Hailey-Hailey Disease Masquerading as Intertriginous Candidiasis for 10 Years

Miguel Villacorta, DO, MPH,* Brittany P. Smirnov, DO,** Jennifer Moscoso Conde, DO,** Carlos H. Nousari, MD***

*Traditional Rotating Intern, PGY-1, Broward General Medical Center, Fort Lauderdale, FL
**Dermatology Resident, PGY-3, Broward General Medical Center, Fort Lauderdale, FL
***Program Director, Dermatology Residency Program, Broward General Medical Center, Fort Lauderdale, FL

Abstract

Hailey-Hailey disease (HHD) is a rare, autosomal-dominant genodermatosis that presents as erosive erythematous plaques commonly present with crusting, maceration and fissures in intertriginous locations. HHD may be difficult to distinguish from other intertriginous diseases. Additionally, bacterial or fungal infection can be superimposed on the affected areas, convoluting diagnosis and complicating management of the disease. Making a correct diagnosis and individualizing treatments are important to decrease patient morbidity and reduce complications.

We present a patient with HHD that was misdiagnosed as intertriginous candidiasis for 10 years. The proper diagnosis was made after a thorough history was taken and a biopsy was performed. Clinical differences between diseases and common treatment modalities are discussed as well. We highlight the new treatment modalities to improve physician awareness of available interventions.

Introduction

In 1939, the Hailey brothers were the first to describe Hailey-Hailey disease (HHD), or benign familial pemphigus.1 Diagnosis of HHD can prove difficult, as it can present similarly to other intertriginous diseases and with a superimposed infection. It is important for a clinician to be able to distinguish HHD from other intertriginous diseases. Herein, we describe a case of HHD that had been misdiagnosed for 10 years as candidiasis. We focus on differentiating HHD from other diseases and summarize current treatment modalities published in the literature.

Case Report

A 63-year old Haitian female with a past medical history of hypertension and diabetes presented with complaints of a painful, irritated rash on her posterior neck, bilateral axillary, inframammary, intergluteal and inguinal folds. The patient reported waxing and waning of the eruption for approximately 10 years, occasionally resolving entirely, but eventually recurring. Prior treatments included betamethasone cream to affected areas, as well as oral and topical antibiotics, antifungals, and topical corticosteroids for the treatment of intertrigo and candidiasis. She originally denied a family history of skin disorders or cancers.

Suspecting possible Hailey-Hailey disease, a 4-mm punch biopsy was performed in the left axilla. Histopathologic examination revealed a large focus of acantholytic dyskeratotic cells in a “dilapidated brick wall” pattern, with perinuclear eosinophilia (Figures 4, 5). PAS stain was negative for dermatophytes, and fungal and bacterial cultures performed at the time of biopsy were positive for only light growth of Pseudomonas aeruginosa.

A complete blood count, comprehensive metabolic panel, and lipid panel were ordered in preparation for possible soriatane treatment. She was prescribed oral fluconazole and doxycycline in the interim. At the one-month follow up, the patient stated that she noted some improvement with the medical regimen. Nystatin powder and ciprofloxacin were added. Three months later, active areas on the patient’s left axilla and...
inframammary folds remained. Clobetasol was added to improve the persistent lesions. Unfortunately, one month later, there was no improvement with clobetasol. At this point the patient had persistent lesions with only some minor improvement in her symptoms. Her prescriptions were adjusted to include fluconazole, tacrolimus, clotrimazole and betamethasone. She returned three months later with improvement in her lesions. The lesions consisted of hyperpigmented patches and mild erythema on her bilateral axilla and inframammary folds without any evidence of maceration. At this point the patient was only using nystatin powder and the topical clotrimazole with betamethasone.

As of her last visit, the patient has been following with our clinic for nine months without any additional flares in her disease. While her blood work for CBC, CMP, and lipid panel returned unremarkable, the patient has not been started on soriatane treatment since she had achieved considerable improvement with her current medical regimen. She was advised to follow up in an additional four months and, if her symptoms worsen, soriatane treatment would be considered.

Discussion

Hailey-Hailey disease (HHD), also known as benign familial pemphigus, is a rare genodermatosis first described by the Hailey brothers in 1939.1 The disease is inherited in an autosomal-dominant fashion with complete penetrance but variable phenotypic expression. It can also present as a de novo mutation.2 Affecting males and females equally, HHD typically presents in the second or third decade of life, with an overall estimated incidence of 1 in 50,000.3,4 The disease is caused by a mutation of the ATP2C1 gene, which encodes the ATP-powered calcium pump protein, hSPCA1, that sequesters calcium into the Golgi apparatus.5 The impaired calcium pump leads to lower calcium levels inside the Golgi apparatus, causing impaired production of calcium-binding transmembrane glycoproteins and subsequent loss of cellular adhesion in the stratum spinosum.6 Histologically, the acantholysis is classically described as having a “dilapidated brick wall appearance” with the retention of basal layer adherence to the dermis.7 Other histologic features include suprabasal decomposition, intraepidermal bullae, epidermal hyperplasia, parakeratosis, and lymphocytic infiltration.7 Direct immunofluorescence testing is negative.8

Hailey-Hailey disease presents as flaccid vesicles or bullae in intertriginous locations such as the axilla, groin, gluteal cleft, and inframammary folds. These fragile vesicles are easily ruptured and are often absent on physical examination. The remaining erosive erythematous plaques commonly present with crusting, maceration and fissures. Patients can experience increases in morbidity as affected areas can become painful, pruritic, and malodorous. The disease course fluctuates between episodic remission and exacerbation aggravated by friction, heat, sweat, tight clothing, increased weight, and infection.1 Additionally, bacterial or fungal infection can be superimposed on the affected areas, convoluting diagnosis and complicating management of the disease. Longitudinal leukonychia has been described in approximately 70% of individuals with the disease and, if present, can aid in the diagnosis.9

Differential Diagnosis

The clinical differential diagnosis of Hailey-Hailey disease includes candidiasis, inverse psoriasis, intertrigo, tinea cruris, contact dermatitis, seborrheic dermatitis, hidradenitis suppurativa, and erythrasma. Histologic differential diagnosis includes other intraepidermal acantholytic processes such as pemphigus vulgaris, Darier’s disease, and Grover’s disease. An extensive history and physical examination along with a biopsy, especially if little or no improvement is seen with treatment, help to support the diagnosis (Table 1).

A fungal infection, such as intertriginous candidiasis, may present clinically by the presence of satellite lesions with peripheral papules and pustules.9 A potassium hydroxide stain will help to confirm the diagnosis, but care should be taken as a superimposed fungal infection can lead to misdiagnosis by masking the underlying Hailey-Hailey disease.

Inverse psoriasis presents in intertriginous areas, similarly to HHD. It presents as erythematous, sharply demarcated, smooth, non-scaly, moist plaques with or without maceration and fissures.10 Typically, patients have a family history of psoriasis and psoriasiform lesions with evidence of typical psoriatic nail involvement, including onycholysis and nail pitting.11 Interttrigo clinically appears very similar to HHD, as erythematous plaques with maceration and inflammation of the skin folds. These lesions are prone to bacterial or fungal infections such as candida. A Wood’s light can help to distinguish a pseudomonal infection from cutaneous erythrasma caused by C. minutissimum. Pseudomonas fluoresces green under Wood’s light, while C. minutissimum fluoresces as coral red patches with well-defined borders.12 Tinea corporis typically presents clinically by the appearance of a raised and annular active border of pustules or vesicles with either central scale (in early lesions) or central clearing (in advanced lesions).13 Tinea cruris may appear similar, as well-demarcated erythematous plaques with central clearing and elevated scaling borders that may be active with pustules or vesicles, and may be confirmed by KOH examination.14

Treatment

Hailey-Hailey disease has no known cure, and treatment therapies are aimed at reducing exacerbations and increasing periods of remission. Many treatment modalities have been attempted, with most modalities demonstrating Level III evidence in the literature. Some patients are refractory to treatment, thus individual therapy must be tailored to each patient (Table 2).

General measures should be considered for each patient, such as avoidance of hot and humid weather, use of bleach or chlorhexidine baths, weight loss, and use of lightweight, loose clothing such as cotton. The use of absorbent pads, barriers, and drying agents such as zinc oxide, petrolatum, aluminum sulfate, and talcum powder may be used to keep skin dry and clean.15,16

First-line treatment should consist of a combination of topical antimicrobials and topical steroids.3,17,18 Based on Level IIa and Level III evidence, clobetasol should be used for acute flares and topical tacrolimus for maintenance.19 The topical antimicrobials that have shown some degree of success include clindamycin, gentamicin, mupirocin, and ketoconazole.17,20

Systemic therapy may be necessary if a patient fails the topical antimicrobial and topical steroid combination therapy. Doxycycline has been shown to be the most appropriate first-line oral antibiotic with Level IIa and Level III evidence.19 Second-line oral therapy includes erythromycin, penicillin, and dapsone with limited Level III studies.

If a patient is refractory to therapy, additional therapies include surgical excision and botulinum toxin type A injections. These therapies have Level IIa and Level III evidence and have had some degree of success. Other treatment modalities include dermabrasion, NBUSB, and laser therapy. These treatments have limited Level III evidence and have had limited success. Currently, there is a Phase II trial in Italy studying the use of afamelanotide, an analog of alpha-melanocyte stimulating hormone (a-MSH), for the treatment of HHD.

Conclusion

Hailey-Hailey disease is a rare disease that may be difficult to distinguish from other intertriginous diseases. HHD should be considered in patients with recurrent flares of intertriginous lesions. Diagnosis is more difficult if a superimposed bacterial and fungal infection is present. A biopsy and clinical features, such as longitudinal leukonychia, can help distinguish this disease. While there is no known cure, individualized treatments using a combination of antimicrobials and steroids are important to decrease patient morbidity, reduce flares, and limit complications.
Table 1. Clinical differentiation of intertriginous dermatitides

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Differentiation</th>
</tr>
</thead>
</table>
| Hailey-Hailey Disease | - Intertriginous erosive erythematous plaques  
- Crusting, maceration, and fissures  
- 2nd or 3rd decade of life, waxing and waning symptoms  
- Longitudinal leukonychia |
| Intertriginous Candida | - Satellite lesions with peripheral papules and pustules  
- Well-demarcated, erythematous patches  
- + KOH Prep |
| Inverse Psoriasis | - Erythematous, sharply demarcated plaques  
- Smooth, moist, macerated, +/- fissures  
- Absent scales  
- + Nail involvement |
| Tinea Cruris | - Well-demarcated erythematous plaques  
- Central clearing and elevated scaling borders  
- +/- Pustules or vesicles |
| Erythrasma | - Reddish-brown macules coalescing into patches  
- Well-defined borders  
- C. minutissimum - coral red fluorescence (Wood’s)  
- Pseudomonas - green fluorescence (Wood’s) |
| Seborrheic Dermatitis | - Sharply marginated erythematous eruption  
- + Erosions and fissures  
- +/- Yellow greasy scales |

Table 2. Treatment and management of Hailey-Hailey disease

<table>
<thead>
<tr>
<th>Individualized Combination Therapy</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical Steroids</strong></td>
<td></td>
</tr>
<tr>
<td>Acute flare</td>
<td>Clobetasol</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td><strong>plus</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Antimicrobials</strong></td>
<td></td>
</tr>
<tr>
<td>First line: topical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
</tr>
<tr>
<td></td>
<td>Mupirocin</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Second line: systemic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
</tr>
<tr>
<td></td>
<td>Dapsone</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
</tr>
<tr>
<td></td>
<td>Penicillin</td>
</tr>
<tr>
<td><strong>Refractory to Treatment</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excision</td>
</tr>
<tr>
<td></td>
<td>Botulinum toxin A</td>
</tr>
<tr>
<td></td>
<td>Dermabrasion, NBUVB, Laser therapy</td>
</tr>
<tr>
<td><strong>General measures</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bleach or chlorhexidine baths</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Lightweight and loose clothing</td>
</tr>
<tr>
<td></td>
<td>Barrier and drying agents</td>
</tr>
<tr>
<td></td>
<td>Avoidance of hot and humid weather</td>
</tr>
</tbody>
</table>
References