

A Case Report on Generalised Hailey - Hailey Disease (HHD): Inherited Acantholytic Disorder

Dr. Nikhat¹, Suwaiba Zakir Hussain², Syed Abu Hassan³

¹MBBS, MD DVL, Associate professor, Department of Dermatology Venereology and Leprosy, Shadan Institute of Medical Sciences, Teaching hospital and Research centre, Peerancheru, Hyderabad, Telangana, India *Corresponding author
Corresponding Author Email: [dr.nikhat786\[at\]gmail.com](mailto:dr.nikhat786[at]gmail.com)

²MBBS, Junior resident, Department of Dermatology Venereology and Leprosy, Shadan Institute of Medical sciences, Teaching hospital and Research centre, Peerancheru, Hyderabad, Telangana, India

³MBBS, Junior resident, Department of Dermatology Venereology and Leprosy, Shadan Institute of Medical sciences, Teaching hospital and Research centre, Peerancheru, Hyderabad, Telangana, India

Abstract: *Benign chronic familial pemphigus (Hailey - Hailey disease) is a rare autosomal dominant blistering skin disorder characterised by acantholysis of the epidermis. The classical symptoms are manifested as an eruption of vesicles and bullae with multiple crusted erythematous, excoriated erosions and macerated plaques. We report a 40 - year - old female presenting with similar lesions at flexural folds regions over the intertriginous areas on neck folds, axillary folds, antecubital fossa, inframammary folds, and gluteal folds of varying sizes and photosensitivity. The patient was successfully treated with oral antimicrobials, oral steroids, topical steroids, emollients, and multivitamins.*

1. Introduction

Hailey-Hailey disease (HHD), also known as familial benign chronic pemphigus, was first described in 1939 by Howard and Hugh Hailey. ¹It is a rare blistering autosomal dominant acantholytic disease that affects around 1/50, 000 of the general population and occurs equally in both males and females. The disease often has a remitting - relapsing pattern and becomes more noticeable during the third/fourth decade of life, although it can occur at any age. ² The symptoms are usually characterised by scaly erosive crusts, malodorous, painful blistering rashes with thickened macerated fissures, recurrent bullous and flaccid ruptured vesicles resulting in erythematous plaques with varying degree of redness and is generally prompted by excessive sweating, local infections and/or friction with a predilection for flexural areas localised especially to neck, axillary and inguinal regions, often become infected, significantly impairing patients quality of life. ³We report a case of Hailey - Hailey disease (HHD) in a 40 year old female with complete coverage of clinical features, investigation, treatment and follow - up.

2. Case Presentation

We report a case of a 40 - year - old woman from India presented with foul smelling itchy lesions at flexural folds regions like neck folds, inframammary folds, axillary folds, and antecubital fossa bilaterally for twenty days. She gave the history of development of fluid filled vesicles of about 8 - 10 in the number of about 0.5 cm in size. Starting from the neck region which increases in size to form flaccid bulla and gradually progresses towards the chest involving the infra mammary fold, axillary fold, truncal surface and gluteal region. Vesicles were painful, pruritic, and associated with stinging, burning and malodorous discharge which caused discomfort to the patient following which she scratched the site and developed erosions. Each vesicle lasted for one day

and had spontaneously ruptured leaving behind erythematous eroded macerated plaques. She used to have similar lesions below both breasts and the axillary regions for the past two years. She consulted a physician and was treated with multiple courses of antimicrobials, corticosteroids, and antifungals, with only partial relief. There was no family history suggestive of any bullous disorder. A History of photosensitivity is present, aggravated on trauma and was not on any medication. She is a known case of Hypertension for two years and blood pressure is maintained on antihypertensive medicine. Dermatological examination showed multiple crusted erythematous, excoriated erosions and macerated plaques over the intertriginous areas on neck folds, axillary folds, antecubital fossa, inframammary folds and gluteal folds bilaterally of varying sizes [Figure 1]. Post inflammatory hyperpigmentation was present below the right breast symmetrical with the active lesion on the left side. nikolsky sign is negative. A solitary erosion was present on the right forearm with surrounding erythema. There was no nail, mucosal or scalp, palm, and soles involvement. With a clinical suspicion of Hailey - Hailey disease, a skin biopsy was done from the inframammary lesion of the trunk for light microscopy and non lesional specimen for direct immunofluorescence. The section shows epidermis with mild orthokeratosis, and intraepithelial neutrophils. There is a suprabasal cleft with acantholytic cells having a dilapidated brick appearance. The superficial dermis shows mild subepithelial neutrophil, and lymphocytes infiltrate. The deeper dermis and subcutis are unremarkable. The immunofluorescence report shows negative immune reactants and the presence of linear C3 deposits among basement membranes. Investigations revealed normal hemogram, liver, renal functions, and serum lipid profile. Tzanck smear showed few acantholytic cells. Systemic examination was unremarkable. A diagnosis of Hailey - Hailey disease was confirmed based on histopathology and clinical examination and the patient was started on moderate potent oral corticosteroid Wysolone 60 mg once daily for

two weeks and tapered it to 10 mg once daily for the next 15 days, a topical steroid like Clonate - F cream for local application along with emollients and oral antibiotic Amoxiclav 625 mg twice daily for five days and simple measures were explained to reduce skin friction and keep flexures dry, loose cool clothing and use of absorbent pads

in skin folds. By the next visit, her skin lesions started responding in four weeks. Emollients and oral multivitamins were continued twice daily uninterrupted for a total of three months. There was complete regression after a six month follow up. [Figure 2]. She tolerated the medication well without any side effects and had no relapse.



Figure 1: Skin lesions at the time of exacerbation: Vesicles, pustules, and crusted plaques on (a) inframammary region, (b) left upper thigh, and (c) gluteal region

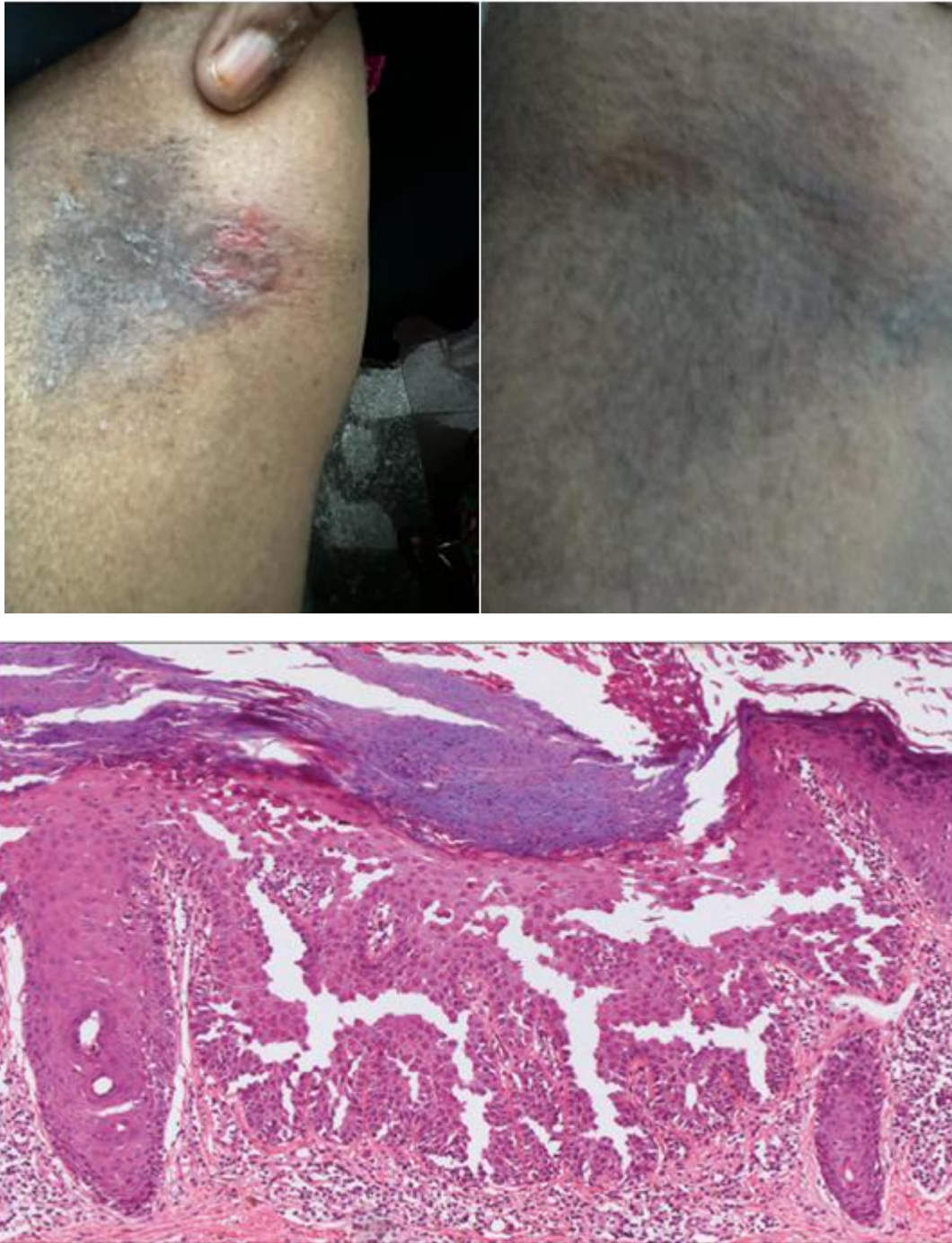


Figure 2: Solitary skin lesion on right arm before treatment and regression of lesion after treatment is shown. Histopathology showing dilapidated brick wall appearance with suprabasal clefts and acantholytic cells (H and E, 10 \times).

3. Discussion

Hailey - Hailey disease is an inherited acantholytic disorder characterised by the development of blisters, warty papules, and flexural erosions. The pathogenesis is linked to mutation of the ATP2C1 gene that codes for chromosome 3q21 which encodes ATP powered intracellular calcium ion transporter protein pump on the golgi complex of epidermal cells leading to disrupted calcium signal altering epidermal integrity between the keratinocytes and desmosomes causing an imbalance in the homeostasis of the ion resulting in intraepidermal acantholysis.^{4, 5} Clinically it can be misdiagnosed as, inverse psoriasis, tinea, impetigo, contact dermatitis, eczema, intertrigo, erythrasma, pemphigus

vulgaris, linear Ig A disease, dermatophytosis, and atypical Darier's disease.⁶ Occasionally, the erosions spread centrifugally with an active inflammatory border in serpiginous patterns, as seen in our case. The lesions generally regress in a few weeks and some lesions follow a chronic course. Less commonly involved sites are the scalp, antecubital or popliteal fossa. Our patient had a solitary bulla creating an erosion over the right forearm and on the upper thigh are the uncommon sites of involvement. Histologically partial loss of the intercellular bridges between keratinocytes gives a dilapidated brick wall appearance to the epidermis with fewer dyskeratotic cells. A red dyskeratotic rim around the nucleus is distinctive and helps to distinguish HHD from other acantholytic disorders.⁷ Direct immunofluorescence is negative. Rare case reports have described C3C deposits at

dermal - epidermal junctions.⁸ Superinfection with bacteria like staphylococcus species, fungi like candidiasis, and viruses play a significant role in exacerbations and persistence of lesions. The disease is associated with serious psychological distress and can severely affect the quality of social life of patients.⁹ Despite progress in our understanding of the molecular genetics of HHD, unfortunately, the response has been variable and existing treatments do not provide a long lasting positive therapeutic benefit.¹⁰ There are various treatment modalities for HHD, including topical corticosteroids, oral and topical antimicrobials and/or topical antimycotics therapy, retinoids, glycopyrrolate, naltrexone, botulinum toxin Type A and modern treatment options include use of topical immunomodulators like Calcineurin inhibitors (cyclosporin A, tacrolimus and Pimecrolimus) and interventional methods like laser ablation, dermabrasion, photodynamic therapy, electron beam radiotherapy and application of Narrow - band (NB) ultraviolet B (UVB).¹¹⁻¹³ Care should be taken with chronic use of corticosteroids as it may lead to skin atrophy, striae distensae and telangiectasia. Additionally, patients with Hailey - Hailey are instructed to avoid conditions such as friction, sunburn and sweating, and to keep the affected areas dry. Cool compresses and dressing have shown they can be effective in treating swelling, redness, and intensity of the blisters.² HHD cases involving large skin areas have been rarely reported as generalised HHD.¹⁴ Hence here's a case of generalised HHD successfully treated with oral antimicrobials, oral steroids, topical steroids, emollients, and multivitamins.

4. Conclusion

Clinicians generally have limited experience with HHD patients and the lack of a strong evidence base can make counselling and treatment of affected individuals difficult. Furthermore, the chronic and recalcitrant nature of HHD greatly impacts a patient's quality of life, making its management challenging for dermatologists. In conclusion, physicians should keep in mind HHD during daily practice as a differential diagnosis.

References

- [1] Hailey H. Familial benign chronic pemphigus; report thirteen years after first observation of a new entity. *South Med J.*1953; 46 (8): 763 - 765. doi: 10.1097/00007611 - 195308000 - 00007
- [2] Reddy S, Brahmbhatt H. A Narrative Review on the Usage of Surgical Skin Grafting, Acitretin, and Tacrolimus in the Treatment of Hailey - Hailey Disease. *Cures.*2021; 13 (11): e19704. doi: 10.7759/cureus.19704
- [3] Farahnik B, Blattner CM, Mortazie MB, Perry BM, Lear W, Elston DM. Interventional treatments for Hailey - Hailey disease. *J Am Acad Dermatol.*2017; 76 (3): 551 - 558. e3. doi: 10.1016/j. jaad.2016.08.039
- [4] Megna M, Scalvenzi M, Russo D, Timoshchuk EA, Costa C, Santoianni P. Hailey - Hailey disease successfully treated with vitamin D oral supplementation. *Dermatol Ther.*2019; 32 (1): e12767. doi: 10.1111/dth.12767
- [5] Tansini PB, Boff AL, Weber MB, Bonamigo RR. Familial "benign" pemphigus? Erythroderma and fatal outcome. *An Bras Dermatol.*2020; 95: 75 - 77. <https://www.scielo.br/j/abd/a/6RPsxBfc5XCxHgqVbTjHg7N/citation/?lang=en>
- [6] Vasudevan B, Verma R, Badwal S, Neema S, Mitra D, Sethumadhavan T. Hailey - Hailey disease with skin lesions at unusual sites and a good response to acitretin. *Indian J Dermatol Venereol Leprol.*2015; 81 (1): 88 - 91. doi: 10.4103/0378 - 6323.148600
- [7] Ho J, Bhawan J. Mimickers of classic acantholytic diseases. *J Dermatol.*2017; 44 (3): 232 - 242. doi: 10.1111/1346 - 8138.13769
- [8] Gu H, Chang B, Chen W, Shao C. Clinical analysis of 69 patients with familial benign chronic pemphigus. *Chin Med J .*1999; 112 (8): 761 - 763. <https://www.ncbi.nlm.nih.gov/pubmed/11601291>
- [9] Konstantinou MP, Krasagakis K. Benign Familial Pemphigus (Hailey Hailey Disease). In: *StatPearls.* StatPearls Publishing; 2022. <https://www.ncbi.nlm.nih.gov/pubmed/36256785>
- [10] Engin B, Kutlubay Z, Çelik U, Serdaroglu S, Tüzün Y. Hailey - Hailey disease: A fold (intertriginous) dermatosis. *Clin Dermatol.*2015; 33 (4): 452 - 455. doi: 10.1016/j. clindermatol.2015.04.006
- [11] Gu K, Silver S. A Case of Hailey - Hailey Disease Managed With Oral Magnesium Citrate and High - Dose Vitamin D3. *J Cutan Med Surg.*2018; 22 (3): 362 - 364. doi: 10.1177/1203475418756377
- [12] Bar - Ilan E, Koren A, Shehadeh W, Mashiah J, Sprecher E, Artzi O. An enhanced transcutaneous delivery of botulinum toxin for the treatment of Hailey - Hailey disease. *Dermatol Ther.*2020; 33 (1): e13184. doi: 10.1111/dth.13184
- [13] 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 (5): 633 - 637. <https://www.ncbi.nlm.nih.gov/pubmed/22051715>
- [14] Marsch WC, Stüttgen G. Generalized Hailey - Hailey disease. *Br J Dermatol.*1978; 99 (5): 553 - 560. doi: 10.1111/j.1365 - 2133.1978. tb02024. x