SKIN

BRIEF ARTICLE

Successful Treatment of Unilateral Hailey-Hailey Disease with Superficial Radiotherapy

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INTRODUCTION

Benign familial pemphigus, also known as Hailey-Hailey disease (HHD), is a rare genodermatosis characterized by impaired epidermal keratinocyte adhesion[1,2]. First described by the Hailey brothers, the clinical hallmarks of HHD include painful vesicles, bullae and papules which evolve into erythematous, macerated erosions and plaques[1–3]. HHD commonly presents in early adulthood with a chronic relapsing and remitting course and a substantial disease burden secondary to severe pain, pruritus, malodor, and risk of secondary infection[1]. The clinical course of HHD may also be exacerbated by perspiration, heat, UV exposure, friction, and secondary infections.

The pathogenesis underlying HHD results from an inherited loss-of-function mutation in the ATP2C1 gene, which encodes the calcium pump protein hSPCA1 ATPase[1,3]. Mutations in this protein disrupt normal calcium transport leading to impaired epidermal keratinocyte adhesion[1–3]. The disease is inherited in an autosomal dominant manner. While most people affected have a family history of the disease, the expressivity is highly variable[4]. De novo mutations or reduced phenotypic expression can account for the absence of family history in some patients[4,5]. Clinical manifestations of the disease vary, but the lesions are typically distributed symmetrically within intertriginous areas. Though rare, unilateral distribution of HHD has been previously reported[6–8]. Whereas the majority of HHD occurs in patients hemizygous for germline mutations in the ATP2C1 gene, unilateral and segmental lesions represent mosaic forms of the disease[6].

While the diagnosis of HHD is largely reliant on clinical hallmarks, histologic analysis is required to confirm the diagnosis. Histopathology of HHD will demonstrate acanthosis with incomplete acantholysis described as a “dilapidated brick wall” appearance[1]. When considering the diagnosis of HHD, it’s important to exclude other diseases with similar pathogenesis and presentation. For example, Darier disease shares similar defects in keratinocyte adhesion but is characterized by keratotic papules localized within seborrheic areas[1]. Additional differential diagnoses include pemphigus vegetans, seborrheic dermatitis, inverse psoriasis, intertrigo, and erythrasma. These diseases may each present with macerated erosions or as lesions localized within intertriginous areas.

Definitive treatment of HHD is largely anecdotal with case reports and clinical

experience guiding treatment. Currently, the use of antibiotics, corticosteroids, naltrexone, dermabrasion, carbon dioxide (CO2) laser ablation therapy, and superficial radiotherapy (SRT) have been reported[1–3]. These treatments, however, are mostly temporarily effective with limited long-term remission of the disease[9]. Herein, we describe a case of unilateral, multifocal HHD with clinical remission after treatment with SRT.

CASE REPORT

A 54-year-old Hispanic woman presented with active bullae in the right inguinal folds and labia (**Figure 1**). Her lesions were pruritic and eroded with a relapsing-remitting course for six years. A biopsy of the right inguinal lesion demonstrated a suprabasilar bullous dermatosis with prominent acantholytic change and a classic “dilapidated brick wall” appearance, confirming the diagnosis of HHD (**Figure 2**). Treatment was initiated with tacrolimus 0.1% and triamcinolone acetonide 0.1 % ointments.

Upon re-evaluation of the patient 2 years later, she continued to report painful bullae with residual hyperpigmentation localized to the right side of her body. Given the lack of response to initial standard therapies, along with specific therapies, a robust literature search was performed looking for novel treatments.

Radiotherapy was found to have had success in achieving remission in a retrospective case-series that included 13 patients,[2] therefore, an informed decision was made to start treatment with SRT. The treatment was divided into two sessions. All affected skin was treated at the same time with molded, site-specific lead shielding to specifically correlate with the lesion parameters including a 3-5 mm treatment margin. At the initial session, seven sites were treated: right anterior proximal upper arm, right medial breast, right rib cage, right lateral abdomen, right anterior proximal thigh (two areas) and right posterior popliteal region. Each of the seven sites received two daily fractions of X-rays at 400.2 centigray (cGy) over 1.74 minutes for a daily total of 800.4 cGy using a 10 cm applicator at 70 kV with a 25 cm SSD. A second treatment was performed four days later at the same dosage. Both sessions were well tolerated. On follow a year later, significant improvement was noted with only mild post residual hyperpigmentation (**Figure 3**).

DISCUSSION

Mosaic manifestations of autosomal dominant skin disease can result from postzygotic mutations in a normal embryo, otherwise known as type-1 mosaicism. The type-1 mosaic form of HHD results in segmental disease due to a localized population of heterozygous cells[7]. Because our patient did not have a family history of HHD, we hypothesize that her clinical presentation could be a result of type -1 mosaicism.

The mechanism of action of SRT is thought to be due to direct ionization resulting in intracellular functional disturbances and ultimately cell apoptosis[2]. This may allow for the regeneration of healthy cells by recruitment of nearby non-mutated keratinocytes[10]. The combined induction of stem cells and recruitment of normal keratinocytes may thus contribute to improved re-epithelialization and ultimate remission.

SRT offers several benefits over other conventional treatments for refractory HHD. For example, carbon dioxide laser ablation is

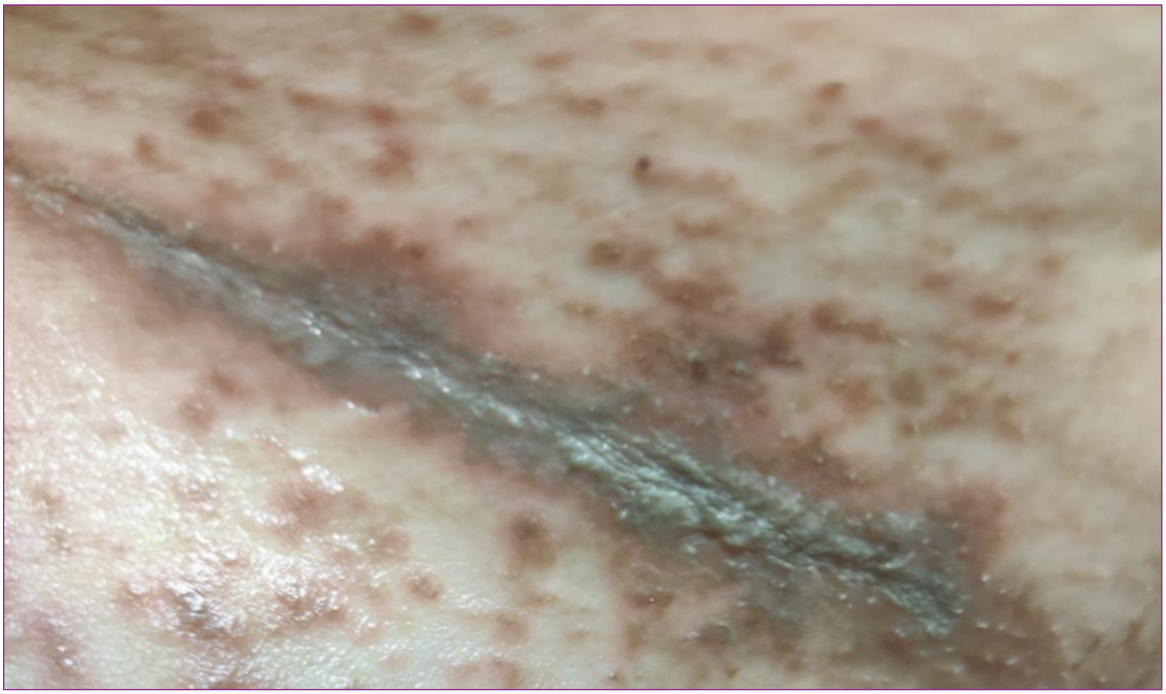

Figure 1. Pre-treatment close-up of active disease in the right inguinal fold.

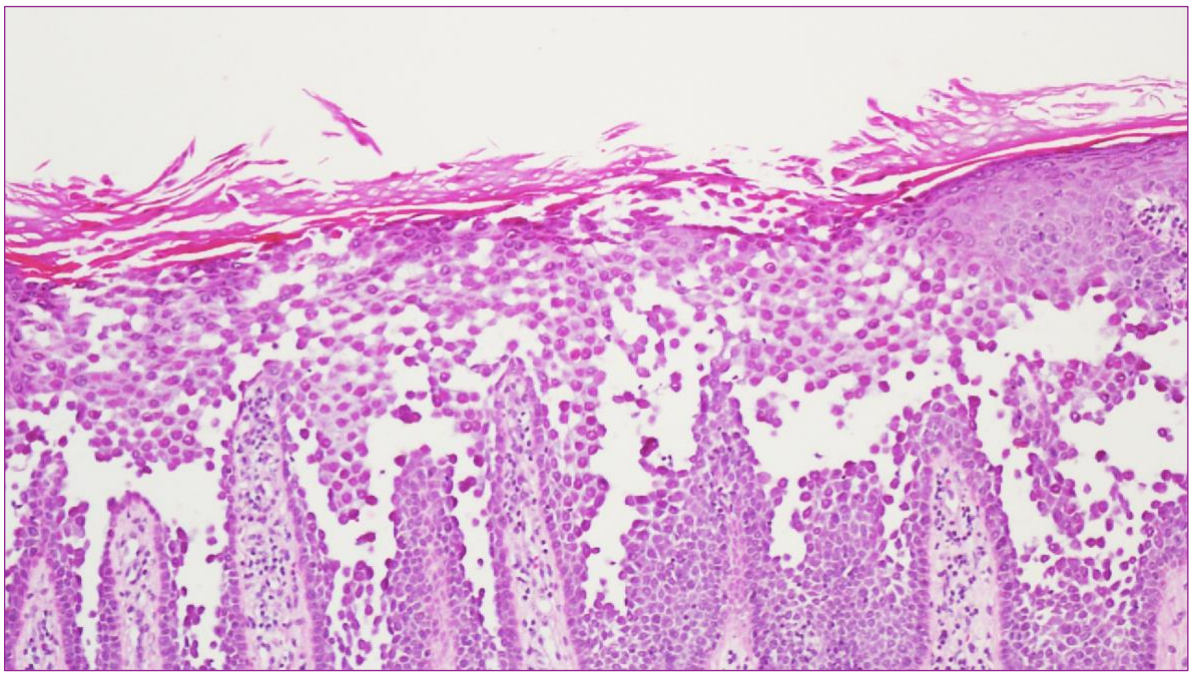

Figure 2. 100X high power view demonstrating extensive acantholysis with classic “dilapidated brick wall appearance”.

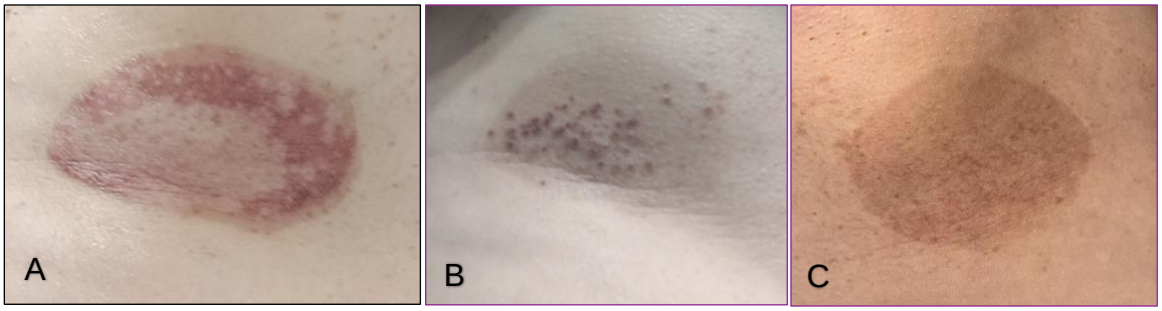

Figure 3. (A) Clinical image before treatment, right side (B) Clinical image after treatment, right side (C) Clinical image after healing, right side. Superficial Radiation Therapy on right medial breast for patient with HHD. Follow-up at 1 month and 1 year respectively, demonstrate significantly improved redness and hyperpigmentation (B) and (C).

known to be painful and can cause inflammation, infection, and scaring[11]. Opposingly, SRT is relatively pain free and has minimal down time[12]. With increased availability in dermatology practices, SRT offers a convenient, office-based treatment for this challenging disease. For patients with HHD refractory to medical treatment, SRT allows for the possibility to discontinue topical treatments which often must be continued indefinity.

While the benefits of SRT are many, it is important to note that SRT has been linked to the development of malignant neoplasms[2]. The risks and benefits of this treatment must be weighed carefully. Future studies are needed to standardize safe dosages of radiotherapy and to validate the efficacy of SRT for treatment in HHD. Based on the results of this case report, we believe SRT has strong potential to become the standard of care for recalcitrant HHD. Though there are risks to this treatment, the overall risks are minor compared to the decades of antibiotics, recurring infections, long term scarring and loss of self-esteem that arise from chronic recalcitrant HHD.

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