

A Rare Case of Atypical Recalcitrant Hailey-Hailey Disease and a Literature Review

Udoka Ogbuneke¹, Emmanuel Odega², Yakub Wahab Ibrahim³, Mustapha Abubakar¹

¹Internal Medicine Trainee Southend Hospital, Mid and South Essex NHS Foundation Trust, Southend on Sea, UK

²Internal Medicine Trainee, Morriston Hospital, Swansea Bay University Health Board, Swansea, UK

³Emergency Medicine, Southend Hospital, Mid and South Essex NHS Foundation Trust, Southend on Sea, UK

Email: Iw.yakub@gmail.com

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Abstract

Hailey-Hailey disease also known as familial benign chronic pemphigus is a rare bullous genodermatosis that affects intertriginous area symmetrically. It presents with flaccid blisters, erosions and maceration resulting in increased morbidity, reduced quality of life for affected patients. It is rare in occurrence with an incidence of rate of 1 in 50,000. It is diagnosed with a combination of clinical and histopathological findings. While there is no known cure, its re-lapsing remitting course can be managed with medication. This case describes an unusual presentation of familial benign chronic pemphigus with a late age of onset of symptoms, atypical distribution and resistant to multiple therapies.

Keywords

Internal Medicine, Dermatology, Atypical Hailey-Hailey's Disease, Benign Chronic Pemphigus

1. Introduction

First described by the Hailey brothers in 1939, Hailey-Hailey disease also known as familial benign chronic pemphigus is a rare genodermatosis inherited in an autosomal dominant fashion with complete penetrance and variable expressivity [1] [2] [3] [4]. Though the exact aetiology factor is unknown, defect in keratinocyte adhesion had been noted in the pathophysiology of the condition [5]. It could also coexist with other medical conditions with skin manifestations which could add to the difficulty in diagnosis [6] [7].

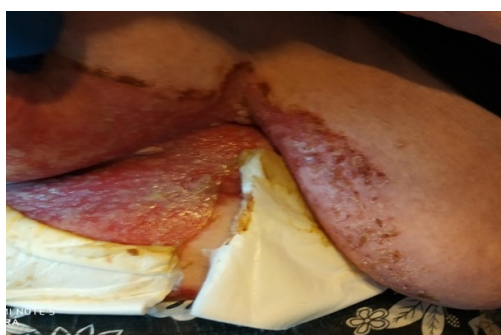
Given its rare nature, diagnosis may be missed, and commencement of treatment delayed often prolonging patient's distress [8]. A combination of clinical

and histopathological findings is needed to confirm diagnosis. We present a unique case of atypical Hailey-Hailey disease with onset of symptom in the fifth decade of life with the condition resistant to multiple medical therapies.

2. Case Presentation

A 61-year-old Caucasian female patient presented to the department complaining of skin rash associated with burning sensations, unpleasant odour which get worse with stressful activities and increased temperature. She also reports a poor quality of life as she avoids activities predisposing her to heat. Her past medical history includes Asthma, hypothyroidism, and hypertension. She has a family history the similar condition in her father. Three years ago, she presented with skin lesions that started as a blister which subsequently ruptured resulting in skin maceration in intertriginous areas. Like this presentation, the skin lesions got worse in warm environmental condition. Diagnosis was confirmed with histopathologic examination of skin biopsy. She had been treated with several courses of topical corticosteroids, antibiotics, and steroid sparing agent (cyclosporine, methotrexate, acitretin and dapsone) with minimal or no improvement.

On examination, she was tachycardic with heart rate of 102 bpm, respiratory rate of 18/minutes with blood pressure of 114/81 mmhg and temperature of 36.6 degrees Celsius. There was extensive erythematous, weepy, macerated rash primarily affecting flexural areas including both axillae, sub-mammary areas, and groin (**Figure 1**, **Figure 2**).



(a)



(b)

Figure 1. (a): Depicting skin excoriation around the mammary gland region and (b) shows erythematous, weepy, erosion with associated crusts and scaling



Figure 2. Picture of the lower back region showing erythematous erosion with associated crusts and scaling.

Blood test on admission showed a C-reactive protein (CRP) of 117 mg/L, (<5 mg/L), white cell count of $19.4 \times 10^9/L$ ($4.0 - 11.0 \times 10^9/L$) and neutrophils of $17.25 \times 10^9/L$ ($1.7 - 7.5 \times 10^9/L$). Other blood results were unremarkable. Patient was commenced on intravenous hydrocortisone 100 mg three times daily for 24 hours which was tapered off with the introduction of 20 mg of oral prednisolone daily for five days, and pain control medication. Five days post admission, a repeat blood showed CRP of 4 mg/l white cell count of $4.1 \times 10^9/L$ and neutrophil count of $5.2 \times 10^9/L$ with significant improvement in skin condition. The patient was discharged home on Dermovate cream, prednisolone, dermol lotion with an outpatient dermatology follow up.

3. Discussion

Our patient had Hailey Hailey's disease, a rare skin condition with an estimated incidence of 1/50,000 without any predilection for any gender or ethnic group. [2] it would initially present as painful flaccid vesicle and blistering lesions on a background of erythematous skin, resulting in erosions, fissures, scales, and maceration, these lesions often occur symmetrically in intertriginous regions [5]. Most patients will present in the second to third decade of life and very rarely as in our patient, it can present in the fifth decade of life [9].

The pathogenesis of Hailey-Hailey disease is due to a mutation in the ATP2C1 gene on 57 chromosome 3q21-24 which encodes the human secretory-pathway calcium/manganese-ATPase isoform 1 (hSPCA1) of epidermal cells. The hSPCA1 protein transports calcium ions (Ca^{2+}) into the Golgi apparatus, where they engage in the post-translational modification of the newly synthesized proteins, including structural ones. Calcium ion is involved in cellular differentiation, skin barrier repair, assembly of functional adherens junctions and desmosomes, and keratinocyte motility. The resultant mutation alters the homeostasis of this ion, resulting in abnormal keratinocyte adhesion, desmosomal decomposition, and acantholysis of the epidermis occur [3] [4].

Clinically, it presents with painful, flaccid vesicles and blisters on a background of erythematous skin resulting in erosions, fissures, scales, and maceration. Malodorous discharges and yellow crust can be seen with superinfection. The lesions are distributed symmetrically in intertriginous areas, such as the axillae, inguinal areas, nape, lateral aspect of the neck, inframammary folds, retro-auricular fold, perineum, and back [10]. Rarely, it presents with unilateral as well as mucosal or vulvar involvement [2]. It has chronic, relapsing-remitting course and frequently exacerbated by excessive sweating, heat, sun exposure, skin trauma, friction from cloths, patch testing, moisture, and herpes infection [11]. These exacerbations worsen during the summer months and may be reduced by wearing loose-fitting, light-weight clothing and avoiding activities that result in sweating or skin friction [12]. Common complication associated with HHD is colonization and secondary infections with bacterial, fungal, or viral microorganism. However, on rare occasion these patients may have an increased risk of squamous cell carcinoma [10].

The diagnosis is suggested clinically based on characteristic distribution of lesion with involvement of intertriginous areas, and a positive family history. Confirmation of diagnosis is made with histology, which shows characteristic pathologic feature of intraepidermal vesicles and bullae with suprabasilar acantholysis. This has been described as dilapidated brick wall appearance [2].

Due to its rare, chronic relapsing and remitting course, and lack of gold standard treatment despite myriad of options, this condition poses a significant challenge to physicians and greatly affects the patient's quality of life [3]. Different therapeutic modalities have been used for the treatment of HHD. However, no cure is available as the various therapeutic strategies used are for symptoms control, reducing recurrence and improving patient's quality of life [4].

Nonpharmacological measures that can improve outcomes in patients with HHD include lifestyle modifications and patient education. This involves avoiding or limiting exposure to exacerbating factors. Example of these measures include wearing of soft and loose clothing and underwear, weight control, and reduced physical activity that increase friction against skin surface [3].

Pharmacological therapies may show short-term benefit, but generally do not induce prolonged remissions, and are limited by their long-term use and side effect. They include topical/intralesional corticosteroids, topical and/or systemic antibiotics, and antifungals. Reports have shown some benefit with topical vitamin D analogues, dapsone, cyclosporine, methotrexate, Naltrexone, alitretinoin, azathioprine, intradermal botulinum toxin, thalidomide, and topical tacrolimus, in recalcitrant cases [9] [10].

Long term treatment measures shown to achieve prolonged remission and even cure in some cases include surgical treatment (wide excision with split-thickness grafting, primary closure, healing by secondary intention) and dermabrasion. However, they are associated with increase morbidity such as scar contractures, limited mobility, venous thromboembolism, graft failure, infections, and cosmetic issues [13].

On the other hand, laser therapy (CO₂ Lasers, Erbium: YAG Lasers, Radio-frequency Ablation, Vascular Lasers, and Diode Lasers) are less invasive, safe, and effective treatment for HHD with good side effect profile [14]. While this therapy provides faster healing, less scarring and can be done as a day case in an outpatient setting using local anaesthetic, dyspigmentation is common side-effects [14].

With onset of symptom at 59 years, our patient presented with late-onset HHD compared to the typical age of onset in the third decade of life [1]. Furthermore, she had a mixture of the classic presentation of HHD, with symmetrically distributed, recurrent erosions in the axillae, sub-mammary areas, groin, and atypical presentation in the lower back area. Hailey-Hailey disease involving the back skin is unusual, as it typically occurs in intertriginous area [1] [3] [8].

4. Conclusions

This case clearly highlights the challenge behind the treatment of HHD, which can be refractory to multiple known therapies and can significantly reduce patients' quality of life.

It should be noted that though rare, Hailey Hailey's disease can occur in non-intertriginous areas such as the back.

Clinicians should have a high index of suspicion in diagnosing patients presenting with late onset disease.

Conflicts of Interest

We have no competing interest.

Authors' Contributions

Udoka Ogbuneke, Emmanuel Odega, Yakub Ibrahim and Mustapha Abubakar contributed equally to gathering information, literature search, writing this case, overall supervision, and review of the piece. We have read and agreed to the final manuscript.

Informed Consent

Our patient gave her consent for the use of her clinical information and images for this case report.

Written consent was taken from the patient prior to the preparation of this manuscript.

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