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Review

Epidermodysplasia Verruciformis

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ABSTRACT

Epidermodysplasia verruciformis (UV) is an extremely rare skin disease with autosomal recessive inheritance. This disease is because of susceptibility to certain types of human papilloma virus and mutations of two genes named EVER1/TMC6 and EVER2/TMC8. Epidermodysplasia verruciformis is characterized by various skin lesions, such as flat warts and reddish papules, which have been seen since childhood. There is a high risk of these lesions becoming malignant in the areas exposed to UV radiation in the following years. This transformation, usually seen in the fourth decade of life, is most commonly associated with squamous cell carcinoma. Although various treatment methods have been proposed for this disease so far, there is no definitive treatment.

Keywords: Carcinoma, epidermodysplasia verruciformis, human papilloma viruses.

Epidermodysplasia verruciformis (EV) was first described by Lewandowsky and Lutz in 1922, and is a rare autosomal recessive inherited skin disease with a rate of less than one millionth.[1] Epidermodysplasia verruciformis patients are caused by a genetically determined susceptibility to specific human papilloma viruses (HPV), which are considered to be harmless for general population.[2] The disease has a pleurorphic presentation with the development of verrucous tumors of flat plague warts and thin plaques similar to pityriasis versicolor, which usually develop in childhood, leading to the resembling of the tree stump of the hands and feet of the patients.[3] Therefore, this disease is also called Tree Man Syndrome. In a review written by Imahorn et al. In 2017, it was reported that there were approximately 500 patients with this disease in the literature.[4]

ETİOLOGY

More than 200 HPV types have been identified so far. The main capsid protein is divided into different HPV types, genera and species according to their sequence in L1. The first two members of the beta HPV genus, about 50 types, are HPV5 and HPV8. Both were first isolated from the skin lesions of EV patients.[5] Epidermodysplasia verruciformis is usually caused by mutations of the EVER1 (TMC6) and EVER2 (TMC8) genes that allow susceptibility to infections by some β-HPV viruses.[6] In a study, it was found that these two genes mutated in 75% of EV patients.[7] However, no mutation is detected in 25% of patients, indicating the genetic heterogeneity of the disease and may also indicate that in some cases the genes responsible for the development of the disease have not yet been identified.[8] The initial symptoms of EV typically develop on the patient's skin during infancy or childhood.[2] These symptoms usually appear as verrucae planae-like squamous reddish skin lesions on the extremities, and reddish or brownish plaques, as well as pityriasis versicolor-like lesions, often distributed on the trunk.[1] The size and severity of these skin lesions increases over time.[9] Precancerous lesions with malignant transformation and invasive non-melanoma skin cancer (NMSC) develop later, especially in areas exposed to UV radiation.[5] This transformation from healthy skin to malignancy can take approximately 20 years and generally corresponds to the fourth decade of life.[9,10] No bias has

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been identified for gender or specific geographical distribution.[4] HPV5 is the most common virus found in malignant lesions, followed by HPV8, 12, 14, 17 and 20.[7] HPV5 and HPV8 were found to be present in 90% of EV-related skin cancers.[4]

The genes EVER1 (TMC6) and EVER2 (TMC8) are located adjacent to chromosome 17q25. The products of these genes belong to a new family of 8 members and are transmembrane channel-like proteins localized in the endoplasmic reticulum.[5] TMC6 and TMC8 proteins form a trimeric complex with Zn Transporter (ZnT1) and affect zinc homeostasis in cells.[11] Zinc is an important mediator of the activity of several cellular proteins, such as enzymes and transcription factors.[5] It is assumed that the level of Zn2 + controlled by the ZnT1 complex leads to a reduced activity of the transcription factors necessary for the replication of EV-HPVs. Due to the mutated and incomplete TMC/ZnT1 complex, the levels of transcription factors increase and allow the EV-HPVs to proliferate. This leads to the EV phenotype.[12]

Patients with an acquired form, known as an atypical form, often have a history of treatment-related immunodeficiency. Regarding immune deficiency, this EV formation (other than that of the hereditary type) is thought to result from T cell-mediated immunodeficiency in patients with predetermined genetic mutations, among others, such as RHOH and STK4. Not all immunosuppressive patients with these mutations have EV-like disease. This is very different from the typical EV, where the characteristic mutations are hereditary and show full penetration.[4]

HISTOPATOLOGY

EV-HPV warts have characteristic microscopic properties.[13] The histology of EV shows moderate acanthosis in the epidermis, mild hyperkeratosis, blue-gray cytoplasm, and prominent keratohvalin granules and characteristic large keratinocytes.[13,14] These scattered or clustered keratinocytes in the granular layer or upper stratum spinosum appear to be swollen with blue-gray foamy cytoplasm.[15] Histopathological findings of blue cells in EV are pathogonomic for HPV-infected keratinocytes and the ''blue'' appearance of these cells can be used as an indicator of EV-related disease. ''Blue'' appears as a pale blue cytoplasm with abundant basophilic keratohyaline granules.[4] Apart from these characteristic lesions, Actinic keratosis and Bowen type lesions may also be encountered. Actinic keratoses are seen as irregular and atypical keratinocytes in the superficial epithelium. These lesions may turn into squamous cell carcinomas, especially in sun-exposed areas, but should not have full-thickness epidermal atypia.[4,15] Bowen type lesions have pagetoid spread of highly atypical keratinocytes in the epidermis.[4] Patients develop malignant lesions diagnosed with Bowen's Disease and invasive squamous cell carcinoma (SCC) in the third or fourth decades of life. In addition, basal cell carcinomas and Merkel cell tumors have been identified in some patients with EV.[3]

CLINICAL FINDINGS

Epidermodysplasia verruciformis was first described by Lewandowsky and Lutz in 1922 as pityriasis versicolor-like macules or verruca plana-like papules.[1] This is a rare polymorphic skin disease characterized by similar brownish papules.[13] These lesions are common and heterogeneous genodermatosis that can develop in the face, extremities, back and all other body parts exposed to the sun.[9,14] Patients may present with verruca plana-like flat wart-like papules located in the sun-exposed areas. Another common appearance is saline-colored, hyperpigmented or hypopigmented macules, papules, or plaques spread on it, similar to tine. At the same time, the clinical appearance of the lesions can sometimes change by mimicking other disease processes.[15]

Symptoms of these lesions, which begin in childhood, can also be seen immediately after birth, but usually occur between the ages of 5 to 12 years. Dark warts that start straight in this process and only grow and multiply rapidly can cause itching and burning sensations when exposed to the sun. In the fourth decade, cutaneous malignant transformation occurs in 30-60% of patients.[9]

TREATMENT

There is absolutely no effective treatment for EV.[4] Since it is difficult to treat EV, there is a search for more effective treatment. The treatment is not only aimed at cosmetic healing but also decreases the conversion to malignancy.[16] Currently, combined treatment of acitretin, imiquimod, interferons, and retinoids, as well as surgical excision, is recommended for a number of possible treatments, such as cimetidine (although there is debate about the efficacy of this treatment) and topical calcipotriol.[4] Current radiation therapy is contraindicated in patients with EV, although it is frequently used in EV patients with conjunctival

squamous cell carcinoma, since it is observed to cause more invasive and serious lesions.[17] In non-conjunctival squamous cell carcinoma cases with metastasis, radiation therapy may be considered in addition to other treatments.[4,18]

Since EV lesions tend to occur in sun-exposed areas of the skin, sun exposure protection counseling and compliance are also important for managing this condition. At the same time, any suspected malignant lesion should be excised for histopathological evaluation.[4] Patients with EV will need annual or more frequent check-ups with dermatologists to assess the development of new worrying lesions.[4,19-22]

Conclusion

Epidermodysplasia verruciformis is a rare autosomal recessive genodermatosis with a high risk of developing skin cancer. The disease is caused by mutations in the TMC genes that make them susceptible to specific HPV species. Subsequently, skin cancer, especially squamous cell carcinoma, develops on the skin exposed to UV rays. Surgical excision is usually used in patients with no definite treatment. Although EV serves as a disease model for the development of SCC in the general population, EV is an unexplained disease. Because of this feature, it will be the subject of many future research.

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REFERENCES

1. Lewandowsky F, Lutz W. A case of a not previously described skin disease (epidermodysplasia verruciformis). Arch Dermatol Syph 1922;141:193-203. [Abstract]
2. Burger B, Itin PH. Epidermodysplasia verruciformis. Curr Probl Dermatol 2014;45:123-31.
3. Uitto J, Vahidnezhad H. Expanding genetics and phenotypic spectrum of epidermodysplasia verruciformis. Br J Dermatol 2016;175:1138-9.
4. Myers DJ, Fillman EP. Epidermodysplasia Verruciformis. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019.
5. Tommasino M. The biology of beta human papillomaviruses. Virus Res 2017;231:128-38.
6. Edwards L, Reutter JC, Foster TE, Rady PL, Tyring SK. Perianal epidermodysplasia verruciformis associated with human papillomavirus 5 after a renal transplant. J Low Genit Tract Dis 2017;21:e35-e6.
7. Orth G. Genetics of epidermodysplasia verruciformis: Insights into host defense against papillomaviruses. Semin Immunol 2006;18:362-74.
8. Kalińska-Bienias A, Kowalewski C, Majewski S. The EVER genes - the genetic etiology of carcinogenesis in epidermodysplasia verruciformis and a possible role in non-epidermodysplasia verruciformis patients. Postepy Dermatol Alergol 2016;33:75-80.
9. Kim C, Hashemi P, Caglia M, Shulman K. Treatment of imiquimod resistant epidermodysplasia verruciformis with ıngenol mebutate. J Drugs Dermatol 2016;15:350-2.
10. Majewski S, Jablonska S. Skin autografts in epidermodysplasia verruciformis: human papillomavirus-associated cutaneous changes need over 20 years for malignant conversion. Cancer Res 1997;57:4214-6.
11. 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;205:35-42.
12. Lazarczyk M, Cassonnet P, Pons C, Jacob Y, Favre M. The EVER proteins as a natural barrier against papillomaviruses: a new insight into the pathogenesis of human papillomavirus infections. Microbiol Mol Biol Rev 2009;73:348-70.
13. Mattos MSG, Oliveira WR, Sotto MN. Comparative study of p16 protein expression in squamous cell carcinomas from patients with epidermodysplasia verruciformis and patients without the disease. Arch Dermatol Res 2017;309:479-83.
14. Bushara O, Miller D, Giubellino A, Schomaker M, Thyagarajan B, Nelson AC. Diagnosis of epidermodysplasia verruciformis: Two cases highlighting the role of direct HPV L1 gene sequencing. J Cutan Pathol 2019;46:436-41.
15. Kupiec PM, Hossler EW. Progressive widespread warty skin growths. Cutis 2017;99:82;99;100.
16. Donaldson SL, Purnell JC, Pavlidakey PG, Atkinson TP, Kissel R. Epidermodysplasia verruciformis in a young adult with activated PI3Kδ syndrome. JAAD Case Rep 2019;5:195-7.
17. Yutsudo M, Hakura A. Human papillomavirus type 17 transcripts expressed in skin carcinoma tissue of a patient with epidermodysplasia verruciformis. Int J Cancer 1987;39:586-9.
18. Kirchhof MG, Au S. Brazilian waxing and human papillomavirus: a case of acquired epidermodysplasia verruciformis. CMAJ 2015;187:126-8.
19. Rajabi MT, Ghasemi H, Safizadeh M, Jamshidi S, Asadi-Amoli F, Abrishami Y, et al. Conjunctival squamous cell carcinoma with intraocular invasion after radiotherapy in epidermodysplasia verruciformis. Can J Ophthalmol 2014;49:e43-6.
20. Vohra S, Sharma NL, Shanker V, Mahajan VK, Jindal N. Autosomal dominant epidermodysplasia verruciformis: a clinicotherapeutic experience in two cases. Indian J Dermatol Venereol Leprol 2010;76:557-61.
21. Nindl I, Gottschling M, Stockfleth E. Human

papillomaviruses and non-melanoma skin cancer: basic virology and clinical manifestations. Dis Markers 2007;23:247-59.

22. Adachi A, Kiyono T, Hayashi Y, Ohashi M, Ishibashi M. Detection of human papillomavirus (HPV) type 47 DNA in malignant lesions from epidermodysplasia verruciformis by protocols for precise typing of related HPV DNAs. J Clin Microbiol 1996;34:369-75.