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Case Series

Familial epidermodysplasia verruciformis with intrafamilial phenotypic variability: a case series of three siblings

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ABSTRACT

Epidermodysplasia verruciformis is a rare inherited skin disorder characterized by persistent susceptibility to selected beta human papillomavirus types. The disease usually begins in childhood and follows a slow, progressive course, with lesions increasing in number and distribution over time. Clinical severity is variable and often unpredictable, even within the same family, and the risk of later malignant transformation remains a major concern. We describe three siblings from a single family diagnosed with epidermodysplasia verruciformis to demonstrate intrafamilial variability in clinical presentation. All patients underwent detailed clinical evaluation and family history assessment. Histopathological confirmation was obtained in one sibling, while diagnosis in the remaining two was made on the basis of characteristic clinical features in a familial setting. The index patient, a 19-year-old female, developed hypopigmented and hyperpigmented lesions at six years of age, with gradual involvement of the face, trunk, limbs, and external genitalia. Her elder brother had a similar age of onset but more extensive cutaneous involvement. The younger brother presented later, at ten years of age, with fewer lesions largely confined to the limbs. None of the siblings showed clinical evidence of malignant change at evaluation.

Keywords: Epidermodysplasia verruciformis, Genodermatoses, Papillomavirus infections, Siblings, Skin neoplasms

INTRODUCTION

Epidermodysplasia verruciformis is an uncommon inherited cutaneous disorder first brought to notice by Lewandowsky and Lutz in 1922.[1,2]

Subsequent observations have shown that affected individuals exhibit a persistent and selective susceptibility to certain cutaneous human papillomavirus types, predominantly beta human papillomaviruses. Among these, types 5 and 8 are most frequently implicated, despite being clinically silent in individuals with intact immune function.[3-5]

Most reported patients follow an autosomal recessive pattern of inheritance, though sporadic cases without a documented family history and rare X-linked variants have also been described.[6] The disease usually manifests during childhood and follows a slowly progressive course.

Lesions tend not to regress and instead accumulate over time, both in number and extent. Clinical morphology is often mixed, with hypopigmented or hyperpigmented macules coexisting with flat wart-like papules, verrucous plaques, or seborrheic keratosis–like lesions, sometimes in the same individual.[7,8]

A major issue in long-term management is the risk of malignant transformation. Squamous cell carcinoma has been reported in a considerable proportion of patients, particularly involving sun-exposed sites, most often in early to mid-adulthood, though the timing and severity vary widely.[9]

Familial clustering with marked variability among siblings is a recognized feature.

Differences in age of onset, lesion type, distribution, and overall disease burden have been documented within the same family, suggesting complex interactions between genetic factors, environmental exposure, and host response.[10]

In the present report, we describe three siblings with epidermodysplasia verruciformis, emphasizing the intrafamilial clinical variability, supported by histopathology in one patient and photographic documentation.

CASE SERIES

Case 1: index case (female patient)

A 19-year-old female presented with multiple light and dark colored skin lesions involving almost the entire body, including the face, scalp, neck, trunk, both upper and lower limbs, axillae, groin, buttocks, and external genitalia. According to the patient, the lesions first appeared when she was around six years old and increased slowly over the years, eventually becoming widespread.

The lesions were asymptomatic. There was no history of itching, pain, burning sensation, or photosensitivity. She had received intermittent oral and topical treatment about four years prior, following which some improvement was noted.

However, after stopping treatment, the lesions gradually reappeared. There was no history suggestive of recurrent infections, systemic illness, or known immunodeficiency. The parents were non-consanguineous.

On cutaneous examination, multiple well-defined hypopigmented and hyperpigmented macules were seen along with verrucous papules and plaques of varying sizes. Facial involvement was marked, with dense hyperpigmented macules and papules over the cheeks, perioral area, chin, eyelids, and forehead, producing a mottled appearance (Figure 1 A-C).

Discrete hyperpigmented papules were also noted over the helix and lobule of the external ears, indicating involvement of sun-exposed sites (Figure 1 D).

Oral examination showed angular erythema with fissuring, but no mucosal plaques were present (Figure 1 B).

Over the trunk and back, hypopigmented macules were interspersed with multiple hyperpigmented verrucous papules and plaques, more prominent over the upper back and interscapular region (Figure 1 E). The lesions were non-tender and non-indurated.

Both upper limbs showed numerous discrete as well as confluent verrucous papules and plaques, distributed symmetrically over the extensor aspects of the forearms, elbows, wrists, and dorsal hands (Figure 1 F and G).

Similar lesions were present over the thighs and legs. Genital examination revealed multiple small verrucous papules over the labia majora and minora, without ulceration or discharge, suggesting extensive disease involvement (Figure 1 H).

A skin biopsy was taken from a lesion on the right forearm. Histopathological examination revealed fairly circumscribed epidermal hyperplasia with mild papillomatosis, thickening of the granular layer, compact orthohyperkeratosis, and minimal inward curving of peripheral rete ridges.

In the clinical context, these findings supported the diagnosis of the epidermodysplasia verruciformis (Figure 2).

Case 2: elder brother

The elder brother developed asymptomatic skin lesions at around six years of age. The disease showed extensive involvement of the face, trunk, and both upper and lower limbs, closely resembling the distribution and morphology seen in the index case. The lesions progressed gradually in early years and later appeared clinically stable.

Cutaneous examination revealed multiple hyperpigmented and hypopigmented macules along with flat-topped verrucous papules, predominantly over sun-exposed areas. There was no history of ulceration, bleeding, or features suggestive of malignant change. The patient did not consent for skin biopsy.

Considering the classical morphology and strong familial background, a clinical diagnosis of epidermodysplasia verruciformis was made.

Case 3: younger brother

The younger brother presented with similar lesions at approximately ten years of age. Compared to the elder siblings, the disease was less severe.

The lesions were mainly confined to both upper and lower limbs, with relative sparing of the face and trunk.

The cutaneous findings consisted predominantly of discrete hypopigmented macules with only a few verrucous papules.

The patient declined biopsy. Diagnosis was made clinically based on typical lesion morphology and positive family history.

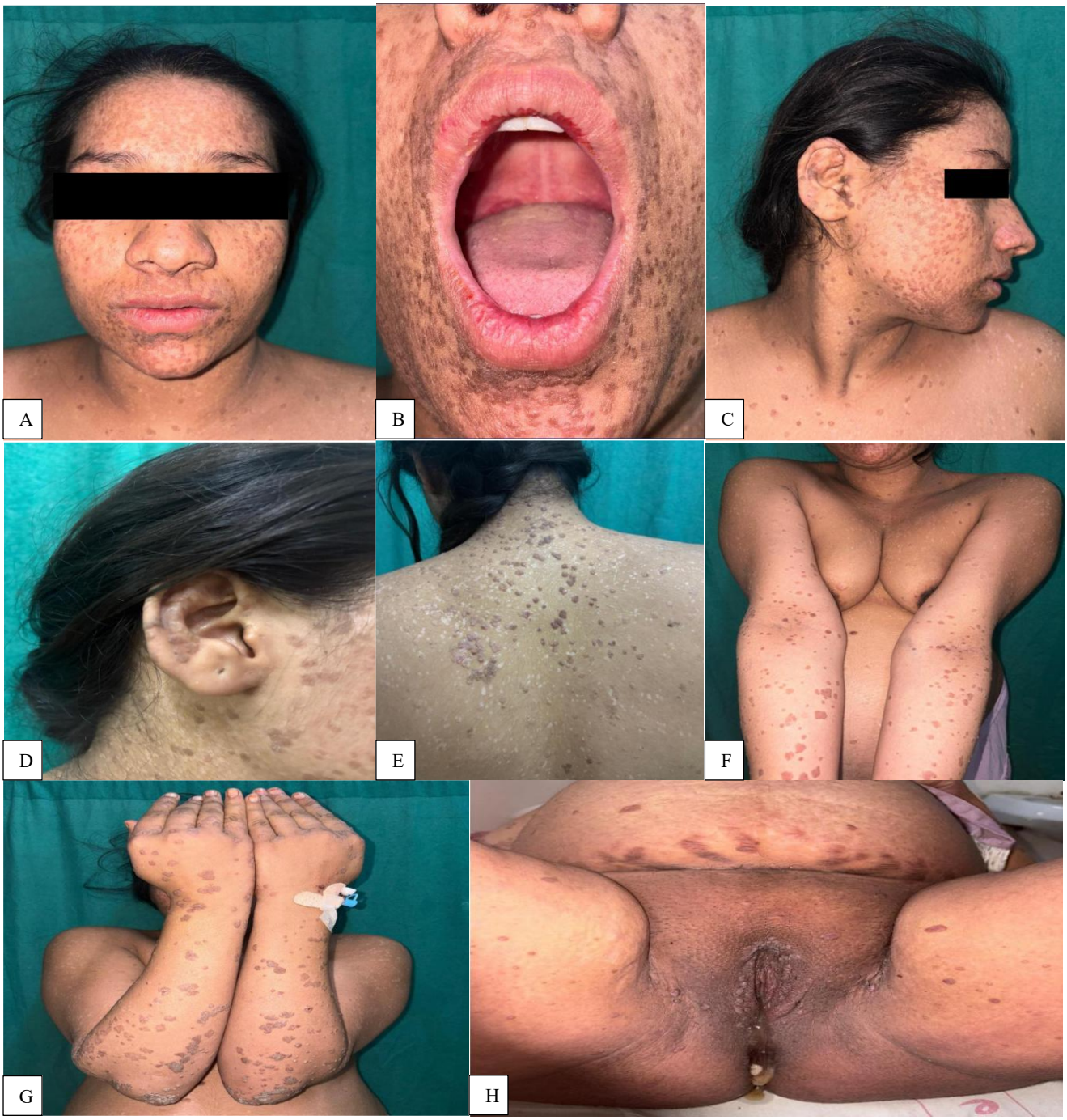

Figure 1 (A-H): A: Frontal view of the face showing multiple hyperpigmented macules and flat-topped papules distributed over the forehead and cheeks. B: Close-up of the perioral region demonstrating hyperpigmented macules with associated erythema and fissuring at the angles of the mouth. The periorificial skin is prominently involved, while the oral mucosa appears normal. C: Lateral facial view showing dense aggregation of hyperpigmented macules and papules over the cheek, jawline, and preauricular area, indicating chronic facial involvement. D: Auricular and periauricular involvement with multiple hyperpigmented papules over the pinna, helix, and lobule, highlighting the predilection for sun-exposed sites. E: Upper back showing numerous hypopigmented macules resembling pityriasis versicolor, interspersed with hyperpigmented verrucous papules and plaques. The presence of mixed lesion morphology is characteristic of epidermodysplasia verruciformis. F: Anterior view of both forearms revealing symmetrical distribution of multiple discrete and coalescent verrucous papules and plaques over extensor surfaces, with variation in size and pigmentation. G: Dorsal view of the hands and wrists showing clustered, flat-topped hyperpigmented papules, supporting a diagnosis of epidermodysplasia verruciformis rather than isolated acquired warts. H: External genital examination demonstrating multiple small verrucous papules involving the labia majora and labia minora, reflecting extensive disease involvement.

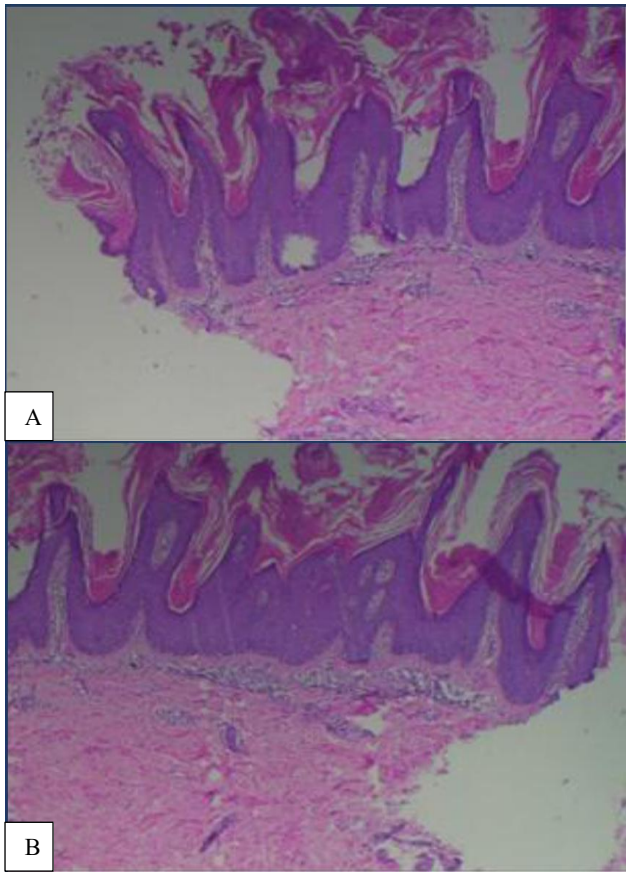

Figure 2 (A and B: A: Low-power histopathological image showing epidermal hyperplasia with gentle papillomatosis and mild compact orthohyperkeratosis (H and E, low power). B: Higher-power view demonstrating a thickened granular layer with minimal incurving of the rete ridges, findings consistent with epidermodysplasia verruciformis (H and E, high power).

DISCUSSION

Epidermodysplasia verruciformis represents a distinctive condition in which genetically determined susceptibility allows persistent infection by specific HPV types.[11] Defects affecting cell-mediated immunity play a central role, and mutations involving the EVER1 (TMC6) and EVER2 (TMC8) genes have been most frequently implicated.[12] These abnormalities interfere with normal keratinocyte defense mechanisms against beta-HPV infection.

In the present family, all three siblings showed features consistent with epidermodysplasia verruciformis, but with clear variation in age of onset, extent of involvement, and severity. The index case and elder brother developed lesions early in childhood with extensive and widespread disease, while the younger brother had a later onset and comparatively limited involvement. Such intrafamilial variability has been described earlier and reflects the heterogeneous expression of EV, even among individuals sharing a similar genetic background.[13]

The female patient demonstrated a broad spectrum of lesion morphology, including hypopigmented macules resembling pityriasis versicolor, plane wart-like papules, and seborrheic keratosis-like plaques, all of which are well-recognized patterns in EV.[14] The marked facial involvement observed in this case is typical and often contributes to cosmetic concern and psychosocial distress. Genital involvement, though less frequently reported, has been described previously and suggests widespread cutaneous susceptibility rather than site-specific disease limitation.[15]

Histopathological confirmation was obtained only in the index case and showed features consistent with EV. While biopsy is not essential in every patient, histopathology is useful in excluding close clinical differentials such as verruca plana, seborrheic keratosis, and epidermal nevus.[16] In familial settings with classical clinical features, a clinical diagnosis may be considered acceptable when biopsy consent is not provided.

The risk of malignant transformation remains a major concern in epidermodysplasia verruciformis, particularly squamous cell carcinoma arising on sun-exposed areas. HPV types 5 and 8 have been strongly linked to oncogenesis in EV, especially in the presence of chronic ultraviolet exposure.[17] Although none of the patients in this series showed evidence of malignancy at the time of presentation, the young age of the patients necessitates long-term surveillance.

Management of EV continues to be difficult, as no definitive curative treatment is available. Various therapeutic options such as systemic retinoids, interferon, topical imiquimod, and strict photoprotection have been used with inconsistent results.[18,19] In our patients, emphasis was placed on counseling regarding sun avoidance and the need for regular follow-up, which remains essential to reduce future morbidity.

CONCLUSION

This case series describes three siblings affected by epidermodysplasia verruciformis, showing clear differences in age at onset and overall disease burden within the same family. Although histopathological confirmation was available only in the female patient, the clinical features and family background were sufficiently characteristic to support the diagnosis in all three cases. The photographic findings highlight the wide morphological range and extensive distribution of lesions that can be seen in EV. Recognition of the condition at an early stage, along with proper counseling, consistent photoprotection, and long-term follow-up, remains important to limit disease-related morbidity and to reduce the future risk of malignant change.

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