ISSN : (Online): 3008-038X
Abbreviation: J Derm Cse Rep
DOI: 10.61705/jdcr.19.2.2026.79.84

Journal of Dermatological Case Reports

Late-Onset Hailey-Hailey Disease Complicated by Infection: A Case for Integrating Antimicrobial Therapy and Dupilumab

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Abstract:

Hailey-Hailey disease (HHD) is a rare autosomal dominant genodermatosis that typically presents in mid-adulthood but may be underrecognized in older patients with atypical or late-onset disease. We report a 71-year-old woman with no family history who presented with a one-year history of painful, malodorous intertriginous erosions refractory to standard therapies. Histopathology confirmed HHD, demonstrating suprabasal acantholysis with a "dilapidated brick wall" pattern. Her course was complicated by Staphylococcus aureus and HSV-2 superinfection, which improved with targeted antimicrobial therapy. Due to persistent disease activity, dupilumab was initiated, resulting in rapid and sustained clinical improvement with near-complete resolution at one month and continued remission at six months. This case highlights the diagnostic challenge of late-onset HHD and supports dupilumab as a promising therapeutic option for refractory disease.

Keywords:
Hailey-Hailey disease, dupilumab

Received : 16-04-2026 **Revised : 20-04-2026** **Accepted: 26-04-2026** **Published : 29-04-2026**

Introduction

Hailey-Hailey disease (HHD), or familial benign chronic pemphigus, is a rare, autosomal dominant genodermatosis caused by a mutation in the *ATP2C1* gene. This mutation impairs the function of the Ca^{2+}-ATPase pump, leading to defective calcium regulation in keratinocytes [1]. The resultant impaired desmosomal adhesion manifests clinically as recurrent vesicles, erosions, and painful fissures, primarily in intertriginous areas, with histological findings of suprabasal acantholysis [2-4]. Exacerbating factors include friction, heat, UV exposure, stress, and secondary infection [5].

While HHD is typically diagnosed in mid-adulthood, its recurrent nature often leads to misdiagnosis as more common conditions such as intertrigo, candidiasis, and atopic dermatitis [2]. This diagnostic challenge is especially pronounced in older adults, as an atypical age of onset and presentation, sometimes affecting non-intertriginous sites, may further delay recognition [6].

Management of HHD currently focuses on controlling exacerbating factors, particularly superimposed infections. Treatment ranges from topical steroids and antimicrobials to systemic

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agents for severe cases [2-4]. Biologics like dupilumab are emerging as promising options for severe or treatment-resistant cases [7-9]. We present a case of HHD in a woman in her 70s characterized by a rare, late-onset sporadic presentation with no family history, underscoring the diagnostic difficulty in this age group. Furthermore, this report highlights the significant role of dupilumab in achieving complete disease control when used in conjunction with standard treatment for superimposed infections, thereby supporting its use as an effective targeted therapy for severe, recalcitrant HHD.

Case Report

A 71-year-old woman presented to the emergency department with a one-year history of recurrent, painful lesions. She reported worsening pain, purulent drainage, and a foul odor emanating from extensive lesions in her axillae, inframammary folds, and groin. Prior outpatient treatment, including super-potent topical steroids, antiperspirants, and oral prednisone, resulted in only partial improvement. A skin biopsy had not been performed prior to this admission.

On examination, she exhibited extensive macerated plaques with flaccid vesicles, fissuring, and exudative crusting across all intertriginous regions **(Figure 1A & 1B)**. Given the severity of her symptoms, the patient was admitted for systemic treatment and required intravenous (IV) opioids for pain control.

Upon admission, the patient was treated empirically for superimposed infections, starting on an IV antibiotic and an oral antifungal agent. Cultures were positive for *Staphylococcus aureus*, and HSV-2 PCR returned positive, leading to the initiation of IV acyclovir.
Two 4-mm punch biopsies were performed on the left inframammary fold. Histology revealed suprabasilar and intraepidermal clefting with keratinocyte acantholysis in a classic “dilapidated brick wall” pattern, which was definitively consistent with HHD **(Figure 2A & 2B)**. Direct immunofluorescence was negative, and no viral cytopathic effect was seen. The patient showed significant clinical improvement in pain and lesion severity with antimicrobial treatment and was discharged home.

At her first dermatology follow-up three weeks later, the patient still presented with persistent macerated and eroded areas. Given the refractory nature of the disease and the patient's failure to respond fully to conventional therapies, she was started on dupilumab, which has a favorable safety profile and has shown promise in treating severe, treatment-resistant HHD **(Figure 3A & 3B)**. Pimecrolimus cream was added as maintenance therapy.

At her second follow-up, one month after initiating dupilumab, she showed significant improvement with near-complete resolution of inflammation in the affected folds **(Figure 3C & 3D)**. Six months after initiating dupilumab, the patient continues to have disease control and has experienced no disease flares.

Discussion

Late-onset Hailey-Hailey Disease (HHD) is a rare form of the condition that typically manifests in late adulthood. When HHD presents in older individuals, the diagnosis can be delayed, as clinicians may not immediately consider this condition in adults with new-onset erosive or intertriginous skin issues [3]. Furthermore, late-onset HHD may present with atypical features, such as involvement of non-intertriginous areas, unilateral or localized plaques, or morphologies resembling infectious or inflammatory dermatoses [6]. This clinical diversity emphasizes the importance of considering HHD in the differential diagnosis of chronic or recurrent erosive lesions across all age groups.

Despite the potential for atypical presentations, our patient exhibited the classic involvement of intertriginous areas, which are most susceptible to friction, heat, and moisture—known precipitating factors for disease activity [3]. Histological examination confirmed the diagnosis, revealing the characteristic suprabasal acantholysis with a "dilapidated brick wall" appearance, consistent with HHD [2,3].

Managing disease triggers is central to controlling HHD. The condition is highly sensitive to external

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factors such as friction, sweating, and infections. Among these, bacterial and candidal infections are the most common and clinically significant triggers for disease flares [5]. Secondary infections can rapidly exacerbate the disease, transforming mildly symptomatic plaques into painful, widespread erosions [8, 9]. Early recognition and treatment of these infectious triggers are crucial to preventing severe exacerbations.

Although HSV superinfection is uncommon, our patient had concomitant HSV-2 along with a *Staphylococcus aureus* infection. This underscores the importance of performing both HSV/VZV and bacterial swabs in patients presenting with an HHD flare to identify treatable triggers.

In addition to addressing infectious triggers, controlling underlying disease inflammation is vital. Emerging therapies such as dupilumab have shown promise, particularly in patients with recurrent or treatment-resistant HHD [7-9]. While dupilumab does not directly correct the underlying calcium-pump defect, it may reduce inflammation and barrier dysfunction, thereby diminishing the frequency and intensity of flares [7]. Moreover, dupilumab is a very safe option, with no need for regular laboratory monitoring, making it a convenient and low-risk choice for long-term management.

Although current evidence is limited to case reports and small studies, these early findings suggest that dupilumab could serve as a valuable steroid-sparing option, warranting further investigation in larger cohorts. Like our patient, who showed marked improvement and complete resolution of lesions after starting dupilumab therapy, such treatments offer hope for better disease management in patients with severe or refractory HHD.

Conclusion

This case illustrates the importance of considering Hailey-Hailey disease in older adults presenting with recurrent intertriginous eruptions, including sporadic cases without a known family history. Prompt recognition, histologic confirmation, and evaluation for superimposed infections remain essential for guiding management. The patient's sustained response to dupilumab supports its potential as a safe and effective option for severe, treatment-resistant HHD. Further studies are needed to better define its long-term efficacy and role in clinical practice.

Funding Sources: None

Conflicts of Interest: No conflicts to disclose

Patient Consent: The authors obtained written consent from the patient for their photographs and medical information to be published in print and online, with the understanding that this information may be publicly available. Patient consent forms were not provided to the journal but are retained by the authors.

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Figure Legends

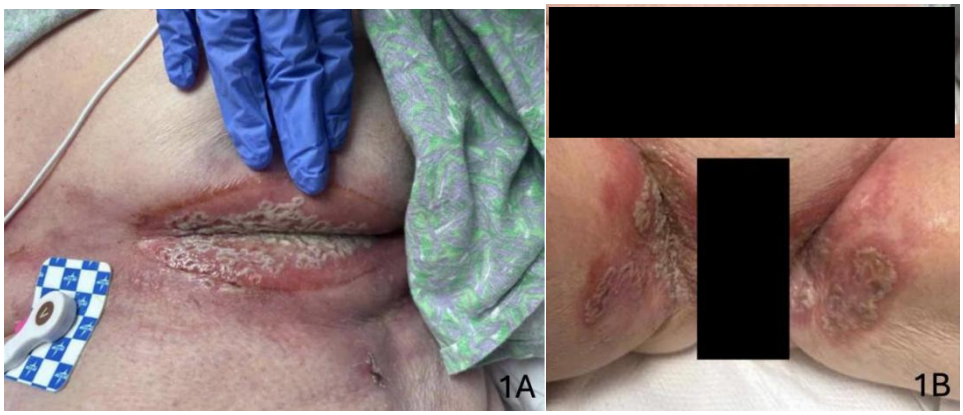
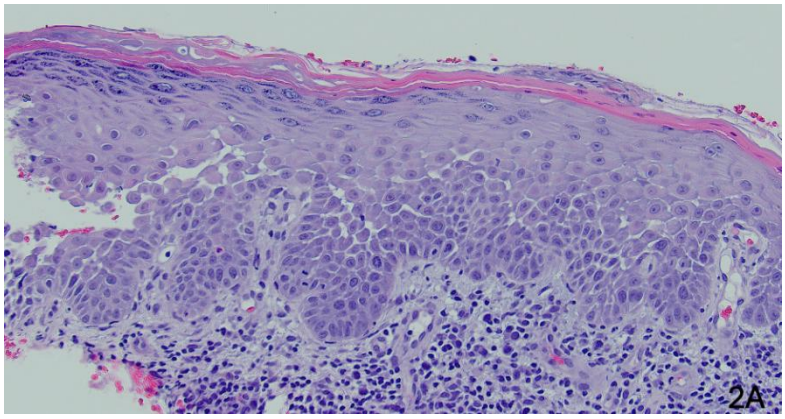


Figure 1. 1A, 1B: Erythematous plaques with whitish scale, erosions, and maceration before dupilumab.



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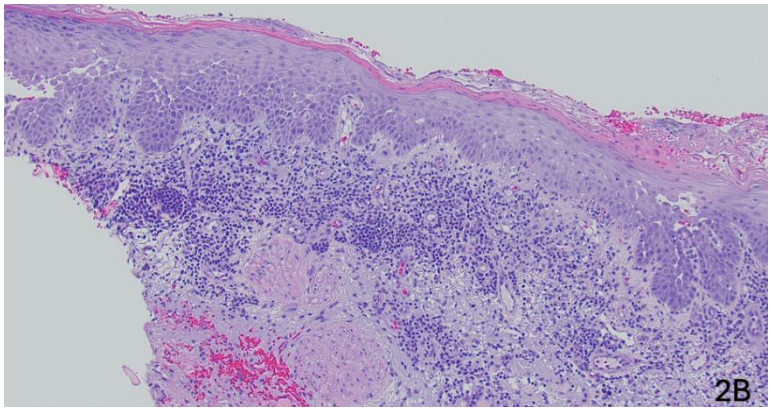
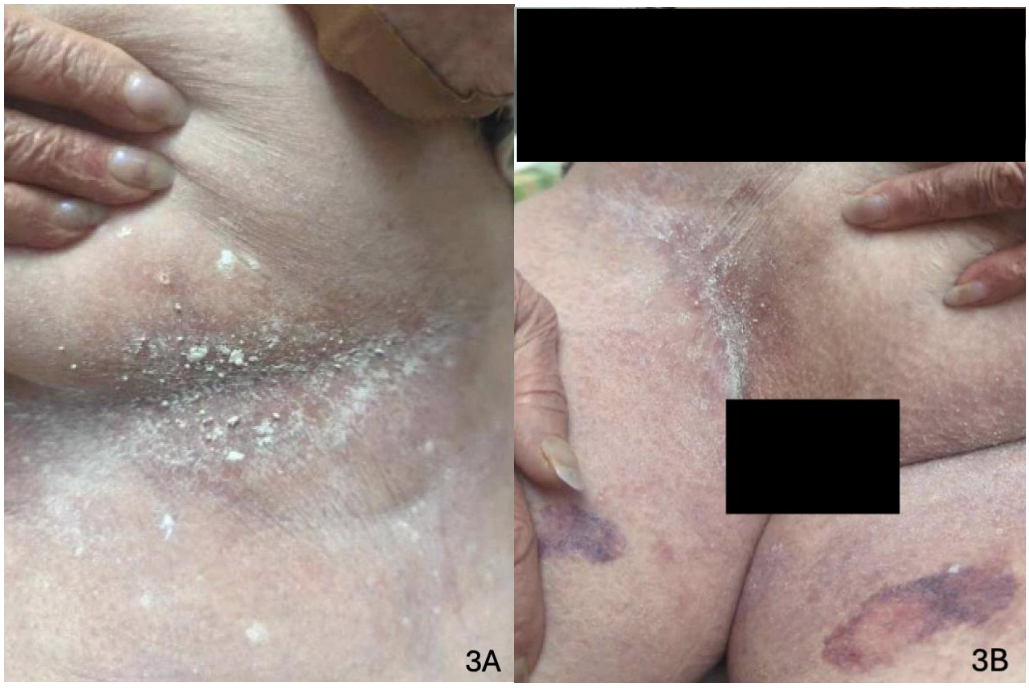


Figure 2. Histopathology: 2A: Suprabasilar and intraepidermal clefting with keratinocyte acantholysis. 2B: Higher power view showing suprabasilar and intraepidermal clefting with keratinocyte acantholysis.



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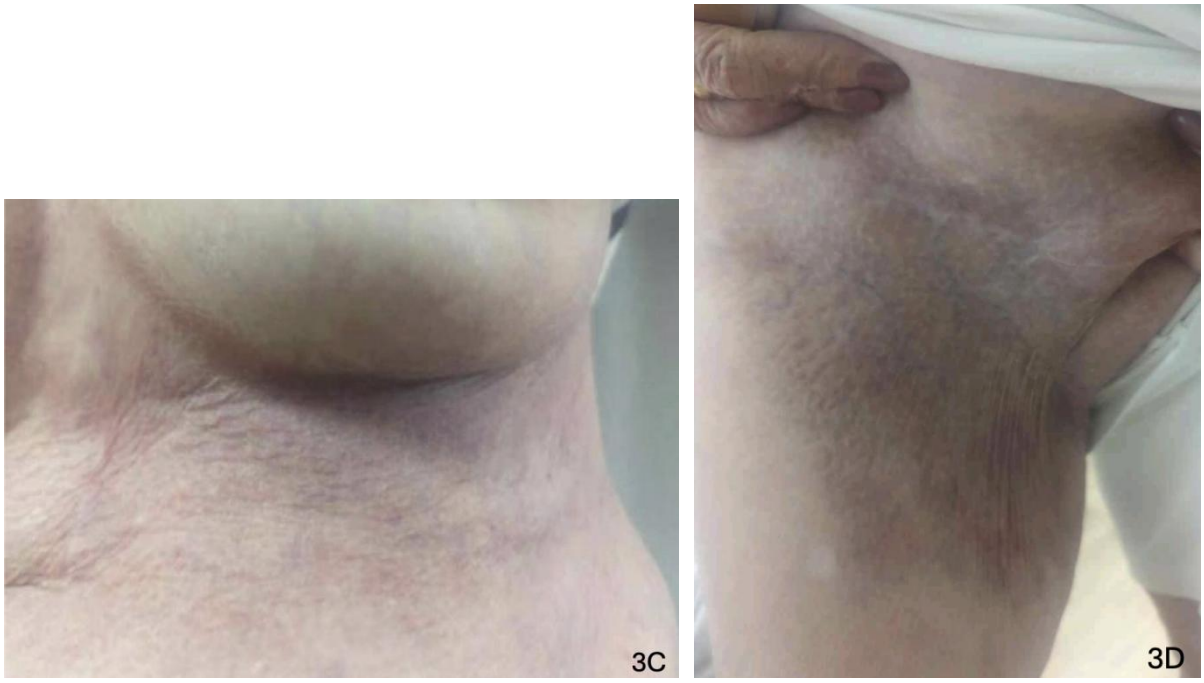

Figure 3. 3A: Left inframammary fold three weeks after hospitalization, showing post-inflammatory erythema and fine scaling with near-complete resolution of vesicles and erosions. 3B: Left groin (and right inguinal region) three weeks after hospitalization, showing post-inflammatory erythema and fine scaling with near-complete resolution of vesicles and erosions. 3C: Left inframammary fold one month after starting dupilumab, showing complete resolution of the eruption and resolution of underlying erythema. 3D: Left inguinal region one month after starting dupilumab, showing complete resolution of the eruption and resolution of underlying erythema.