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Case Series: Hailey Hailey Pemphigus - A Familial Malady

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Abstract

Hailey-Hailey disease (HHD) or Familial Chronic Benign Pemphigus (FBCP) is an uncommon autosomal-dominant bullous disorder characterized by recurrent vesicular and erosive lesions at friction prone inter-triginous sites. It runs in families. Diagnosis is by strong suspicion in any chronic intertriginous dermatoses with similar disease running in parents & siblings with typical histopathology showing extensive acantholysis described as characteristic dilapidated brick wall - appearance. Often treated with various therapeutic options with various periods of remission. Here we describe two cases with itchy red rash in disease prone areas over several areas with impartial relief, strong family history, on examination showing typical clinical picture, confirmed by biopsy. Both are managed with non-steroidal drugs like oral MgD3, low dose oral naltrexone with short course of intermittent topical mid potent steroid with antifungal / antibacterial combination creams leading to a dramatic improvement. These twin case series highlight the ways to avoid unnecessary delay in diagnosis so as to cut short, prolonged use of steroids (oral & topical) especially in flexural dermatoses prone for striae atrophicans. Non - steroidal / non immunosuppressive therapy given in them helped in avoiding long term deleterious side effects.

Keywords: ***Hailey Hailey Pemphigus; Oral MgD3; Lowdose naltrexone***

1. Introduction

Hailey-Hailey disease (HHD), also known as familial benign chronic pemphigus, is a rare autosomal-dominant blistering disease with an estimated incidence of approximately 1/50,000 [1]. It is characterized by recurrent vesicles, erosions, and macerated plaques involving the intertriginous areas, such as the lateral neck, axillae, groins, and perianal areas. The disease usually causes severe discomfort and chronic relapse, which affects the individual's quality of life. The affected patients usually

present with clinical findings between the third and fourth decades of life. HHD is caused by mutations in the ATP2C1 gene on chromosome 3q21 encoding the human secretory pathway Ca2+/Mn2+ ATPase isoform 1 (hSPCA1) in the Golgi apparatus. hSPCA1, a calcium transporter protein, regulates the concentration of both Ca2+ and Mn2+ in the Golgi complex [2]. The intracellular Ca2+ stores play a pivotal role in maintaining epidermal integrity. The loss-of-function mutation in the ATP2C1 gene leads to defective calcium homeostasis, loss of cell-cell adhesion of keratinocytes, and acantholysis [3]. We report two cases with classical skin manifestations, biopsy findings with a strong family history showing dramatic improvement after cost effective therapy.

2. Case Report

2.1 Case no 1

A 54-year-old business man presented to the OPD with complaints of pruritic skin lesions in his groin and intergluteal regions with occasional burning sensation for 4 years. On physical examination, multiple greyish and dull red warty moist papules were noticed in his nape, bilateral axilla, bilateral inguinal region, perineum, and perianal region (FIG. 1 A-C). Nails showed multiple longitudinal white bands. His general condition was normal with no systemic co-morbidities. Mycological examination of scales with 10% KOH was negative under low power light microscope. All routine investigations were negative. Histopathology of 5 mm punch skin biopsy from his right inguinal region showed epidermal hyperkeratosis, parakeratosis, and downward proliferation with a finger-like projection and acantholysis with the characteristic appearance of dilapidated brick-wall with a blister in the epidermis.

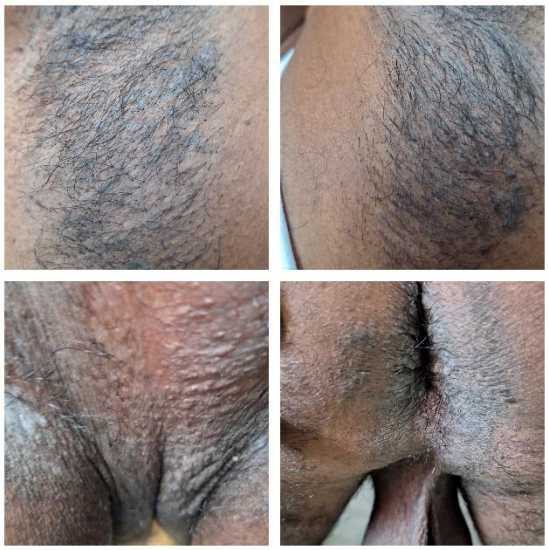

FIG. 1. **Multiple dull red warty moist papules in armpits, crura, perineum & perianal region.**

In addition, there were vascular dilatations in the dermal papilla and inflammatory infiltrate consisting of lymphocytes and eosinophils in the dermis (FIG. 2). His mother was a 75-year-old woman, who presented with relapsing flares of mild erythema under her infra-mammary region, axilla, and crissum for more than 40 years. His father was normal. His siblings and maternal relations were also affected from same condition and were on various modalities of treatments from different dermatologists.

Direct Immunofluorescence (DIF) staining and serum autoantibodies by ELISA yielded only negative results. We could not do gene analysis as the patient was not willing. On the basis of history, clinical examination and laboratory findings we confirmed the diagnosis of Hailey-Hailey disease. He was administered with oral MgD3, low dose naltrexone (LDN - 50 mgm of tablet in 10 ml of potable water - 1 ml at bed time), a course of broad-spectrum antibiotics (Doxycycline 100 mgm B.D for 7 days) with topical application of midpotent steroids with antifungal and antibiotic combination creams as and when needed. Oral controlled release preparation of hydroxyzine hydrochloride 50 mgm (SR) was given at night to relieve itching and burning sensation. The skin disease dramatically improved after 8 weeks. Few asymptomatic skin lesions were still present after a month of follow up (FIG. 3). The patient is still on therapy with monthly follow up.

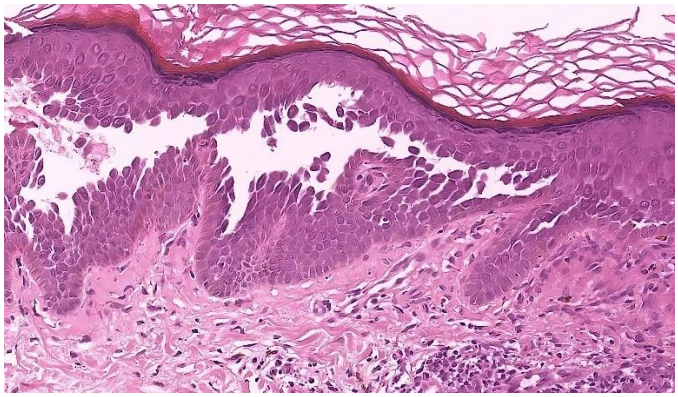

FIG. 2. **Histopathology depicting dilapidated brickwall appearance.**

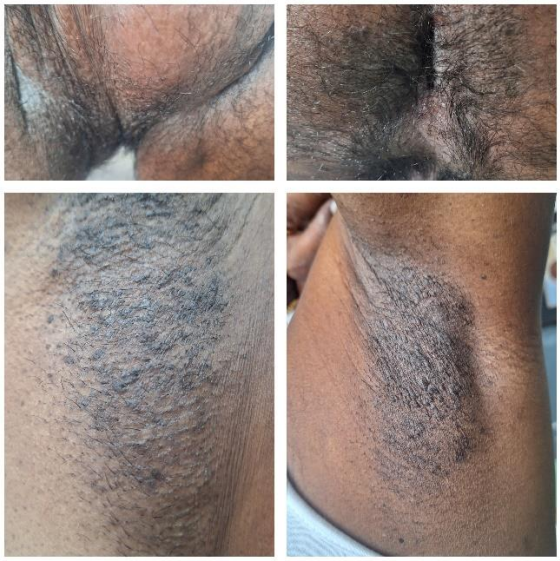

FIG. 3. **Lesions are reduced in size with hyperpigmentation after therapy.**

2.2 Case no 2

A 42-year-old house wife presented with complaints itchy red rash over neck, armpit, underneath breasts and flanks over past 12 yrs with no relief. Her mother, grandmother were suffering from same flexural skin disease of various duration. General

physical and systemic examinations were un remarkable. Dermatological examination revealed pruritic erythematous erosions and crusts over nape, sides of neck, cubital fossa, inframammary region. Flanks and around the hip areas where petticoat is worn (FIG. 4). Skin biopsy was confirmatory (FIG. 5). DIF was negative. After routine investigations, she was treated with same drugs as above with significant improvement (FIG. 6). She is on close follow up.

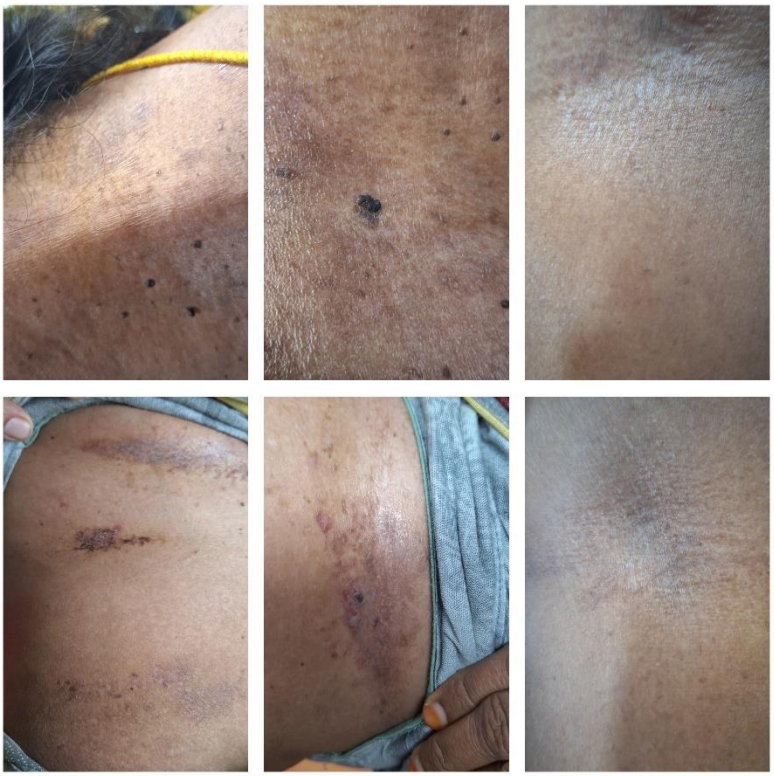

FIG. 4. **Pruritic red moist erosions & crusts over nape, sides of neck, cubital fossa, inframammary region, flanks and around the hip areas on diagnosis.**

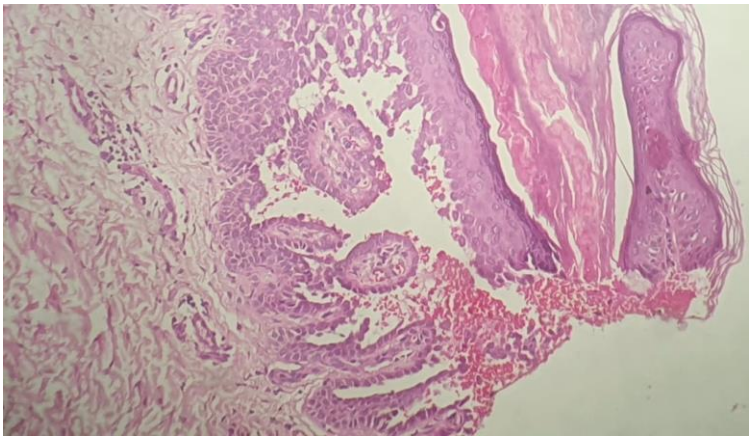

FIG. 5. **Histopathology depicting parakeratosis, dyskeratosis & suprabasal acantholysis.**

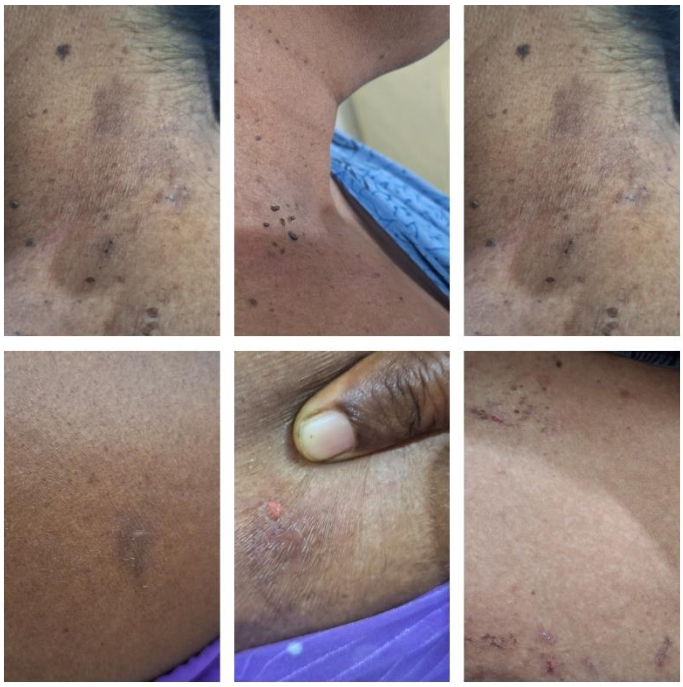

FIG. 6. **Improvement with ongoing therapy with reduction in lesions.**

3. Discussion

Typically, the patients with HHD present with flaccid vesicopustules, crusted erosions, macerations, or fissures in the friction-prone skin folds. Vulva, back, or inframammary areas may also be affected [4-7]. Rarely, mucosal involvement was observed including conjunctival, oral, esophageal, and vaginal mucosa [8-10]. In our study, the affected presented with multiple dull greyish red soft warty papules and plaques over intertriginous areas. HHD, a papular acantholytic dyskeratotic disorder with specific histopathology such as epidermal parakeratosis, dyskeratosis, suprabasal acantholytic cleft or bulla, and the typical appearance of “dilapidated brick-wall.” Intercellular deposition of IgG and complement 3 (C3) is not usually seen in the epidermis of HHD patients in contrast to pemphigus vulgaris. The antibodies may be rarely present [11,12]. The formation of anti-desmoglein antibodies, anti-desmocollin antibodies, and immune complexes is mostly associated with the unmasking of desmosomal antigens due to acantholysis. These conditions suggest that immunological factors are implicated in the pathogenesis of HHD in addition to a genetic defect. These factors provide a plausible explanation for the use of steroids or immunosuppressants in HHD. In addition, abnormally elevated oxidative stress levels have been noticed in the keratinocytes of HHD, hence antioxidant drugs can be used to give relief [13].

Unfavorable factors aggravating HHD intermittently were identified as sun exposure, skin infection, high temperature, sweating, friction, trauma, menstruation, and parturition [14]. So, these factors should be avoided or eliminated. There is no effective cure for HHD. Conventional treatments include topical antibacterial or antifungal agents, oral antibiotics, moderate to potent topical corticosteroids, topical tacrolimus ointment, and topical vitamin D3 analogs. Some patients respond well to narrow-band UVB phototherapy where areas most patients experience exacerbation [15,16]. Systemic corticosteroids,

cyclosporine, methotrexate, acitretin, or alitretinoin are the other options in widespread FBCP [17,18]. Prolonged use should be curtailed due to severe side effects for this relatively benign disorder. Newer therapeutic armamentarium includes with various efficacy especially in refractory disease include botox, naltrexone, dupilumab, apremilast, photodynamic therapy, common or fractional CO2 laser, 595-nm pulsed dye laser, and electron beam radiotherapy [19]. Long-term improvement was observed in some patients treated with various laser ablation or electron beam radiotherapy.

4. Conclusion

To conclude, we describe two cases of clinically diagnosed and biopsy proven HHD with extensive involvement responding to non - immunosuppressive therapy. Such therapy should be chosen over steroids or cytotoxic drugs due to persistence of disease in milder forms even in remission and to avoid long term adverse effects of the drug. Our observations will help to broaden the pharmacologic treatment of HHD with minimal side effects and improve the dermatological quality of life index.

5. Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

7. Conflicts of Interest

There are no conflicts of interest.

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