

Generalized Hailey-Hailey Disease Triggered by Nonsteroidal Antiinflammatory Drug-Induced Rash: Case Report

INTRODUCTION

Hailey-Hailey disease (HHD) is a chronic recurrent blistering disorder, first described in 1939 (1). HHD is inherited as an autosomal dominant disease, characterized by mutation in the ATP2C1 gene encoding the secretory pathway of Ca (2+)/Mg (2+) ATP-ase found in the Golgi apparatus (2). This gene defect results in calcium-pump dysfunction and loss of intracellular adhesion in the epidermis, and in subsequent development of skin lesions. The clinical picture comprises painful, erythematous, fissured, malodorous lesions localized typically in the skin folds, axillae and groins, aggravated by friction, ultraviolet radiation, warmth and moisture, and superficial bacterial, viral or fungal infections (3,4). Generalized or disseminated forms are observed extremely rarely, and they are usually induced by superficial bacterial skin infection (3).

CASE REPORT

A 53-year-old male Caucasian with extensive skin lesions was referred to our Department. Clinical examination revealed erythematous plaques, pustules, vesicles and scales localized on the neck, trunk and extremities. In the intertriginous areas (axillae,

groins), erosive, fissured malodorous plaques were observed (Fig. 1). On admission, the patient gave a history of recurrent pruritic and painful rash, which appeared for the first time in the axillary and perianal region about 4 years before and resolved after potent steroid cream (mometasone furoate) application. The lesion reappeared not only in the intertriginous areas but also on the neck, on the trunk, in the submammary region, and under the knees (Fig. 2a,b), several days after allergic skin reaction triggered by administration of ibuprofen (200 mg). The lesions tended to exacerbate after sun exposure and remitted in winter. The patients' history was irrelevant; however, he was allergic to nonsteroidal anti-inflammatory drugs (NSAID).

Skin biopsy obtained from the erythematous plaque on the trunk revealed acantholysis with less pronounced dyskeratosis, inflammatory cell infiltration composed of polymorphic neutrophils in the superficial dermis, and blister formation in the suprabasal region (Fig. 3). Direct immunofluorescence was negative. All routine hematology investigations were normal. Based on the clinical and histologic picture, we arrived to the diagnosis of HHD. The patient's family history was negative for this disorder.

Initially, the patient was treated with topical and systemic steroids (prednisone 0.4 mg/kg) and occasionally with topical and oral antibiotics, having achieved transient remission in the first year of the diagnosis. With gradual withdrawal of oral prednisone, the skin lesions tended to reappear. In 2006, oral retinoid therapy (isotretinoin 0.4 mg/kg) was introduced. The skin changes showed some improvement within two weeks; however, the patient developed hepatic dysfunction with increased levels of ALT, AST, ALP, total cholesterol, triglycerides, and total bilirubin. The levels of liver enzymes and total bilirubin decreased when the retinoids were discontinued; however, the levels of cholesterol and triglycerides remained elevated. Subsequently, cyclosporin (3 mg/kg) was administered and discontinued after 4 days because of severe adverse effects (hypertension, blood pres-



Figure 1. Typical erythematous, fissured plaques on the left groin.

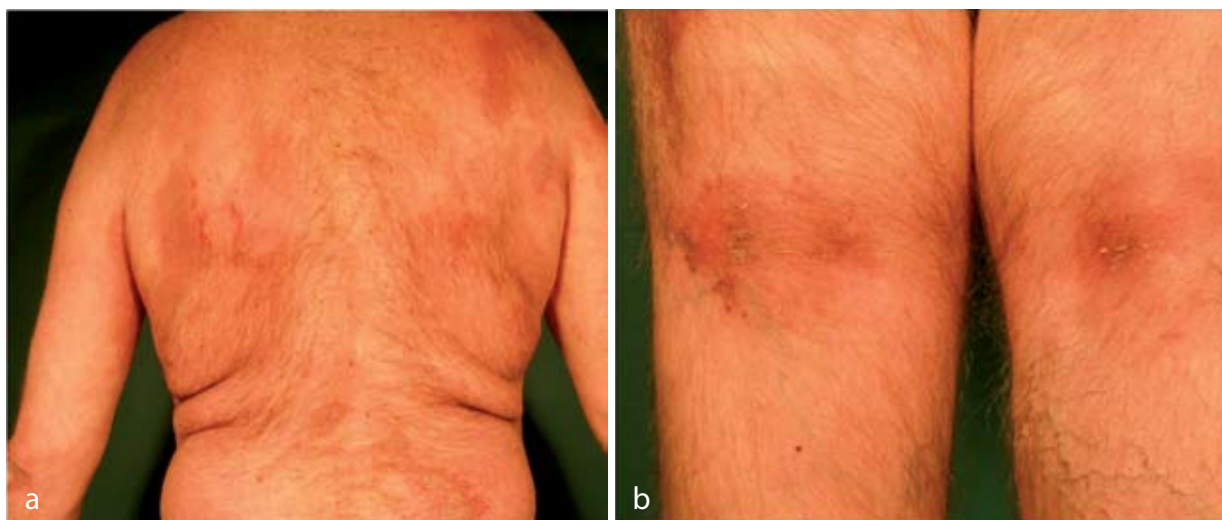


Figure 2. (a) Numerous disseminated erythematous plaques on the trunk; (b) erythematous plaques typical for Hailey-Hailey disease in atypical localization under the knees.

sure 200/100 mm Hg). The patient improved on oral methotrexate (7.5 mg/week), but he developed widespread staphylococcal skin infection followed by rapid generalization of the lesions. Systemic antibiotics (doxycycline 200 mg/day) and prednisone (0.3 mg/kg) dramatically improved the skin condition. In view of his NSAID hypersensitivity, the main difficulty in the management of this patient was to combat pain

associated with persistent axillary lesions. Therefore, excision of the affected skin followed by split skin graft was performed. The skin grafts in both axillae remained clear nine months after surgical treatment, and the patient is generally satisfied because of diminished sweating and pain.

Nevertheless, the new lesion formation is observed in the surrounding areas. The patient is on maintenance therapy with oral steroids (prednisone 30 mg/day) and methotrexate 15 mg weekly.

DISCUSSION

To the best of our knowledge, the presented patient is the first case of generalized HHD in Poland. In the world literature, there are few reports of the generalized type of the disease usually induced by bacterial infection (3,5,6). Most of these cases were provoked by superficial bacterial or viral cutaneous infections. In our patient, drug eruption triggered generalization of the lesions through a Koebner-like reaction. We observed close time correlation between ibuprofen administration and development of skin changes typical for HHD, which appeared every time after the drug intake. Careful evaluation of other potential trigger factors did not reveal any of them to be involved. To our knowledge, it is the first reported case of generalized HHD provoked by ibuprofen 200 mg tablet. The biopsy specimen obtained from the skin changes on the trunk confirmed clinical suspicion of HHD.

In addition, the severe side effects of systemic therapies administered to the patient posed a major therapeutic problem and serious challenge for further

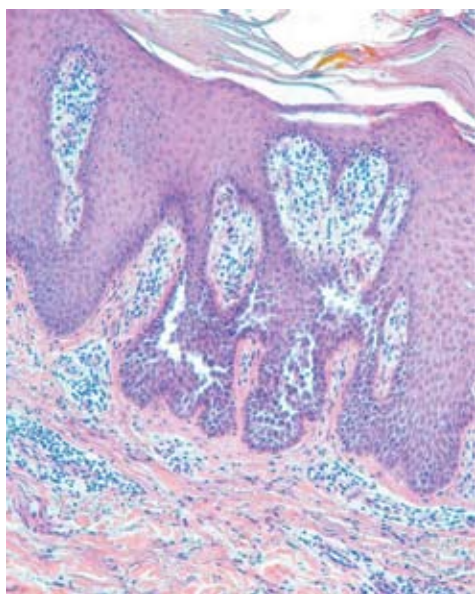


Figure 3. Histopathology revealed prominent suprabasal acanthosis, perivascular inflammatory infiltrations in the dermis composed mostly of lymphocytes, and hyperkeratosis (H&E, X40).

treatment choice. Many therapeutic options are used in the standard treatment of HHD. Oral and topical steroids and oral and topical antibiotics are most common. Alternative treatment modalities comprise oral retinoids (3), oral and topical cyclosporin (7), methotrexate, dapsone, topical tacrolimus (8,9), and thalidomide (10). Successful treatment with alefacept has been recently described (11). In our patient, systemic treatment with oral steroids and methotrexate helped to achieve partial remission, while surgical procedures enabled control of recalcitrant lesions in the armpits.

**Iwona Chlebicka, Alina Jankowska-Konsur,
Joanna Maj, Ewa Plomer-Niezgoda, Jacek
Cezary Szepietowski**

Department of Dermatology, Venereology and
Allergology, Wrocław Medical University, Po-
land

Corresponding author:

Iwona Chlebicka, MD
Department of Dermatology, Venereology and
Allergology
Wrocław Medical University
ul. Chalubinskiego 1
50-368 Wrocław
Poland
iwonak4wsk@interia.pl

Received: October 24, 2011

Accepted: May 25, 2012

References

1. Hailey H, Hailey H. Familial benign chronic pemphigus. *Arch Dermatol Syphilol* 1939;39:679-85.
2. Vanoevelen J, Dode L, Raeymaekers J, Wuytack F, Missiaen L. Diseases involving the Golgi calcium pump. *Subcell Biochem* 2007;45:385-405.
3. Mashiko M, Akiyama M, Tsuji-Abe Y, Shimizu H. Bacterial infection-induced generalized Hailey-Hailey disease successfully treated by etretinate. *Clin Exp Dermatol* 2006;31:57-9.
4. Schirren H, Schirren CG, Schlüppen EM, Volkenandt M, Kind P. Exacerbation of the Hailey-Hailey disease with herpes simplex virus. Detection with polymerase chain reaction. *Hautarzt* 1995;46:494-7.
5. Chave TA, Miligan A. Acute generalized Hailey-Hailey disease. *Clin Exp Dermatol* 2002;27:290-2.
6. Amagai M., Kobayashi M, Wakabayashi K, Hakuno M, Hashiguchi A, Nishikawa T, Hata J. A case of generalized Hailey-Hailey disease with fatal liver injury. *Keio J Med* 2001;50:109-16.
7. Berth-Jones J, Smith SG, Graham-Brown RA. Benign familial chronic pemphigus (Hailey-Hailey disease) responds to cyclosporin. *Clin Exp Dermatol* 1995;20:70-2.
8. Rocha Paris F, Fidalgo A, Baptista J, Caldas LL, Ferreira A. Topical tacrolimus in Hailey-Hailey disease. *Int J Tissue React* 2005;27:151-4.
9. Peršić-Vojinović S, Milavec-Puretić V, Dobrić I, Radoš J, Špoljar S. Disseminated Hailey-Hailey disease treated with topical tacrolimus and oral erythromycin: case report and review of the literature. *Acta Dermatovenerol Croat* 2006;14:253-7.
10. Schnitzler L. Beneficial effect of thalidomide in a case of Hailey-Hailey pemphigus. 1-year trial. *Ann Dermatol Venereol* 1984;111:285-6.
11. Hurd DS, Johnston C, Bevins A. A case report of Hailey-Hailey disease treated with alefacept (Amevive). *Br J Dermatol* 2008;158:399-401.