

Lewandowski & Lutz Syndrome: A Rare Case Entity

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Abstract

Epidermodysplasia verruciformis (EV), first described in 1922 by Lewandowski and Lutz, is a rare inherited genetic disease. The disease usually manifests in childhood with highly polymorphic, widespread lesions.¹

We report a case of a fifteen year old boy, who presented to us with multiple flat topped, hypopigmented papules of a seven year duration on his body. He was diagnosed with EV on a skin biopsy, after ruling out differential diagnosis of pityriasis versicolor, verruca vulgaris and acrokeratosisverruciformis. The patient was resistant to known treatment options.

Key message: sun protection and lifelong observation for diagnosis and improved prognosis of malignant or premalignant lesions of EV.

Key words: pityriasis versicolor, verruca-like lesions, sun exposed sites

Introduction

Epidermodysplasia verruciformis is a rare genodermatosis characterized by a unique susceptibility to cutaneous infection by a group of phylogenetically related human papilloma viruses (EV-HPVs).² These patients show a defect in cell-mediated immunity specific toward the causative HPVs that lead to lifelong disease. The defect is usually inherited as autosomal recessive trait and presents clinically with plane warts, pityriasis versicolor-like lesions and reddish verrucous plaques. Dysplastic and malignant changes in the form of actinic keratoses, Bowen's disease and squamous cell carcinoma (SCC) are common but metastasis occurs rarely. A totally effective treatment against EV is as yet highly desirable. The mode of inheritance is often autosomal recessive and a mutation in EVER1 or EVER2 genes located in chromosome 17 causes underlying cell mediated immune deficiency.³ We are presenting a case of EV in a 15 year old male patient, to document and share our clinico-therapeutic experience.

Conflict of Interest: No

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Case Discussion

A fifteen year old boy (Figure.1) presented with raised hypopigmented, flat-topped, non pruritic, non tender, wart-like, slowly progressive skin eruptions on the whole body since the last seven years. The lesions initially presented on the forehead and gradually progressed in a caudal direction, to involve most of the body in a span of seven years. He was otherwise normal clinically. No other family members had similar complaints. All the baseline investigations including complete blood count, liver function tests, and lipid profile and serological test for HIV were normal.

Pityriasis versicolor was ruled out with a potassium hydroxide of the lesional skin scrapings. A differential diagnosis of Acrokeratosisverruciformis and Verruca Vulgaris were made.

Skin biopsy from one of the lesions showed (Fig.2a,2b,2c) diffuse vacuolization, swelling and numerous round, basophilic keratohyalin granules in the stratum Malpighi, and granular layer.

The patient was unresponsive to treatment (Fig.3), with daily 10mg Acitretin, sunscreen, topical azelaic acid and zinc supplements, even after five months duration.

Though, the patient's lesions didn't seem to be progressive in nature, they also appeared to be resistant to the given treatment. No side effects were

reported by our patient during therapy or follow-up. All the oral medications were stopped and patient

was advised to continue sun protection. He is under regular follow up and the lesions are non-progressive presently.



Figure 1 : Initial presentation of patient

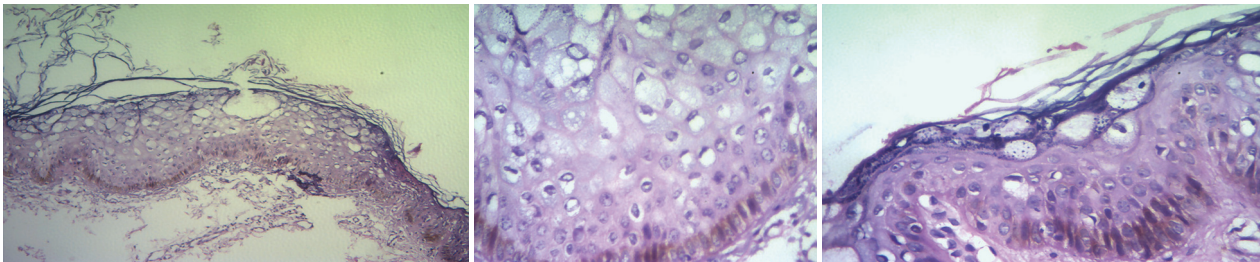


Figure 2a: H&E stain (40x magnification) showing acanthosis in the stratum Malpighi, and diffuse vacuolization of the cells in the granular layer.

Figure 2b: H&E stain (100x magnification) showing few cells in the granular layer with pyknotic nuclei and other cells have nuclei that are round empty with peripherally condensed chromatin.

Figure 2c: H&E stain (100x magnification) showing cells in the granular layer which are swollen, irregularly shaped, have abundant slightly basophilic cytoplasm and numerous round, basophilic keratohyalin granules



Figure 3 : the patient, five months after treatment

Discussion

Clinically, it presents with a characteristic combination of pityriasis versicolor-like lesions, reddish verruca-like and seborrheic keratosis-like plaques with a potential for malignant transformation.² EV is characterized by widespread human papilloma virus (HPV) infection.⁴ HPV 5 and 8 are the main types incriminated for the malignant transformation in about 25% of EV patients.⁵⁻⁷ EV occurs worldwide but doesn't display any gender or geographic predisposition. Its frequency is 11% in Europe and USA and 40% among Japanese,⁸ but reported infrequently from India. A PubMed and IndMed search on 26 Oct 2009 revealed only 12 reports appearing between 1971 and 2009.⁸⁻¹¹

The disease has no preference for gender or race and can be sporadic or familial. The disease usually begins in childhood. The hallmark lesions of EV are preferentially located on sun-exposed sites of face, neck, trunk and extremities. The malignant transformation of EV lesions into Squamous Cell Carcinoma occurs in 30–70% cases; this may require over 20 years for such conversion or occurs when the lesions have been present for 10 years or so, or usually in third and fourth decades of life.¹²⁻¹³ Immunological changes occur in patients with this disease, especially in their cellular immunity. These patients show a defect of cell-mediated immunity that is specific toward the causative HPVs.¹⁴ This deficiency appears to be local and specific, which causes the generation of several cytokines which prevent the immune system from recognizing HPV. This inability to recognize and reject HPVs leads to lifelong lesions/ disease. Interestingly, these EV associated HPVs are also involved in both benign and malignant proliferation of keratinocytes, as in the early stages of carcinogenesis.¹⁵ Hence, the convincing oncogenic potential of HPV 5 and 8 in cutaneous malignancies of EV patients has evoked a considerable interest among clinicians and basic researchers for this rare genetic disorder as a model of cutaneous carcinogenesis.^{2,8}

However, the underlying defect in EV is still not well understood. This susceptibility of human keratinocytes to the HPV in EV is usually inherited through an autosomal recessive gene, and pathogenic mutations have been detected in *EVER1/TMC6* and *EVER2/TMC8* genes mapped to a locus on chromosome 17q 25 that encodes integral membrane proteins of unknown significance in the endoplasmic reticulum.¹⁶ A high frequency of parental consanguinity is usual in most reported cases, and more than 30% of the siblings acquire the disease at some or the other stage. The

absence of the disorder in either of the parents, unusual for disorders with autosomal dominant inheritance, can be explained on the basis of “lack of penetrance” wherein a person inheriting the defective gene may not develop the disorder.² Nevertheless, cases with autosomal dominant or X-linked inheritance too have been reported.¹⁷ Mutated *EVER1* and *EVER2* genes in EV patients may control the infection of other viruses.¹⁸ It is often associated with IgM deficiency and HIV infection.¹⁴

The dysplastic and malignant changes in the EV lesions usually occur in the form of actinic keratosis, Bowen's disease or Squamous cell carcinoma having a low metastatic potential.¹² However, all types of lesions seen in EV patients should be subjected to histopathology for early detection of any malignant changes, as clinically benign appearing lesions can demonstrate atypia. Early identification and appropriate treatment of actinic keratoses is also important as these are increasingly being recognized as an early clinical manifestation of biological continuum that may ultimately lead to invasive Squamous cell carcinoma.²

Because Human Papilloma Virus infection is non-lytic, antigen presentation occurs very slowly. HPV infection does not induce inflammatory cytokines therefore, therapeutic options aimed at modulating the immune system and facilitating the production of cytokines have been proposed.¹⁹ Morbidity and mortality associated with EV may be avoided by early recognition of the disease, sun avoidance, monitoring by a dermatologist, and treatment of premalignant and malignant lesions. Treatment options of epidermodysplasia verruciformis are limited, and to date no specific treatment exists. Treatment aims primarily to prevent the progression of benign lesions to malignancy. Medical management for EV includes topical imiquimod and 5- fluorouracil, systemic retinoids, interferon-alpha, cimetidine, zinc, and combination therapy.¹⁷

Acitretin 0.5–1 mg/day has been effective and is perhaps the drug of choice currently.²⁰

Prescribing zinc is due to its immunomodulatory effects. Zinc is a micronutrient that is necessary for the normal functioning of cells. More importantly, this element modulates DNA and RNA related enzymes and is also involved in many immunologic processes. Kitamura *et al.* proposed that toll-like receptors mediated regulation of zinc homeostasis which influences dendritic cell function. Zinc may be administered as acetate, gluconate or sulphate, but

the latter seems to be better tolerated. One 100 mg capsule of zinc sulphate has 22.5 mg of elemental zinc. Normal plasma levels of zinc are 70-110 µg/dl.²¹

Cimetidine's inhibitory effect on T- suppressor cell function and ability to depress mitogen-induced lymphocyte proliferation are among the mechanisms by which its usefulness has been justified.²²

Interferons have been used effectively for the treatment of warts in EV, with their antiviral action and ability to inhibit malignant cell growth and stimulate natural killer cells and T cells.²³ Genetic counseling and frequent dermatologic monitoring of patients should be undertaken.²⁴

These non-surgical modalities, which are only palliative and improve quality of life, need large controlled studies for recommending their lifelong use.

Our patient was unresponsive to the preferred treatment, and hence, he was advised to discontinue oral medications.

Stringent sun protection and lifelong observation for early diagnosis of malignant/premalignant lesions, which then can be treated early with surgical excision/grafting or ablated locally, is imperative for improved prognosis/survival of EV patients.² The same was advised for the present patient also.

Conclusion

This case is being reported to bring to light, the unresponsiveness and resistance to known treatment options. There is a need for further investigations of new treatment modalities for EV. Physicians should monitor patients of EV regularly for early detection of malignant transformation.

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