The coexistence of Darier's disease and Hailey-Hailey disease symptoms

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Darier's disease (keratosis follicularis) is an autosomal dominantly inherited genodermatosis characterized by greasy hyperkeratotic papules in seborrheic regions, nail abnormalities, and mucous membrane changes. Worldwide prevalence is estimated between 1 : 30,000 and 1 : 100,000. Darier's disease is not apparent at birth. Usually, it starts either in the first or second decade of life. The sites of predilection are the seborrheic areas of the trunk and face, particularly the scalp margins, forehead, ears and nasolabial furrows, and scalp. The flexures, notably the anogenital region, the groins and the axillae, are often involved [1].

The distinctive lesion of Darier's disease is a firm rather greasy crusted papule that is skin-colored, yellow-brown or brown. Coalescence of the papules produces irregular warty plaques or papillomatous masses which, in the flexures, become vegetating and malodorous. On the scalp, the heavy crusting simulates seborrhea but has a characteristic spiny feel to palpation. Loss of hair is exceptional but has occasionally been extensive and permanent. In Darier's disease, the palms and soles may show punctuate keratoses or minute pits. Nails may display longitudinal ridges, red and white lines, and V-shaped nicks [2].

The lesions may cause persistent itchiness (pruritus). Exacerbations have been reported following exposure to UV radiation and herpes simplex infections. Spontaneous remissions do occur but the condition usually runs a chronic relapsing course with fluctuations, which may be seasonal and hormonal in origin. The general health normally remains unaffected.

Darier's disease and Hailey-Hailey disease are often discussed together because of some similarities in their etiopathology. Both diseases are autosomal dominantly inherited genodermatosis with incomplete penetrance and are caused by abnormal epidermal calcium homeostasis. They are mapped to different chromosomal locations. Darier's disease is caused by mutations in the ATP2A2 gene found on chromosome 12q23-24.1. Hailey-Hailey disease is caused by mutations in the ATP2C1 gene, located on chromosome 3q21–24 [3, 4].

Clinically, Hailey-Hailey disease includes recurrent eruptions of vesicles and bullae, crusted erosions and warty papules. Lesions develop mainly in areas exposed to friction such as the sides of the neck, axillae and groins. The condition usually starts in adolescence. This contrasts with patients suffering from Darier's disease where the age at onset is often earlier.

Spontaneous remissions occur in cold weather and most patients find heat and sweating aggravating the condition. The disease only rarely subsides permanently, but long remissions are common and it becomes less severe as the patient ages [1, 4] (Table 1).

A 38-year-old female patient was admitted to the Department of Dermatology at the beginning of December 2015. The dermatological examination revealed hyperkeratotic, skin-colored to hyperpigmented, grouped as well as scattered papules on the seborrheic areas of the trunk, back, abdomen, upper and lower extremities. On further examination, eruptions of vesicles and bullae, crusted erosions were seen over groins and the left popliteal fossa (Figures 1 A, B).

Furthermore, the medial surface of the thigh showed some stretch marks. Nail examination did not show any abnormality and the oral mucosa was also normal (Figures 1 C, 2 A).

The eruption first appeared in the right groin as some vesicles and bullae, crusted erosions and had remained relatively stable for about 15 years. Exacerbations of lesions in groins have been reported during the luteal

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Table 1. Differences between Darier's disease and Hailey-Hailey disease

Comparison of symptoms	Darier's disease	Hailey-Hailey disease
Clinical features	Greasy hyperkeratotic papules and/or warty plaques, palmoplantar in seborrheic areas; palmoplantar pits, and distinctive nail abnormalities	Groups of small flaccid vesicles, at first with clear contents, becoming turbid on normal or erythematosus skin
Sites of predilection	Seborrheic areas of the trunk, face, palmoplantar pits and distinctive nail abnormalities	Neck, axillae, groin, and other flexures and intertriginous areas
Mucous membranes	Yes	Not present in the oral cavity
Nails	Longitudinal ridges, red and white lines, and V-shaped nicks	Less frequent
Itchiness	May occur	Less frequent
Main exacerbating factors	UV radiation, herpes simplex infections	Heat, sweating, UV radiation, secondary infections
Onset	Mostly at the ages of 10–20	Adolescence
Prognosis	Chronic relapsing course with fluctuations, which may be seasonal and hormonal in origin	Exacerbations and remissions
Genetic basis	ATP2A2 gene found on chromosome 12q23-24	ATP2C1 gene located on chromosome 3q21–24
Histopathology	Dyskeratosis' domination	Acantholysis' domination

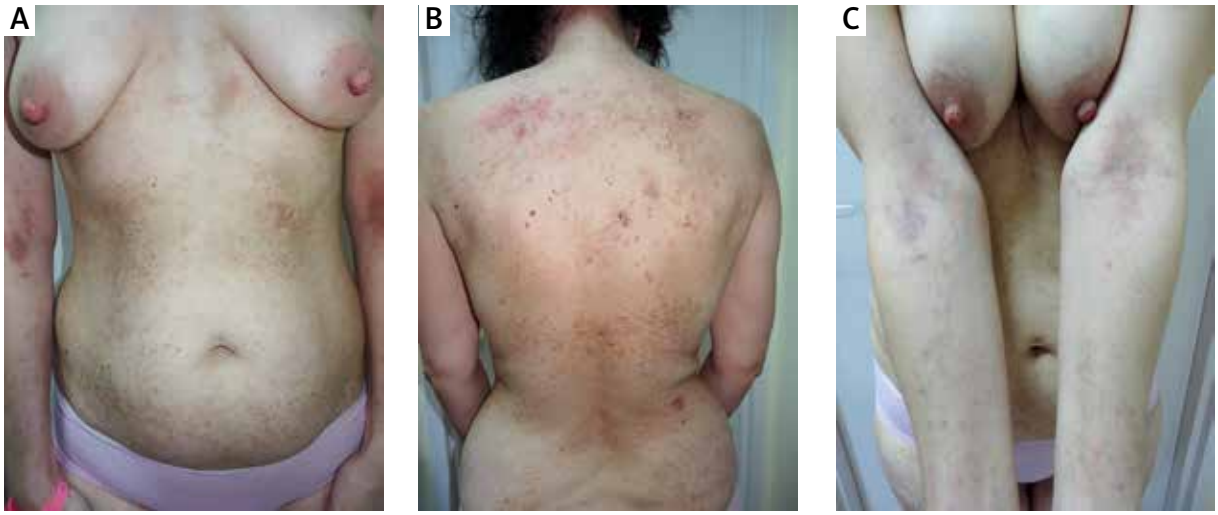

Figure 1 A–C. Hyperkeratotic papules on the seborrheic areas of the trunk, back, abdomen, upper and lower extremities

phase of the menstrual cycle and the pregnancy in 2007 (Figure 2 B).

A skin biopsy specimen was obtained in 2006 from a groin lesion and it showed characteristic histopathological findings consistent with a diagnosis of Hailey-Hailey disease.

Regarding her family history, her father, deceased, also had similar cutaneous disorders in the groin area.

Since September 2015 after a sun exposure, the lesions have spread to involve the seborrheic areas of the trunk, back, abdomen and limbs.

The patient was treated with multiple courses of conventional topical treatments, including emollients, topical corticosteroids, antibiotics and topical antifungal ointment, with only partial relief.

The histopathological examination revealed a circumscribed area of hyperkeratosis with acantholytic dyskeratosis and suprabasal cleft formation. Within the focus, the epidermis showed scattered acantholytic dyskeratotic cells (corps ronds). The stratum corneum showed an array of parakeratotic dyskeratotic cells (grains). Given the above findings, a diagnosis of Darier's disease was made.

The patient started a course of oral acitretin 25 mg daily to which her skin lesions responded. The treatment was well tolerated and produced no side effects.

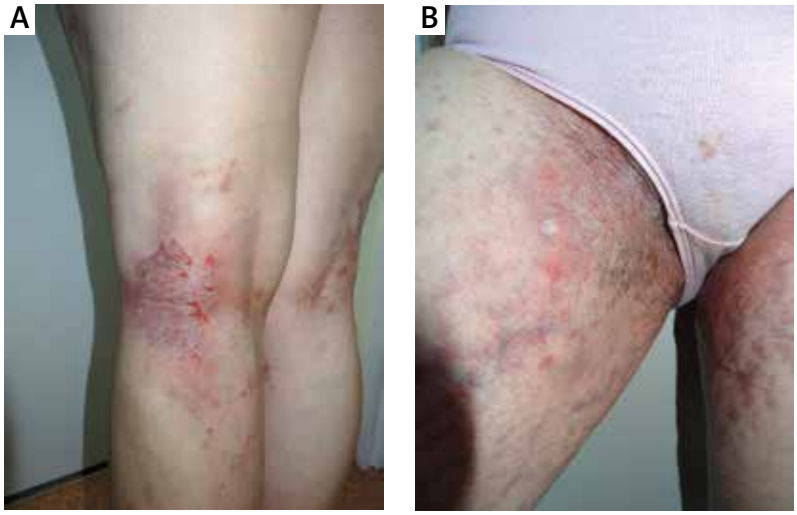

Figure 2 A, B. Eruptions of vesicles and bullae, crusted erosions in the skin folds (groins and the left popliteal fossa)

The patient was referred to the Genetic Department for further investigations.

Darier's disease (keratosis follicularis) and Hailey-Hailey disease (familial benign pemphigus) are autosomal dominantly inherited genodermatosis, caused by abnormal epidermal calcium homeostasis. Linkage analysis in affected families mapped the Darier's disease locus to chromosome 12q23-24.1. ATP2A2 encodes the sarco/endoplasmic reticulum Ca^{2+}ATPase isoform 2 (SERCA2) and is highly expressed in keratinocytes [3]. SERCA2 belongs to a large family of P-type cation pumps. SERCA pumps play an important role in Ca^{2+} signal transduction by generating Ca^{2+} oscillations which mediate cell responses to extracellular signals. SERCA actively transports Ca^{2+} from the cytosol back into the ER lumen using energy from ATP hydrolysis [5]. Although it is not clear how the loss of SERCA2 function causes Darier's disease, selective inhibition of SERCA pumps has been shown to interfere with the formation of intercellular junctions and cell-cell adhesion [6].

Hailey-Hailey disease is caused by mutations in the ATP2C1 gene, located on chromosome 3q21–24 [7, 8]. The protein encoded by this gene is human secretory pathway calcium/manganese-ATPase (hSPCA1), calcium and manganese pump. The hSPCA1 is implicated in the transport of Ca^{2+} and Mn^{2+} in the Golgi lumen, playing an important role in the cytosolic and intra-Golgi concentration of Ca^{2+} and Mn^{2+} [9]. The mutations in ATP2A2 and ATP2C1 affect Mn^{2+} and Ca^{2+} homeostasis. Ca^{2+} mediates stability and adhesion of desmosomes. Desmosomal adhesion between keratinocytes is abnormal in this autosomal dominantly inherited skin disorders. It is possible that alteration in calcium regulation affects the synthesis, folding or trafficking of desmosomal proteins [10–12]. Some studies *in vitro* showed that desmosomes are not assembled in low Ca^{2+} condition [13].

Darier's disease and Hailey-Hailey are autosomal dominant calcium ATPase disorders. A better understanding of the molecular mechanisms involved in the disruption of the balance leading to the clinical symptoms has the potential to identify new therapeutic targets. Even if these diseases have similar features, clinically, genetically and histopathologically they are distinct entities. The diagnosis of genodermatosis imposes a multidisciplinary approach.

Conflict of interest

The authors declare no conflict of interest.

References

1. Rook's Textbook of Dermatology. 5th ed. Griffiths C, Barker J, Bleiker T, et al. (eds.). Wiley 1992; 1362-1365, 1636-1637.
2. Sehgal VN, Srivastava G. Darier's (Darier-White) disease/keratosis follicularis. Int J Dermatol 2005; 44: 184-92.
3. Sakuntabhai A, Ruiz-Perez V, Carter S, et al. Mutations in ATP2A2, encoding a Ca2+ pump, cause Darier disease. Nat Genet 1999; 21: 271-7.
4. Burge SM. Hailey-Hailey disease: the clinical features, response to treatment and prognosis. Br J Dermatol 1992; 126: 275-82.
5. Periasamy M, Kalyanasundaram A. SERCA pump isoforms: their role in calcium transport and disease. Muscle Nerve 2007; 35: 430-42.
6. Savignac M, Edir A, Simon M, Hovnanian A. Darier disease: a disease model of impaired calcium homeostasis in the skin. Biochim Biophys Acta 2011; 1813: 1111-7.
7. Buteica E, Burada F, Stoicescu I, et al. Darier disease and Hailey-Hailey disease. Rom J Morphol Embryol 2007; 48: 423-6.

8. Ikeda S, Welsh EA, Peluso AM, et al. Localization of the gene whose mutations underlie Hailey-Hailey disease to chromosome 3q. Hum Mol Genet 1994; 3: 1147-50.
9. Missiaen L, Raeymaekers L, Dode L, et al. SPCA1 pumps and Hailey-Hailey disease. Biochem Biophys Res Commun 2004; 322: 1204-13.
10. Dhitavat J, Cobbold C, Leslie N, et al. Effect of sarco(endo) plasmic reticulum Ca2+ ATPase (SERCA) dysfunction on the distribution of desmosomal proteins. J Invest Dermatol 2002; 119: 742.
11. Dhitavat J, Fairclough RJ, Hovnanian A, Burge SM. Calcium pumps and keratinocytes: lessons from Darier's disease and Hailey-Hailey disease. Br J Dermatol 2004; 150: 821-8.
12. Fairclough RJ, Dode L, Vanoevelen J, et al. Effect of Hailey-Hailey Disease mutations on the function of a new variant of human secretory pathway Ca2+/Mn2+–ATPase (hSPCA1). J Biol Chem 2003; 278: 24721-30.
13. Burdett ID. Aspects of the structure and assembly of desmosomes. Micron 1998; 29: 309-28.