



Hailey-Hailey disease misdiagnosed as candidal intertrigo: Case report of a rare skin disease

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Abstract

Hailey–Hailey disease (HHD) is a rare autosomal-dominant blistering disorder characterized by macerated velvety, fissured, hypertrophic plaques with characteristic involvement of the intertriginous areas. The diagnosis is often suspected by the clinical appearance of the lesions in intertriginous areas as well as positive family history and confirmed by histological analysis of the lesional skin biopsy. A diagnosis of HHD is rarely made in this environment due to its resemblance to other dermatoses of the intertriginous areas and the rarity of the condition itself. We present a case report of HHD, a rare hereditary disease, involving two unrelated Nigerians seen in our dermatology clinic, who were diagnosed and successfully managed at our centre.

Introduction

Hailey-Hailey disease, also refers to as familial benign pemphigus, is a rare chronic autosomal-dominant genodermatosis that affects the intertriginous areas of the skin.^{1,2} The incidence of the disease is 1 in 50,000 individuals among the general population³ but the prevalence in Nigeria is not known as the disease is very rare. Hailey-Hailey disease occurs in the third decade of life without predilection for sex or race. It runs a chronic course with reports of the symptoms abating in severity with increasing age.⁴⁻⁶

Studies have revealed that Hailey-Hailey disease is caused by mutations of the ATPase secretory pathway Ca²⁺ transporting 1 gene, ATP2C1.⁷ The alteration of calcium homeostasis results in dysfunction of epidermal desmosomes seen histologically as supra-basilar acantholysis often described as a 'row of tombstones'.⁸ Clinically, the

affected individual presents with localized, symmetrical, painful recurrent blisters which form macerated erosions and crusted plaques. These presenting complaints are often exacerbated by heat, moisture, friction, and microbial infections.^{5,8,9}

Hailey-Hailey disease is a rare dermatological condition. To the best of our knowledge, this case report represents the first to be reported from Nigeria. Few case reports and case series have been published from North Africa.¹⁰ In our report, we highlight the importance of clinicians' high index of suspicion for HHD in patients presenting at Dermatology clinic with intertriginous blister and maceration. Our patients presented at the clinic after protracted years of developing the symptoms. Variabilities in their epidemiological history include the age at onset, family history, and aggravating factors. The first patient was a 22-year-old man with a positive family history of similar lesions, while the second patient was a 60-year-old woman with no known family history HHD.

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Case Presentations

Case 1: A 22-year-old male with painful erythematous pruritic blisters in the axilla, groin and intergluteal cleft.

The patient presented to our Dermatology outpatient clinic with a 4-year history of recurrent erythematous pruritic blisters in his axilla, groin and intergluteal cleft. The itching was aggravated by an increase in ambient temperature and the pain was severe enough to limit normal arm abduction and caused the patient great discomfort while sitting and walking. The patient's occupation (manual yam pounding) is strongly associated with axillary friction and generalized sweating. The lesion was described to be worsened by long hours of yam pounding as well as the hot environmental conditions of the tropical dry season. There was a discharge of clear fluid from the lesion. Prior to his presentation, the patient had been using topical ketoconazole to treat as a case of candidal intertrigo without resolution of symptoms. There is a history of similar blisters in his mother which has been recurrent for about 10 years. Other aspects of the patient's history were unremarkable.

The lesions in both axillae were 8cm by 5cm in dimension. They appeared erythematous with areas of erosions and macerated plaques, giving it a vegetative appearance, as shown in Figures 1.1a and 1.2a below. There was a similar pattern in the intergluteal cleft (16cm by 4cm) and the groin (10cm by 5cm), which were associated with right tender inguinal lymph node enlargement. The mucous membranes were spared and the patient had no signs suggestive of systemic illness. A presumptive diagnosis of familial benign pemphigus (Hailey-Hailey Disease) was made and a biopsy of the lesion was taken and sent for histopathological diagnosis.

Biopsy of the section showed supra-basilar and intra-epidermal clefting with acantholysis, resembling a dilapidated brick wall and epidermal hyperplasia. The dyskeratotic keratinocytes have a well-defined nucleus and preserved cytoplasm with normal skin adnexal structures. There was variable chronic inflammatory infiltrate in the dermis (Figure 1.0). Histopathological features were consistent with Hailey-Hailey Disease. The patient was counselled on the diagnosis and placed on twice daily topical betamethasone cream, oral cefuroxime 500mg every 12 hours for 10 days to control a suspected secondary bacterial infection, oral loratadine 10mg daily, oral paracetamol 1g every 8 hours for 3 days for pain relief and was asked to return in 2 weeks for follow up.

The patient returned in 2 weeks following consistent use of the prescribed medication with a resolution of erythema, pruritus and pain. The lesions in his axilla, groin and intergluteal cleft had also improved considerably with a limited mild erythematous patch. The patient was counselled to continue the topical betamethasone valerate and return in 4 weeks for follow-up. Post-treatment images are shown in Figures 1.1b and 1.2b below.

Case 2: A 60-year-old female with recurrent blisters in the axillae, inframammary areas, the groin and the nape of the neck.

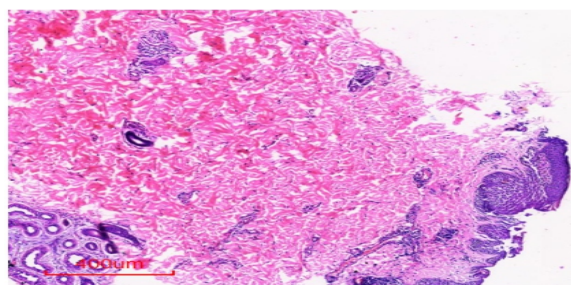


Figure 1.0: Histological section from axillary tissue biopsy (Case 1) showing hyperkeratosis and dilapidated brick-wall appearance.

Images from case 1



Figure 1.1a: Left axilla (pre-treatment)



Figure 1.1b: Left axilla (two weeks of treatment)



Figure 1.2a: Right axilla (pre-treatment)



Figure 1.2b: Right axilla (two weeks of treatment)

Images from case2



Figure 2.1a: Left axilla (pre-treatment)

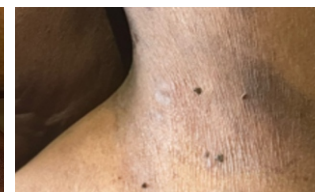


Figure 2.1b: Left axilla (post-treatment)



Figure 2.2a: Right axilla (pre-treatment)



Figure 2.2b: Right axilla (post-treatment)

Before treatment



Figure 2.3a: Abdomen and part of the groin

After treatment



Figure 2.3b: Abdomen and part of the groin



Figure 2.4a: Nape of the neck (pre-treatment)



Figure 2.4b: Nape of the neck (post-treatment)

The patient presented to our Dermatology clinic with a 6-year history of recurrent bullous eruptions which were localised to both axillae, inframammary areas, groin and nape of the neck. Blisters were preceded by itching in the affected regions and they subsequently ruptured, creating areas of erosion. There were no oral lesions and the patient did not report a family history of similar lesions.

Physical examination of the axillary lesions revealed a macerated erythematous plaque, measuring 10cm by 8cm with multiple erosions. The lesions in the inframammary areas, the groin and the nape of the neck measure 8cm by 4cm, 10cm by 6cm and 8cm by 7cm respectively, had a similar appearance (see Figures 2.1-2.4(a) below). There was no mucosal involvement or any signs of systemic illness. A diagnosis of Hailey-Hailey disease was made on clinical grounds and the patient was counselled on the need for a skin biopsy which she declined.

Other investigations such as full blood count and electrolytes were reported to be normal with the exception of the hepatitis B surface antigen (HBsAg), which was positive and necessitated her

referral to the Gastroenterology unit. The patient was placed on topical betamethasone, topical mupirocin, and oral doxycycline 100mg twice daily after thorough counselling and education on the diagnosis, its treatment and prognosis. She was asked to return in 3 weeks for review.

She presented for follow-up with moderate improvement in the lesions evidenced by the absence of maceration but with the persistence of a few erosions in the inframammary region. Prescribed medication was continued and she returned 4 weeks later with significant improvement and subsequently in 1 month with complete resolution of the lesions. See Figures 2.1-2.4(b) for post-treatment state.

Discussion

The defective keratinocyte adhesion observed in HHD is the result of a loss of function mutation in the *ATPC*²¹ gene located on chromosome 3q²¹⁻²⁴ which encodes the Ca²⁺/Mn²⁺ ATPase protein 1 (hSPCA1).⁷ The mutation of this gene causes haploinsufficiency of hSPCA1, resulting in the abnormal release of calcium from the Golgi apparatus thereby altering the intracellular calcium gradient.⁸ The resultant decrease in the intracellular calcium concentration disrupts desmosomal protein processing, assembly, and trafficking to the cell membrane.¹¹ The consequence of this is the formation of abnormal keratinocyte adhesion and eventual suprabasilar acantholysis with preservation of the dermal layer.^{7,11-13}

The diagnosis of HHD is often based on clinical presentation and confirmed by characteristic histopathological findings on skin biopsy.¹⁴ Affected individuals present with localized, symmetrical, painful blisters in the intertriginous areas which rupture easily to form macerated, crusty erosions. This progresses to velvety, fissured, hypertrophic plaques.¹⁵ Our patients presented in this clinical evolutionary pattern. None of the patients had mucosal involvement and this was not surprising as mucosal surfaces are rarely involved in HHD and the overall health of the individual is preserved.¹⁶ Histological findings demonstrate a loss of cohesion between keratinocytes often described as a 'row of tombstones' or 'dilapidated brick wall'.¹⁷ In addition, dyskeratosis may be present.¹⁸ These classical features were present in

the first patient. Although the dermal layer is preserved, there can be lymphocytic infiltration of its vascular structures. Direct immunofluorescence distinguishes this condition from pemphigus vulgaris, an unrelated immunobullous condition due to the presence of antidesmosomal autoantibodies.¹⁷

The morphology of both cases was similar, affecting the intertriginous areas. There was no mucosal involvement or any sign of systemic illnesses. A diagnosis of HHD was made on clinical grounds and the histopathological result from the skin biopsy of the first patient supported this diagnosis.

The management of our patients was aimed at the resolution of pruritus with loratadine, suppression of inflammation with topical betamethasone, treatment of superimposed infection with antibiotics, and pain control with paracetamol. Both patients diagnosed in our facility responded well to corticosteroids and antibiotics which are believed, by most experts, to be the first-line treatment for HHD.¹⁹ Despite the numerous therapeutic options for HHD, a cure has remained elusive. Options for management include symptomatic control of relapses with steroids, antibiotics, and antifungal agents.²⁰ The underlying inflammatory component is managed with anti-inflammatory agents and immunosuppressants. These include topical steroid-sparing agents such as tacrolimus 0.1% ointment²¹ and pimecrolimus, topical tacalcitol²² and topical and oral ciclosporin for cases refractory to tacrolimus and tacalcitol.²³⁻²⁴ Intra-dermal botulinum toxin type A, methotrexate, isotretinoin, dapsone and thalidomide have been used by several Dermatologists with reports of resolution of symptoms.^{20,25-29} Alefacept, which was approved for the treatment of chronic plaque psoriasis, showed promising results in the resolution of inguinal and perineal lesions which have been refractory to other treatments.³⁰ However, the production and distribution of the drug ceased by the manufacturer. In recalcitrant HHD, laser therapy has shown significant results in resolving the condition with the added benefit of reducing the rate of recurrence. The most effective laser therapy documented is with CO₂ laser.³¹⁻³² Dermabrasion treatment has also been used and there are several reports of its superiority over medical treatment. The patients who benefitted from the procedure had a better cosmetic effect with

no recurrence of the condition in the areas treated except in the axillae.³⁴⁻³⁵

A good long-term control of the disease was achieved in our patients with topical steroid and they are currently being monitored and followed-up as outpatients.

Conclusion

Hailey-Hailey disease may actually be more common than previously thought and family history may not be present. Clinicians should, therefore, have a high index of suspicion for it while evaluating any patient with flexural and/or intertriginous lesions.

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