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Case Report

Dermatological Enigma: Hailey-Hailey Disease

Ryan Albrecht, DO[1]; Farzana Hoque MD, MRCP, FACP, FRCP [2]

[1] Saint Louis University School of Medicine, St. Louis, MO, USA

[2] Associate Professor of Medicine, Saint Louis University School of Medicine, St. Louis, MO, USA

Corresponding Author: Farzana Hoque MD, MRCP, FACP, FRCP, Associate Professor of Medicine, Saint Louis University School of Medicine, St. Louis, MO, USA.

E-mail: farzanahoquemd@gmail.com

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Abstract

Hailey-Hailey disease (HHD), an autosomal dominant disorder resulting from ATP2C1 gene variants, manifests as skin blisters and erosions, typically emerging in the 3rd or 4th decade of life. The absence of a specific therapy underscores the pivotal role of trigger identification and avoidance in HHD management, necessitating lifestyle adjustments such as weight loss and loose clothing. Treatment modalities vary from topical antimicrobials, corticosteroids, and tacrolimus for mild cases to oral antibiotics and emerging therapies like low-dose naltrexone for moderate to severe instances. For mild cases, treatment involves the use of topical antimicrobials, corticosteroids, and tacrolimus. In moderate to severe instances, oral antibiotics are considered, while emerging therapies like low-dose naltrexone show promise but necessitate further investigation. Surgical interventions, botulinum toxin injections, and low-dose naltrexone demonstrate varying success rates; however, HHD remains chronic and recurrent, significantly impacting quality of life. This case report underscores the importance of clinician and patient awareness regarding triggers in HHD management, emphasizing the timeliness of interventions such as antibiotics and corticosteroids. It further highlights the ongoing imperative for effective therapeutic research in Hailey-Hailey disease

Introduction

Hailey-Hailey disease (HHD), or familial benign pemphigus, is a rare, autosomal dominant disorder characterized by skin blisters, macerations, and erosions. Usually presented in the 3rd or 4th decade of life, it is caused by a variant in the ATP2C1 gene encoding an ATP-powered calcium pump. This results in altered intercellular and extracellular connections of the epidermis, specifically desmosomal cadherin and E-cadherin (adherens junction associated protein), and a faulty calcium pump action leads to disorganized function of desmogleins, which are calcium-dependent adherence proteins (cadherins).[1,3] While HHD is autosomal dominant with complete penetrance, it is variably expressed which leads to an estimated two-thirds of individuals unaware of a family history of HHD.[2]

Case Report

A 75-year-old African American female with a past medical history of Hailey-Hailey disease, end-stage renal disease (ESRD) on hemodialysis, and coronary artery disease presented to the emergency department with an extensive skin rash and associated pain concerning an acute Hailey-Hailey flare. She reported her flare had been ongoing for the past three weeks, however during dialysis the pain became so unbearable that she could not tolerate her session, prompting her presentation to the hospital. Her baseline regimen for HHD included gentamicin and topical steroid ointments as well as apremilast, a PDE4 inhibitor. She reported that flares are usually managed with topical antibiotics, but she could not get a prescription for her current flare. On arrival at the Emergency Department, the patient was afebrile and hemodynamically stable. Her exam was notable for significant weeping, macerated and malodorous plaques along her bilateral

sides, axillae, groin, back, and neck along with severe skin pain with minimal movement or palpation. The complete blood count (CBC) was remarkable for anemia of chronic disease with no other findings. The basic metabolic panel (BMP) showed findings consistent with end-stage renal disease (ESRD) and no acute electrolyte changes. Given the severity of the weeping lesions on the exam, she was admitted to the hospital for the management of wounds and pain control. Broad spectrum antibiotics were initiated with ceftriaxone and vancomycin due to concern of superimposed secondary skin infection as the patient had a history of MRSA skin infection.

The dermatology team recommended continuing broad antibiotics, adding triamcinolone and gentamicin ointments, and dakin's solution soaks. Nephrology consulted for inpatient hemodialysis. The patient developed an altered mental status two days after admission which improved after adjusting home medications, gabapentin, and cinacalcet. Lesion cultures obtained grew methicillin-sensitive staphylococcus aureus. Antibiotics were de-escalated to cefazolin. The following day, she had worsening encephalopathy. Labs demonstrated leukocytosis of 15.7 x 10^9 /L and a lactic acid level of 9.9 mmol/L. Blood cultures were obtained. Vancomycin, piperacillin/tazobactam were started, and added micafungin for empiric anti-fungal coverage. She was transferred to the intensive care unit (ICU) for vasopressor support due to concern for distributive shock secondary to sepsis. Hemodialysis transitioned to continuous renal replacement therapy (CRRT). Cultures were unremarkable, although the leucocyte count was rising. Her clinical course continued to deteriorate significantly, and after shared decision-making (SDM) her family elected to transition to comfort care.

Discussion

This case illustrated the importance of early recognition and management of Hailey-Hailey disease (HHD) to prevent severe, life-threatening complications. As there is no specific therapy for HHD, the key step of management is the recognition and avoidance of common triggers. The most common triggers of flares include excessive heat, moisture, and friction. Accordingly, lifestyle modifications such as weight loss, wearing loose-fitted clothing, avoiding excess sun and heat exposure, and applying absorbent pads to skin folds can minimize cutaneous flares. Despite acknowledging common and individual triggers, flares are still difficult to predict both in frequency and severity. Mild disease can be managed in the outpatient setting with topical antimicrobials and topical corticosteroids to reduce inflammation and overgrowth of bacteria. Topical tacrolimus, a calcineurin inhibitor, has also been utilized to some benefit. The efficacy of these treatment modalities is largely based on small, observational studies and case reports.[2,4,5] In cases of moderate to severe disease or frequent exacerbations, oral antibiotics may be prescribed to better control disease activity.

Tetracyclines have been advocated in part due to additional anti-inflammatory properties.[8] Additional systemic therapies such as methotrexate,[9] oral tacrolimus,[10] and apremilast[11] have been anecdotally reported to provide benefit. Our case patient had been prescribed apremilast for chronic management. Surgical options have been explored including surgical excision of lesions, superficial radiation therapy, and argon plasma coagulation.[12] These surgical interventions generally have associated long healing times, additional scars, and an unclear long-term benefit. Intermittent injections of botulinum toxin type A have been shown in several case studies [6,13] to reduce flares and even show sustained improvement over months, however high cost is a restrictive factor to routine use.[13] An emerging therapy in the management of HHD is low-dose naltrexone,[7, 14] although case reports are limited and require further studies.

One report of three patients with recalcitrant HHD were treated with naltrexone alone for three to four months.[14] All patients achieved a reduction in lesions and improvement in quality of life within two weeks and resolution of lesions within two months. However, once naltrexone was discontinued, all patients developed cutaneous HHD flares which then cleared within a few days of restarting low-dose naltrexone. The exact mechanism of naltrexone specific to HHD is not well understood. One hypothesis is its action is through opioid or toll-like receptors to influence intracellular calcium homeostasis.[2] Although many therapies have been tried for Hailey Hailey disease, no specific therapy has emerged as the definitive choice. The disease course is characterized by a chronic recurrence of cutaneous flares which can greatly impair quality of life.

Conclusion

The clinician and patient's awareness of common triggers such as prolonged sun exposure, excessive sweating, and skin friction from tight-fitted clothing is a critical step in the overall care of Hailey-Hailey disease patients. Prompt management of flares includes topical/oral antibiotics, topical corticosteroids, and anti-fungal coverage. This case illustrates the importance of early recognition and management of Hailey-Hailey disease to prevent severe life-threatening complications.

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