EPIDERMODYSPLASIA VERRUCIFORMIS WITH SQUAMOUS CELL CARCINOMA IN A FAMILY

Vinod K Sharma, Surrinder Kaur, Bhushan Kumar and Shobha Sehgal

Three Indian sibs with epidermodysplasia verruciformis (EV), born of consanguineous marriage, are described. The lesions were hypopigmented, erythematous, flat papules present over the face, neck, trunk and upper extremities. Multiple Bowen's keratosis over the face in case 1 and 2, and squamous cell carcinomas over the forehead in case 1 and the scalp in case 2 were also present at the time of presentation. Cell-mediated immunity was depressed in all the three cases. Viral particles were demonstrated in the nucleus by electronmicroscopy in the lesion of EV. No direct association with any HLA type could be established.

Key words : Epidermodysplasia verruciformis, Bowen's keratosis, Squamous cell carcinoma, Cell-mediated immunity, Human papilloma virus (HPV).

Epidermodysplasia verruciformis (EV) was first described in 1922 by Lewandowsky and Lutz.[1] It is a rare disease characterised by wart-like lesions occurring over the face, neck, trunk and the extremities. The lesions are more verrucous on the exposed parts,[2] appear during childhood and persist for decades. However, spontaneous regression after two successive pregnancies has been observed.[3] The causative micro-organism is human papilloma virus(HPV), different from the virus of common or venereal warts.[4,5] HPV 3,4[6] and rarely HPV 8[7] are responsible, HPV 4 is presently referred to as HPV5.[8] In an individual case, the infection may be caused by HPV 3 or HPV 5 and rarely both.[2] The lesions caused by HPV 3 are similar to the flat warts, whereas those of HPV 5 infection are hypo or hyperpigmented and scaly, akin to the lesions of pityriasis versicolor and show increased propensity for malignant change. Viral particles were first demonstrated in the lesions by Ruiter ad Van Mullem.[9] The finding has subsequently been confirmed by numerous workers.[10-17] Malignant transformation, generally over the exposed parts occurs at a relatively young age.[10,18] Multiple Bowen's keratosis, squamous and basal cell carcinomas and rarely rhabdomyosarcoma[19] may develop. The cell mediated immunity (CMI) is depressed in a majority of the patients.[8,15,20,21]

In the present communication, three cases of EV occurring in an Indian family are reported. Two had squamous cell carcinomas and multiple Bowen's keratosis at the time of presentation.

Case Reports

Case 1

A 23-year-old male presented with non-pruritic skin lesions since the age of ten years. The lesions initially appeared on the forehead, and sides of the face and later over the neck, trunk and extremities. Gradually, these increased in number and size. No lesion had regressed spontaneously. Some lesions over the face became crusted and turned dark brown during the past one year. Three lesions on the right cheek grew into miniature horns and recurred within three months of local excision by a practitioner. A fast growing fleshy growth developed over one of the brown crusted lesions over the forehead since six months. In addition, the patient suffered from frequent attacks of cold since early childhood.

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He was born of a consanguineous marriage, the parents being second degree cousins (Fig. 1). A younger brother (case 2) and sister (case 3) were similarly affected. There was no history of a similar disease in the parents or grand parents.

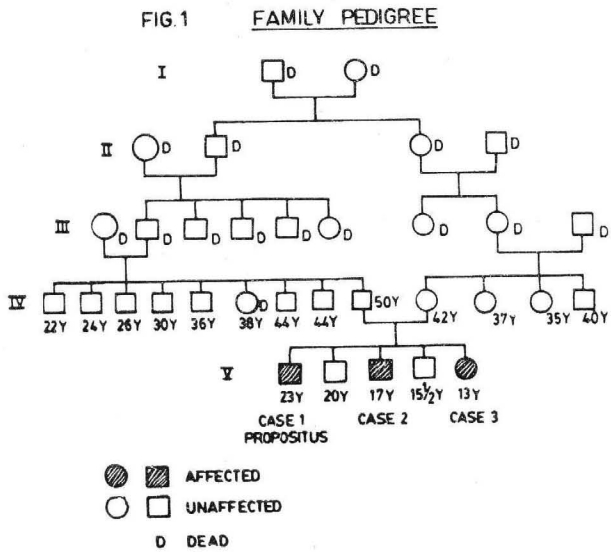

Fig. 1. Family pedigree.

General and systemic examination was normal except for left chronic suppurative otitis media. Cutaneous examination revealed multiple hypopigmented, erythematous, flat papules with irregular borders and rough surface. Lesions varied from 1-10 mm in size and were maximum on the face, neck, trunk and upper extremities. Lesions were sparse on the lower extremities, and were more verrucous on the dorsa of hands. Genitalia and perineum were involved but axillae, groins, popliteal fossae, palms, soles, oral and genital mucosae were spared. A rounded fleshy growth, 4×5 cm in size and with rolled out borders was present over the forehead (Fig. 2). It bled on touch and was not fixed to the underlying structures. Regional lymph nodes were not enlarged. Three dark brown, horny growths were present on the right cheek and multiple dark brown crusted lesions 3-8 mm in size were present over the forehead and sides of the face. Removal of crusts left raw, moist surfaces.

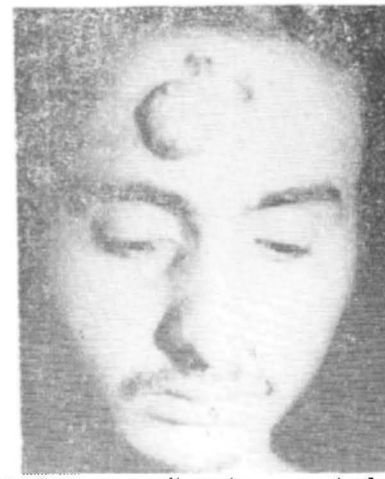

Fig. 2. Squamous cell carcinoma on the forehead and multiple Bowen's keratosis (case 1).

Case 2

A 17-year-old younger brother of case 1, developed hypopigmented flat papular lesions

over the face, neck and extremities at the age of ten years. The evolution and distribution of the lesions was similar to case 1 except for mild pruritus. Multiple hyperkeratotic lesions had developed on the scalp during the last five years which recurred after local excision. Subsequently, many dark brown crusted lesions of irregular shape and size between 2-8 mm appeared on the forhead and sides of the face. A rapidly growing, bleeding, fleshy growth developed on the right side of the scalp during the last five months. With onset of the skin lesions, the patient also started having frequent attacks of cold and cough with mucoid expectoration. There was intermittent purulent discharge from both the ears for the last five years. General examination showed mild anaemia and right chronic suppurative otitis media with attic perforation. Systemic examination was essentially normal. The tumour over the scalp was 6×4 cm in size (Fig. 3) and was not fixed to the underlying bone. Regional lymph nodes were not enlarged. Koebner's phenomenon was noticed over the trunk and the forearms.

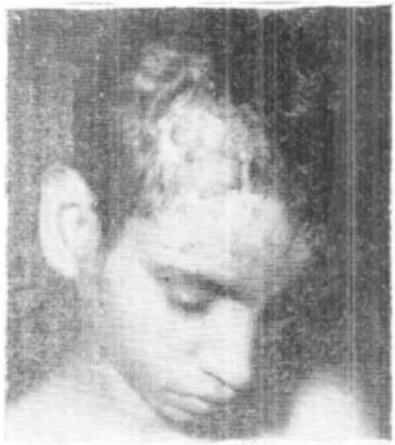

Fig. 3. Squamous cell carcinoma on right side of scalp and multiple Bowen's keratosis (case 2).

Case 3

A 13-year-old sister of these patients developed non-pruritic, hypopigmented, slightly erythematous flat papules on the face, neck, trunk, forearms and dorsa of hands, and scattered lesions over the lower extremity for three years. The lesions on the trunk resembled pityriasis versicolor (Fig. 4). The lesions were more on the extensor than the flexure surfaces. There were no growths or crusted brown lesions. She had occasional ear discharge, and cough with mucoid expectoration for three years. However, ENT examination was normal.

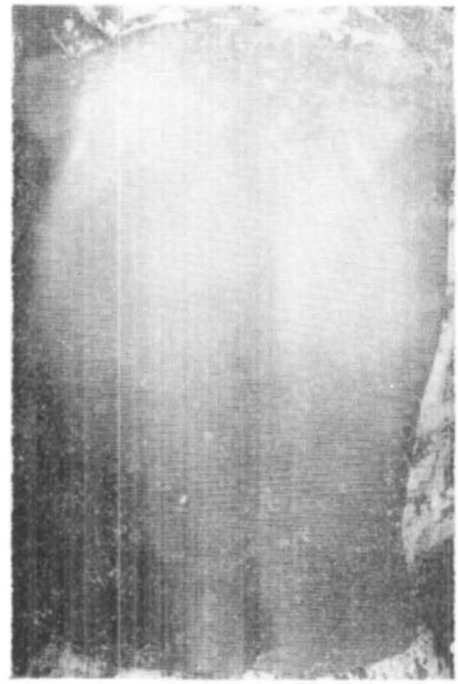

Fig. 4. Pityriasis versicolor like lesions on the back (case 3).

The parents and the other three sibs were found to be normal.

The following investigations were carried out in all the 3 patients : complete blood counts, haemoglobin, erythrocyte sedimentation rate, peripheral blood smear, serum electrolytes, creatinine, blood urea, liver function tests, total and differential proteins, serum electrophoresis, immunoelectrophoresis and urinalysis. Skiagrams of the chest, dorso-lumbar spine, hip joint and skull were done. Skin biopsy was taken from a verrucous lesion on the forearm

in all cases, the fleshy growth and brown crusted lesions were biopsied in cases 1 and 2. Biopsy of the horny lesion on the cheek was taken in case 1. The material was studied by light and electron microscopy.

Intradermal tests were carried out with tuberculin, candidin and aspergillin. The readings were taken at 24 and 48 hours. DNCB (dinitrochlorobenzene) sensitization was done by the method of Filber and Morton.[22] Venous blood was collected for T and B cell counts by the method of Jondal et al,[23] and blast transformation was studied in response to PHA (phytohaem-agglutinin), Con A (concanavalin A) and PWM (pokeweed mitogen). HLA studies were conducted in the patients, the three normal sibs and the parents.

Results

Routine investigations were within normal limits in all the patients except for mild anaemia present in case 2. Spina bifida was present in case 3, all other skiagrams were normal. Intradermal tests with tuberculin, candidin and aspergillin were negative in all three cases and DNCB sensitization could not be achieved in any. T cell counts were lower than normal whereas B cell counts were within normal limits in all three cases. Blast transformation in response to PHA, Con A and PWM was diminished in all three cases. Light microscopic examination of biopsies from forearm showed basket weave hyperkeratosis, mild acanthosis and presence of vacuolated cells in groups in the granular and prickle cell layers (Fig. 5). The dermis was unremarkable. These changes are consistent with the diagnosis of EV. The dark brown crusted lesion showed histopathologic changes consistent with both EV and Bowen's disease. The fleshy growths in case 1 and case 2 showed moderately differentiated squamous cell carcinoma. The horny growth from case 1 showed changes of cutaneous horn with a few atypical cells. Electron microscopy showed intranuclear viral particles arranged in a crystalline pattern

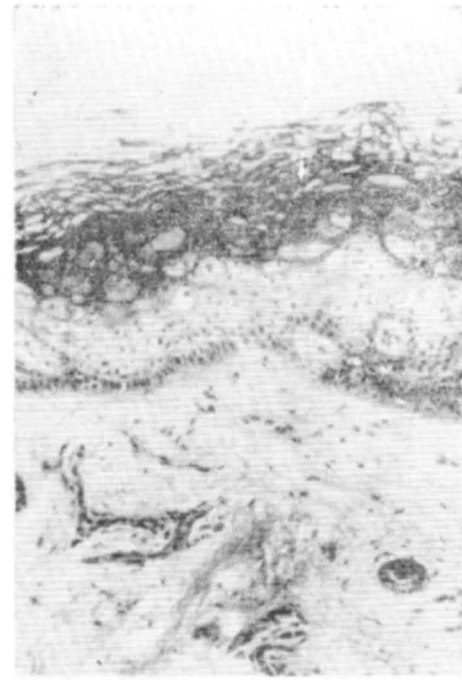

Fig. 5. Basket weave hyperkeratosis and vacuolated cells in the prickle and granular cell layers of epidermis (Haematoxylin-eosin×140).

(Fig. 6). HLA typing revealed that affected sibs were sharing the identical haplotypes.

Comments

All the three patients had characteristic clinical features of EV, the diagnosis was confirmed by histopathology and demonstration of viral particles by electron microscopy. Clinical features such as pityriasis versicolor like lesions, premalignant lesions i.e. Bowen's keratosis, cutaneous horn, and squamous cell carcinomas in case 1 and case 2 are suggestive of HPV type 5 infection. EV caused by HPV 5 has a high incidence of malignancies.[4] Malignancies have been reported to develop in 20-30%,[13,24] to almost all cases if followed for sufficiently long periods.[18] Squamous cell carcinoma and multiple Bowen's keratosis were present at the time of presentation in cases 1 and 2 but not in case 3. No case of EV with malignancy has been reported from India.[25-28] Malignancies developed on the

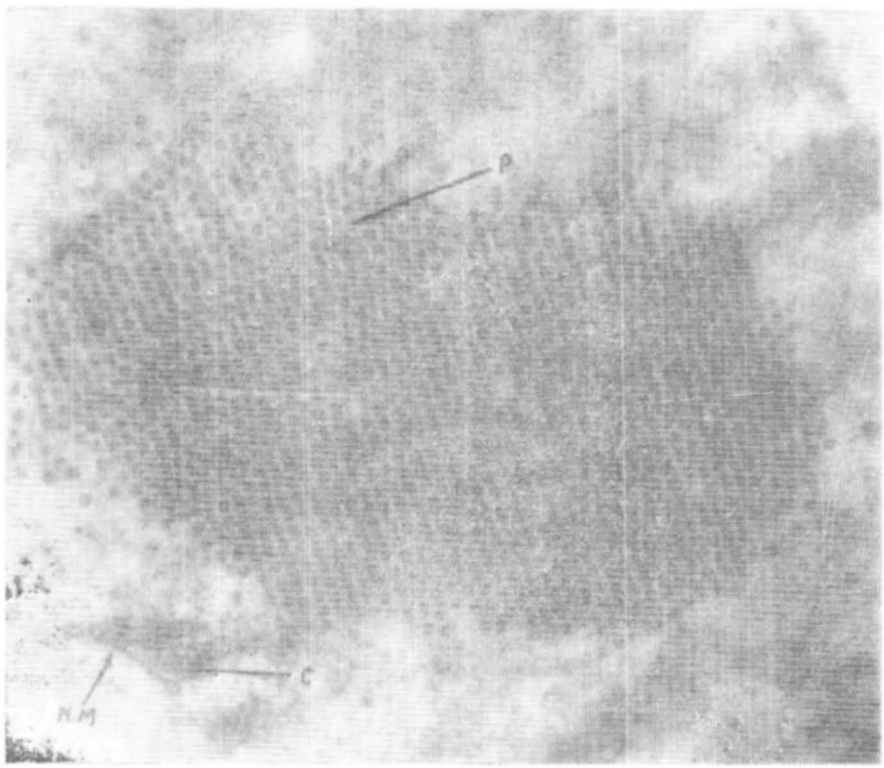

Fig. 6. Electron micrograph showing crystalline arrangement of viral particles (P) in the nucleus, nuclear membrane (NM) and chromatin (C) (X 30,000).

sun exposed areas i.e. forehead and scalp, as has been reported by others.[2,13] Factors believed to be responsible for malignant transformation are oncogenicity of the virus,[13] ultraviolet light, impaired DNA repair[12] and depressed CMI.[15]

Cell-mediated immunity (CMI) was depressed both in vivo and in vitro in all the three cases. DNCB sensitization was negative in all the cases. Similar findings have been reported by other workers.[8,15,20,21] Depressed CMI may be responsible for persistence of the virus infection. However, it is not known whether the depressed CMI is the cause or the effect of virus infection. Serum immunoglobulins were normal in all the cases as has been reported by Prawer et al.[15] However, Pyrhonen et al[21] found lower values of serum antibodies against HPV in EV as compared to patients with other HPV infections. CMI was depressed both in patients with and without malignancy. Similar findings were reported by Prawer et al[15] and Glinski et al.[20] All the three cases occurred in the sibs born of consanguineous marriage. Familial occurrence and consanguinity have been reported by other workers.[5,29-31] Mode of inheritance is probably autosomal recessive with equal occurrence in males and females but a Chinese family of six females with sex-limited autosomal recessive inheritance has been documented.[32] HLA studies showed that the affected sibs were sharing the identical haplotype. As both the parents were disease free, it was difficult

to attribute the direct genetic linkage with HLA. There is need for further investigation on this aspect of EV. It will also be interesting to find whether the patients of EV are susceptible to other viral or bacterial infections. Two patients under report had chronic suppurative otitis media, one of them also had an episode of broncho-pneumonia during hospital stay. Recently, two sibs with EV having lepromatous leprosy have also been reported from Sudan.[33] The authors had suggested that because of depressed CMI due to lepromatous leprosy, the patients developed EV. However, it is also likely to be a coincidence.

Excision of the squamous cell carcinoma and cutaneous horns followed by grafting was done with good results. Bowen's keratoses were either excised or treated with cryotherapy. Attic perforation necessitated mastoidectomy in case 2. All the cases were treated with levamisole 150 mg on two consecutive days per week for eight weeks with the aim of stimulating CMI, but there was no clinical or immunological response. Patients were explained about the disease and advised regarding protection from sunlight, use of reflectant sunscreens and followed up every three months. Within three months, the lesions of EV developed in the grafted skin, and in case 2 after a period of nine months, a new growth developed at the edge of the previously excised lesion. Excision and grafting was done again. Histopathologically, it was a squamous cell carcinoma. Further follow up for nearly two years, revealed new Bowen's keratosis in cases 1 and 2 which were treated.

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