Invasive squamous cell carcinoma of the eyes in patients with epidermodysplasia verruciformis

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ABSTRACT

We described 3 male patients with epidermodysplasia verruciformis seen in the Department of Dermatology and Venereology, Baghdad Teaching Hospital; their ages were 25, 30 and 34 years subsequently. They developed frequent multiple basal and squamous cell carcinoma, all of them had periorbital squamous cell carcinoma that invaded the orbit and ended with enucleation of their eyes. All available therapeutic measures failed to inhibit the progressiveness of these tumors. Great awareness and early management must be performed regarding any periorbital lesion in epidermodysplasia verruciformis patients.

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Epidermodysplasia verruciformis (EV) is an autosomal recessive skin disease characterized by early onset, numerous, widespread and persistent human papillomavirus (HPVs) infection, giving rise to characteristic combination of plane warts, pityriasis versicolor-like lesions and reddish plaques.[1-4] These HPV types are called EV, HPVS and include HPV (5,8,9,12,15,17,19-25,28,29,36-38,47,49,50).[2-8] In addition, HPV 3 and 10, which cause ordinary plane warts are found in EV patients.[2-7] There may be more than 1 HPV type in the same patient.[5,6,8] Squamous cell carcinoma develops in 30-60% of epidermodysplasia verruciformis patients.[1-4,8-10] These dysplastic and malignant changes arise in pityriasis versicolor-like lesions on sun-exposed skin, commonly as actinic keratosis and Bowen's disease suggesting that ultraviolet is an important factor.[1-4,8-10] Most of the malignant tumors remain local,[1,3] but regional and distant metastasis may occur.[1,3] The aim of the present report is to record 3 cases of EV with locally invasive squamous cell carcinoma that invaded the orbit and unfortunately ended with eyes enucleation.

Case Report. *Patient one.* A 34-year-old man from Diayla Governorate in Iraq, attended to the Department of Dermatology and Venereology, Baghdad Teaching Hospital on July of 2001, with classical presentation of EV with negative family history. The condition started at the age of 6 years, as extensive, multiple skin rash with some warty lesions affecting the face mainly forehead, cheek, and periorbital area. Then, the rash extended gradually to involve the whole trunk and lower parts of extremities. The number and size of lesions was gradually increasing. At the age of 25, he developed multiple pigmented basal cell carcinoma and solar keratosis affecting the sun exposed parts of the body. Frequent excisional biopsies showed pigmented basal cell carcinoma and solar keratotic changes (**Figure 1a**). Some lesions were curettaged and cauterized. Examination at presentation revealed numerous pigmented papular, nodular, and ulcerative types of basal cell carcinoma, seborrheic keratosis-like, solar keratosis and cutaneous horns in different size and locations of the face and v-area of the chest. In addition, there were diffuse plane warts and reddish to brown pityriasis versicolor-like lesions affecting the face, the whole trunk and dorsum of the hand and feet. A trial of oral zinc sulphate in a dose of 600 mg /day for 6 months without benefit. Monthly Bacille-Calmette-Guerin (BCG) vaccination was also carried out 3 times on successive month without any response.[11] Oral acitretin in a dose 75 mg/day for 6 months failed to achieve a reasonable result.[1,12,13]Interferon-α, was not available at the time of seeing the patient. Later on, the rash around the right eye progressively enlarged in size until it became a fungating mass that covered the eye lids (**Figure 1b**). Biopsy from the mass denoted invasive squamous cell carcinoma. Further ophthalmological assessment revealed deeper invasion of the orbit that justified complete enucleation of the damaged eye.

Patient 2. A 25-year-old man from Basrah Governorate in Iraq attended to the Department of Dermatology and Venereology, Baghdad Teaching Hospital on February of 2002, with clinical features of EV since the age of 6. His family composed of 8 members (5 females and 3 males), 2 brothers were affected. He developed multiple pigmented maculopapular rashes with some warty lesions affecting the face, upper trunk, forearms and dorsum of the hands. Over time, the lesions increased in size and number. In 1991, he presented with multiple basal cell carcinoma and solar keratosis affecting the face and v-area of the chest. In 1993, he was seen by plastic surgeon due to a small, pinkish, and fungating mass on the right eyebrow. The size of mass was approximately 1.5 x 1.5 cm which gradually increased over time. Biopsy with histopathological examination showed invasive squamous cell carcinoma. Systemic evaluation showed no internal involvement. Complete excision and graft was performed. Later on, in 1996, the mass relapsed on the same site for which another wide resection and graft was carried out. In the year 2000, he developed an invading mass at the same location towards the orbit and there was no regional lymph node enlargement. It was difficult to save the right eye and urgent enucleation of it was arranged (**Figure 2**). The histopathological examination revealed invasive squamous cell carcinoma infiltrating the deep through facial skeletal muscles. The patient gave no history of receiving systemic treatment like zinc sulphate, monthly BCG, acitretin and interferon-α.

On February 2002, full clinical examination showed many warty lesions, pigmented basal cell carcinoma, seborrheic keratosis-like, actinic keratosis and cutaneous horns in different size and locations of the face and v-area of the chest, with plane warts lesions on the chest and dorsum of the hands. Depressed scar approximately 4 x 5 cm in size, as a result multiple operations on the right frontal region. He lost his right eye with brow and there was a pigmented basal cell carcinoma at the end of scar line of operation. We prescribed him a systemic zinc sulphate in a dose of 600 mg/day. However, his compliance was insufficient and never return back to us for follow-up.

Patient 3. A 30-year-old man from Salah Al-Din Governorate in Iraq, attended to the Department of Dermatology and Venereology, Baghdad Teaching Hospital on June of 2002, with typical presentation of EV since early childhood with positive family history as he had 5 sisters and 2 brothers were affected by the same skin problem. He had multiple basal cell carcinoma and solar keratotic changes on the face. Both hands and legs were covered with big warty lesions coalescing together to form a sheet, in addition to tinea versicolor-like picture on the neck and upper trunk. He received systemic zinc sulphate in a dose of 600 mg/day,[11,12] in addition to that, we curettaged and cauterized some other lesions. Unfortunately, we lost him and then he arrived to our department on February of 2004 with extensive locally destructive tumor affecting the right orbit. The histopathological study revealed invasive

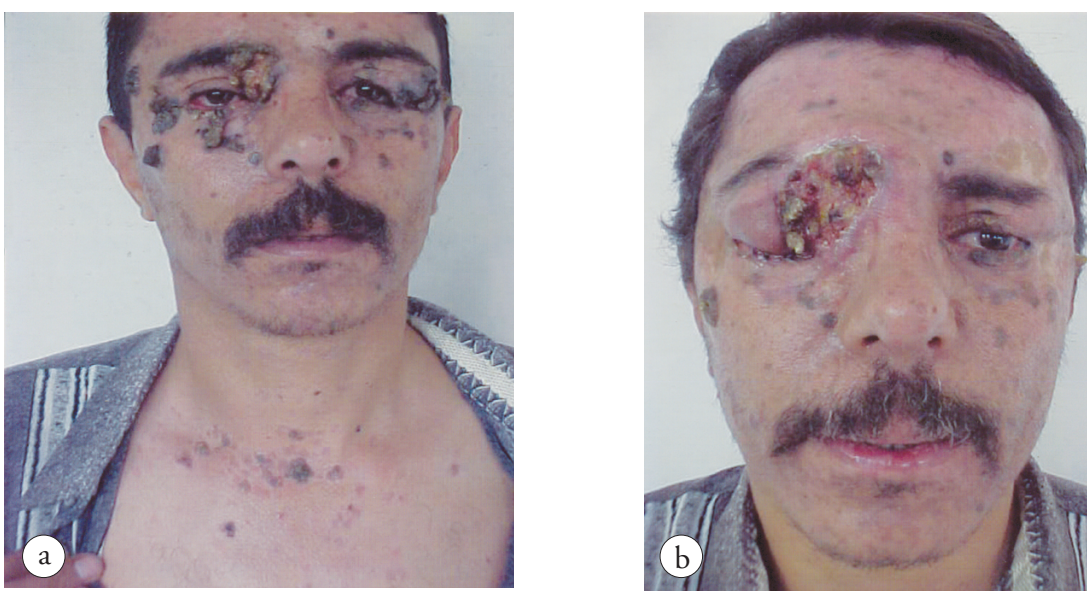

Figure 1 - Photograph showing **a)** case of extensive lesions of basal cell carcinoma and squamous cell carcinoma. **b)** the same patient with invasive squamous cell carcinoma of the right eye that ended with enucleation .

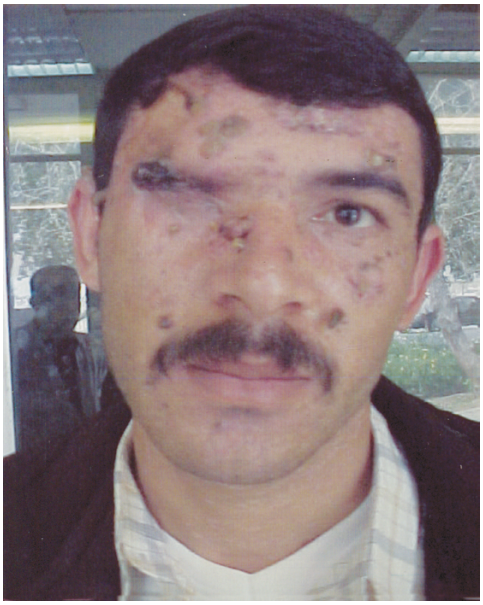

Figure 2 - Showing the second case with enucleation of the right eye.

squamous cell carcinoma. Enucleation of the right eye was carried out in April 2004. However, he died after 1 month of operation for no obvious reason.

Discussion. Epidermodysplasia verruciformis is an inherited disorder in which there is early onset, numerous, widespread, persistent and refractory infection with HPVs giving rise to characteristic combination of plane warts, pityriasis versicolor like lesions and reddish plaques. The susceptibility to the virus is inherited usually autosomal recessive gene.[1-4] The individual lesions typically have either the appearance of the warts or flat scaly red-brown macules; resemble lesions of pityriasis versicolor or pityriasis rosea. The first type of lesion is usually caused by the same HPV types as those found in flat warts in the general population such as HPV 3 and 10, while the second one is usually caused by EV, HPV types (for example: HPV 5,8,9,12,15,17,19-25, and 47).[2-7] There may be more than one HPV type in the same patient.[5,6] The pathogenesis of this disease is unknown but felt to be a specific impaired cell mediated immunity.[2-4] Some patients are at high risk of developing malignancy especially squamous cell carcinoma. These tumors usually arise in pityriasis-like lesions caused by any EV, HPV type on the sun-exposed parts of the body.[1-4] The risk appears to be greatest for those caused by HPV-5,8, and 47.[1-4] In Iraq, although consanguineous marriages are common among Iraqi societies,[14] but fortunately there are only 2 foci, in Sammara (North of Baghdad) and Diayla where the disease seems to be common among their families, although sporadic cases could be seen from other Iraqi areas. From our clinical observation, approximately 4-6 families were seen every year from these areas attending our department. The management of this disease is very difficult, although trials of many drugs have been used orally or topically like retinoid, 5-flurouracil, imiquimod, interferon-α, photodynamic therapy, and sunscreen. Substantial clinical improvement is often achieved by using etretinate in a dose of 1 mg/kg/day, but signs of viral infection persist histologically. The effect is dose dependent and relapse occurs if the drug is stopped.[1] Interferon has been effective in reducing warts but lesions return when therapy stopped. Malignancy is a common complication of this disease such as basal and squamous cell carcinoma.[1-4] In our cases, multiple basal and squamous cell carcinomas were commonly present. Unfortunately, the squamous cell carcinoma around the orbits invaded the eyes and urgently needed eye enucleation as a radical therapy for this lesion in these 3 cases. Therefore, we recommend urgent destructive and removal of EV lesions especially around the vital organs like the eye. As mentioned in the literatures, most of malignant tumors remain local, while regional and distant metastasis rarely occur.[1,3] However, in our clinical practice, we have seen only these 3 cases with regional metastasis. In addition, as most of malignancies of EV occur on the exposed part of the body, sun exposure might trigger the onset of tumors. Avoiding complete sunlight and using sunscreen is mandatory as a prophylactic measure against malignancies.[1-4] Also, it is essential to give chemo-preventive agents to stop the progression of this disease and appearance of new lesions by using these drugs such as retinoid, 5-flurouracil, imiquimod, interferon-α and photodynamic therapy.[1-4] We conclude that EV is still a very difficult and annoying problem; until now, there is no beneficial therapies available to fight this disease. These patients should be cautioned against sun light exposure and should watch carefully on regular bases for malignancies in order to save important organs such as the eye.

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