/day acitretin for a period of almost half year improved skin features like lesions slightly is reported. However, upon discontinuation of treatment, the lesions returned, and the patient declined further treatment [14].
- An another case was reported in which pegylated interferon alfa2b and acitretin was given to a 43 year old female with multiple squamous cell carcinomas in the oral and genital mucosa and widespread verrucous lesions. The patient saw a marked reduction of flat warts and no recurrence of cancer during treatment [15].
- Hayashi et al. treated a patient with intolerable retinoid side effects with topical tacalcitol, a vitamin D analog. Not only did the largest lesion regress within six months of therapy, but it also prevented new carcinomas over the following three years [16].
- Other therapies include cimetidine (a histamine type 2 receptor antagonist), which has demonstrated immune modulating properties. It has been used in a dose of 40 mg/kg per day to treat planar, plantar, and common warts in patients not responding to other therapies. The patient demonstrated a marked improvement after 3 months of therapy, with no relapse at a 6 month follow up [17]. But de Oliveira et al. used the same treatment regimen in eight EV patients with contra indicatory results [18].
- Berthelot et al. described a patient with EV and a novel homozygous gene mutation of an EVER2 gene that was treated successfully with topical imiquimod application for 5 days/week for 3 months [19]. Imiquimod is a topical immune modulator that is usually used for common and genital warts, as well as squamous cell carcinoma and Bowen's disease.
- This topical therapeutic result was also used along with systemic interferon therapy in an EV patient with Bowen's disease and actinic keratoses [20].
- In a novel therapy, Karrer et al. performed photo dynamic therapy (PDT) using a 20% 5 –Amino laevulinic acid ointment applied for 6 h to the lesions and irradiating using an incoherent light source (wavelength approximately in the visible region 580–740 nm, 160 mW/cm<sup>2</sup>, 160 J/cm<sup>2</sup>). Following PDT, blistering and crusting of the lesions occurred, but these healed completely within 2–3 weeks without scarring, and the cosmetic result was excellent. Six months after PDT a skin biopsy was taken. In situ hybridization was positive for HPV type 8 in skin, which was clinically and histologically normal. Twelve months after PDT, a few lesions had recurred on the hands. The authors conceded that though permanent cure of EV cannot be achieved by any therapy at present and single lesions continued to

appear in this patient, annual PDT might result in better control of HPV induced lesions [21].

- Though traditional therapies such as cidofovir may be effective against other papilloma virus associated conditions, it has been unsuccessful in treating an EV patient with multiple cutaneous lesions [22].
- Treatment in epidermodysplasia verruciformis patients with concurrent HIV infection requires specialized attention as several studies have shown most treatments to be ineffective. Topical imiquimod in two HIV positive half brothers did not show improvement [23].
- Davison et al. tried imiquimod, 5-fluorouracil, and isotretinoin, all without success [24]. The effects of highly active antiretroviral therapy (HAART therapy) in the improvement of EV disease states have not been clearly defined. One group found it to have no effect [25], while Haas et al. reported a patient being treated with highly active antiretroviral therapy who experienced improvement of EV lesions [26].

### **SURGICAL INTERVENTION**

The surgical intervention that may be performed for isolated carcinomas is the auto transplantation of skin from unaffected areas. This method has shown promising results in prevention of further carcinomas. In addition, employment of cryo probes to remove benign lesions on the skin, as well as grafting of the skin from areas of lesser or no exposure to the sun, may also be utilized. However, if the epidermodysplasia verruciformis has already progressed into a carcinoma that is invasive in nature, then a surgical excision may be necessary to prevent further problems.

### **SUPPORTIVE CARE AND/OR PREVENTIVE APPROACH**

The medical management of epidermodysplasia verruciformis does not guarantee full resolution of the disorder, as one lesion removed may only recur along the course of the patient's life. Thus, the medical management of the condition is primarily directed to a preventive approach such as-

- Avoidance of oncogenic factors, like UV lights A and B; and X-ray radiation among others.
- The health care provider should provide patient counseling and education, and counseling to the patient's significant others as well.
- The use of sun block or sun protection may also be necessary as a defense from the sun's harmful UV rays.

- Assistance to the patient in maintaining good hygiene should also be provided.
- A balanced healthy diet coupled with fresh fruits and vegetables should also be observed, as this may be beneficial to the patient's skin health, as well as overall health.

### **REFERENCES**

1. Ramoz N, Rueda LA, Bouadjar B, Montoya LS, Orth G, Favre M. Mutations in two adjacent novel genes are associated with epidermodysplasia verruciformis. *Nature Genetics* 2002; 32 (4): 579–81.
2. Lewandowsky F and L.W. A case of a previously undescribed skin disease (epidermodysplasia verruciformis) [in German]. *Arch Dermatol Syphilol.* (141): 193–203
3. Lazarczyk M, Pons C, Mendoza JA, Cassonnet P, Jacob Y, Favre M. Regulation of cellular zinc balance as a potential mechanism of EVER-mediated protection against pathogenesis by cutaneous oncogenic human papillomaviruses. *The Journal of Experimental Medicine* 2008; 205 (1): 35–42.
4. Orth G (1986). "Epidermodysplasia verruciformis: a model for understanding the oncogenicity of human papillomaviruses". *Ciba Foundation Symposium.* 120: 157–74. PMID 3013521.
5. Antonsson A, Forslund O, Ekberg H, Sterner G, Hansson BG. The ubiquity and impressive genomic diversity of human skin papillomaviruses suggest a commensalic nature of these viruses. *Journal of Virology* 2000; 74 (24): 11636–41.
6. Gül U, Kiliç A, Gönül M, Cakmak SK, Bayis SS. Clinical aspects of epidermodysplasia verruciformis and review of the literature. *International Journal of Dermatology* 2007; 46 (10): 1069–72.
7. Lowy DR, Androphy EJ. "Warts". In *Freedberg IM, Eisen AZ, Wolff K, et al. Fitzpatrick's Dermatology in General Medicine.* Ed 6. McGraw-Hill. New York City 2003 pp. 2119–2131.
8. Pereira de Oliveira WR, Carrasco S, Neto CF, Rady P, Tyring SK. Nonspecific cell-mediated immunity in patients with epidermodysplasia verruciformis HPV. *The Journal of Dermatology* 2003; 30 (3): 203–9.
9. Androphy EJ, Dvoretzky I, Lowy DR. X-linked inheritance of epidermodysplasia verruciformis. *Genetic and virologic studies*

- of a kindred. *Arch Dermatol.* 1985 Jul. 121(7):864-8.
10. Gober MD, Rady PL, He Q, Tucker SB, Tying SK, Gaspari AA. Novel homozygous frameshift mutation of EVER1 gene in an epidermodysplasia verruciformis patient. *J Invest Dermatol* 2007; Apr. 127(4):817-20.
  11. Sun XK, Chen JF, Xu AE. A homozygous nonsense mutation in the EVER2 gene leads to epidermodysplasia verruciformis. *Clin Exp Dermatol* 2005; Sep. 30(5):573-4.
  12. Li SL, Duo LN, Wang HJ, Dai W, Zhou EH, Xu YN, et al. Identification of the LCK mutation in an atypical epidermodysplasia verruciformis family with T cell defects and virus-induced squamous cell carcinoma. *Br J Dermatol* 2016; Apr 18.
  13. Anadolu R et al. Treatment of epidermodysplasia verruciformis with a combination of acitretin and interferon alfa2a. *J Am Acad Dermatol* 2001; 45(2): 296–299.
  14. Iraj F and Faghihi G. Epidermodysplasia verruciformis: association with isolated IgM deficiency and response to treatment with acitretin. *Clin Exp Dermatol* 2000; 25(1): 41–43.
  15. Gubinelli E et al. Epidermodysplasia verruciformis with multiple mucosal carcinomas treated with pegylated interferon alfa and acitretin. *J Dermatolog Treat* 2003; 14(3): 184–188.
  16. Hayashi J et al. Treatment of localized epidermodysplasia verruciformis with tacalcitol ointment. *Int J Dermatol* 2002; 41(11): 817–820.
  17. Micali G et al. Cimetidine therapy for epidermodysplasia verruciformis. *J Am Acad Dermatol* 2003; 48(2 Suppl): S9– S10.
  18. de Oliveira WR, Neto CF and Rivitti EA. The lack of a clinical effect of cimetidine in the treatment of epidermodysplasia verruciformis. *J Am Acad Dermatol* 2004; 50(6): e14;author reply e15.
  19. Berthelot C et al. Treatment of a patient with epidermodysplasia verruciformis carrying a novel EVER2 mutation with imiquimod. *J Am Acad Dermatol* 2007; 56(5): 882–886.
  20. Baskan EB et al. A case of epidermodysplasia verruciformis associated with squamous cell carcinoma and Bowen's disease: a therapeutic challenge. *J Dermatolog Treat* 2006; 17(3): 179–183.
  21. Karrer S et al. Epidermodysplasia verruciformis treated using topical 5aminolaevulinic acid photodynamic therapy. *Br J Dermatol* 1999; 140(5): 935–938.
  22. Preiser W et al. No apparent effect of cidofovir in epidermodysplasia verruciformis. *J Clin Virol* 2000; 16(1): 55–57.
  23. Hu W et al. Epidermodysplasia verruciformis in two half brothers with HIV infection. *J Cutan Med Surg* 2004; 8(5): 357–360.
  24. Davison SC et al. Epidermodysplasia verruciformislike eruption associated with HIV infection. *Clin Exp Dermatol* 2004; 29(3): 311–312.
  25. Carre D et al. Epidermodysplasia verruciformis in a patient with HIV infection: no response to highly active antiretroviral therapy. *Int J Dermatol* 2003; 42(4): 296–300.
  26. Haas N et al. Remission of epidermodysplasia verruciformis like skin eruption after highly active antiretroviral therapy in a human immunodeficiency virus positive patient. *Br J Dermatol* 2001; 145(4): 669–670.