

Oral methotrexate in the treatment of Hailey–Hailey disease: a case report

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Abstract

Hailey–Hailey disease is a rare chronic autosomal-dominant blistering disease characterized by erosions, fissures, and vegetations occurring in intertriginous regions. To date, there is no specific treatment and there are no therapeutic guidelines, which makes management of the disease challenging. We present the case of a 43-year-old man unsuccessfully treated for Hailey–Hailey disease with topical and systemic corticosteroids, antibiotics, and surgical debridement. At presentation he had erosions, vegetations, and infection in the axillae and groin. We introduced oral methotrexate, 10 mg weekly, and complete remission was achieved in 3 weeks. After 8 weeks, we decided to discontinue methotrexate due to lesion absence. Over 3 years of follow-up, mild flares were effectively managed with topical miconazole or mild steroid creams. We conclude that oral methotrexate is safe and effective for achieving long-term remission in Hailey–Hailey disease.

Keywords: Hailey–Hailey disease, methotrexate, treatment

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Introduction

Hailey–Hailey disease (HHD), or familial benign chronic pemphigus, is a chronic autosomal-dominant blistering dermatosis caused by a mutation in the *ATP2 C1* gene that encodes a Ca^{2+} ATPase protein, leading to weakened keratinocyte adhesion in the epidermis and acantholysis (1). It is characterized by vesicles and blisters that rupture and form erythematous eroded plaques with fissures and vegetations in intertriginous regions. Secondary superinfections are common. Onset is usually between the 3rd and 4th decades, and the prevalence is estimated to be around 1:50,000 (2). Despite progress in understanding the molecular basis of HHD, there are no therapeutic guidelines or specific treatment, and so management of the disease remains challenging. We report a 43-year-old male treated with 10 mg of methotrexate weekly.

Case report

A 43-year-old man was admitted to our hospital in June 2019, with a 4-year history of blisters and erosions in the axillae and the inguinal folds. In his family history, his uncle had a similar condition. He was previously treated by several dermatologists with topical and systemic corticosteroids, oral antibiotics, including tetracyclines, antibiotic ointments, and surgical debridement, with limited and transient improvement.

At presentation, the erosions and vegetations were distributed symmetrically in the axillae and inguinal region, on approximately 4% of the skin (Fig. 1). Histopathology showed diffuse acantholysis, involving full thickness of the epidermis in a dilapidated brick wall pattern (Fig. 2). Oral methotrexate 10 mg per week was introduced alongside folic acid, and a complete clinical response was achieved within 3 weeks. Topical treatment included miconazole cream. Methotrexate was tapered and stopped 2 months later. No adverse effects were reported during the treatment. Sub-

sequently, the patient remained asymptomatic during a 3-year follow-up period. Mild relapses were infrequent, and control was achieved with occasional use of topical preparations containing betamethasone, gentamicin, and miconazole.



Figure 1 | Erythematous eroded plaques with a fissured appearance in the axillae.

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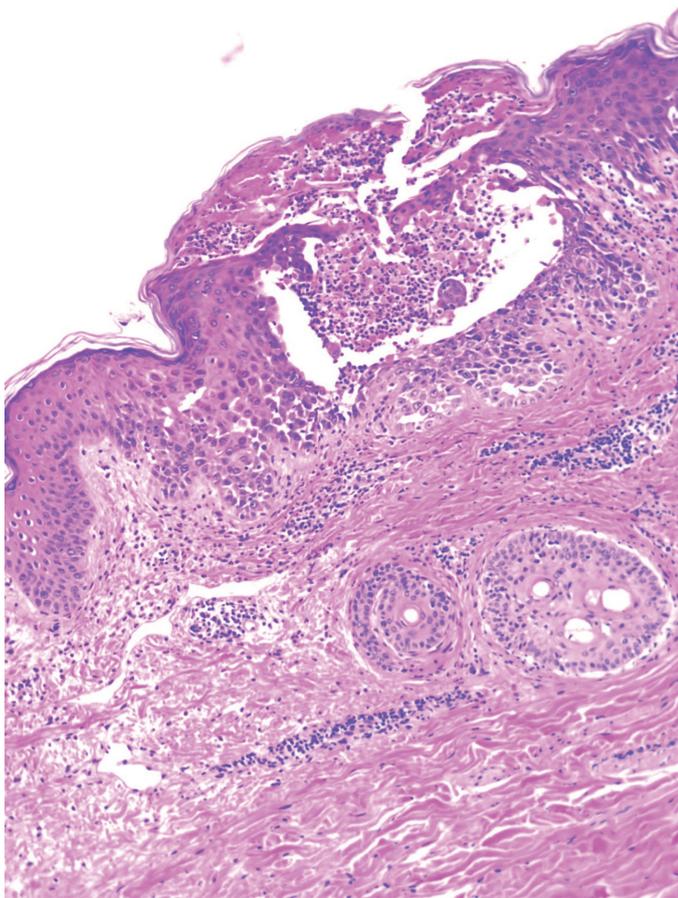


Figure 2 | Diffuse acantholysis in the epidermis compared to a dilapidated brick wall.

Discussion

To date, no official therapeutic guidelines have been published for the management of HHD, which makes assessment of treatment options more difficult (2). Given the lack of randomized clinical studies, therapeutic recommendations primarily rely on retrospective analyses, case reports, and the physician's personal experience. Topical corticosteroids, antibiotics, calcineurin inhibitors, and vitamin D analogs are considered first-line therapy in most cases (1). In addition to its antifungal properties, miconazole is also known to have an antibacterial and anti-inflammatory effect (3). Systemic treatment comprises antibiotics, retinoids, corticosteroids, dapsons, and naltrexone. Immunomodulators, such as cyclosporine, methotrexate, thalidomide, and apremilast, are considered in cases for which standard treatment options are not effective. Procedural therapies include botulinum toxin type A, laser ablation, pulsed dye laser, photodynamic therapy, and radiofrequency surgery (2).

HHD is a chronic relapsing-remitting disease exacerbated by friction and heat and complicated by bacterial, fungal, or viral superinfection (4). Although the main event in HHD is acantholysis, the treatment targets cutaneous inflammation (5). The loss of *ATP2C1* function leads to DNA damage and accelerates keratinocyte differentiation. Keratinocytes produce inflammatory cytokines

which—alongside DNA alteration, superinfections, and friction—have been suggested to trigger the release of inflammatory mediators in HHD (1). Methotrexate is used in numerous dermatoses due to its anti-proliferative and anti-inflammatory properties. At low doses, methotrexate has shown potent anti-inflammatory effects by acting on multiple target cells of the immune system. The safety profile of methotrexate is high when administered in commonly used doses in dermatology, and folic acid supplementation improves its tolerance even more (5). Recent studies have shown no evident superiority of subcutaneous methotrexate administration versus oral regarding adverse events and efficacy (6).

To our knowledge, 11 cases of patients with HHD treated with methotrexate have been published in the literature. Six of 11 reported cases showed therapeutic success.

Fairris et al. were first to report the case of a 50-year-old patient with HHD successfully treated with 15 mg of intramuscular methotrexate per week in 1986 (7). D'Errico et al. and Vilarinho et al. each achieved complete and long-lasting remission using oral methotrexate in a patient with HHD at 7.5 mg per week (4) and 15 mg per week (8), respectively. Arjona-Aguilera et al. reported two cases of recalcitrant HHD treated with 15 mg of subcutaneous methotrexate per week (5). Recently, Mestre et al. published a case report of a patient with rheumatoid arthritis and HHD treated with 10 to 20 mg of methotrexate weekly (1). All patients had good clinical response and tolerance. Vilarinho et al. discontinued treatment after 2 months, as did we in our patient, whereas others continued treatment with methotrexate up to 12 months. Mild flares after discontinuation of therapy were well managed with standard topical treatments, as in the case of our patient.

In contrast, Bedi et al. (9) reported a case of a 71-year-old woman that, during a 2-month course of methotrexate, 15 mg weekly, showed minimal improvement and had new extensive lesions. Similarly, Hurd et al. (10), Narbutt et al. (11), and Kieffer et al. (12) all reported treatment failure with the use of methotrexate in treating HHD, but they did not specify the dose or duration of the therapy because they reported patients successfully treated with other forms of therapy previously unresponsive to methotrexate.

Due to contradictory reports in the literature, we believe that the treatment response of each patient with HHD treated with methotrexate should be reported.

Conclusions

In conclusion, we reported a case of HHD successfully treated with oral methotrexate, with excellent tolerance, which showed rapid lesion healing and long-lasting remission after methotrexate discontinuation. We believe that this case report may increase knowledge of dermatologists about using methotrexate as a therapeutic option for HHD.

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