

Case Report

A man with familial flexural rash: a case of Hailey-Hailey disease

男患者的家族性屈側皮疹：黑利—黑利二氏病一例

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A 38-year-old gentleman presented with erythematous patches over neck, axillae, and groin. The family history was positive with his mother having similar rash over neck and axillae. Histology showed 'delapidated brick wall appearance'. The diagnosis of Hailey-Hailey disease was made.

38歲男患者於頸部、腋下及腹股溝出現紅色斑片。其家族史呈陽性，即患者母親於頸部及腋下出現類似皮疹。組織學檢查顯示“破牆徵”。診斷為黑利—黑利二氏病。

Keywords: Familial benign chronic pemphigus, Hailey-Hailey disease

關鍵詞：家族性良性慢性天疱瘡，黑利—黑利二氏病

Case report

A 38-year-old male developed mild itchy rash over his groin, buttock, and neck for 1 year. He tried various topicals and herbs but to no avail. He was therefore referred to our unit for further assessment. On examination, he was found to have scaly erythematous patches with maceration

over groin (Figure 1) and perianal areas and scaly erythematous papules and patches over left lateral neck. The axillae were also involved.



Figure 1. Erythematous patch with macerations over right groin.

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A biopsy was done on the right thigh. The specimen revealed suprabasal separation of the epidermis due to acantholysis. The acantholytic keratinocytes had round, condensed cytoplasm, and loss of intercellular bridges were seen. In some areas, the acantholysis was incomplete and the cells retained some connections and cellular orientation, with 'dilapidated brick wall' appearance (Figure 2). Aggregates of dyskeratotic cells were found in the superficial portion of the skin. There was no evidence of acanthosis nigricans, Paget's disease or malignancy. The findings were compatible with Hailey-Hailey disease. It was later found that the mother of the patient also had similar rash over the neck and axillae. The patient was treated with topical Fucidin cream, potassium permanganate dressing and the condition was stable.

Discussion

Hailey-Hailey disease (HHD), also known as familial benign chronic pemphigus, is an uncommon genodermatosis. It is inherited in an autosomal dominant mode with variable penetrance. About 70% of the patients have a

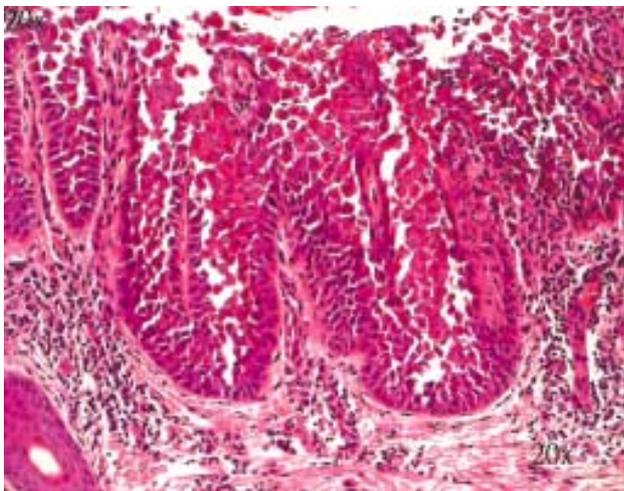


Figure 2. The characteristic "dilapidated brick wall" appearance of the acantholysis (H&E Original magnification x 20).

definite family history. It favours the intertriginous areas, such as the neck, axillae, inframammary areas and groin. Initial lesions include flaccid vesicles on erythematous skin which rupture easily and give rise to macerated or crusted erosions. The lesions spread peripherally producing a circinate border with crusts and small vesicles. The lesions develop into chronic, moist, malodorous vegetations with painful fissures. They heal without scarring leaving postinflammatory hyperpigmentation. Pain may be noted in the intertriginous erosions and crusting. The lesions may be pruritic or burning. Sometimes, they may also be malodorous. The lesions may be induced by trauma, heat, sweating, UV light, and infections caused by scabies, bacteria, herpes virus, and yeasts. Periods of spontaneous remission with subsequent exacerbations are noted in this disease. Our case had macerated erythematous patches over the axillae, groin and neck. They were itchy at times.

The pathology of early lesions include lacunae formed by suprabasilar clefting with acantholytic cells either singly or in clumps lining the clefts and lying free within them. The lacunae progress to broad, acantholytic vesicles and bullae. Intercellular oedema leads to partial acantholysis and gives rise to areas with a 'delapidated brick wall' appearance. This characteristic appearance was also noted in our case. Acantholytic, dyskeratotic cells are found within the epidermis. Epidermal hyperplasia is commonly seen.¹

Family linkage studies had already linked Hailey-Hailey disease to chromosome 3q21-q24. In 2000, Hu et al amplified DNA samples from affected patients from 51 unrelated kindreds of European descent and 10 of Japanese descent, all with typical clinical and histological findings, and identified 21 abnormalities. Of the abnormal sequences, a high frequency of prematurely truncated products through frameshifts or single base-pair substitution was found.²

ATP2C1 encodes the human secretory pathway Ca^{2+} Mn^{2+} -ATPase protein 1 (SPCA1). This pump is found in the Golgi apparatus. It supplies the Golgi apparatus, and possibly other more distal components of the secretory pathway, with both Ca^{2+} and Mn^{2+} . Various mutations including missense, frameshift, splice site and nonsense mutations were found scattered throughout the coding regions of these genes. These mutations disrupt the functional domains of the encoded proteins in Hailey-Hailey disease. There is no clear correlation established between phenotype and genotype. Human keratinocytes rely mainly on SPCA1 pumps for loading the Golgi stores with Ca^{2+} . This explains partially why mutations in Hailey-Hailey disease preferentially affect the skin.³ Acantholysis in Hailey-Hailey disease is associated with varying degrees of dyskeratosis and papillomatosis as desmosome formation is critical for cell growth, cell differentiation and formation of the cornified cell envelope. A spectrum of ATP2C1 gene mutations was reported since the discovery that mutation of this gene led to Hailey-Hailey disease.^{4,5}

The differential diagnoses of Hailey-Hailey disease included fungal infection, intertrigo, psoriasis, extramammary Paget's disease, acanthosis nigricans, pemphigus vegetans, and Darier's disease. However, in our case, there were no satellite pustules or active margin, fungal culture was negative and there was no response to antifungal, thus making fungal disease an unlikely possibility. In intertrigo, the lesions are usually not so well demarcated as those seen in this patient. In psoriasis, there are fewer macerations or erosions, less crusting, sharper borders, additional sites of involvement, and nail pitting. In extramammary Paget's disease, it is rare to have simultaneous symmetrical involvement of several sites. In acanthosis nigricans, the lesions are warty, velvety, and hyperpigmented. In pemphigus vegetans, it might be possible to find mouth erosion. Darier's disease usually occurs in seborrhoeic area. Palmar pits and V-shaped

notches of nail plate and oral papules might be found.

In the management of HHD patients, general measures should not be neglected. These include wearing light weight clothes and treatment of infections if any.

It was reported that topical tacrolimus was found to be effective in HHD.⁶ Partial clearing was seen in HHD after treatment with tacrolimus or cyclosporine. This might be due not to immunologic mechanisms, but instead to these agents' ability to inhibit calcineurin. Cyclosporine-induced calcineurin inhibition induces tolerance to high extracellular Ca^{2+} .⁷

Previous reports have documented the efficacy of systemic calcitriol on HHD. The effect might be due to the inhibitory effect of calcitriol on T cells and on some inflammatory mediators. More recently, tacalcitol, another vitamin D3 derivative, was also found to be topically effective. It might affect the calcium gradient in differentiating keratinocytes and could regulate and preserve the desmosome assembly and integrity. The lesions cleared after twice daily application for one month and remission was continued to be noted at three months' observation.⁸

Reducing sweat in all intertriginous regions could effectively improve lesions of Hailey-Hailey disease. Botulinum toxin is a good treatment option for hyperhidrosis. It was found that patients with axillary Hailey-Hailey disease treated with botulinum toxin type A showed good response.⁹ Other available topical modalities include topical antibiotics, topical steroids, and topical cyclosporine.

A relatively short-course treatment with oral erythromycin for three to four weeks induced a long-lasting remission for eight months. The clinical improvement might be due to the anti-inflammatory properties inherent to its macrolide

structure. It may act through inhibition of cytokine release.¹⁰ In addition to antibiotics such as erythromycin, other options of systemic treatment include steroids, cyclosporine, dapsone, methotrexate, and thalidomide.

More aggressive approaches like dermabrasion or laser abrasion may also be effective in severe HHD. However, they may need a longer period of postoperative care and may be inconvenient. Wide excision and grafting can also be used. These have all provided sustained remission of the disease.

Since 1959, the use of Grenz-rays, very low-energy X-rays, has been found to offer temporary relief. However, it is an unproven option.

Recently, it was reported that photodynamic therapy was also effective in the treatment of Hailey-Hailey disease. In two patients, 5-aminolevulinic acid was applied to the lesions. This was followed by exposure to incoherent light of 590 to 700 nm. Clinical clearing was noted after two treatments. However, the underlying mechanism was not clear.¹¹

Thus, we reported a gentleman with lesions involving the flexural areas with positive family history. Pathology shows characteristic 'delapidated brick wall' appearance. This is a case of Hailey-Hailey disease.

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