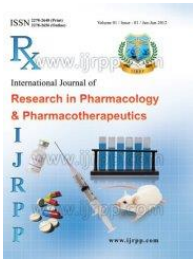
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 IJRPP |Vol.11 | Issue 2 | Apr - Jun - 2022
ISSN Online: 2278-2656 Journal Home Page: www.ijrpp.com

Case Study Open Access

An Overview of Epidermodysplasia Verruciformis

Gaddam Raghu Goud, Anantha Lakshmi Jakka*, Patha Rasagna, Mantripragada Bhagavan Raju

Sri Venkateswara College of Pharmacy, Madhapur, Hyderabad, Telangana, India

***Corresponding author: Anantha Lakshmi Jakka**

ABSTRACT

Epidermodysplasia Verruciformis (EV), often known as tree man disease, is a frightening, rare, and genetically transmitted skin ailment caused by the human papillomavirus (HPV). It is characterised by the development of a variety of flat, wart-like lesions and confluent plaques on the skin, as well as an increased risk of developing skin cancer. Cancer is primarily caused by the HPV-5 and HPV-8 viruses. Susceptibility to HPV was recently linked to a 1cm area on chromosome 17q25 by a biallelic loss-of-function mutation in either the EVER1/TMC6 or EVER2/TMC8 genes. Histological analysis of the afflicted tissue reveals acanthosis and hyperkeratosis. Amplification of the polymerase chain reaction (PCR) can be performed to detect the virus in lesions. Although there is no cure for EV, symptoms can be reduced with vitamins, antiviral medications, cryotherapy, and surgical excision of lesions.

Keywords: Skin cancer, DNA,

INTRODUCTION

Epidermodysplasia verruciformis (EV) is a rare, life-threatening autosomal dominant genodermatosis caused by the human papilloma virus (HPV). It is an autoimmune disorder (1) that manifests itself through the formation of various forms of flat, wart-like lesions and confluent plaques on the skin, which are connected with an increased risk of skin cancer. This condition is also known as Lutz-Lewandowsky verruciformis epidermodysplasia (2) or, more often, tree man disease (3). The disorder is referred to as genodermatosis due to the fact that it usually runs in families. It frequently results in multifocal neoplastic proliferation, most frequently of the Bowen's carcinoma type, over a period of years (4). EV pathogenesis is complicated by genetic (5), immunological (6), and extrinsic (7,8,9) factors. These people have a hereditary immunological deficiency that predisposes them to papillomavirus infections (10). HPV is susceptible to truncating mutations (biallelic loss-of-function mutations) in either the EVER1 or EVER2 genes (11), which regulate the interaction of epidermal keratinocytes with HPVs

(12). Currently, 86 HPV genotypes have been fully sequenced, with around a fifth of those belonging to the EV-HPV type (13). EV-HPV kinds were discovered initially in lesions on the skin of EV patients (14). While HPV types are detectable in the general population, they are harmful only in EV patients (15). Around 30% of these EV patients acquire skin cancer, most commonly on sun-exposed areas, implying that UV light may act as a cocarcinogen. However, it appears as though only HPV-5 and -8 are strongly related with these skin malignancies (16,17). This condition is most prevalent between the ages of 20 and 40 years and is most prevalent in people who inherited it through consanguineous marriages (3).

Fig 1: Lesions of EV

Epidermodysplasia verruciformis was first reported in 1922 by dermatologists Lewandowsky and Wilhelm Lutz. (18). This syndrome has been recorded in over 50 cases. It is classed as genodermatosis and is characterised by an inherited proclivity for dysplasia of the epidermis's top layer. Epidermodysplasia verruciformis had been documented in 42 cases prior to 1939. Mashikillesion originally reported the first 24 occurrences in 1928 (19), and Sullivan and Ellis collected the remaining 28 cases in a 1939 publication. (20). It's worth mentioning that over 40% of patients with reported cases were Japanese, Russians, or Asians, while the remainder, save for one, were Europeans (21).

Sahana Khatun, 10, may be the first female in the world to be diagnosed with epidermodysplasia verruciformis, a rare hereditary disorder, according to Sky News (a US-based broadcaster). She was sent to a Dhaka hospital with "bark-like warts" on her nose, chin, and ears (22). Ajul Bajandar (25 years old), a Bangladeshi rickshaw driver, has been driving an electric vehicle since he was ten years old. He received free treatment at Dhaka Medical College Hospital, where he underwent surgery to remove more than 5kg of growths from his hands and feet, followed by 24 treatments. However, a relapse happened after a year (23).

EPIDEMOLOGY

The prevalence of epidermodysplasia verruciformis (EV) is unknown. There have been 501 reported cases worldwide; the majorities are sporadic, while there have been numerous reports of familial cases (24). In 2017, a review of the literature indicated that approximately 500 cases of this condition had been identified worldwide (18).

ETIOLOGY

Epidermodysplasia verruciformis (EV) is a condition caused by human papilloma viruses (HPVs) (25). EV-HPV kinds are HPVs related with this disease. When exposed to ultraviolet light, HPV-induced papillomata transformed into carcinomas (26). Two distinct families of EV-HPVs have been found. Which one (HPV types 5, 8, 10, and 47) has a higher risk of developing skin cancer than the others? (HPV types 14, 20, 21, and 25). This disorder has been linked to nonsense mutations (biallelic loss-of-function mutations) in two new genes next to one another, EVER1 and EVER2 (28,29). A case of EV was recently recorded with a remarkable CD8+ T-cell lymphocytopenia (30). EV was recently recognised as an innate immune deficit associated with specific HPV genotypes (31).

RISK FACTORS

Recently, an EV-like syndrome was described in patients with the following conditions: Immunocompromised patients (HIV), Organ transplantation, Lepromatous leprosy, Hodgkin's disease, Systemic lupus erythematosus, Lymphedema, Anogenital dysplasia syndrome (wild syndrome), Immunoglobulin M deficiency, and adult t-cell leukaemia. Biological substances used in treatment.

SIGNS AND SYMPTOMS

Lesions that resemble warts, widespread skin eruptions with papillomatous characteristics, and reddish to brownish pigmented plaques in various locations on the body are all typical indicators and symptoms. In some circumstances, white patches on the trunk resemble tinea and pityriasis versicolor. In the early stages, patients present with flat, slightly scaly, red-brown macules on the face, neck, and body, most frequently 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, whereas the malignant form has a higher rate of polymorphic skin lesions (32,33). HPV type 1 (HPV-1) was identified as a cause of deep, painful plantar warts (34, 35). HPV type 2 (HPV-2) was shown to be more prevalent in common warts (36, 37).

THE EXTREME SYMPTOMS ARE

Thick, stiff, twisted yellow-brown branches reaching up to three feet are visible on the hands and feet. The disease is called Tree-Man Disease or Tree-Man Syndrome (TMS) because to the skin's appearance, which resembles tree bark or tree roots.

TYPES OF EPIDERMODYSPLASIA VERRUCIFORMIS LESIONS

a) Flat lesions: The first form consists of flat or even lesions with flat-topped papules, verruca plana with rough surfaces and hypo- or hyperpigmented elongated regions that resemble warts. Small patches may combine to form large, irregularly edged areas with a reddish to brownish hue.

b) Seborrheic-like or verrucous types: The look of this type is similar to that of a wart. The wounds often form a linear column in sun-exposed areas of the body, such as the upper and lower limbs, neck, face, and even the earlobes. Additionally, lesions can be detected on the soles of the feet, the vaginal region, and the axillae, or underarm area. Infrequently, the moist regions of the body, such as the oral mucosa and conjunctiva, are implicated.

PATHOPHYSIOLOGY

Mutations in two neighbouring locations of the EVER1 and EVER2 genes have been identified as pathogenic (38,39). These genes, which are found on chromosome 17q25, are responsible for EV (40,41). These enzymes regulate the interaction of epidermal keratinocytes with HPVs. Due to frameshift mutations in four amino acid sites of this gene, EVER1 (Arg94 and Glu 576), and EVER2 (Leu283 and Glu362), aberrant sensitivity to human papilloma virus is observed (42). The fact that only about 10% of persons with epidermodysplasia verruciformis have consanguineous marriage progeny suggests that genetic inheritance is largely autosomal recessive. There have been only a few reports of X-linked inheritance (43). A unique hallmark of tree man sickness is a cell-mediated immune deficit linked with suppression of natural cytotoxicity and proliferation of T lymphocytes against HPV-infected squamous cells (27). In adults with the horrible disorder epidermodysplasia verruciformis, sun exposure mixed with immunologic dysfunction is likely to result in a drastic change in the genetic composition of the tumour suppressor gene protein (p53), culminating in the development of malignant skin cancer (27). It is well established that excessive production of immunosuppressive cytokines such as tumour 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, is associated with UV-B–induced local immunosuppression on the skin of patients with epidermodysplasia verruciformis (27). Graft vs host disease and common variable immunodeficiency has been associated with epidermodysplasia verruciformis lesions (44).

DIAGNOSIS

If we notice any warts or lesions on our skin, we should consult a dermatologist promptly, even if the

symptoms are moderate. If the physician suspects EV, a tissue biopsy will be performed to detect HPVs in the sample (47). A skin biopsy indicates mild hyperkeratosis, hypergranulosis, and acanthosis of the epidermis. HPVs can also be detected in keratinocytes using in situ hybridization or immunohistochemistry with anti-HPV antibodies (48). The polymerase chain reaction (PCR) can be utilized to detect a single-stranded confirmational polymorphism in the EVER1 and EVER2 genes in leukocyte DNA (46). (47). Histopathology: HPVs associated with premalignant and malignant disease are discovered early through tissue biopsy. The epidermis exhibits the distinguishing characteristics. Verruca plana-like lesions like as acanthosis and moderate hyperkeratosis are histological symptoms of EV. Keratinocytes have perinuclear halos and a blue grey pigmentation (see image below). Perinuclear cells are transparent cells with abnormal nuclei that are occasionally larger, hyperchromatic, and aberrant (45) (46).

DIFFERENTIAL DIAGNOSIS (48)

- Cutaneous Squamous cell carcinoma
- Acro keratosis verruciformis
- Tinea versicolor
- Nongenital Warts

TREATMENT

At the moment, there is no specific treatment for EV. Management entails a combination of medicinal and surgical interventions, as well as patient counseling, education, and follow-up (particularly for immuno-compromised patients) (49).

Vitamins and antiviral medicine can help reduce the symptoms of EV. Three cases of Tree-Man Sickness were investigated by scientists and physicians, including Dr. Anthony Gaspari of the University of Maryland, in order to uncover a genetic link that could be used to treat the sickness. There is currently no specific treatment for EV. Numerous therapy have been offered; however, patient education, early detection, and removal of tumoral lesions are favoured to prevent the establishment of cutaneous malignancies. When this type of cell proliferation is recognised, the rate and severity of the illness dictate the course of treatment. Localized epidermal growths of carcinoma can be surgically removed; however more extensive nonmalignant lesions require a more practical therapy (27).

TOPICAL THERAPY

Topical medications (retinoids, steroids, immunomodulators), cryotherapy, and electrosurgery are the treatment options for treating acquired EV (49,50).

SYSTEMIC THERAPY

Oral retinoids and interferon-alpha (IFN-a) therapy for acquired EV has been documented (49). Iraji and Faghihi used acitretin at a dose of 1 mg/kg per day for 4 months followed by 0.5 mg/kg per day for 2 months in a 25-year-old female with isolated IgM deficiency; a slight improvement in skin lesions was observed, but lesions relapsed upon discontinuation of treatment.

COMBINED THERAPIES

Three months of IFN-a-2a (9 MIU/day) and zidovudine (600 mg/day) treatment resulted in a small improvement in EV lesions with no recurrence (50).

PHOTODYNAMIC THERAPY (PDT)

PDT has been used to treat skin cancers of the superficial layer (basal cell carcinoma, Bowen's disease, actinic keratoses), as well as psoriasis and condyloma acuminate (44,50). It is critical to keep in mind that HIV patients are frequently less susceptible to treatment, and the efficiency of highly active antiretroviral therapy (HAART) is still unknown.

SEVERAL RESEARCHES OFFER A VARIETY OF THERAPEUTIC OPTIONS FOR THE HEINOUS SICKNESS

According to Anadolu et al., retinoids are employed for their endogenous antiproliferative impact via improved epithelial cell differentiation control. The author provided a case of a patient who improved significantly after ninety days of treatment with acitretin and interferon alfa2a. Though the wounds reappeared following treatment cessation, the patient resumed combined therapy for four months, followed by three months of acitretin alone (50). A 25-year-old lady was treated with acitretin at a daily dose

of 0.5–1 mg/kg/day for nearly half a year and reported a small improvement in skin characteristics such as lesions. However, after medication was discontinued, the lesions reappeared, and the patient declined further treatment (51). Another case was reported in which a 43-year-old female was treated with pegylated interferon alfa2b and acitretin for numerous squamous cell carcinomas in the oral and vaginal mucosa, as well as widespread verrucous lesions. Throughout treatment, the patient noticed a significant reduction in flat warts and no recurrence of malignancy (52). Hayashi et al. used topical tacalcitol, a vitamin D analogue, to treat a patient who was experiencing unacceptable retinoid side effects. Not only did the largest tumour regress within six months of treatment, but it also prevented the development of additional carcinomas over the next three years (53). Additional medications include cimetidine (a histamine type 2 receptor antagonist), which has been shown to modulate the immune system. It has been used in patients who have failed to respond to conventional medications at a dose of 40 mg/kg per day to treat planar, plantar, and common warts. After three months of therapy, the patient showed significant improvement, with no relapse at the six-month follow-up (54) However, de Oliveira et al. employed the identical treatment regimen in eight EV patients and obtained contrary indicators (55). Berthelot et al. identified a patient with EV with an unique homozygous EVER2 gene mutation who was successfully treated with topical imiquimod treatment five days per week for three months (56). 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. Additionally, this topical medication was administered in conjunction with systemic interferon therapy in an EV patient with Bowen's disease and actinic keratoses (57). In an unique therapy, Karrer et al. used a 20% 5 –Amino laevulinic acid ointment applied to the lesions for 6 hours and irradiated with an incoherent light source (wavelength approximately in the visible region 580–740 nm, 160 mW/cm2, 160 J/cm2). After PDT, blistering and crusting of the lesions occurred, but they recovered entirely without scarring after 2–3 weeks, and the cosmetic outcome was outstanding. A skin biopsy was performed six months following PDT. HPV type 8 was detected by in situ hybridization in skin that was clinically and histologically normal. Twelve months after PDT, a few lesions on the hands had recurred. The authors acknowledged that, while there is no treatment for EV at the moment and single lesions continued to occur in this patient, annual PDT may result in improved control of HPV-induced lesions (58). While conventional medications such as cidofovir may be beneficial in treating other papilloma virus-related illnesses, they have been ineffective in treating an EV patient with numerous cutaneous lesions (59). Treatment of epidermodysplasia verruciformis patients who also have HIV requires special care, as multiple studies have demonstrated that the majority of medications are ineffective. Topical imiquimod did not improve the condition of two HIV-positive half-brothers (60). Davison et al. unsuccessfully attempted imiquimod, 5-fluorouracil, and isotretinoin (61). The effects of highly active antiretroviral therapy (HAART therapy) on EV disease stages remain unknown. One group concluded that it had no impact (62), whereas Haas et al. reported an improvement in EV lesions in a patient receiving highly active antiretroviral treatment (63).

PREVENTIVE APPROACH (27)

Avoiding carcinogenic elements such as UVA and UVB light, as well as X-ray radiation; and • Patient counselling and education should be offered by a health care provider. Sunblock or sun protection may also be necessary to protect yourself from the sun's harmful UV radiation. Assist the patient in maintaining proper hygiene. Additionally, a healthy, balanced diet rich in fresh fruits and vegetables should be followed, as this may assist the patient's skin and overall health.

CASE STUDIES

For one year, a ten-year-old kid came with chronic cough and asymptomatic widespread truncal hyperpigmented and hypopigmented macules with pityriasiform scales on the eyelids and chin (Figure 1-B1 and B2). Immunological evaluation revealed persistent leucopenia with persistently low CD4/CD8 T-cells and B-cells. He was eventually diagnosed with primary immunodeficiency, Medellian Susceptibility to Mycobacterial Disease (MSMD), and pulmonary tuberculosis-related bronchiectasis. There was no history of consanguinity in the family. Similar lesions were observed on his older sister, his only sibling, but not on his father. His mother had died of colorectal

cancer eight years prior. Biopsies of the patient's chin and torso confirmed the viral wart diagnosis. Histopathological analysis revealed larger cells with bluish grey cytoplasm in the granular and spinous layer, consistent with HPV) infection. Additionally, larger keratohyaline granules and koilocytes were observed. HPV typing on paraffin-embedded skin biopsy tissues was not available in our context. Both siblings' lesions were successfully treated with regular cryotherapy and oral isotretinoin. To avert malignant transformation, sunscreen use and sun avoidance were advised.

DISCUSSION

HPV infections have the potential to cause cancer in EV patients. This malignant change occurs gradually, with cancers typically manifesting on sun-exposed skin in the fourth decade of life, around 20 to 30 years after the disease's inception. HPV infection is required, but not sufficient, for malignant transformation in EV. UVR is a significant factor in the development of SCC in EV patients. In EV patients, the majority of skin malignancies grow on sun-exposed areas. The carcinogenic potential of EV-HPV and how it interacts with UVR to cause carcinogenesis remain unknown. It is well established, however, that UVR, specifically UVB, destroys keratinocyte DNA and impairs the skin's immune system. The majority of SCCs have UVB-specific mutations in the p53 tumour suppressor gene, including the creation of pyrimidine dimer photoproducts.

Numerous interventions have been attempted, with varying degrees of success, in the treatment of congenital and acquired EV. All treatments for common verrucae have been proven to be ineffective, including electrodesiccation, cryotherapy, topical retinoids, contact sensitization, imiquimod, 5-fluorouracil, podophyllotoxin, and topical cidofovir. There was a transitory decrease in the number of lesions in a case report of an EV patient treated with systemic retinoids (etretinate at 1 mg/kg daily for 4 months). After 9 months of treatment, a combination of oral retinoids (acitretin 50 mg/day) and recombinant interferon alfa-2a (subcutaneously at 3 million units 3 days/wk) resulted in improvement in one case of EV. Three months after therapy, lesions on the hands recurred, while the face remained free at one year. In our patients, we used a combination of isotretinoin and cryotherapy to control the warts. Additionally, patient education regarding photoprotection and periodic skin examinations is critical for early cancer detection (65).

CONCLUSION

After careful consideration, we have established that tree man illness, also known as epidermodysplasia verruciformis (EV), is a genetic hereditary skin disorder caused by the Human Papilloma Virus (HPV). EV is characterised by the formation of flat, wart-like lesions and plaques on the skin, and it has been linked to skin cancer. This disease, including its causes and prevention actions, should be known by everyone. Because there is no cure for EV, only the symptoms can be relieved by taking vitamins, antiviral medications, and anti-cancer drugs, among other things. We can protect ourselves from this deadly disease if we are aware of the precautions to take.

REFERENCES

1. Emsen IM, Kabalar ME. Epidermodysplasia verruciformis: an early and unusual presentation. Can J Plast Surg. 2010;18(1):21-4. doi: 10.1177/229255031001800105, PMID 21358870.
2. Lewandowsky F, LW. A case of a previously undescribed skin disease (epidermodysplasia verruciformis) [in German]. Arch Derm 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. J Exp Med. 2008;205(1):35-42. 4. doi: 10.1084/jem.20071311, PMID 18158319.
4. Jablonska S, Milewski B, Kenntnis Z. Epidermodysplasia verruciformis Lewandowsky-Lutz. Dermatologica. 1957;115:1-22.
5. Rajagopalan K, Bahru J, Loo DS, Tay CH, Chin KN, Tan KK. Familial epidermodysplasia verruciformis of Lewandowsky and Lutz. Arch Dermatol. 1972;105(1):73-8, PMID 5009624.
6. Gliński W, Jablonska S, Langner A, Obalek S, Haftek M, Proniewska M. Cell-mediated immunity in epidermodysplasia verruciformis. Dermatologica. 1976;153(4):218-27. doi: 10.1159/000251060, PMID 1017532.

7. Jablonska S, Dabrowski J, Jakubowicz K. Epidermodysplasia verruciformis as a model in studies on the role of papovaviruses in oncogenesis. Cancer Res. 1972;32(3):583-9. PMID 5061309.
8. Hammar H, Hammar L, Lambert L, Ringborg U. A case report including EM and DNA repair investigations in a dermatosis associated with multiple skin cancers: epidermodysplasia verruciformis. Acta Med Scand. 1976;200(6):441-6. doi: 10.1111/j.0954-6820.1976.tb08261.x, PMID 1015352.
9. Maddiboyina, Desu, Mallikarjun Vasam, Veerendra Teja Challa, Amareswarapu V Surendra, Sridhar Rao, Shanmugarathinam Alagarsamy, Jhawat. An insight of nanogels as novel drug delivery system with potential hybrid nanogel applications. J Biomater Sci Polym Ed. 2022;33(2):262-78. doi: 10.1080/09205063.2021.1982643, PMID 34547214.
10. Pfister H. Human papillomaviruses and skin cancer. Semin Cancer Biol. 1992;3(5):263-71. PMID 1335790.
11. Ramoz N, Taïeb A, Rueda LA, Montoya LS, Bouadjar B, Favre M, Orth G. Evidence for a nonallelic heterogeneity of epidermodysplasia verruciformis with two susceptibility loci mapped to chromosome regions 2p21-p24 and 17q25. J Invest Dermatol. 2000;114(6):1148-53. doi: 10.1046/j.1523-1747.2000.00996.x, PMID 10844558.
12. Orth G. Epidermodysplasia verruciformis. In: Howley PM, Salzman NP, editors. The papillomaviruses. New York: Plenum Press; 1987. p. 199-243.
13. Maddiboyina B, Jhawat V, Desu PK, Gandhi S, Nakkala RK, Singh S. Formulation and evaluation of thermosensitive flurbiprofen in situ Nano gel for the ocular delivery. J Biomater Sci Polym Ed. 2021;32(12):1584-97. doi: 10.1080/09205063.2021.1927460, PMID 33977874.
14. Jablonska S, Orth G. Epidermodysplasia verruciformis. Clin Dermatol. 1985;3(4):83-96. doi: 10.1016/0738-081x(85)90052-5, PMID 2850863.
15. Zahir A, Craig L, Rady P, Tyring S, Ehrlich A. Epidermodysplasia verruciformis associated with HPV 10. Dermatol Online J. 2013;19(4):2. doi: 10.5070/D379B2760C, PMID 24021362.
16. Orth G. Epidermodysplasia verruciformis. In: Salzman NP, Howley PM, editors, The Papovaviridae. The papillomaviruses. New York: Plenum Press; 1987. p. 199-243.
17. Pfister H. Human papillomaviruses and skin cancer. Semin Cancer Biol. 1992;3(5):263-71. PMID 1335790.
18. Lewandowsky F, Lutz W. ein Fall einer bisher nicht beschriebenen Hauterkrankung (Epidermodysplasia verruciformis) [Epidermodysplasia verruciformis]. Arch f Dermat. 1922;141(2):193-203. doi: 10.1007/BF01938833.
19. Mashkilleison J. N: Ist die epidermodysplasia verruciformis (Lewandowsky-Lutz)ein stelbastandige Dermatos. IHRE beziehungen zur Verrucositas, Dermat, Wchnschr. 1931;92:569.
20. Sullivan M, Ellis F. A: epidermodysplasia verruciformis (Lewandowsky and Lutz). Arch Dermatol Syph. 1939;40 (Sep):422.
21. sayer A, Schweig J. Epidermodysplasia verruciformis (Lewandowsky – Lutz)report of a case with all the essential; Aug 1942.
22. abdullah A, EPA. United States today. Network of European World Shops 10-years-old girl may be 1 female with extremely rare' tree man syndrome'.
23. Warts starts to regrow on Bangladesh tree man after 24 surgeries.update on February 2, 2018.
24. Imahorn E, Yüksel Z, spoerri I, Gürel G, Imhof C, Saraçoğlu ZN, Koku Aksu AE, Rady PL, Tyring SK, Kempf W, Itin PH, Burger B. Novel TMC8 splice site mutations in epidermodysplasia verruciformis and review of HPV infections in patients with the disease. J Eur Acad Dermatol Venereol. 2017;31(10):1722-6. doi: 10.1111/jdv.14431, PMID 28646613.
25. Pfister H. Human papillomaviruses and skin cancer. Semin Cancer Biol. 1992;3(5):263-71. PMID 1335790.
26. Rowson KEK, Mahy BWJ. Human papova (wart) virus. Bacteriol Rev. 1967;31(2):110-31. doi: 10.1128/br.31.2.110-131.1967, PMID 5342713.
27. Epidermodysplasia verruciformis: A dreadful disease.
28. Ramoz N, Rueda LA, Bouadjar B, Montoya LS, Orth G, Favre M. Mutations in two adjacent novel genes are associated with epidermodysplasia verruciformis. Nat Genet. 2002;32(4):579-81. doi: 10.1038/ng1044, PMID 12426567.
29. Orth G. Genetics of epidermodysplasia verruciformis: insights into host defense against papillomaviruses. Semin Immunol. 2006;18(6):362-74. doi: 10.1016/j.smim.2006.07.008, PMID 17011789.
30. Azzimonti B, Mondini M, De Andrea M, Gioia D, Dianzani U, Mesturini R, Leigheb G, Tiberio R, Landolfo S, Gariglio M. CD8+ T-cell lymphocytopenia and lack of EVER mutations in a patient with clinically and virologically typical epidermodysplasia verruciformis. Arch Dermatol. 2005;141(10):1323-5. doi: 10.1001/archderm.141.10.1323, PMID 16230580.
31. Notarangelo L, Casanova JL, Fischer A, Puck J, Rosen F, Seger R, Geha R, International Union of Immunological Societies Primary Immunodeficiency diseases classification committee. Primary

immunodeficiency diseases: an update. J Allergy Clin Immunol. 2004;114(3):677-87. doi: 10.1016/j.jaci.2004.06.044, PMID 15356576.
32. Lowy DR, Androphy EJ. Warts. In: Freedberg IM, Eisen AZ, Wolff K, et al, editors. Fitzpatrick's dermatology in general medicine. 6th ed. McGraw-Hill. New York City 2003 pp. p. 2119-31.
33. Pereira de Oliveira WR, Carrasco S, Neto CF, Rady P, Tyring SK. Nonspecific cellmediated immunity in patients with epidermodysplasia verruciformis HPV. J Dermatol. 2003;30(3):203-9. doi: 10.1111/j.1346-8138.2003.tb00372.x, PMID 12692356.
34. Favre M, Orth G, Croissant O, Yaniv M. Human papillomavirus DNA: physical map. Proc Natl Acad Sci U S A. 1975;72(12):4810-4. doi: 10.1073/pnas.72.12.4810, PMID 174077.
35. Favre M, Breitburd F, Croissant O, Orth G. Chromatin-like structures obtained after alkaline disruption of bovine and human papillomaviruses. J Virol. 1977;21(3):1205-9. doi: 10.1128/JVI.21.3.1205-1209.1977, PMID 191643.
36. Orth G, Breitburd F, Favre M' & Croissant, 0. Cold Spring Harbor conferences on CellProliferation. In: Vol. 4B. Cold Spring Harbor, NY: Cold Spring Harbor Laboratories; 1977. p. 1043-68.
37. Orth G, Favre M, Croissant. J Virol. 1977;24. PMID 108120.
38. Gober MD, Rady PL, He Q, Tucker SB, Tyring SK, Gaspari AA. Novel homozygous frameshift mutation of EVER1 gene in an epidermodysplasia verruciformis patient. J Invest Dermatol. 2007; Apr;127(4):817-20. doi: 10.1038/sj.jid.5700641, PMID 17139267.
39. Sun XK, Chen JF, Xu AE. A homozygous nonsense mutation in the EVER2 gene leads to epidermodysplasia verruciformis. Clin Exp Dermatol. 2005; Sep 30;30(5):573-4. doi: 10.1111/j.1365-2230.2005.01858.x, PMID 16045695.
40. Ramoz N, Rueda LA, Bouadjar B, Montoya LS, Orth G, Favre M. Mutations in two adjacent novel genes are associated with epidermodysplasia verruciformis. Nat Genet. 2002;32(4):579-81. doi: 10.1038/ng1044, PMID 12426567.
41. Burger B, Itin PH. Epidermodysplasia verruciformis. Curr Probl Dermatol. 2014;45:123-31. doi: 10.1159/000356068, PMID 24643182.
42. Nature Publishing Group. Available from: http://www.nature.com/naturegenetics,mutations. In: two adjacent novel genes are associated with epidermodysplasia verruciformis.
43. Androphy EJ, Dvoretzky I, Lowy DR. Xlinked inheritance of epidermodysplasia verruciformis. Genetic and virologic studies of a kindred. Arch Dermatol. 1985 Jul;121(7):864-8, PMID 2990354.
44. 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.
45. Assoc prof Emanuel P. dermatopathologist,New Zealand, 2013. Epidermodysplasia verruciformis pathology.
46. Nat Pernick MD, skin nontumer/clinical dermatology infectious disorders epidermodysplasia verruciformis.
47. Medically reviewed by Xixi Luo, M.D. on May 24, 2017-written by Jamas Roland, epidermodysplasia verruciformis: what is it and how is it treated?
48. Expert reviewer: Pr Giovanna Zambruno,Lutz-Lewandowsky epidermodysplasia verruciformis.
49. Ngan V, staff writer,2006.updated by doctor Jannet Gomez,dec,2016. Epidermodysplasia verruciformis.
50. Anadolu R, Oskay T, Erdem C, Boyvat A, Terzi E, Gürgey E. Treatment of epidermodysplasia verruciformis with a combination of acitretin and interferon alfa2a. J Am Acad Dermatol. 2001;45(2):296-9. doi: 10.1067/mjd.2001.114575, PMID 11464195.
51. Iraji F, Faghihi G. Epidermodysplasia verruciformis: association with isolated IgM deficiency and response to treatment with acitretin. Clin Exp Dermatol. 2000;25(1):41-3. doi: 10.1046/j.1365-2230.2000.00570.x, PMID 10671971.
52. Maddiboyina B, Nakkala RK. Formulation development and characterization of enteric coated tablets of lansoprazole. Pharm Lett. 2020;12:22-38.
53. Hayashi J, Matsui C, Mitsuishi T, Kawashima M, Morohashi M. Treatment of localized epidermodysplasia verruciformis with tacalcitol ointment. Int J Dermatol. 2002;41(11):817-20. doi: 10.1046/j.1365-4362.2002.01642.x, PMID 12453013.
54. Micali G, Nasca MR, Dall'Oglio F, Musumeci ML. Cimetidine therapy for epidermodysplasia verruciformis. J Am Acad Dermatol. 2003;48(2);Suppl:S9-S10. doi: 10.1067/mjd.2003.111, PMID 12582373.
55. de Oliveira WR, Neto CF, 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. doi: 10.1016/j.jaad.2003.12.037, PMID 15153919.
56. Berthelot C, Dickerson MC, Rady P, He Q, Niroomand F, Tyring SK, Pandya AG. Treatment of a patient with epidermodysplasia verruciformis carrying a novel EVER2 mutation with imiquimod. J Am Acad Dermatol. 2007;56(5):882-6. doi: 10.1016/j.jaad.2007.01.036, PMID 17368633.

57. Maddina BY, Asthana GS, Asthana A. Formulation and Development of polysaccharide based mesalamine Nanoparticles. Int J Pharm Clin Res. 2016;8(7):676-84.
58. Karrer S, Szeimies RM, Abels C, Wlotzke U, Stolz W, Landthaler M. Epidermodysplasia verruciformis treated using topical 5aminolaevulinic acid photodynamic therapy. Br J Dermatol. 1999;140(5):935-8. doi: 10.1046/j.1365-2133.1999.02830.x, PMID 10354037.
59. Preiser W, Kapur N, Snoeck R, Groves RW, Brink NS. No apparent effect of cidofovir in epidermodysplasia verruciformis. J Clin Virol. 2000;16(1):55-7. doi: 10.1016/s1386-6532(99)00069-4, PMID 10680741.
60. Hu W, Nuovo G, Willen M, Somach S. Epidermodysplasia verruciformis in two half-brothers with HIV infection. J Cutan Med Surg. 2004;8(5):357-60. doi: 10.1007/s10227-005-0022-6, PMID 15868315.
61. Davison SC, Francis N, McLean K, Bunker CB. Epidermodysplasia verruciformislike eruption associated with HIV infection. Clin Exp Dermatol. 2004;29(3):311-2. doi: 10.1111/j.1365-2230.2004.01503.x, PMID 15115519.
62. Maddiboyina B, Asthana A, Asthana GS, Singh S, Sunnapu O, Kotla N. Formulation and characterization of polycarbophil coated mucoadhesive microspheres of repaglinide. J Pharm Sci Res. 2015;7(11):972-7.
63. Haas N, Fuchs PG, Hermes B, Henz BM. 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):669-70. doi: 10.1046/j.1365-2133.2001.04426.x, PMID 11703302.
64. Maddiboyina B, Jhawat V, Sivaraman G, Sunnapu O, Nakkala RK, Naik MH, Gulia M. Formulation Development & Characterization of controlled release core in cup matrix tablets of venlafaxine HCl. Curr Drug Ther. 2020;15(5):503-11. doi: 10.2174/1574885515666200331104440.
65. Maddiboyina B, Jhawat V, Ramesh K, Nakkala RK, Jakka AL. A review on nanoparticle-based herbal remedies for the management of alopecia. Pharm Lett. 2020;12(5):1-17.