Recalcitrant vulvar Hailey-Hailey disease treated with alitretinoin and onabotulinumtoxinA: A case report

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Abstract
Hailey-Hailey disease is an autosomal dominant genodermatosis leading to chronic hyperkeratotic and fissured lesions in the intertriginous areas. We present a 53-year-old woman with a case of vulvar and inguinal Hailey-Hailey disease resistant to usual treatments. She was efficiently treated with alitretinoin 10 mg daily combined with injections of onabotulinumtoxinA every 9 months. The combination led to an almost complete resolution of the lesions and symptoms at follow-ups.

Keywords
Hailey-Hailey disease, alitretinoin, onabotulinumtoxinA

Introduction
Hailey-Hailey disease (HHD), or familial benign chronic pemphigus, is an autosomal dominant genodermatosis caused by a mutation in the ATP2C1 gene on chromosome 3q1. This leads to a dysfunction in the Golgi-associated human secretory pathway Ca\(^{2+}\)/Mn\(^{2+}\) ATPase (hSPCA1) that explains the typical epidermal acantholysis that causes recurrent blisters and erosions in intertriginous sites. Isolated vulvar lesions are also possible. This causes pain, pruritus and the development of chronic malodorous vegetations at risk of infection with Staphylococcus aureus and Candida albicans. The symptoms are typically exacerbated with sweating, friction and heat and will have an impact on patient’s quality of life.

Treatments can be challenging and are mostly symptomatic with topical or oral corticosteroids, topical calcineurin inhibitor, antihistamines, antifungal and antimicrobial agents, including tobramycin and gentamicin. Patients carrying a premature stop mutation of the gene can particularly benefit of topical gentamicin. It has demonstrated its capacity to induce readthrough of premature stop mutation and possibly prevent the formation of a truncated form of the protein hSPCA1. However, several resistant cases have been described and treated with methotrexate, vitamin D analogues, cyclosporine, dapsone, onabotulinumtoxinA (OnA), alitretinoin, lasers (mostly erbium:YAG and CO\(_2\)) or dermabrasion. Lately, the use of low-dose naltrexone was also described. As a Toll-like receptor 4 antagonist, naltrexone can lead to a lower production of tumor necrosis factor (TNF)-alpha, interleukin-6 and nitric oxide, which are known to play a role in the calcium homeostasis known to be dysregulated in HHD. In rare cases, surgical excisions have also been described.

We present the case of a 53-year-old woman with a vulvar and inguinal HHD that failed topical treatments for several years and was successfully treated with a combination of alitretinoin and OnA injections.

Case report
A 53-year-old woman was referred to the vulvar disease clinic for distressful inguinal and vulvar lesions associated with an HHD. She was only known for hypertension and obesity, for which she had a gastric surgery. Her HHD was confirmed with a vulvar biopsy showing typical acantholysis within the epidermis. She had been treated with several courses of topical corticosteroids and calcineurin inhibitors along with oral antihistamines and showed only mild improvement.

She initially presented with chronic erythematous keratotic and fissured plaques on the labia majora, the groins and the
inner thighs, as well as on the neck and the axillary regions. An attempt at optimizing her topical therapy was made by combining different regimens which included a moderate strength topical corticosteroid, fusidic acid ointment, clotrimazole cream, oral antihistamines and a course of oral fluconazole. The neck and axillae lesions were controlled, leaving the patient’s vulvar and inguinal areas still significantly affected and symptomatic (see Figure 1). It was decided to introduce alitretinoin at 10 mg daily, combined with a topical treatment. A 75% reduction of the lesions was noticed at the 5-month follow-up visit, and up to 90% at 15 months. Pruritus was still occasionally bothersome with the occasional exacerbations during the summer months. An increase in the dose of alitretinoin at 20 mg daily was not tolerated because of xerosis and fatigue. It was then decided to add OnA injections to her treatments. A total of 200 U were initially injected in the inguinal area and labia majora (100 U per side). Injections were then repeated every 6–9 months. This combination led to a complete resolution of the active lesions, as well as the resolution of pruritus and pain. She now only presents a mild exacerbation a few weeks before her scheduled OnA injections, which correlates with the estimated lasting efficacy of the injections of 6–9 months (see Figure 2). During follow-ups, an attempt at tapering alitretinoin to 10 mg every other day failed with a recurrence of the lesions and symptoms. Subsequently, a daily 10-mg dose of alitretinoin was reintroduced.

Both treatments are well tolerated and no side effects were noted at these doses. Laboratories were monitored every 3 months for alitretinoin and only a mild and non-significant increase in the total cholesterol was seen.

Discussion

HHD can be quite distressing for the patients’ quality of life with important symptoms of pruritus and pain, accompanying the recurrent blisters, erosions and plaques in the intertriginous areas.5 Management can be a challenge in some cases since there is still no cure other than the symptomatic treatments.

In the case of our patient, the only satisfying treatment was achieved with a combination of alitretinoin 10 mg daily and OnA injections every 9 months. Alitretinoin has been described in three other patients up to now by Sardy and Ruzicka,6 and Vanderbeck et al.7 They were all treated with a dose of 30 mg and responded positively, although two of them needed a combination, one with oral prednisone and the other with narrowband ultraviolet B (UVB). One case was also successfully treated with etretinate, which is no longer available.8 Alitretinoin, a first generation oral retinoid, is known to interact with the nuclear retinoic acid receptors (RAR) and retinoid X receptors (RXR), therefore having anti-proliferative and anti-inflammatory properties on the keratinocytes. This mechanism of action can explain a potential effect on the hyperkeratotic component of the lesions. This treatment, alone or in combination, has also been described for Darier’s disease.

OnA injections have been used in several published case reports or series for HHD, mostly in combination with topical treatments.9–13 A significant improvement was noted in all of them, even with complete resolutions.14–17 Knowing that sweating is a typical exacerbating factor, the benefit can be explained by the inhibition of the release of acetylcholine in the sweat glands, which can reduce the sweating and prevent flares of the disease.

This treatment combination for our patient allowed the use of a lower dose of alitretinoin compared to the other cases documented to date which is better for the tolerability profile and long term treatment. The case of this patient highlights the challenge behind the treatment of HHD, which...
can be refractory to several known therapies. We suggest that alitretinoin combined with OnA injections can be an efficient therapeutic option for refractory cases of HHD.

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**Informed consent**
The patient provided informed consent for publication of the case report.

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