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Review article

Epidermodysplasia Verruciformis-A Genetic Disorder

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ABSTRACT
Epidermodysplasia verruciformis also known as Tree man disease. It is recognized as an inherited disorder with wide spread and persistent with human papilloma virus causes defect in cell mediated immunity. It is a rare, lifelong, cutaneous, autosomal recessive genetic disorder of the immune system manifested by (HPV) infection beginning in the early years of life. This disorder was first described by Lewandowsky and Lutz [1] in 1922 as an epidermal nevus. In 1939, Sullivan and Ellis[2] described a close relationship between EV and high risk of skin cancer. In EV, there are mutations in the EVER1 or EVER2 genes on chromosome 17q25, which, due to a defect of cell-mediated immunity, lead to an abnormal susceptibility of the patients to a specific group of HPV genotypes known as EV HPV. Most of these are HPV 5 and 8; more rarely, HPV 14,17, 20 and 47, and all have oncogenic potential[3] In the addition, there is a link with squamous cell carcinoma. A tree man syndrome is a rare disorder happening more frequently at a younger age in the general population. It is an unusual Geno dermatosis characterized by an autosomal recessive inheritance pattern. Non-surgical therapies and surgical therapies are known to treat this disorder, but it is known to be lifelong disorder. Recent surgery was performed in Bangladesh which is known to be successful.

Key words: Genodermatosis, Human papilloma virus, Oncogenic potential.

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INTRODUCTION

Epidermodysplasia verruciformis colloquially known as tree man illness is an extremely rare autosomal recessive genetic[4] hereditary skin disorder associated with a high risk of carcinoma of the skin. It is characterized by abnormal susceptibility to human papilloma virus of the skin.[5] 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.[4] The condition usually has an onset of between the ages of one and 20,[6] but can occasionally present in middle age.[6] It is named after the physicians who first documented it, Felix Lewandowsky and Wilhelm Lutz (de).[7] Epidermodysplasia verruciformis is a rare Geno dermatosis characterized by abnormal susceptibility to infection with specific serotypes of human papillomavirus (HPV). EV HPVs are thought to be ubiquitous and non-pathogenic in the normal population, while EV patients develop disseminated cutaneous lesions early in childhood. Lesions are heterogeneous and may resemble verruca plana, or be macular and either hyper- or hypo pigmented resembling the lesions of pityriasis versicolor.[7] Mucous membranes are spared. These lesions are most often initially asymptomatic although non-melanoma skin cancer may develop in the third, fourth, and fifth decades of life in sun-exposed skin. Classic histologic findings include enlarged keratinocytes present in the spinous layer of the epidermis with abundant, vacuolated pale blue cytoplasm[8,9] Other, less specific, histologic findings include abundant The disease was first described by Lewandowski and Lutz in.[9] Approximately half of all patients with EV will develop cutaneous malignancies, predominately Bowen's type carcinoma in situ and invasive squamous cell carcinomas that occur mainly on sun-exposed areas in the fourth or fifth decade of life.[10]

Literature Survey

- Epidermodysplasia verruciformis usually begins in infancy or early childhood, with the development of various types of flat, wartlike lesions and confluent plaques on the skin, especially on dorsal hands, extremities, face, and neck. Patients may also develop tinea versicolor–like lesions on the trunk.
- Epidermodysplasia verruciformis lesions may progress to form verrucous plaques and nodules, or they may transform into invasive squamous cell carcinomas,[11] most commonly between the ages of 20 and 40 years.
- The clinical course of epidermodysplasia verruciformis is protracted. As the disease progresses, some lesions disappear, while new lesions may appear on other areas of the body. The rate of appearance of new lesions varies considerably.
- The diagnosis of epidermodysplasia verruciformis should be suspected in the clinical setting of numerous verrucous lesions or when lesions are resistant to appropriate therapy.[12]
- Epidermodysplasia verruciformis variants may be suspected when a patient has the typical clinical presentation in the setting of epidermodysplasia verruciformis–associated HPV but lacks nonmelanoma skin cancers at a young age or has late-onset disease.

Etiology

Epidermodysplasia verruciformis–associated HPVs can be divided into 2 groups. One group has high oncogenic potential (HPV types 5, 8, 10, and 47). More than 90% of epidermodysplasia verruciformis–associated skin cancers contain these 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 autosomal recessive mode of inheritance is supported by the finding that 10% of patients with epidermodysplasia verruciformis are offspring of consanguineous marriages. X-linked inheritance has rarely been reported.[13] A clear mode of inheritance is not evident in all cases.
- Pathogenic mutations in 2 adjacent genes, *EVER1* and *EVER2*, have been identified.[14]
- Major histocompatibility complex (MHC) class II alleles (DR-DQ) have been found in a large series of patients with epidermodysplasia verruciformis from Europe, Africa, and America.

- Neither chromosomal abnormalities nor the relationship to any specific MHC class I antigens has been found in patients with epidermodysplasia verruciformis.
- The exact mechanisms involved in the keratinocytic transformation within epidermodysplasia verruciformis skin lesions are unclear. Transcripts of the early region of viral genomes (E6 and E7 gene proteins) have been detected in epidermodysplasia verruciformis tumors. However, in most carcinomas, viral sequences are not integrated into the host genome.
- Studies have shown that interactions occur between oncogenic HPVs and the anti-oncogene products, p53 and pRb, in cell cycle regulation, DNA repair, and the execution of programmed cell death (apoptosis). Failure of programmed cell death to eliminate cells with DNA damage may play an important role in the malignant transformation of squamous epithelium, with resultant proliferation, disruption of epithelial structural order, and development of cellular atypia. A decrease in UV-induced DNA repair synthesis, coupled with anti-oncogenes 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 epidermodysplasia verruciformis.
- Chronic sun-exposure coupled with immunologic defects in patients with epidermodysplasia verruciformis is likely to induce mutations 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.
- Studies have implicated a defect within keratinocytes. The activity of Langerhans cell antigen presentation appears normal in epidermodysplasia verruciformis, thus suggesting other cells cause immunotolerance to epidermodysplasia verruciformis–associated HPVs.

Genetics

The cause of the condition is an inactivating PH mutation in either the EVER1 or EVER2 genes, which are located adjacent to one another on chromosome 17.[15] The precise function of these genes is not yet fully understood, but they play a role in regulating the distribution of zinc in the cell nuclei. Zinc is a necessary cofactor for many viral proteins, and the activity of EVER1/EVER2 complex appears to restrict the access of viral proteins to cellular zinc stores, limiting their growth.[16] Other genes have also rarely been associated with this condition. These include the ras homolog gene family member H.[17] Genetic Many researches shown thatpredisposed deficiencies in cutaneous immunity make patients of this disease more vulnerable to HPV infection Any mutations in the family of genes called EVER genes whose deficiency cause tree man syndrome and also acquire following.

- Squamosal cell carcinoma,
- Acrokeratosis verruciformis,
- Tinea versicolor,
- Generalized verrucosis,[18]
- Immunosuppression,
- Profound CD8+T cell lymphocytopenia[19]

PATHO PYSIOLOGY

The pathophysiology of epidermodysplasia verruciformis is linked to defective cell-mediated immunity, with elucidation of mutations in *EVER1* and *EVER2* genes (band 17q25).[20] Their gene products are integral membrane proteins localized to the endoplasmic reticulum. Although the role of *EVER1* and *EVER2* genes in the pathogenesis of epidermodysplasia verruciformis remains unclear, one hypothesis is that they are involved in the control of HPV infection within keratinocytes, or they play a role in the immune response to the infection itself. Intracellular zinc homeostasis regulated by a complex of EVER proteins and zinc transporter proteins may play a role in inhibiting EV-HPV expression.[21] However, an estimated 25% of patients with epidermodysplasia verruciformis lack mutations in *EVER1* and *EVER2*, with the genetic defect in these patients not yet elucidated.[22] Sporadic reports have described patients with the epidermodysplasia verruciformis phenotype who exhibit mutations in other genes. In 2012, two siblings who were homozygous for a mutation that created a stop codon in the Ras homolog gene family member H (*RHOH*) gene exhibited an epidermodysplasia verruciformis phenotype and their T cells exhibited impaired T-cell receptor (TCR) signaling.[23] A report also described a 19-year-old with an autosomal recessive MST1 (or STK4, serine/threonine kinase 4) deficiencyf8b} who exhibited the epidermodysplasia verruciformis phenotype as well as a global immune deficiency with susceptibility to other bacterial and viral infections.[24] MST1 deficiency leads to naive T-cell lymphopenia and an impaired egress of mature T lymphocytes from the thymus to secondary lymphoid organs, associated with an impaired chemotactic response to several chemokines, including the CCR7 ligands CCL19 and CCL21.[24] Lastly, a report describes three siblings who lacked *EVER1*/*EVER2* mutations and exhibited atypical epidermodysplasia verruciformis, but who exhibited a homozygous splicing deficiency in the gene encoding LCK (lymphocyte specific kinase), resulting in a deletion of three exons of this gene.[25] These three siblings exhibited T-cell defects and epidermodysplasia verruciformis phenotype, including skin cancers. These reports indicate that there are multiple genetic defects that can be associated with an epidermodysplasia verruciformis phenotype, and that genes resulting in T-cell defects play a permissive role in allowing the epidermodysplasia verruciformis–associated HPV to cause skin lesions. Several epidermodysplasia verruciformis variants have been described, and the majority of these cases occur in association with immunosuppression, such as HIV infection, organ transplantation, or idiopathic lymphopenia.[26] In cases of the acquired epidermodysplasia verruciformis phenotype, such as HIV infection or organ transplantation, the status of *EVER1* or *EVER2* has not been evaluated. Whether these patients harbor previously silent mutations, epigenetic changes, or splice variants of *EVER1* or *EVER2* is not known, but it is clear that in these cases, global immune suppression allows the phenotype to develop. Zavattaro *et al* reported a rare case of an epidermodysplasia verruciformis patient who had clinical features of epidermodysplasia verruciformis but lacked the *EVER1* or *EVER2*mutation.[27] This patient was older at diagnosis and had no premalignant or malignant lesions upon examination. Defective Fas protein function (CD95, apoptosis receptor) was identified along with perforin gene variations, suggesting that this combination resulted in increased susceptibility to HPV infection owing to defective viral clearance. In addition, a profound $CD8^+$ T-cell lymphocytopenia was identified, a finding also described by Azzimonti *et al* in a patient who also had a clinical diagnosis of epidermodysplasia verruciformis but who lacked *EVER1* or *EVER2* mutations.[28] The papillomavirus genus is a member of the Papovaviridae family. HPVs are small, no enveloped viruses, measuring approximately 55 nm in diameter. Their icosahedral capsid is composed of 72 cap Somers, with a 56,000-d major protein, which is the genus-specific antigenic determinant of the virus, and a

76,000-d minor protein. The HPV genome contains a double-stranded circular DNA of approximately 7900 base pairs, functionally divided into an early region (E) of 5-7 open reading frames E1-E7, a late region (L) of open reading frames L1 and L2, and a noncoding upstream regulatory region. The HPV types are primarily classified on the basis of their DNA homology. Patients with epidermodysplasia verruciformis have a defective cell-mediated immune response to HPV infection. In classic, autosomal recessive epidermodysplasia verruciformis, the immune defect is very specific, as these patients do not exhibit global defects in cell-mediated immunity, and there is no evidence that there are any defects in controlling other types of viral infections or bacterial or fungal challenges. Many HPV types found in epidermodysplasia verruciformis lesions are nonpathogenic to the general population. The exact mechanism by which cancer occurs frequently in patients with epidermodysplasia verruciformis is unclear. The role of HPV in cancer development is supported by the identification of viral DNA within epidermodysplasia verruciformis–induced malignancies. Carcinogenic cofactors, such as ultraviolet B and x-ray irradiation, are probably involved in the progression from benign warts (verrucae) to cancer. Cells with early signs of malignant transformation have been found closely connected with virus-infected epidermal regions. The exact mechanisms involved in the malignant transformation of keratinocytes in skin lesions of patients with epidermodysplasia verruciformis are still unclear. Studies have shown that interactions occur between oncogenic HPVs and anti-oncogene proteins, such as p53 and pRb, in cell cycle regulation, DNA repair, and the execution of programmed cell death (apoptosis).The persistence of HPV infection in epidermodysplasia verruciformis is thought to be the result of an immunogen etic defect, which generates several cytokines capable of down-regulating cell-mediated immunity. Patients with epidermodysplasia verruciformis reportedly show an increased rate of low-production genotypes of interleukin 10 compared with control subjects. Patients with epidermodysplasia verruciformis and skin cancer are more likely to have low-production interleukin 10 genotypes than patients with benign forms of epidermodysplasia verruciformis.[29] In epidermodysplasia verruciformis tumors, gene products transcripts of E6 and E7 (the early region of viral genes) are detected. Within the early region of the HPV genome, E6 and E7 code for major oncoproteins responsible for the oncogenic potential of HPV. These viral proteins are crucial for tumorigenesis. In cancerous lesions, the high-risk HPV types, such as HPV types 5, 8, and 47, selectively retain and express the E6 and E7 portions of the viral genome. Working together, these E6/E7 regions cause cell immortalization, or failure of programmed cell death, resulting in transformation of normal human keratinocytes into malignant cells.[30] Both E6 and E7 are multifunctional proteins that promote cell growth via multiple mechanisms. Each has the ability to neutralize an anti-oncogene product, specifically p53 and pRb, that is essential for intracellular defense mechanisms against the development of neoplasms. However, the exact mechanism of carcinogenesis of E6 and E7 oncoproteins and the effects of these oncoproteins on p53 and pRb are unclear. Failure of programmed cell death to eliminate cells with DNA damage may play an important role in malignant transformation of squamous epithelium. A decrease in UV-induced DNA repair synthesis, coupled with an oncogenic viral infection, further enhances the susceptibility toward somatic mutations and malignant transformation in patients with epidermodysplasia verruciformis.[31] Renal transplant recipients and immunosuppressed patients have an increased risk of developing lesions of epidermodysplasia verruciformis.

Diagnosis

Making a diagnosis for a genetic or rare disease can often be challenging. Healthcare professionals typically look at a person's medical history, symptoms, physical exam, and laboratory test results in order to make a diagnosis. The following resources provide information relating to diagnosis and testing for this condition.

Testing Resources

The Genetic Testing Registry (GTR) provides information about the genetic tests for this condition. The intended audience for the GTR is health care providers and researchers. Patients and consumers with specific questions about a genetic test should contact a health care provider or a genetics professional.

Symptoms

- **Epidermodysplasia verruciformis** (EV) colloquially known as **tree man illness** is an extremely rare autosomal recessive geneticherediatary skin disorder associated with a high risk of carcinoma of the skin.
- It is characterized by abnormal susceptibility tohuman papillomaviruses (HPVs) of the skin.
- Thick visible warts all over the body as well as inside of the skin,the skin becomes thick and hardened.
- The hands and feet, the extremities, are enlarged and it is difficult to use them. Hands and feet have been described as looking like contorted, yellow-brownbranches extending upto 3 feet Skin looks like tree bark or tree roots, hence the name Tree-Man Disease or Tree-Man Syndrome (TMS) Clinical diagnostic features are lifelong eruptions of pityriasis versicolor-like macules, flat wart-like papules, and development of cutaneous carcinomas.
- 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

Table 1: Signs and Symptoms

Signs and Symptoms	Approximate number of patients (when available)
Pustule	90%
Seborrheic dermatitis	90%
Skin ulcer	90%
Verrucae	90%
Cafe-au-lait spot	50%
Hypo pigmented skin patches	50%
Telangiectasia of the skin	7.5%
Abnormality of metabolism/homeostasis	-
Basal cell carcinoma	-

extremities, and face.

- The benign form of EV presents with only flat, wart-like lesions over the body, whereas the malignant form shows a higher rate of polymorphic skin lesions and development of multiple cutaneous tumors.
- The Human Phenotype Ontology (HPO) provides the following list of features that have been reported in people with this condition. Much of the information in the HPO comes from Orphanet, a European rare disease database. If available, the list includes a rough estimate of how common a feature is (its frequency).

Risk Factors

Human papillomaviruses (HPVs) are found in normal skin and in benign and malignant skin conditions. Epidermodysplasia verruciformis (EV) HPV types are those most plausibly linked to the development of squamous cell carcinomas of the skin.

Epidemology

Epidemiology is the study and analysis of the patterns, causes, and effects of health and disease conditions in defined populations, race, sex, age.

United States

The exact frequency of epidermodysplasia verruciformis is unknown.

International

The largest series of epidermodysplasia verruciformis reported in the literature includes 195 cases, mainly from Eastern Europe, Poland,[32] and Latin America.

Race

Epidermodysplasia verruciformis is universal and affects persons of all races.

Sex

No sexual preference is noted for epidermodysplasia verruciformis, although sex-linked[33] and autosomal dominant inheritance have been described.

Age

Patients with epidermodysplasia verruciformis typically present early in childhood with flat wartlike lesions of the dorsal hands, extremities, face, and neck. The disease manifests as a congenital form in infancy (approximately 7.5%), during childhood (61.5% in children aged 5-11 y), or at puberty (22.5%). Malignant tumors typically appear during the fourth and fifth decades of life. The reported frequency of malignant change ranges from 30-60%.

Treatment

EV is a lifelong disease. Even though lesions can be treated or removed as they appear, patients with EV will continue to develop these lesions throughout life. In many cases lesions may develop and remain unchanged for years. The greatest risk is that in 30-60% of EV patients these lesions will change into skin cancers. Malignant tumors are usually found in patients between 30-50 years of age.

Currently there is no treatment to prevent new EV lesions from occurring. The management of EV involves a combination of medical and surgical treatments alongside patient counselling and education.

- Stress the importance of following sun protection strategies. Exposure to sunlight (UVB and UVA) has been shown to increase the rate of EV lesions turning into skin cancers.
- Treat and remove warts, as you would treat other viral warts. This includes chemical treatment, cryotherapy with liquid nitrogen and electro surgery.
- Experimental therapies for EV lesions and skin tumors include intraregional interferons and retinoids, combination of isotretinoin and interferon alpha or cholecalciferol (vitamin D) analogues

CONCLUSION

Epidermodysplasia verruciformis is a rare cutaneous disorder that manifests with persistent human papillo virus infection. Genetic inheritance patterns have been implicated, resulting in defective cutaneous immunity against HPV. There is an association with squamous cell carcinoma of the skin, especially in sun-exposed sites. A multitude of specific HPV types have been associated with EV; however, only certain types (primarily HPV-5 and HPV-8) have been associated with carcinoma. Recognition of the cutaneous findings is paramount for the physician. Given their propensity for skin cancer, such patients must be counseled with regard to sun avoidance and strict use of sunscreens.

ABBREVATIONS

EV: Epidermodysplasia verruciformis; **HPV**: Human papilloma virus; **GTR**: Genetic testing registry; **HPO:** Human phenotype ontology.

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