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Case Series

# Case series of hailey-Hailey disease treated with apremilast

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ABSTRACT

Hailey-Hailey disease (HHD) is a rare autosomal-dominant blistering condition caused by heterozygous mutations in the ATP2C1 gene on chromosome 3q21-q24 which encodes ATPase. The typical skin lesions of HHD usually occur in friction or intertriginous areas, tend to form erythematous plaques with worm-eaten erosions and painful fissures or moist vegetations. Treatment includes general measures like weight management to minimize friction and comfortable clothing to prevent heat, moisture and friction. Topical steroids, antibiotics, vitamin D3 derivative and tacrolimus helps to control the disease flares in mild cases. Systemic treatment includes antibiotics, steroids, cyclosporine, dapsone, methotrexate and thalidomide in severe cases. Treatment of this disease till date is far from satisfactory. Here we report 3 cases (two females and one male) presented with macerated, patch with fissures in both axilla and groin. Characteristic "dilapidated brick wall appearance" was observed histologically. The patients were prescribed various therapeutic regimens over the period of one year, the response was unsatisfactory, so they were started on apremilast (phosphodiesterase-4 inhibitor), initially with induction dose and later with maintenance dose of 30mg every 12h, with a very good response in 2 female patients and one lost with the follow-up. We suggest that apremilast may be a low risk therapeutic option for severe cases of HHD. Accumulation of a greater number of similar cases and further research will be required.



## 1. Introduction

An uncommon genodermatosis known as Hailey disease (HHD) was initially reported by the Hailey brothers in 1939.[1] It is a rare autosomal-dominant blistering conditions with an estimated prevalence of 1/50,000, commonly known as familial benign chronic pemphigus.[2] Mutations in ATP2C1 gene that encodes a calcium pump of the Golgi apparatus causes HHD.[3] Intermittent episodes of vesicles that breaks to form painful 'rhagades' and scaly erythematous plaques in the intertriginous region.[4] Factors such as friction, moisture, UV radiation, and superficial bacterial, fungal infections exacerbate HHD.[5] Topical steroids, antibiotics, tacalcitol another vitamin D3 derivative and tacrolimus are the topical modalities of treatment and the systemic treatment includes antibiotics, steroids, dapsone, cyclosporine, methotrexate and thalidomide. Here we report a cases of HHD treated with apremilast, and its outcome.

## 2. Case 1

A 36-year-old married woman presented to skin outpatient department with greyish black coloured macerated lesions associated with pain, over flexural areas. She was having intermittent episodes for past 12 years. Initially, she noticed sudden appearance of multiple itchy vesicles on an erythematous base over her groin region- heals with crusting and hyperpigmentation. Later, she started developing similar lesions over the axilla, inframammary

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region, which worsened in summertime. For past 2 years, there was increase in lesion size, crusting, and ulcer formation. There was no fever, oral or genital lesions, nail involvement. Her mother, brother and her maternal grandmother had history of similar lesions. On examination, Hyperpigmented macerated plaque with fissures and erosion distributed symmetrically over bilateral axilla, groin and inframammary region. KOH of skin scrapping was negative. Biopsy, revealed widespread acantholysis with dilapidated brick wall appearance with separation of keratinocytes, foci of hypergranulosis, orthokeratosis, focal suprabasal cleft with acantholytic cells, upper dermal perivascular infiltrates of lymphocytes was present. Clinical and histopathological features were suggestive of HHD. She was recalcitrant for topical antibiotics, steroids and calcineurin inhibitors and systemic immunomodulators. so she was started on Apremilast, initially with induction dose and later with maintenance dose of 30mg every 12h. She started getting good response in 3weeks of starting apremilast.

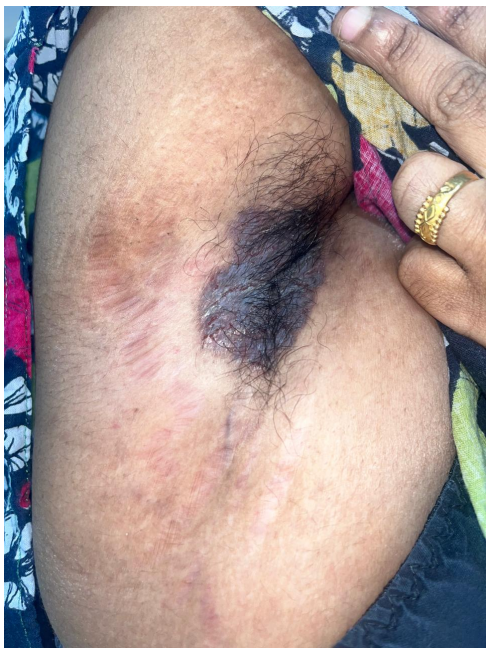

**Figure 1:** Macerated hyperpigmented plaques overright axilla

### 2.1. *Case 2*

58 years old female, mother of case 1 had similar complaints of reddish rash lesion over neck and flexures , associated with itching and irritation for past 25 years. The lesion exacerbates during summer and subsides on taking topical medications. On examination hyperpigmented macerated plaques with erosion present on neck, axilla and groin region. KOH of skin scrapping was negative. Biopsy results were suggestive of HHD. She was treated initially with topical and systemic antibiotics, followed by topical steroids

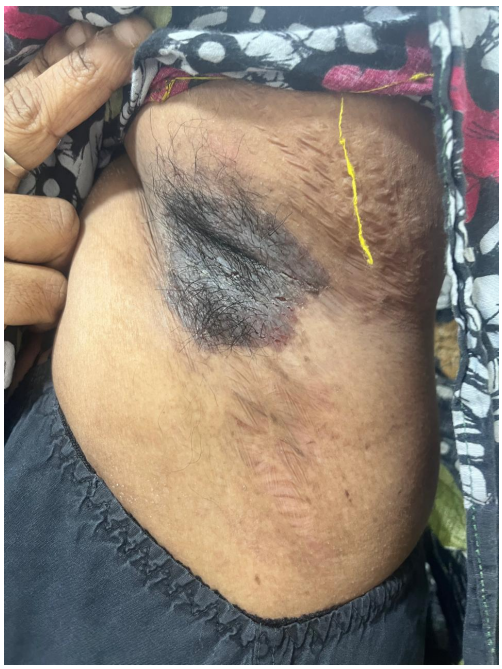

**Figure 2:** Macerated hyperpigmented plaques over leftaxilla

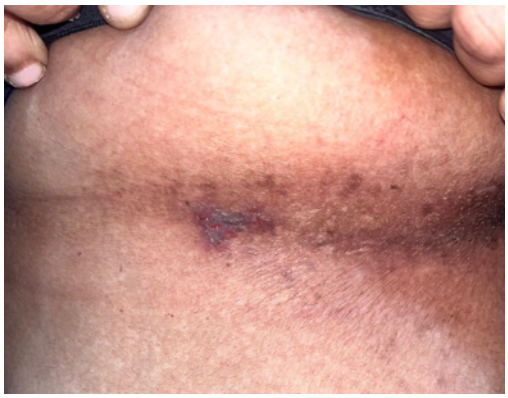

**Figure 3:** Hyperpigmented plaques with erosion and crusting over inframammary region

and calcineurin inhibitors. Since disease was refractory, she was started on Apremilast, initially with induction dose and later continued with maintenance dose. The lesions improved in one month of starting with apremilast.

### 2.2. *Case 3*

34 old male, brother of case 1 had black lesions over his axilla initially for past 10 years, then he developed similar lesions over his axilla and neck which was associated with itching and burning sensation. Lesions aggravates when has excessive sweating and subsides on taking topical medication. On examination erythematous macerated plaque with fissures present on both axilla, groin, and neck region. KOH of skin scrapping was negative.

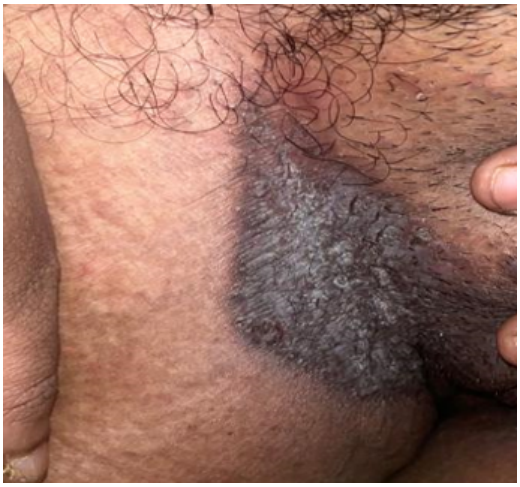

**Figure 4:** Macerated hyperpigmented plaques overright groin

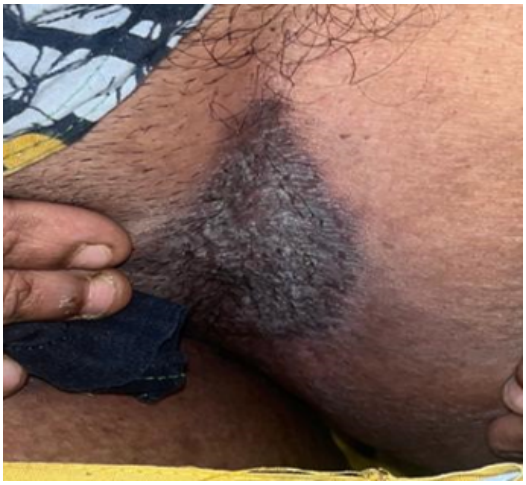

**Figure 5:** Macerated hyperpigmented plaques over left groin

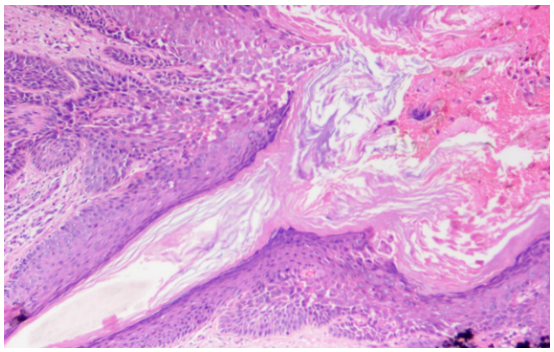

**Figure 6:** HPE- focalSuprabasal cleft with acantholytic cells -Dilapidated brick wall appearance. Dermis- upper dermal perivascular infiltration with lymphocytes

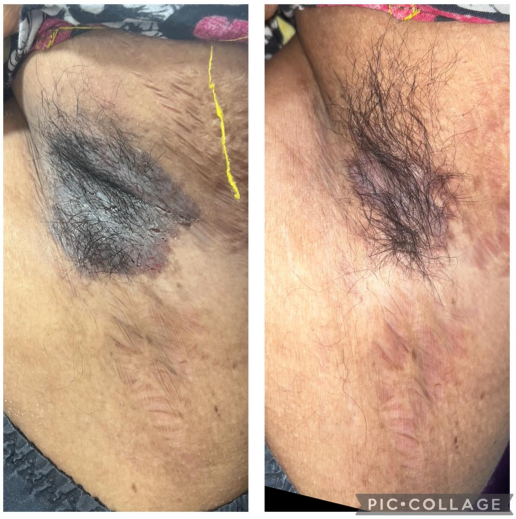


**Figure 7:** Shows before treatment (left) and after treatment (right) 3weeks of apremilast- left axilla

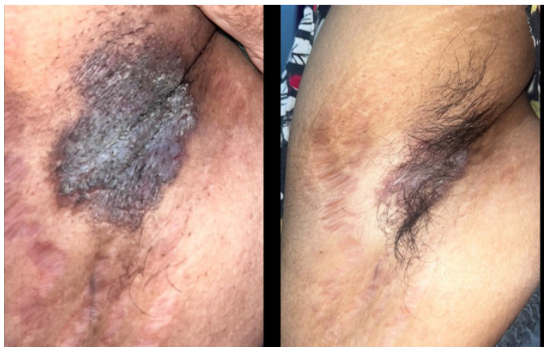

**Figure 8:** Shows before treatment (left) and after treatment (right) 3 weeks of apremilast- right axilla

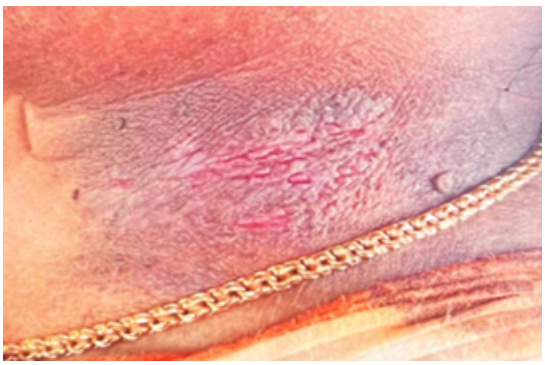

**Figure 9:** Macerated hyperpigmented plaque with rhagades over the neck

Biopsy results were suggestive of HHD. He was treated initially with topical and systemic antibiotics, followed by topical steroids and calcineurin inhibitors. Since there was no improvement, he was started on Apremilast, initially with induction dose and later with maintenance dose. Patient lost follow up.

## 3. Discussion

HHD is also termed as familial benign chronic pemphigus. It results from heterozygous mutations in the ATP2C1 gene, which codes for ATPase1 and is located on chromosome 3q21–q24. Reduced activity of this enzyme in affected people may lead to desmosome instability. This results acantholysis (loss of cohesion between keratinocyte) and vesicle formation. It's unclear how mutant ATP2C1 causes acantholysis.[6] Flaccid grouped vesicles and blisters on an erythematous base or normal skin are the primary lesions. This ruptures to form erosions and crusting with foul-smelling exudate. Chronic lesions, occurs in the intertriginous areas, tend to form erythematous plaques, erosions with worm-eaten apperarance and painful "rhagades" or moist vegetations.[7] A positive family history of HHD is present in many patients.[8] Often the disease is triggered by friction, minor trauma, heat, humidity irradiation, on which secondary infections, leads to acute exacerbations of the disease. Exfoliative toxins produced by Staphylococcus may aggravate acantholysis leading to severe flares.[9] Patients with HHD may go through excruciatingly painful symptoms like itching, burning, and body odour, which can severely impact the quality of life. HHD has a major negative influence on social functioning and is linked to considerable psychological suffering.[10] Typical clinical presentations, positive family history and characteristic histopathological feature of "dilapidated brick wall" appearance, negative immunofluorescent studies are the primary basis for the diagnosis. Intertrigo, Dermatophytosis, Eczema, Darier disease and Pemphigus vegetans are differential diagnosis. Various therapeutic modalities are to be considered as HHD is difficult disease to treat. As general measures, weight of the patient should be maintained to reduce friction and comfortable clothing to prevent friction, heat, and moisture. Antiseptics and topical anti-inflammatory treatments helps to control the disease flares in mild cases of HHD. 50 % Zinc oxide paste prevents the skin from friction and humidity by forming a barrier and it can prevent infection of skin lesions and has been reported to increase in vitro levels of intracellular calcium.[11] Moderate to high-potent topical steroids are often considered as a first-line treatment. Long trem usage can lead to steroid-induced atrophy and striae. Topical calcineurin inhibitors twice a day can be second-line or long-term maintenance treatment to avoid steroid-induced skin atrophy.[12] Exacerbations can be controlled with topical and systemic antibiotics. Wide excision of the lesion, combined with restoration with split-thickness skin grafts is commonly acceptable for recurrent lesions.[13] Carbon dioxide laser ablation and Erbium:YAG (Yttrium-Aluminium-Garnet) have also been reported to be effective.[14] Since the course of HHD is chronic and variable; patients have recurring episodes of aggravation and remission that can extend from months to years. In severe cases of Hailey-Hailey disease resistant to conventional treatments, good response with apremilast have been reported. Apremilast is a drug that selectively inhibits the enzyme phosphodiesterase 4 (PDE4), which prevents the conversion of cAMP to AMP leads to intracellular accumulation of cAMP, which depletes the production of inflammatory mediators such IFN-$\gamma$, chemokines, IL-2, IL-8, IL-12, TNF-$\alpha$, and IL-23 and further reduces the inflammatory response.[15,16] It is FDA approved for psoriatic arthritis, plaque psoriasis, oral ulcers associated with Behcet disease.[17] Apremilast is contraindicated in pregnancy and lactation.[18] Frequently reported adverse effects are diarrhea, nausea, headache, vomiting, weight loss, migraine, frequent bowel movements, mood disorders and suicidal thoughts.[19] Apremilast 10 mg was used as an induction dose, and then the dosage was gradually increased by 10 mg each day for six days, until by day six, to reach the daily dosage of 30 mg twice a day. This dosage titration helps prevent unwanted gastrointestinal adverse effects.[20] In previous studies, 4 patients with HHD, improvement was seen after 1 month with use of apremilast 30 mg twice daily.[21] An early improvement of skin lesion and symptoms of HHD have been reported in 2 weeks of treatment with apremilast. In total of 13 reported cases of HHD[22] treated with apremilast, 8 cases -good response to apremilast, 5 cases- no response.

Two HHD patients who received apremilast did not experience recurrence two years.[22] However, it is also been reported that, five patients treated with apremilast had no improvement.[23] Sometimes apremilast alone is insufficient to reduce inflammation due to a complicated interaction of numerous factors, including seasons, frictional stress and sweat. The possibility of combination treatments, like apremilast with oral steroids, or antibacterial agents ought to be investigated in the future.[24]

## 4. Conclusion

In severe cases of HHD with chronic relapsing course and multiple recurrences, which are resistant to conventional treatments, apremilast can be a useful low-risk therapeutic alternative. We suggest that, compilation of a more number of similar cases and further research with long-term follow-up is required.

## 5. Source of Funding

None.

## 6. Conflict of Interest

None.

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