**INTRODUCTION**

The “Tree Man” phenomenon was made into mainstream media when a man was reported with excessive growth of warts forming tree-like barks mainly on hands and feet and less sporadically on neck and face. The disease was made apparent starting from childhood when the patient suffered a minor knee cut while playing. Small warts emerged from the close vicinity of the wound, and later it progressed rapidly to eventually towards the whole body (figure 1). This attracted a professor from University of Maryland to investigate him with greater details. He was diagnosed with **Epidermodysplasia verruciformis** (EV) and commenced treatment regimens in collaboration with Indonesian doctors to formulate the best therapeutic strategies for the disease. So far, the treatments have been well and the patient is recovering.

**DEFINITION**

**Epidermodysplasia verruciformis** (EV) is a dermal genetic disorder with a very rare occurrence, caused by autosomal recessive genetic disorder with ranges from 10% to 20% of the patients. This genetic trait increased vulnerability to Human Papillomavirus infection manifested in macules and papules growth with different severity. The disease was first documented by Felix Lewandowsky and Wilhelm Lutz, can also be referred as Lewandowsky-Lutz dysplasia. Most cases has an onset from early infancy up to as late as 20 years old, and in some cases, middle ages.¹

**ETIOLOGY**

**Genetic**

EV emerges from genetic disorder which increases patients’ vulnerability to the virus.
The genetic anomaly stems out from the mutation of EVER1 and EVER2 genes which is located on chromosome 17q25. The functions of EVER1/EVER2 genes, which are also named as Transmembrane Channel-like Protein 6 (TMC6) and TMC8 genes, respectively, have been indicated to serve as zinc transporter by interacting with zinc-transporter 1 protein.\(^\text{2}\)

Zinc-binding proteins have been found to be very important in great variety of viruses to maintain virus life cycle such as adenoviruses, retroviruses, rotaviruses, herpesviruses, polyomaviruses and papillomaviruses. Zn\(^{2+}\) ion is required for the activation of AP-1 transcriptional activity through PI3K-Akt and JNK pathway to assist viral proteins production. Also, free zinc ions alter the expression levels of certain cellular genes, and many of which are relevant to the viral life cycle, for example cellular immunity and antiviral responses. The activity of EVER1 and EVER2 has been indicated to assist cellular defense against virus infection by limiting available zinc ions.\(^\text{3}\)

Another factor linked to the progression of the disease is major histocompatibility complex class II (MHC II) located at alleles (DR-DQ) in patients from regions of America, Europe and Africa. MHC class II molecules play huge role in immune system by exposing antigens to stimulate T cells in order to be able to remove those by phagocytosis, or receptor-mediated endocytosis. These molecules are highly variable in general populations. The experts found that –DRB1, -DQA10501, -DQB10301 type of MHC II were greatly more common in patients with EV, which could represent susceptible alleles with stronger predisposition to EV.\(^\text{4}\)

Several cases of EV has also been described with close association with immunesuppression cases such as HIV positive, immunocompromised, organ transplantation or idiopathic lymphopenia.\(^\text{3}\)

**Virology**

Human Papillomavirus (HPV) is a double-stranded DNA (dsDNA), small, non-enveloped virus and contain circular double DNA as viral genome with length of 7,900 base pairs. HPVs infect mainly keratinocytes of the skin or mucous membranes. The infections can be non-symptomatic, benign papillomas in form of warts or squamous cell papillomas, or malignant and life-threatening cancers such as cervical cancer. More than 120 types of HPVs have been identified so far and experts refer those by numbers. In EV case, numerous HPV types, such as HPV-4, -5a, -5b, -8-9, -12, -14, -15, -17, -19, -25, -36, -38, -47, and -50, have been identified. Among EV patients, HPV-5 and HPV-8 are the most abundant causative agents reported.\(^\text{5}\)

HPVs transform keratinocytes, changing the characteristics to be rapidly growing by suppressing cellular anti-oncogenic proteins p53 and pRb, and at the same time promoting pro-oncogenic HPV viral E6 and E7 proteins to alter cell cycle and apoptosis.\(^\text{7}\)

In EV case, HPV proteins of E6 and E7 are detected in abundance, which explains extensive tumorigenesis in EV. In cancerous lesions, the high-risk HPV types, such as HPV types 5, 8, and 47, are able retain and continuously express the E6 and E7 portions of the viral genome to cause cell immortalization by inhibiting apoptotic

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Figure 1  The “Tree Man”. Much advanced stage of Epidermodysplasia verruciformis (EV) which manifests as tree bark-like warts grown mostly on feet and hands area with lesser intensity on face and neck.

Figure 2  *Epidermodysplasia verruciformis* cutaneous lesions on the forehead of an 8-year-old boy characterised by flat macules varying from flesh-colored to reddish brown or brown plaques, with slightly scaly surfaces and irregular borders.

Figure 3  Verrucous or seborrhic keratosis–like lesions of *Epidermodysplasia verruciformis* on (A) head, (B) leg, (C) trunk.
pathway, resulting in transformation of normal human keratinocytes into malignant cells.

CLINICAL PRESENTATION
EV may begin as early as infancy in the form of flat, wart-like lesions and plaques on the face, limbs or neck (figure 2). The clinical course of EV is rather erratic. It may stay benign or progress into verrucous plaques and nodules, even become uncontrolled and transformed to be invasive squamous cell carcinoma, or in other cases, the lesions disappear and replaced by new ones in other areas. Commonly found primary skin lesions in EV consist of two types. The first one is flat, wart-like lesions similar to verruca plana with flat-topped papules with scaly, hyperpigmented or hypopigmented confluent patches or plaques. The second one is flat macules and reddish brown plaques with slightly scaly surfaces and irregular borders resembling tinea versicolor (figure 3). Those papules may coalesce into large plaques on more advanced stage.

Clinical Recognition
The clinical features are assessed based on the symptoms, mainly on cutaneous changes such as plane warts or pityriasis versicolor-like lesions, and red or brownish plaques, with persistent and progressive effect without any involvement of mucous membranes or lymph nodes, and in some cases, malignancies. The more comprehensive diagnosis of EV should be initiated upon the appearance and growth of verrucous lesions and when the condition is not relieved by the administration of ordinary treatment regimen. On the next step, medical practitioners can perform biopsies on the affected regions. The most apparent biopsy findings can be observed on the epidermis. The typical histologic manifestation of EV is a verruca plana-like lesion with mild hyperkeratosis and acanthosis, in which the keratinocytes contain perinuclear halos and blue-gray pallor (figure 4). Perinuclear halos are specific cytopathic effect, which depicted in the figure as clear cells in the granular and spinous layers with occasional enlarged, hyperchromatic, atypical nuclei. Further confirmatory step can be achieved by performing in-situ hybridization targeting HPV DNA on the upper layer on the epidermis (figure 5).

TREATMENT AND MANAGEMENT
There is no consensus on first-treatment therapy for EV. The preventive measures are not limited to using sun-protection or totally avoid sun as soon as the confirmatory diagnosis has been made. The therapeutic measures can be further divided into non-surgical and surgical methods.

Non-surgical Methods
Imiquimod
Imiquimod is a topically applied medication that works by modulating immune response. Imiquimod activates Toll-like receptor (TLR7), one of the cellular receptors that detects foreign and pathogen substances. The cellular activation will then upregulate cytokines, such as interferon-α, interleukin-6 and tumor necrosis factor-α (TNF-α) to activate immune cells like Natural Killer (NK) cells, macrophages, B-lymphocytes and cytotoxic T-lymphocytes to halt viral infection by activating cell death/apoptosis mechanism, viral genetic material...
The outcome of imiquimod treatment has been positive with successful recovery, but shown to be ineffective in patients with defective cell mediated immunity.

5-Fluorouracil (5-FU)

5-Fluorouracil (5-FU) is an anti-metabolic agent mainly used in various cancer treatment, such as colorectal, anal, oesophageal, stomach, breast, pancreatic and skin cancers.

The drug can be administered via intravenous injection and/or topical application. It works by inhibiting thymidylate synthase (TS) activity, which will deprive the cancerous cells of thymidine monophosphate required for DNA replication, triggering thymineless cell death.

The success of treatment of EV with 5-FU has been reported in patients.

Interferons (IFNs)

Interferon treatments works by modulating and mimicking natural body interferons to remove pathogens. IFNs have been known to have antiviral, antiseptic and anticarcinomic properties which are beneficial to the treatment of EV. IFNs are delivered most likely by intramuscular injection. The initial clinical efficacy study to treat EV with interferon-α alone has shown to be effective.

However, combination treatment has been demonstrated to be more successful, such as combination with acitretin, ribavirin on HIV patient.

Derivatives of Vitamin A (acitretin) and Vitamin D analogues

Vitamin A derivatives has been employed to treat many types of diseases, mainly psoriasis, inflammatory skin disorders and skin aging. Acitretin is one of the retinoids generally used to treat EV with high success rate. It comes with trade name Soriatane or Neotigason. It acts by binding to nuclear receptors that regulate gene transcription, hence blocking overproliferating keratinocytes and suppressing epidermal hyperdysplasia. It has been reported to be efficacious in combination with interferon-α2a, peginterferon-α2b, and imiquimod.

Other commonly used Vitamin A derivatives is 13-cis retinoic acid, which is also used in conjunction with interferons.

Vitamin D analogues work with similar mechanism by modulation of epidermal proliferation and differentiation, and inhibition immune induction. Its usage and efficacy with combination of isotretinoin have been demonstrated.

Photodynamic therapy (PDT)

Photodynamic therapy utilizes photosensitizing mediated agents to increase target cells vulnerability to light sources. The photosensitizing agents are generally preferentially absorbed by hyperproliferative cells and have low intake and minimal effects on healthy cells, which is a suitable treatment for EV. The commonly used photosensitizing agent for cancerous skin is 5-aminolevulinic acid (ALA) and methylaminolevulinate (MAL). The body will activate the photosensitizing effect by transforming ALA and MAL into protoporphyrin, which then will excite upon exposure to light and accumulate reactive oxygen species (ROS) which will trigger cell death (apoptosis) and necrosis to malignant cells.

Another advantage is that the accumulated ROS is only confined intracellularly and will not affect adjacent cells. In EV, the usage of 5-ALA and followed by irradiation using lambda light source (580-740 nm wavelength) has been shown to be efficacious.

Surgical Method

Surgical method includes removal and elimination of benign and premalignant skin lesions by surgery or cryosurgery. Many successful removal of the lesions with surgery has been described, for example fusiform excision with a curette and application of trichloroacetic acid (TCA) resulted in no appearance of lesion for 3.5 years, surgical excision and postoperative radiotherapy, liquid nitrogen and excision surgery.

Besides, skin grafting from non-infected and sun protected skin methods are also reported.

SUMMARY

Epidermodysplasia verruciformis is a rare dermal disease caused by rare autosomal recessive hereditary genetic disorder located on chromosome 17q25 which causes mutation on EVER1 and EVER2 genes. These mutations increased vulnerabilities on Human Papillomavirus (HPV) causing prominent and uncontrolled wart growth on arms, neck, and legs. The common initial detection of Epidermodysplasia verruciformis is through biopsy on predicted premalignant and malignant skin lesions. Further confirmatory analysis can be performed by in-situ hybridization and polymerase chain reaction. The medical treatment is generally not definitive; typically with topical drugs such as imiquimod, 5-fluorouracil, vitamin A derivative 13-cis retinoic acid, interferon alpha or cholecalciferol analogues (Vitamin D). For severe cases, surgical procedures to remove excessive warts are necessary.

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