



Epidermodysplasia Verruciformis – A Review with Role of Autoinoculation in the Management

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ABSTRACT

Epidermodysplasia verruciformis is an inherited disorder, characterized by multiple plane warts, pityriasis versicolor-like lesions, defects of cell-mediated immunity and tendency to develop skin malignancies, primarily on sun-exposed areas. In this article, we present a case of epidermodysplasia verruciformis with multiple verruca vulgaris, pityriasis versicolor-like lesions and verrucous carcinoma on non sun-exposed areas of skin and the effect of autoinoculation in the management. Uniqueness of this case report is that the presented case is a known case of multiple systemic disorders on treatment and was diagnosed to have multiple skin diseases including carcinoma.

KEYWORDS

Epidermodysplasia verruciformis, Pityriasis versicolor-like lesions, Autoinoculation, Multiple verruca vulgaris.

CASE REPORT:

A 42 year old male patient, presented to the Dermatology OPD with the complaints of multiple raised lesions all over the body since 20 years. Patient also noticed multiple swellings over hands and legs since 5 years. He is also a known case of type 2 diabetes and bronchial asthma and on treatment for 3 years. He is on treatment for renal calculi, started few months back. He is an occasional smoker and alcoholic for 5 years. There was no history of similar illness in his family members.

On examination, there were multiple hyperpigmented verrucous plaques present over the forehead [fig 1], neck, upper part of chest [fig 2], back present more extensively over the upper part and right side of back [fig 3], dorsal aspect of both hands [fig 4], extensor aspect of both lower limbs [fig 5] and numerous hypopigmented macules, patches and plaques all over the body which remained asymptomatic. There were also multiple skin colored soft outgrowths present over the extensor aspect of both the upper limbs suggestive of collagen naevi [figs 3 & 6] and lower limbs suggestive of verrucous carcinoma [figs 5 & 7] based on biopsies from the respective sites. There was also multiple, hyperpigmented, hyperkeratotic warty papules over the extensor surfaces of both upper and lower limbs [figs 5 & 8] suggestive of multiple verruca vulgaris were present. In the sternal region, there was a large skin colored plaque which was suggestive of keloid [fig 2]. Pityri-

asis versicolor-like patches were seen over the head and neck region [figs 9 & 10] and more extensively over the back region [fig 11]. There was also hyperpigmented, hyperkeratotic nail changes suggestive of onychomycosis of the index and middle fingers of left hand [figs 12 & 13]. Small hypopigmented papules present over all the knuckle pads of all the fingers of both the upper limbs suggestive of 'Acrokeratosis verruciformis of Hopf' [fig 12 & 13]. Patient was obese with sparse body hair present over the chest and the limbs. Mucosa including genitalia were spared.



Fig 1: EDV over the scalp and extending over the hair margin



Fig 2: Mild pityriasis versicolor-like EDV over the neck and upper chest region with keloid in the sternal region



Fig 3: Pityriasis versicolor-like EDV over back, more over the right side and also with multiple collagen-naevi over the lateral aspects of bilateral upper limbs



Fig 4: EDV over the dorsal aspect of hands



Fig 9: EDV over the post-auricular scalp region, ear lobe, right side of face and limited to the beard region



Fig 10: EDV over the post-auricular scalp region, ear lobe, left side of face and limited to the beard region



Fig 5: Multiple verruca vulgaris along with EDV over the extensor aspects of both the lower limbs

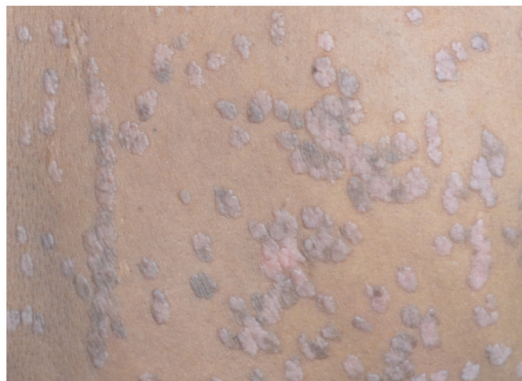


Fig 11: Closer view of EDV of the left side back region in a pityriasis versicolor-like presentation



Fig 6: EDV with collagen naevi over the right upper limb



Fig 7: Closer view of the verrucous carcinoma over the extensor aspect of left lower limb



Fig 12: Acrokeratosis verruciformis of Hopf with distal lateral onychomycosis of the index and middle finger of the left side



Fig 13: Acrokeratosis verruciformis of Hopf with distal lateral onychomycosis of the middle finger of the right side



Fig 8: EDV [right shoulder] with multiple verruca vulgaris [lateral aspect of right upper limb]

The clinical picture was consistent with the diagnoses of:

Multiple verruca vulgaris

Epidermodysplasia verruciformis

Keloid

Collagen nevi

Acrokeratosis verruciformis of Hopf

Onychomycosis of the left index and middle fingers with

Obesity

Type 2 diabetes mellitus

Bronchial asthma

Renal calculi

Verrucous carcinoma

Routine investigations were done and found to be normal including RFT but except with high blood sugar levels. HIV and HbS Ag screening were done and was found to be negative. Skin biopsies were taken from two different sites and were examined. Histopathology from the warts suggested Epidermodysplasia verruciformis by showing the features of hyperkeratosis with keratin forming basket-weave pattern. There was also focal acanthosis and thinning of the epidermis with scattered

inflammatory infiltrate around the blood vessels in the upper dermis.

Histopathologic examination from the nodular growth revealed thinned epidermis with excess collagenisation in the dermal layer where the collagen is formed into nodules and whorls. Adnexa was absent. There was scattered inflammatory cells around the blood vessels. These features were suggestive of collagen naevi.

The procedure of autoinoculation of warts was done twice and the effective response was noticed in 80% of multiple verruca vulgaris lesions. Five sittings of intralesional injection of triamcinolone acetonide were given for the keloid and the effective response was about 75%. Surgical excision of verrucous carcinoma was done by Surgeon after biopsy. Patient was also on treatment for all other systemic complaints and was on regular follow-up by Physician.

DISCUSSION:

Epidermodysplasia verruciformis (EV) is an inherited autosomal recessive gene disorder in which there is early onset, numerous, widespread, persistent, and refractory infection with human papilloma virus (HPV) strains – called EV types^[1-4]. The individual lesions typically have either the appearance of that warts or flat scaly red-brown macules and resemble lesions of pityriasis versicolor or pityriasis rosea. It was first described by Lewandowsky and Lutz in 1922^[5]. It is also known as Lewandowsky and Lutz dysplasia^[6]. Autosomal dominant and X-linked dominant patterns have been reported^[7,8]. There may be more than one HPV type in the same patient. The first type of lesion is usually caused by the same HPV types as those found in flat warts in the general population (e.g. HPV-3 & 10), while the second one is usually caused by EV HPV types (e.g. HPV-5, 8, 9, 12, 14, 15, 17, 19-25, 28, 29, 36-38, 47, 49 and 50). It has no racial or geographic predilection, but increased incidence in consanguineous marriages^[9]. Although EV typically is viewed as a disease of childhood, sometimes presenting in patients with a family history of the disease, it may be seen rarely in immunocompromised adults^[10].

ETIOPATHOGENESIS:

Etiopathogenesis of the disease includes genetic factors, immunologic factors and persistent HPV infections. These patients show a defect in cell mediated immunity. Mutations in two genes EVER1 and EVER2 are linked with the disease in most of the cases. There are at least 20 HPV types characteristic of EV, types most commonly found are HPV 5, 8, 9, 12, 14, 15, 17, 19-25^[11].

More than 100 HPV types are recognised and classified into 3 clinical categories: anogenital or mucosal, cutaneous wart-associated, and -HPV types. -HPV viruses are ubiquitous and nonpathogenic in the normal population^[12].

Patients with EV are known to have defects in cell-mediated immunity, such as anergy to cutaneously applied dinitrochlorobenzene [DNCB] and decreased responsiveness of peripheral T lymphocytes to the nonspecific T-cell mitogen^[13].

Mutations of p53 gene have also been identified^[14]. So the patients should be observed for development of nonmelanoma skin cancers (NMSC).

EV is associated with several types of human papillomavirus, but types 5, 8, and 47 are closely associated with malignant EV lesions which selectively retain and express the E6 and E7 portions of the viral genome. These viral proteins cause cell immortalization, or failure of apoptosis, resulting in transformation of normal human keratinocytes into malignant cells^[15].

RISK FACTORS:

Ultraviolet light is currently considered to be the most important risk factor in the genesis of nonmelanoma skin cancer, but HPV infection also plays a significant role in the development of these neoplasms, especially squamous cell carcinoma.

Other factors, such as smoking, immunosuppression and specific genetic alterations, such as in EV, potentialize HPV's oncogenic effect^[16]. Patients can prematurely show solar elastosis and numerous actinic keratosis-like lesions in the areas of greatest photoexhibition^[17].

CLINICAL PRESENTATION:

There are two main clinical forms [table-1] of EV have been identified, form 1 [benign] and form 2 [malignant]. One form is characterized by multiple plane warts and is associated with HPV-3 and HPV-10. In benign skin lesions, the viral cytopathic effect was only observed in the upper layers of the epithelium. This variant has no tendency for malignant transformation. The second form often occurs in patients with a family history of the disease. Malignant transformation occurs in 30% to 60% of patients with this variant and is associated with HPV-5, HPV-8, and HPV-14^[10].

SECOND FORM:

Second form is considered as autosomal dominant but X-linked recessive modes of inheritance have been reported in one family each, indicating possible genetic heterogeneity.^[18] Malignant changes may occur in the form of actinic keratosis, Bowen's disease, Squamous cell carcinoma, basal cell carcinoma or rarely sweat apparatus carcinoma. Squamous cell carcinoma (in situ or invasive), develop frequently in these patients (30–70%), most commonly on sun-exposed areas starting between the ages of 20 and 40 years^[6].

DIFFERENTIAL DIAGNOSIS:

Clinically, the disease may be confused with verruca plana, seborrheic keratosis and pityriasis versicolor^[10]. Trauner et al reported a case of EV in an HIV-positive patient who presented with scaly erythematous papules and plaques in the groin region that resembled psoriasis^[16].

HISTOPATHOLOGY:

Histopathology shows hyperkeratosis, slightly thickened epidermis, enlarged keratinocytes, some with basophilic and others with eosinophilic cytoplasm, hypertrophic nuclei with perinuclear halos and intracytoplasmic keratohyalin granules^[19].

ASSOCIATIONS:

Patients with defects in cell-mediated immunity are more susceptible to EV and EV has been reported in association with renal transplant, Hodgkin's disease, systemic lupus erythematosus and most recently, human immunodeficiency virus (HIV) infection^[10].

Kidney transplant patients are also commonly associated with viral warts that might change into skin cancers.

Most often, skin cancers appear on sun exposed surfaces, but they can appear on any parts of the body. They begin to appear at ages 20 - 40 years. HPV 5, 8 and 47 are found in more than 90% of EV skin cancers. The squamous cell carcinoma may appear de-novo but usually appear on the background of numerous actinic keratosis and lesions of Bowen's disease, locally and usually aggressive^[20].

Patients with EV have depressed cell mediated immunity to disease-specific keratinocytes. Additionally, an increase in CD8+ and CD57+ T cells (the T cells inhibit cell-mediated cytotoxicity) has been reported in 3 HIV-infected patients with EV^[15].

In a study conducted by Khalifa et al, the results showed that viral warts had been found in 40% of kidney transplant patients, while viral warts admixed up with solar keratosis found in 14% of cases. Skin malignancies mainly squamous cell carcinoma and basal cell carcinoma were seen in 6% cases of kidney transplant patients in combination with viral warts and solar keratosis^[20].

The finding of palmar pits in EV patients is extremely rare and only one case has been reported^[18]. Some rarer associations include Histoplasmosis, Hailey Hailey disease, Sarcoidosis and EV.

A case report has been published with a patient having Astrocytoma, pulmonary tuberculosis, Mantle cell lymphoma, Hepatitis B Virus infection and immunodeficiency after the previous diagnoses of EV represent an interesting uncommon occurrence of these diseases together^[6].

EV has been reported in various immunosuppressed states (sometimes referred to as "EV-like lesions") including HIV, graft versus host disease, renal transplantation, systemic lupus erythematosus, Hodgkin disease, WILD syndrome (warts, immunodeficiency, lymphedema, anogenital dysplasia)^[6].

There are also case reports regarding the association with leprosy and EV, one of them describe an EV patient with a localized form of *M. leprae* infection, confirming that tuberculoid leprosy patients possess a relatively specific and efficient cell-mediated immunity against the bacillus ^[21]. The converse situation occurred in two African sisters with lepromatous leprosy who had EV^[22].

Extracutaneous cancers reported in EV are intestinal adenocarcinoma, plasmablastic lymphoma, natural killer/T cell lymphoma and intestinal lymphoma . A similar instance of EV, disseminated molluscum contagiosum and intestinal diffuse large B cell lymphoma has been published.

Other extracutaneous cancers reported in EV are leiomyosarcoma in a 6-year-old child with an immune defect and Myelodysplastic syndrome also has previously been documented ^[6].

HPV 1 and 2, classically associated with plantar warts, were also isolated in skin biopsies from our patients, together with HPV 5, commonly found in patients with congenital EV^[23].

Mahendra et al reported a case of 23 year old male with plane wart and Pityriasis versicolor-like lesions since the age of 3 years with associated mental retardation and seizure disorder^[24].

SIGNIFICANCE:

Malignant transformation to squamous cell carcinoma has been associated with lesions caused by HPV-5, HPV-8, and HPV-14. [10] UV radiation likely plays role in the progression of EV to cancer because malignancy most often occurs on sun-exposed areas such as the face and hands^[12].

HPVs 5, 8, 9, 12, 14, 15, 17, 19-25 and HPV-5 and 8 are the main type's associated with NMSC. Mutation and abnormal expression of the p53 gene in the viral skin also plays role in carcinogenesis of epidermodysplasia verruciformis.

Table-1:

Features	Form 1	Form 2
Age of onset	Early childhood	Early childhood
Etiology - HPV types	3, 10	5, 8, 14
Family history	Occasionally present	Often present; predominantly autosomal recessive, with susceptibility loci at regions 17q25 and 2p21-24
Clinical presentation	Flat-topped papules	Red, brown or white scaly macules that may coalesce into large patches with polycyclic borders
Sites	Trunk and limbs	Generalized
Histopathology	Hyperkeratosis, acanthosis and vacuolation of cells in granular layer	Few lesions have enlarged keratinocytes with prominent blue-gray cytoplasm and clumping of keratohyalin granules within the granular layer of the epidermis
Malignant transformation	No	Yes; 30%-60% of patients; usually in lesions on UV-exposed areas of the body; after 30 years of age
Differential diagnosis	Verruca plana	Pityriasis versicolor Verruca plana Seborrheic keratosis

TREATMENT:

There is no definitive treatment for EV. Lee et al reviewed the treatment of twenty patients with congenital EV and concluded that oral retinoids (with or without interferon) were effective, as was low-dose oral retinoid maintenance^[25]. Relapses were common upon treatment cessation and caution is advised when prescribing retinoids to adolescents with child-bearing potential due to the recognized teratogenicity . Topical imiquimod, intralesional interferon, 5-fluorouracil, and cimetidine have all been used as treatment, but with variable success^[26]. Previous reports suggest that treatment of HIV-associated EV is less successful than that for classical EV. Haas et al report the resolution of lesions upon starting cART in 1 adult patient^[27]. A recent treatment trial of glycolic acid in HIV-positive children in Botswana showed a trend toward flattening and color normalization in flat warts, although complete resolution was observed in only 10% of patients.

Recently, novel therapies with oral retinoids, interferons or the association of both have been employed with variable results. Systemic or intralesional interferon alpha-2a, in various doses (1-9 million units/day), leads to disappearing of the histological alterations found in EV, through immunomodulating, anti-viral and anti-proliferative actions. Dosage: oral acitretin at 0.75mg/kg/day and interferon alpha-2a, 3,000,000 IU subcutaneously, three times a week^[16].

CONCLUSION:

The diagnosis of EV should be considered in patients with HIV who present with disseminated hypopigmented lesions resistant to treatment with antifungal medications. Patients with EV should be monitored for development of cutaneous malignancy and should be educated about possible serious complications. The concomitant HBV infection is usually discovered incidentally in EV patients, so we should search in relation between co-infection with (HPVs, HBV), immunodeficiency and the development of secondary malignancies in EV patients.

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