

Association of cutaneous malignancy with epidermodysplasia verruciformis: a clinicopathological study

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Abstract *Objective* To find out presence of nonmelanoma skin cancer (NMSC) in a series of 13 patients with diagnosis of epidermodysplasia verruciformis (EDV).

Methods This prospective descriptive study detailed the clinical presentation of patients with EDV associated with nonmelanoma cutaneous malignancy between 2007 and 2010 presenting to Dermatology OPD Pakistan Institute of Medical Sciences, Islamabad. Patients were diagnosed on clinical basis. Patients with all ages and both sexes were included. Skin biopsies were taken from lesions with suspicion of malignancy, stained with hematoxylin and eosin and studied in collaboration with histopathologist. Different histopathological findings were recorded and results analyzed.

Results 13 cases were studied for presence of NMSC. NMSC were found in 3 (23%) out of 13 patients. Actinic keratosis was found in 2 patients and one patient had seborrheic keratosis with suspicious lesions.

Conclusion The clinically suspicious lesions should always be biopsied, as cutaneous malignancy is a well-known, frequent and serious complication of EDV and there is high potential in these patients to develop premalignant conditions.

Key words

Actinic keratosis, epidermodysplasia verruciformis, seborrheic keratosis, squamous cell carcinoma.

Introduction

Epidermodysplasia verruciformis (EDV) is a rare genodermatosis in which there is widespread and persistent infection with human papilloma virus (HPV).^{1,2} It was first described by Lewandowsky and Lutz in 1922.² The susceptibility to the virus is inherited, usually autosomal recessive in manner, though autosomal dominant and X-linked dominant

patterns have been reported.^{3,4} Etiopathogenesis of the disease includes genetic factors, immunologic factors and persistent HPV infections.^{5,6} These patients show a defect in cell-mediated immunity.⁶ Mutations in two genes *EVER1* and *EVER2* are linked with the disease in most of the cases.^{8,9} There are at least 20 HPV types characteristic of EDV, types most commonly found are HPV 5, 8, 9, 12, 14, 15, 17, 19-25.^{7,8}

Clinically, patients present with various types of lesions including plane warts, pityriasis versicolor-like lesions and reddish verrucous

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plaques.⁹ Dysplastic and malignant changes in the form of actinic keratoses, Bowen's disease and squamous cell carcinoma (SCC) are common in adult life.^{8,9}

The first cutaneous lesions usually appear at 4 to 8 years of age usually in the form of warts. They are most numerous on the face, neck, backs of the hands and feet.¹⁰ Squamous cell carcinoma has ultimately developed in one or more lesions in about 20-30% of reported cases mostly in third or fourth decade. HPV-5 and 8 are the main types associated with malignancy.^{9,10} Malignant changes occur mostly on exposed skin, suggesting that ultraviolet radiation is an important factor. Mutations of p53 gene have also been identified.¹¹ So the patients should be observed for development of nonmelanoma skin cancers (NMSC).

This study was carried out to look for burden of NMSC in patients with EDV in our region.

Methods

In this cohort study, after approval from ethical committee of Pakistan Institute of Medical Sciences, Islamabad, patients diagnosed as EDV on clinical grounds were recruited and informed consent was taken from each patient.

Data were collected from each patient including demographics, duration and extent of disease, family history of disease. Biopsy was done from lesions with suspicion of cutaneous malignancy. Clinical details of all the suspicious lesions were recorded along with the change of symptoms and change in morphology of lesions. Clinical photographs of patients with suspicious lesions were also taken as were the slides of diagnostic skin biopsies.

Biopsy specimens were stained with hematoxylin and eosin stain and were examined by dermatologist and dermatopathologist jointly.

Results

13 patients of EDV were included in the study. The age range of patients was 18 to 60 years with 9 (69%) male patients and 4 (31%) female patients. 5 patients were already diagnosed by physicians/dermatologists in their local area as having EDV. 8 other patients were diagnosed afresh after thorough clinical examination by two consultant dermatologists as having EDV. All 13 patients had chronic symptoms and lesions dated back to their childhood. Demographic detail of all the patients was recorded including their place of residence, their profession and sun exposure duration (**Table 1**).

All patients had pityriasis versicolor like lesions and warty lesions dated back to their childhood. 5 already diagnosed patients had been advised avoidance from sun exposure and use of topical sunscreens. But it was not possible for all to observe strict sun avoidance mainly due to their profession. Most of the patients already diagnosed had not been told about proper technique of sunscreen use. All of them belonged to poor socioeconomic class which also lead to nonaffordability of drugs. All the patients were again advised about avoidance of sunlight and proper use of sunscreens. 4 newly diagnosed patients were also advised oral retinoids but none of them used medication due to nonaffordability.

Among 13 patients, skin biopsy was carried out in all patients with suspicious lesions mostly involving sun exposed areas. Clinical lesions with suspicion of cutaneous malignancy were seen in 10 patients. NMSC (squamous cell carcinoma, basal cell carcinoma, basisquamous

Table 1 Demographic detail of patients.

Patient No.	Age (years)	Gender	Place of residence	Occupation	Age of onset	Type of first lesion
1	18	M	Chakwal	Student	18	Warts
2	22	F	Pindi Bhattian	Housewife	22	Pityriasis versicolor-like
3	45	F	Hari pur	Housewife	19	Warts
4	32	M	Rawat	Labourer	21	Warts
5	21	M	Jehlum	Sweeper	18	Warts
6	20	M	Rawalpindi	Hawker	20	Pityriasis versicolor-like
7	57	M	Abbottabad	Cobbler	13	Pityriasis versicolor-like
8	48	F	Kharian	Housewife	15	Warts
9	54	M	Rawalpindi	Labourer	16	Warts
10	60	F	Islamabad	Housewife	22	Warts
11	56	M	Bhera	Labourer	14	Pityriasis versicolor-like
12	49	M	Chashma	Labourer	17	Warts
13	44	M	Rawalpindi	Beggar	21	Pityriasis versicolor-like



Figure 1 Ulcerated lesion below eye on left cheek.



Figure 2 Nonhealing ulcerated lesion involving left upper half of face.

carcinoma) was found in 3 (23%) patients. In 2 patients lesions turned out to be of actinic keratosis and seborrheic keratosis was noted in 1

patient. Biopsy of 4 patients was nonspecific and no malignant change was noted.

Among three patients in which lesions turned out to be malignant, the lesions were persistent lasting for more than 6 months and there was history of bleeding and itching with history of increase in size of lesions. One patient had 6-month history of excoriated lesion which later on ulcerated with history of itching and discharge of pus and blood from lesion involving left cheek (**Figure 1**). There were also pityriasis versicolor-like lesions involving face and upper trunk. Ulcer on cheek was biopsied and it turned out to be squamous cell carcinoma. Other patient presented with nonhealing ulcer on left temporal region for last 8 months which started as a papular lesion and had itching and bleeding off and on for which we did biopsy and it turned out to be basal cell carcinoma (**Figure 2**).

Another patient was 60-year-old male who presented with persistent plaque on left frontoparietal region. Biopsy was done and it turned out to be basisquamous cell carcinoma. He had this recurrence with previous biopsy diagnosis of squamous cell carcinoma done at 35 years of age.

All the patients were Asians. All patients were of wheatish complexion, none was very fair. The most common presentation was discoloration of skin representing pityriasis versicolor-like lesions; other presentations included plaque like or warty lesions and nonhealing ulcers with itching and ulcer formation. Lesions were most commonly seen on sun-exposed areas including hands, forearm, face and trunk.

Family history of similar lesions was not found in any of the patients. All 3 of them were male patients with significant sun exposure related to their occupation. Nonmelanoma skin cancers were seen in patients during third and fourth decade, one patient presenting with recurrence of NMSC during sixth decade.

All these 13 patients were kept on regular long-term follow-up in dermatology outpatient department to observe for any suspicious lesions developing later on.

Discussion

Epidermodysplasia verruciformis (EDV) is an inherited disorder in which there is widespread and persistent infection with HPV.^{11,12} Clinical presentation is in the form of combination of plane warts, pityriasis versicolor-like lesions and reddish plaques.^{13,14} The susceptibility to the virus is inherited, usually autosomal recessive. Impairment of cell-mediated immunity is commonly found.¹⁵

Malignant change is very common in adult life. There are at least 20 HPV types characteristic of EV, including types most commonly found in the skin of these patients: HPVs 5, 8, 9, 12, 14, 15, 17, 19-25 and HPV-5 and 8 are the main type's associated with NMSC.^{15,16} Mutation and abnormal expression of the p53 gene in the viral skin also plays role in carcinogenesis of

epidermodysplasia verruciformis.¹² Other cutaneous features include actinic keratosis, seborrheic keratosis, pigmented warts and Bowens disease.¹⁷

Benign lesions in EV start in late infancy and carcinomas develop after the third decade of life, usually within 20-40 years after onset of the disease.¹⁸ Patients frequently develop squamous cell carcinomas (SCCs) of the skin mainly on sun-exposed sites.^{17,18}

A study was done to find out occurrence of NMSC in 7 patients of EDV.⁶ It showed presence of malignancy in 6 patients. While another study done by Jacy and Villiers in Africa showed presence of NMSC in only one patient, out of 20 patients included in the study.¹⁹ In a case report from India, NMSC was seen in one of two siblings.²⁰

In our study 13 patients with clinical diagnosis of EDV were included. Frequency of NMSC development was 23% occurring during third and fourth decade and one patient presented with recurrence of NMSC in sixth decade.

The prevalence of NMSC is a well-known complication of EDV but its frequency varies in various regions of the world owing to varied exposure to sun light, occupation of patients and variation in other malignancy causing factors in different populations. Patient's education, early presentation to dermatologist, accurate and early diagnosis etc. also contribute to the results of various studies in different parts of the world.

In the present study, although all patients were diagnosed in childhood or adulthood but still on inquiring it was obvious that none of them used effective sun protection either in form of physical barrier or regular sunscreen usage. They all knew about sun protection but did not

realize its importance. All patients lost to follow-up to their respective hospitals or doctors. This led us to ponder whether it was fault on behalf of clinicians who did not make patients realize the importance and seriousness of situation or it was carelessness on part of patients, since it is a chronic disease or was it simply due to nonaffordability of patients for sunscreens and oral retinoids. This study is an eye opener for the clinicians practicing in this region to emphasize the need for good communication making patients realize the seriousness of situation and giving them good guidance to identify those factors which lead to the serious complications like NMSC and how to prevent them if possible.

Treating physicians should give some printed material for awareness of patients not only for EDV, its complications and prevention but for many other chronic dermatological diseases which have serious long-term complications which can easily be prevented by education of patients.

The present study not only reflects a part of disease burden but gives some idea of the magnitude of illness. It emphasizes for early detection and accurate diagnosis of the condition along with a need of prompt necessary action to treat malignancy with emphasis on regular monitoring of such patients.

Conclusion

Nonmelanoma skin cancer is a well-known and frequent complication in patients with EDV in our region. Patients with EDV should be monitored for development of cutaneous malignancy and should be educated about possible serious complications.

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