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EPIDERMODISPLASIA VERRUCIFORMIS ASSOCIATED WITH LOW-RISK HPV- CASE REPORT

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Abstract

Epidermodysplasia verruciformis (EV) is a hereditary skin disorder that affects the body's ability to eliminate and protect against certain types of human papillomavirus (HPV), resulting in a higher risk of abnormal tissue growth and skin cancer.

Typically, the signs and symptoms of this condition are presented during childhood and may include flat warts, macules that resemble pityriasis versicolor, or lesions resembling seborrheic keratoses. An 11-year-old female patient came for examination with viral verrucae that first appeared at the age of 4, on the forehead and hairline. The consulted dermatologist diagnosed verruca plana and proposed local treatment with a topical retinoid (adapalene), with limited efficacy.

Over time, the verrucae spread to other areas and the patient received various treatments including cryotherapy, CO2 fractional laser, and several topical creams and oral medications. Due to suspicion of Epidermodysplasia Verruciformis (EV), a skin biopsy was performed.

The histopathological findings suggested the presence of Epidermodysplasia verruciformis. The immunological analyses showed the presence of antibodies IgE and IgG At to Ebstein Barr Virus (EBV), and Cytomegalovirus (CMV). A DNA sample was taken from the patient with a biopsy and skin smear, which was subjected to HPV amplification in real-time PCR. Low-risk HPV types 6 and 44 were detected. High-risk HPV was not found. The patient was subsequently given 3 doses of the 9-valent HPV vaccine.

Although some improvement was observed in certain areas, new verrucae appeared elsewhere. Patients with EV require frequent check-ups with dermatologists to evaluate for the development of new lesions and malignant transformation.

Keywords: Human papillomavirus (HPV), genetic dermatologic condition, autosomal recessive inheritance, cutaneous dysplasia.

Introduction

Epidermodysplasia verruciformis, also known as “Lutz-Lewandowsky disease” (1922), is a genetic dermatologic condition in which patients show a decreased immunologic ability to defend against and eradicate certain types of human papillomavirus, like the beta-HPV, leading to persistent infection and increased lifetime risk of development of cutaneous dysplasia and malignancy[1].

There are 2 forms of EV, the inherited or primary type, which is inherited in an autosomal recessive pattern (mutation in TMC6/EVER1 or TMC8/EVER2), and the secondary sporadic type observed mainly in HIV-infected, immunocompromised individuals [2].

Other mutations associated with EV include RAS homolog gene family member H, MSTI deficiency, and LCK (lymphocyte-specific kinase). Clinical manifestations of primary epidermodysplasia verruciformis begin in childhood (between the ages of 5 and 11), unlike sporadic EV, which tends to occur later in life and is thought to result from somatic mutations that arise spontaneously during an individual's lifetime. If the clinical manifestation is limited to flat warts, EV is classified as a “benign form” and it is usually associated with non-oncogenic HPV types 3 and 10.

The "malignant form" is characterized by polymorphic lesions, with a tendency to malignant transformation and it is usually associated with HPV types 5, 8, and 14 [3]. Many of these lesions take on the appearance of tree bark or tree roots, typically on the face, neck, torso, hands, and feet. Because of this, EV is sometimes referred to as "tree-man disease" or "tree-man syndrome."

EV is a rare disease, with no predisposition to gender, race, or geographic distribution. A review of the literature performed by Imahorn et al. in 2017 found about 500 patients with this disease were reported in the literature worldwide [4]. A frequency of 11% is estimated in Europe and the USA [5].

Epidermodysplasia verruciformis (EV) can be diagnosed by obtaining a thorough patient history, analyzing clinical findings, reviewing family history, conducting a skin biopsy for histopathological examination, performing immunological assays, utilizing HPV typing (PCR), and conducting genetic analyses [6].

Case report

An 11-year-old female patient presents for evaluation, subsequent inquiry, and medical intervention. Anamnestic data gave information about viral verrucas that appeared at the age of 4, on the upper part of the forehead and the hairline. The consulted dermatologist diagnosed verruca plana (Figure 1).

She was treated with retinoid (Adapalene cream) with minimal effect. Spontaneous regression was expected to occur in 2 years but did not occur (Figure 2). Instead, a larger part of the forehead was affected and the verrucas reached the eyebrow line, a few isolated verrucas also appeared behind the ears.

The patient was then treated with cryotherapy (liquid nitrogen) on three occasions with minimal effect. Segmented treatment was done with a CO2 fractional laser on the neck and the forehead (Figure 3). Topical Imiquimod cream 5% was used for local treatment for 3 months, along with UV protection creams. A skin biopsy was performed almost five years after the initial appearance.

The histopathological findings suggest the presence of Epidermodysplasia verruciformis. The immunological analyses showed the presence of antibodies IgE and IgG At to Ebstein Barr Virus (EBV), and Cytomegalovirus (CMV). The detection and typing of high-risk and low-risk Human Papillomavirus (HPV) were performed, and no high-risk HPV was found. Low-risk HPV types 6 and 44 were detected with a DNA sample taken from the patient with a biopsy and skin smear.

The HPV-typing swabs are stored in a suitable medium - PBS (Phosphate buffered saline) until the DNA extraction procedure. The DNA sample was subjected to HPV amplification in real-time PCR.

The patient started with combined therapy with caps, Acitretin 20 mg/per day (for 9 months), cryotherapy twice a week, and Fluorouracil 5% cream (for 2 months). Additionally, 3 doses of the 9-valent HPV vaccine were administered (Figure 5, 6, 7). Currently, she is being treated per os with caps. Isotretinoin, 20mg per day with a combination of cryotherapy and laser.

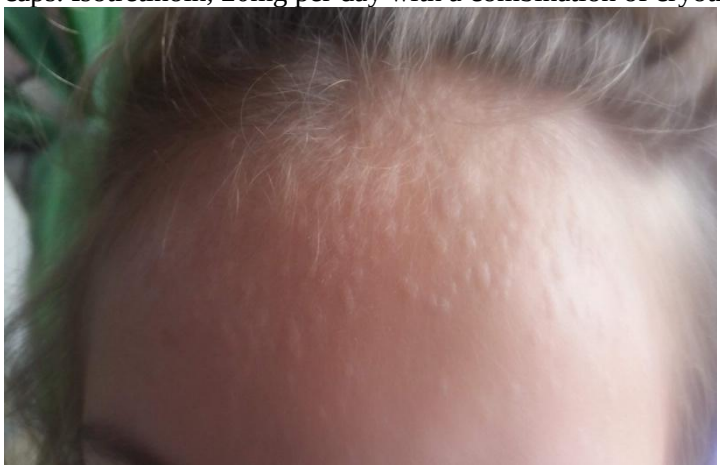

Figure 1. Before any treatment.

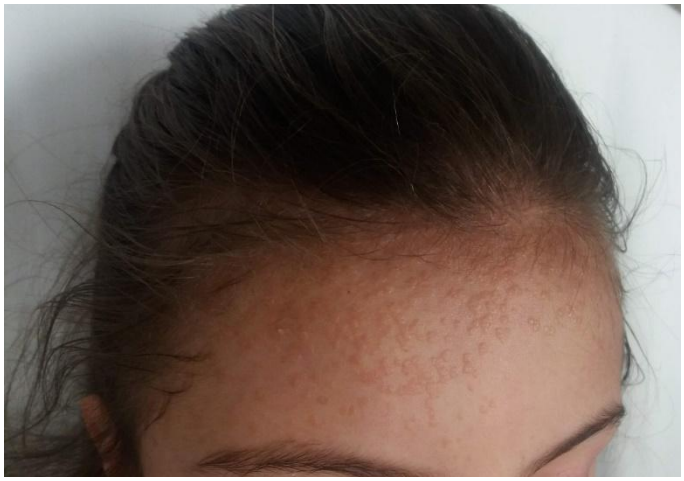

Figure 2. After 2 month treatment with local retinoid.

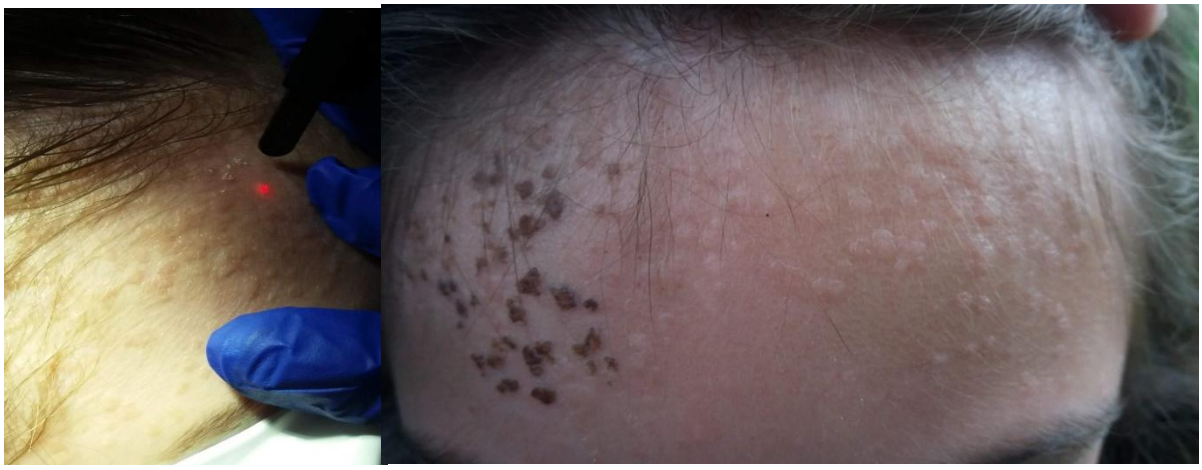

Figure 3. Segmented treatment with CO2 fractional laser.

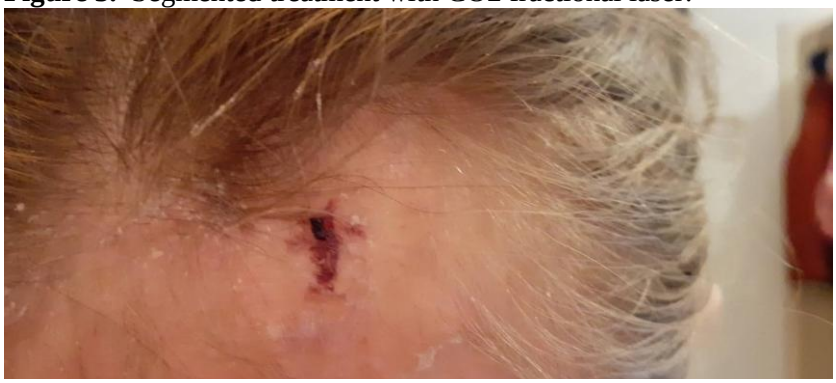

Figure 4. After biopsy.

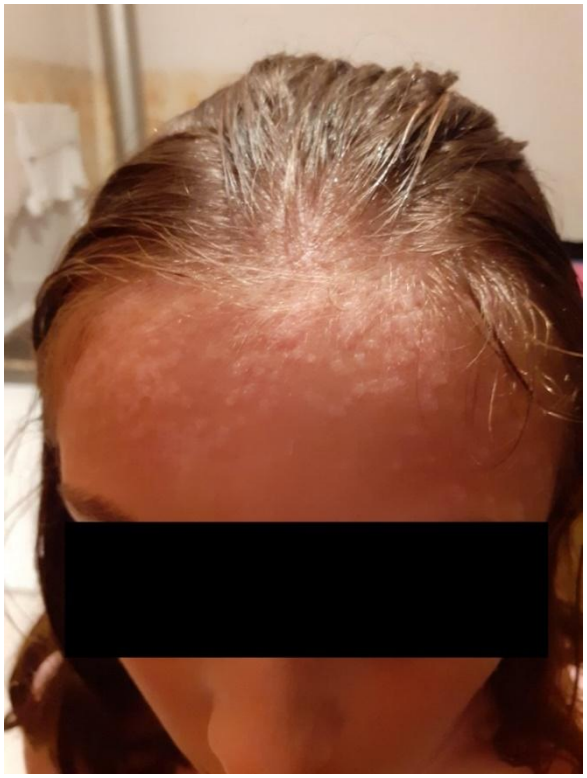

Figure 5. After first dose of of 9-valent HPV vaccine and cream Imiquimod 5%.

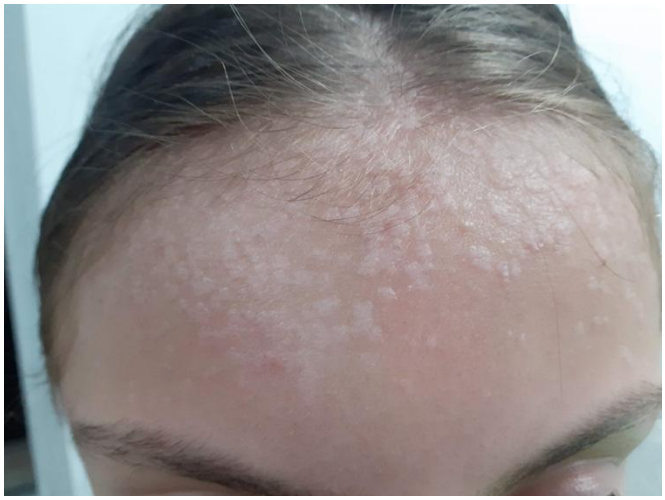

Figure 6. 2 months after treatment with caps, Acitretin, Cryotherapy,Imiquimod 5% and second dose of 9-valent HPV vaccine.

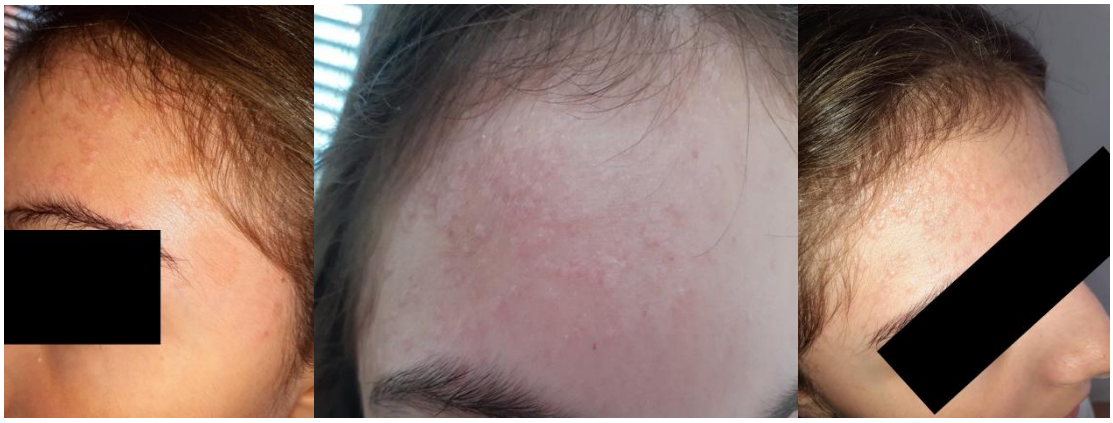

Figure 7. 9 months after treatment with caps. Acitretin, Cryotherapy, Imiquimod 5% and third dose of 9-valent HPV vaccine.

Discussion

Epidermodysplasia verruciformis (EV) is a rare genetic disorder characterized by the development of multiple benign and malignant cutaneous lesions associated with the human papillomavirus (HPV). The onset of EV lesions typically occurs in childhood and persists throughout life, with a strong association between specific HPV types and the progression of dysplasia to malignancy [7]. The prevalence of EV is not influenced by gender or geographical location [8].

In the general population, HPV infections in cutaneous keratinocytes are typically cleared without malignant progression [9]. However, HPV types 5 and 8 are the most commonly implicated in EV-related cancers, with a prevalence of up to 90%. (10) Malignant transformation of cutaneous epidermal lesions in EV is usually observed in patients in their 30s. [11, 12, 13, 14].

In some cases, 30-50% of EV patients' lesions may undergo malignant transformation, most commonly into cutaneous squamous cell carcinoma (SCC). Basal cell carcinoma (BCC) and adnexal tumors are less frequently observed. The incidence of malignancy increases with age, and it is typically observed in patients between 30 and 50 years old [15].

The characteristic histopathologic appearance of EV lesions includes hyperkeratosis, parakeratosis, acanthosis with koilocytic cellular atypia, and pale eosinophilic cytoplasm. Pathognomonic "blue cells" are observed in HPV-infected keratinocytes in EV and serve as an indication of EV-related disease. Accurate diagnosis of EV requires dermatologic clinical evaluation and histopathologic examination of suspected EV-like lesions. Molecular analysis can also identify known mutations associated with EV [16].

While no definitive cure exists for EV, multiple treatment options are available, including excision and other therapies such as acitretin and imiquimod, interferons with retinoids, cimetidine, and topical calcipotriol. Several experimental therapies have been investigated for the treatment of EV-related skin cancers. These include intralesional interferon injections, a combination of isotretinoin and interferon alpha, or cholecalciferol (vitamin D) analogues [17].

However, the efficacy of these treatments is not yet established, and further research is needed to determine their safety and effectiveness.

As EV lesions tend to occur in sun-exposed areas, sun protection counseling and adherence are important aspects of management [18, 19, 20]. Patients with EV require frequent check-ups with dermatologists to evaluate for the development of new lesions and malignant transformation.

Conclusion

After undergoing various therapies, it was observed that the verrucas partially receded from certain regions while appearing in other locations.

Factors that influence the progression or regression of the disease remain unclear. Multiple studies have established the role of beta-HPV in the development of squamous cell carcinoma (SCC) in patients with epidermodysplasia verruciformis (EV). The effectiveness of the 9-valent HPV vaccine has also been demonstrated against cutaneous papillomaviruses, proving to be immunogenic and able to prevent the formation of skin tumors, including non-melanoma skin cancer and SCC. [21].

Early detection of the disease, reducing sun exposure and the use of combined therapies for suspicious lesions is crucial in preventing disease progression and the development of more severe malignancies. Successful treatment outcomes can be achieved by utilizing these strategies in managing patients with EV.

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