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Hailey-Hailey disease treated with methotrexate

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Abstract

Background: Hailey-Hailey disease (HHD) is a chronic, recurrent blistering disorder characterized clinically by erosions occurring primarily in intertriginous regions and histologically by suprabasal acantholysis.

Main observations: We report a long standing case of HHD initially unresponsive to cyclosporin, multiple topical and systemic steroids. Good response was achieved with methotrexate 7,5 mg weekly for 16 week, intramuscularly, and topical steroids as needed.

Conclusion: In conclusion, we suggest that methotrexate could be considered a therapeutic option for the treatment of HHD and in particular as a maintaining therapy to control the disease flares. (*J Dermatol Case Rep*. 2012; 6(2): 49-51)

Introduction

Hailey-Hailey disease (HHD), also known as familial benign chronic pemphigus, is an autosomal dominant disease that is characterized by vegetating and malodorous intertriginous lesions with recurrent blistering and erosions. Mutations in the ATP2C1 gene, which encodes a Golgi apparatus Ca2+-ATPase protein, lead to the inappropriate processing of desmosomal proteins. This results in deficient cell adhesion with acantholysis occurring in intertriginous sites that are prone to heat and friction. We report a 65-year-old female presenting several long standing lesions with an involvement of the axillary, inframammary and inguinal areas.

Case Report

A 65 year-old white woman presented to our Hospital in February, 2011, with a 25-years history of vesicles and crusted erosion of the intertriginous folds mainly involving axillae, inframammary and inguinal and sacroiliac regions (Fig. 1).

Since 1986, skin blisters and crusts with preceding pruritus and a sensation of burning have recurred approximately every year, during summer, in the same areas. The patient reported that, in the past, the eruption flared around the time of her menstrual periods but she also denied any other modifying factors such as heat, friction, moisture or sweating. There were no known blood relatives with a similar condition. The patient had consulted several dermatologists prior to her visit and had one previous biopsy confirming HHD. Prior treatments had included cyclosporin, topical and systemic steroids, but both of them provided only minimal relief. Some months before our consultation she experienced a flare in the inframammary region treated with oral steroids and an improvement in the recurrence and quality of erosions was seen. However, this medication was discontinued because she could not tolerate side effects of detent and stomach upset.

At the presentation to our clinic, considering disease extension and also the failure of the other standard treatments, oral methotrexate, 7,5 mg per week, was started. Lesions improved and were nearly cleared 3 months later, leaving some post-inflammatory hyperpigmentation. Methotrexate

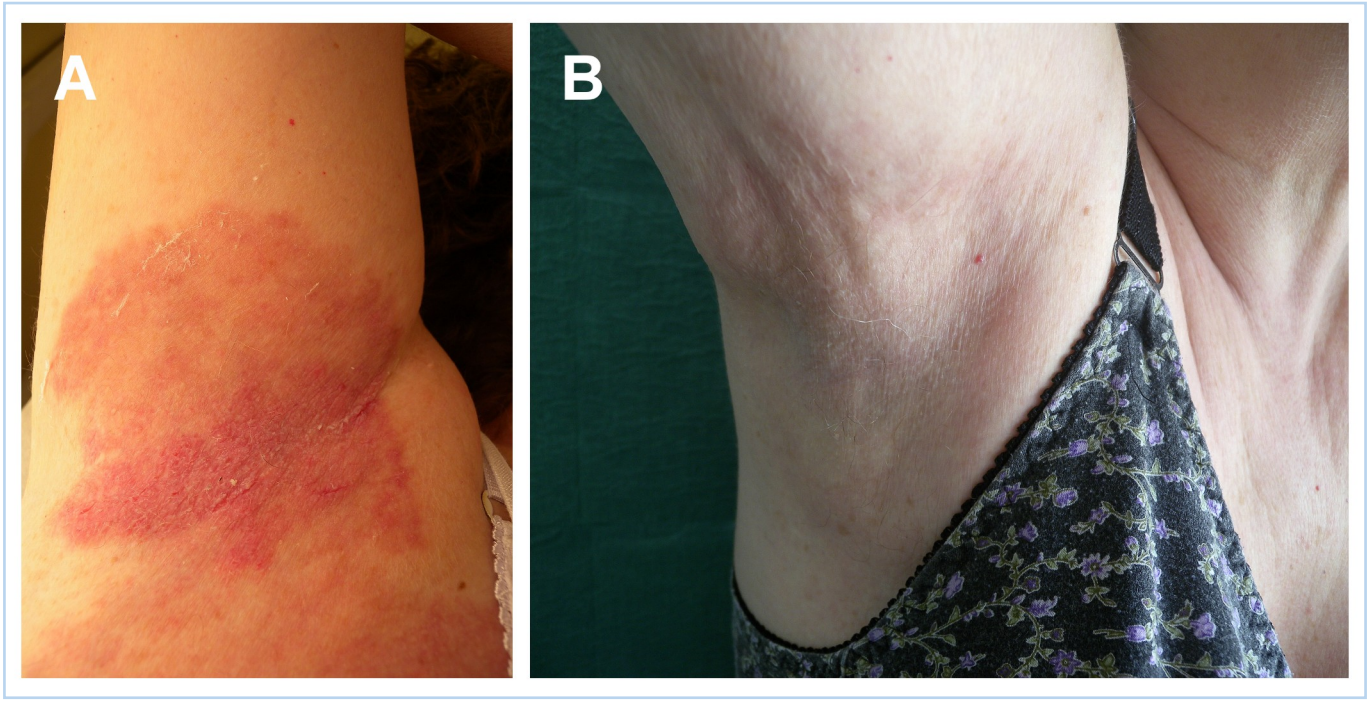

Figure 1
Erythematous and macerated lesions at the axillary fold (A); the lesions were cleared after a course with methotrexate (B).

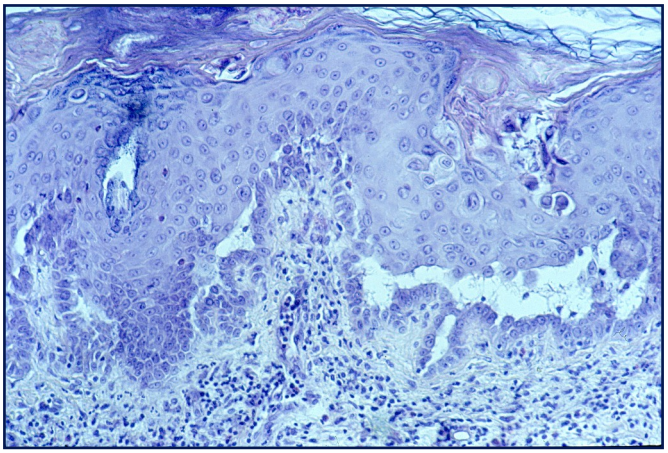

Figure 2
Intraepidermal detachment within the full width of epidermis with acantholytic cells and dyskeratosis.

was tapered and finally stopped 2 months later. Since then she remained asymptomatic and topical corticoseroids were sufficient to control developing lesions.

Discussion

HHD, which was first described in 1939 as familiar benign chronic pemphigus, is an autosomal dominant acantholytic disorder that manifests with recurrent episodes of painful or pruritic, flaccid vesicles and erosions.[1] HHD has a chronic, relapsing-remitting course exacerbated by heat, sweat, moisture, friction and ultraviolet radiation or by fungal, bacterial, yeast and parasitic superinfection. Recent studies have discovered that HHD is caused by heterozygous mutations in the ATP2C1 gene which leads to a malfunction of the encoded protein hPMR1. hPMR1 is a high-affinity calcium transport ATPase pump of the Golgi complex.[2]

Most patients experience initial symptoms during the second or third decade of life suffer from chronic, relapsing outbreaks. Although any individual's disease course may be difficult to predict, the majority of patient, who have suffered from the condition for greater than 20 years, felt that their disease became less burdersome with advancing age. The lesions of HHD characteristically favor the axillary, genitocrural and inframammary folds and commonly involve the back and the nape and lateral aspects of the neck. Lesions are typically symmetric although post-zygotic loss of gene function can result in asymmetric type. Additional unusual presentations of HHD include erythroderma and involvement of the vulva, conjunctivae or mucosae.[3]

Our patient demonstrated a classic presentation of HHD, with symmetrically distributed, recurrent erosions that were limited to the upper chest, anterior aspects of the upper arms and inguinal areas.

Complications associated with HHD include colonization and secondary infections with bacterial, fungal or viral microorganism, including eczema herpeticum and rare instances of squamouse-cell carcinoma. In general, patients experience a relapsing and remitting disease course, with a substantial impact on their quality of life. The frequency of exacerbations may be decreased by wearing light-weight clothing and avoiding activities that result in sweating or skin friction. Nowadays, to our knowledge, there are no international guidelines to HHD's treatment. Therapeutic option for HHD are many and they vary in their approach to this

troubling disease. While there have been a few treatments that provide a long-lasting positive therapeutic impact, nowadays there is no known cure. Topical antimicrobials, oral antimicrobials, topical glucocorticoids, and intralesional glucocorticoids are routinely used to control symptoms. Anecdotal drug therapies have been used for control the underlying inflammatory immune response associated with HHD. These therapies include topical tacrolimus, topical tacalcitol, topical and oral cyclosporin, intradermal botulinum toxin type A, dapsone, isotretinoin, etretinate, alefacept and thalidomide. In some patients, disease can be recalcitrant to medical treatments, and more invasive approaches may be required like surgical excision of intertriginous folds or carbon dioxide laser ablation.[4,5] In literature only two other cases of refractory HHD successfully treated with methotrexate were reported.[6,7] Accordingly to these other two cases even in our patient, treatment with methotrexate, achieved a good clinical response and a remission of 9 months from the initial course of methotrexate therapy, moreover any further developing lesion was controlled with topical steroid used as needed.

In conclusion, we suggest that methotrexate could be considered a therapeutic option for the treatment of HHD and in particular as a maintaining therapy to control the disease flares.

References

1. Luo S, Ni H, Li Y, Hou S, Li X, Liu Q. Novel clinical and molecular findings in Chinese families with Hailey-Hailey disease. *Clin Exp Dermatol*. 2011; 36: 814-816. PMID: 21623880.
2. Dobson-Stone C, Fairclough R, Dunne E, Brown J, Dissanayake M, Munro CS, Strachan T, Burge S, Sudbrak R, Monaco AP, Hovnanian A. Hailey-Hailey disease: molecular and clinical characterization of novel mutations in the ATP2C1 gene. *J Invest Dermatol*. 2002; 118: 338-343. PMID: 11841554.
3. 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: 821-828. PMID: 15149492.
4. Vilarinho C, Ventura F, Brito C. Methotrexate for refractory Hailey-Hailey disease. *J Eur Acad Dermatol Venereol*. 2010; 24: 106. PMID: 19627406.
5. Fairris GM, White JE, Leppard BJ, Goodwin PG. Methotrexate for intractable benign familial chronic pemphigus. *Br J Dermatol*. 1986; 115: 640. PMID: 3790441.
6. Hurd DS, Johnston C, Bevins A. A case report of Hailey-Hailey disease treated with alefacept (Amevive). *Br J Dermatol*. 2008; 158: 399-401. PMID: 17941942.
7. Tchernev G, Cardoso JC. Familial benign chronic pemphigus (Hailey-Hailey Disease): use of topical immunomodulators as a modern treatment option. *Rev Med Chil*. 2011; 139: 633-637. PMID: 22051715.