

## Case Report

# Epidermodysplasia verruciformis in a young Chinese male

## 疣狀表皮發育不良——年輕華籍男子病例一宗

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A 22-year-old Chinese male patient presented with eighteen years history of extensive asymptomatic erythematous and hypopigmented papules over his hands, neck, back and knees. A diagnosis of epidermodysplasia verruciformis was made based on the characteristic clinical findings and the histopathological features. Regular follow-up was arranged to detect the development of premalignant and malignant skin lesions.

22歲華人男患者呈手、頸、背及膝部廣泛無症狀性紅色及脫色性低色素丘疹達18年。經臨牀及組織學的特徵性表現診斷為疣狀表皮發育不良。患者需接受定期覆診以發現皮膚的癌症及癌前病變。

**Keywords:** Chinese, Epidermodysplasia verruciformis

**關鍵詞:** 華人, 疣狀表皮發育不良

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### Introduction

Epidermodysplasia verruciformis is a rare genetic condition which is associated with a high risk of skin malignancy due to abnormal susceptibility to infection by specific EV-related types of human papilloma viruses (HPV). The condition has

attracted much interest because it serves as a model for the study of cutaneous HPV oncogenesis.<sup>1</sup>

### Case report

A 22-year-old Chinese male presented with extensive erythematous papules which had been present since the age of four. These papules were located over the dorsal aspect of both hands and the extensor surface of both knees. There were also other hypopigmented macules and papules over the neck, back and buttock. The lesions were asymptomatic. The patient had received no previous treatment for them. There was no family history of similar lesions. His past medical history and drug history were unremarkable.

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Physical examination showed multiple slightly erythematous papules with well-defined edges over the dorsum of both hands and knees (Figures 1 & 2). Each papule ranged from 5-8 mm in diameter. Some were flat-topped and resembled plane warts. They were confluent in areas. There were other hypopigmented, pityriasis versicolor-like macules scattered over the nape of neck, back and buttock (Figure 3). No significant scaling was



**Figure 1.** Plane wart-like papules over the dorsal aspects of hands and fingers.



**Figure 2.** Plane wart-like papules over the knees.



**Figure 3.** Pityriasis versicolor-like lesions over the back.

noted. There was no nail scalp or oral mucosal involvement. The main clinical differential diagnoses included epidermodysplasia verruciformis, multiple plane warts, lichen planus, pityriasis versicolor and guttate psoriasis.

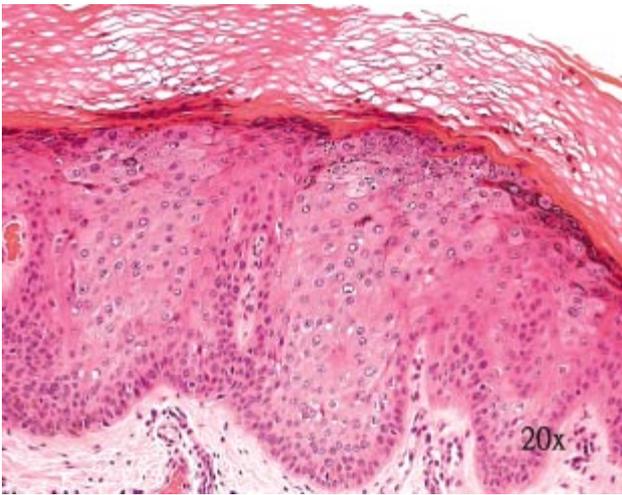
An incisional skin biopsy was taken from a plane wart-like papule over the knee. The histopathology showed orthokeratosis, acanthosis and clusters of large, pale keratinocytes with blue-grey staining cytoplasm within the epidermis (Figure 4). Some of these keratinocytes contain perinuclear vacuoles. Coarse keratohyaline granules were easily found in the granular layer. There was also a focus where the keratinocytes were large, more hyperchromatic and crowded with mildly disturbed orientation (Figures 5 & 6). No invasive tumour was seen. The overall features were consistent with epidermodysplasia verruciformis with mild dysplasia.

## Discussion

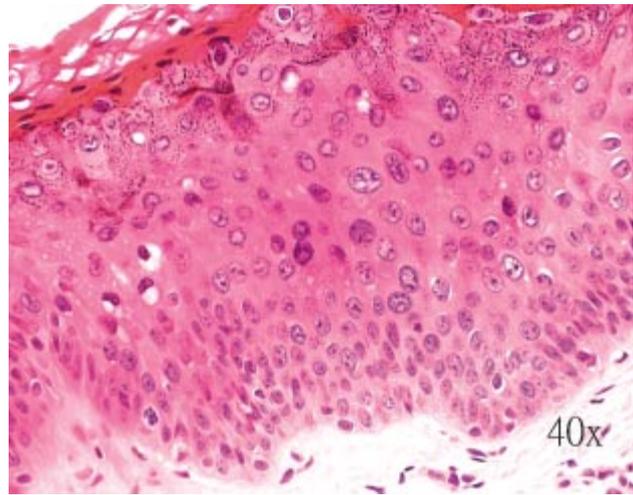
Epidermodysplasia verruciformis (EV) is also known as Levandowsky-Lutz syndrome. This rare genetic condition is associated with a high risk of skin malignancy due to an abnormal susceptibility to infection by specific HPV. It serves as a model to study the interaction between genetic factors in HPV-associated skin cancer.



**Figure 4.** Hyperkeratotic papule in low power view. (H&E, Original magnification x 2.5)



**Figure 5.** Characteristic large pale keratinocytes of EV. (H&E, Original magnification x 20)



**Figure 6.** Focal dysplasia indicated by mild nuclear enlargement and loss of polarity. (H&E, Original magnification x 40)

The incidence of EV is unknown and there is no sexual or racial preference. More than 20% of the cases are inherited as autosomal recessive, whilst the others are mostly sporadic. There have also been X-linked and autosomal dominant cases reported. The condition usually manifests during childhood between 4-8 years of age.<sup>2</sup> The infection with HPV is life-long. Clinically, the widespread and persistent lesions are distributed over the dorsal aspects of hands, palms, forearms, face, trunk, legs, soles, axillae and external genitalia. The benign lesions are polymorphic. Usually, the first lesions to appear resemble plane warts, localised on the hands and fingers. A few years after the initial lesions appear, red-brown flat macules resembling pityriasis versicolor develop.<sup>3</sup> Red-brown plaques, papilloma- and verruca seborrhoeica-like lesions can also be present. 30-50% of the patients with benign lesions go on to develop premalignant and malignant lesions, which usually start to appear in the third to fourth decades over sun-exposed areas.<sup>4</sup> They include actinic keratoses, Bowen's disease and squamous cell carcinoma. Metastases have been reported but are rare. The development of malignancy depends on the genetic predisposition, HPV type and other cofactors, especially UV irradiation.

The diagnosis of EV is based on the clinical recognition of characteristic cutaneous changes and location of the lesions. A positive family history may be present. Skin biopsy is helpful for histopathological confirmation and for the identification of premalignant and malignant lesions. The characteristic findings include swollen pale keratinocytes with perinuclear vacuolation arranged in clusters or columns within the granular and spinous layers of the epidermis. The cytoplasm of these large, blue-grey staining pale keratinocytes often contain keratohyaline granules of various sizes and shapes. These changes are due to the specific cytopathic effect of the virus. As the lesion progresses to atypicality, the nuclei of the keratinocytes become larger and hyperchromatic. Cellular maturation also becomes more disorderly, and these dysplastic changes can further progress to malignancy. HPV typing is not routinely performed for diagnostic purpose. However, it can be useful to find out whether the patient is infected with the high oncogenic type of HPV.

The pathogenesis of EV is only partially understood. It is known that genetic predisposition, HPV infection and exposure to the sun all play a

part. The inherited predisposition results in a defect in cell-mediated immunity, where the immune system fails to recognise and does not reject HPV-harbouring keratinocytes.<sup>5,6</sup> At least two susceptibility loci have been mapped to chromosome 17 (EV1) and chromosome 2 (EV2).<sup>7</sup> A recent study shows that two genes, *EVER1* and *EVER2*, within EV1 are mutated in EV patients. Although their function is still unclear, the gene products have features of integral membrane proteins and are localised in the endoplasmic reticulum.<sup>8</sup> The causative HPVs in EV are different from other genital or cutaneous HPVs. They are collectively referred to as EV-specific HPVs (EV-HPVs). There are more than twenty known EV-HPVs, many of which have a low oncogenic potential and are present in benign lesions. One patient is often simultaneously affected by several types of EV-HPVs. This contrasts with the EV-associated malignant cutaneous lesions, where predominantly the high oncogenic potential EV-HPVs are identified, namely HPV 5 and HPV 8. Previously, EV-HPV was thought to be specific to the condition of EV. By using nested PCR technique, it is now known that EV-HPV is in fact ubiquitous and can cause widespread and inapparent infection in the general population. However, its role in non-EV related benign and malignant skin condition in the general population is still controversial.<sup>9</sup>

The malignant transformation in EV is a slow and multistep process. Although the mechanism behind this transformation is still unclear, it is likely that EV-HPVs influence cell biology in a manner different to genital HPVs in causing malignancy. Studies show that a high level of E6 and E7 transcripts, the early oncoprotein of HPV, are detected in the EV-associated malignant cutaneous lesions. However, unlike genital HPVs, E6 of EV-HPV does not degrade p53, and E7 cannot transform keratinocytes.<sup>10,11</sup> The EV-HPV DNA is not integrated into the host DNA except in metastases. Recent evidence shows that E6 of several cutaneous HPVs promotes the degradation

of a pro-apoptotic protein, Bak.<sup>12</sup> This protein is induced in keratinocytes by UV irradiation. In other words, E6 has an anti-apoptotic effect, favouring the accumulation of UV-induced mutation.

There is no definitive treatment for EV. However, it is important to advise patients to avoid exposure to UV irradiation and to regularly monitor them for the development of premalignant and malignant skin lesions. Many of the therapies tried are experimental and based only on case reports. Oral retinoids,<sup>13</sup> topical vitamin D analogue,<sup>14</sup> photodynamic therapy with 5-aminolaevulinic acid,<sup>15</sup> intralesional and systemic interferon<sup>16</sup> have resulted in only a partial or transitory effect. It is also unclear whether they prevent malignant progression. Surgical removal, cryotherapy, curettage can be used in the treatment of benign and premalignant lesions. Locally destructive methods, however, are not ideal for extensive and resistant lesions. Surgery is also indicated for malignant lesions.

EV is a rare genetic condition of great interest, both for basic research and clinical practice, because it serves as a model for studying the interplay of oncogenic viruses, genetic factors and UV irradiation in cutaneous carcinogenesis.

## References

1. Majewski S, Jablonska S. Epidermodysplasia verruciformis as a model of human papillomavirus-induced genetic cancer of the skin. *Arch Dermatol* 1995;131:1312-8.
2. Lutzner MA, Blanchet-Bardon C. Epidermodysplasia verruciformis. *Curr Probl Dermatol* 1985;13:164-85.
3. Lutzner MA, Blanchet-Bardon C, Orth G. Clinical observations, virologic studies, and treatment trials in patients with epidermodysplasia verruciformis, a disease induced by specific human papillomaviruses. *J Invest Dermatol* 1984;83(1 Suppl):18s-25s.
4. Orth G, Jablonska S, Jarzabek-Chorzelska M, Obalek S, Rzesza G, Favre M, et al. Characteristics of the lesions and risk of malignant conversion associated with the type of human papillomavirus involved in epidermodysplasia verruciformis. *Cancer Res* 1979;39:1074-82.

5. Cooper KD, Androphy EJ, Lowy D, Katz SI. Antigen presentation and T-cell activation in epidermodysplasia verruciformis. *J Invest Dermatol* 1990;94:769-76.
6. Majewski S, Skopinska-Rozewska E, Jablonska S, Wasik M, Misiewicz J, Orth G. Partial defects of cell-mediated immunity in patients with epidermodysplasia verruciformis. *J Am Acad Dermatol* 1986;15(5 Pt 1):966-73.
7. Ramoz N, Taieb A, Rueda LA, Montoya LS, Bouadjar B, Favre M, et al. Evidence for a nonallelic heterogeneity of epidermodysplasia verruciformis with two susceptibility loci mapped to chromosome regions 2p21-p24 and 17q25. *J Invest Dermatol* 2000;114:1148-53.
8. Ramoz N, Rueda LA, Bouadjar B, Montoya LS, Orth G, Favre M. Mutations in two adjacent novel genes are associated with epidermodysplasia verruciformis. *Nat Genet* 2002;32:579-81.
9. Harwood CA, Suretheran T, McGregor JM, Spink PJ, Leigh IM, Breuer J, et al. Human papillomavirus infection and non-melanoma skin cancer in immunosuppressed and immunocompetent individuals. *J Med Virol* 2000;61:289-97.
10. Steger G, Pfister H. In vitro expressed HPV 8 E6 protein does not bind p53. *Arch Virol* 1992;125(1-4):355-60.
11. Hiraiwa A, Kiyono T, Segawa K, Utsumi KR, Ohashi M, Ishibashi M. Comparative study on E6 and E7 genes of some cutaneous and genital papillomaviruses of human origin for their ability to transform 3Y1 cells. *Virology* 1993;192:102-11.
12. Jackson S, Storey A. E6 proteins from diverse cutaneous HPV types inhibit apoptosis in response to UV damage. *Oncogene* 2000;19:592-8.
13. Lutzner MA, Blanchet-Bardon C. Oral retinoid treatment of human papillomavirus type 5-induced epidermodysplasia verruciformis. *N Engl J Med* 1980;302:1091.
14. Hayashi J, Matsui C, Mitsuishi T, Kawashima M, Morohashi M. Treatment of localized epidermodysplasia verruciformis with tacalcitol ointment. *Int J Dermatol* 2002;41:817-20.
15. Karrer S, Szeimies RM, Abels C, Wlotzke U, Stolz W, Landthaler M. Epidermodysplasia verruciformis treated using topical 5-aminolaevulinic acid photodynamic therapy. *Br J Dermatol* 1999;140:935-8.
16. Androphy EJ, Dvoretzky I, Maluish AE, Wallace HJ, Lowy DR. Response of warts in epidermodysplasia verruciformis to treatment with systemic and intralesional alpha interferon. *J Am Acad Dermatol* 1984;11(2 Pt 1):197-202.