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Case Report

Case Report of Hailey-Hailey Disease Successfully Treated with Topical Roflumilast 0.3% Cream

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Abstract

Hailey-Hailey Disease, also called Benign Familial Pemphigus, is a genetic acantholytic blistering condition that most commonly affects the intertriginous areas. There are many treatments, both on and off label, for the treatment of this life-long, uncomfortable condition. More efficacious treatments are needed. We believe we are the first to report successful treatment with topical roflumilast, a PDE-4 inhibitor. This helps us to further understand and speculate beyond the genetics, other mechanisms of action that trigger this disease.

Keywords: PDE-4; Roflumilast; Hailey-Hailey; Pemphigus; Blister; Inflammation; Neutrophils; Immunofluorescence; Familial

Introduction

Hailey-Hailey Disease (HHD) also called Benign Familial Pemphigus is a rare, acantholytic, inheritable, chronic blistering condition that most commonly affects the intertriginous areas often worsened by heat and friction. The incidence is unknown but thought to impact 1 out of 50,000 individuals [1]. Hailey-Hailey Disease is due to multiple defects of the ATP2C1 gene on chromosome 3q21-24. These genetic aberrations disrupt the Ca^{2+}/Mn^{2+}-ATPase secretary pathway of the golgi apparatus within the cytoplasm. This defect results in impaired formation of desmosomes which leads to acantholysis and blistering. To date, there has been no cure nor consistent, reliable treatment for HHD. This is perceived due to a wide array of oral and topical treatments that have been attempted including but not limited to corticosteroids, vitamin D analogues, calcineurin inhibitors and tetracyclines. Other oral medications that have been used include cyclosporin, methotrexate and dapsone [1]. Off-label treatments have been attempted with the advent of newer therapies such as the biologic, dupilumab [2,3]. There have been several reports of apremilast, an oral Phosphodiesterase-4 (PDE-4) inhibitor, being successfully used in the treatment of HHD [4-7]. We report the first case of successful treatment of HHD with topical roflumilast, a PDE-4 inhibitor. The patient had a dramatic response to therapy on a fairly large body surface area of the trunk after four weeks of treatment.

Case Report

A 75-year-old established male patient with a 50-year history of HHD presented with an exacerbation of HHD on the trunk and axillae (Fig. 1). Previous therapies that have been attempted included mid to super-potent topical steroids, vitamin D analogues, calcineurin inhibitors and topical clindamycin. He had some improvement with previous therapies but never had complete clearance. Due to the large body surface area and discomfort, topical roflumilast 0.3% cream daily was attempted. The patient returned four weeks later with significant improvement presenting as post inflammatory hyperpigmentation (Fig. 2). Additional biopsies to confirm diagnosis and rule out other immunobullous conditions were obtained from untreated areas for hemotoxin

and eosin (H&E) and Direct Immunofluorescence (DIF). Biopsy for H&E displayed a prominent suprabasilar acantholytic change with associated dyskeratosis, resembling a "dilapidated brick wall." This demonstrated focal erosion and associated impetiginized neutrophilic crusting. Solar elastosis and chronic inflammation were also present (Fig. 3). DIF showed no significant immune deposits (Fig. 4). The patient had maintained clearance at 16 weeks of treatment.

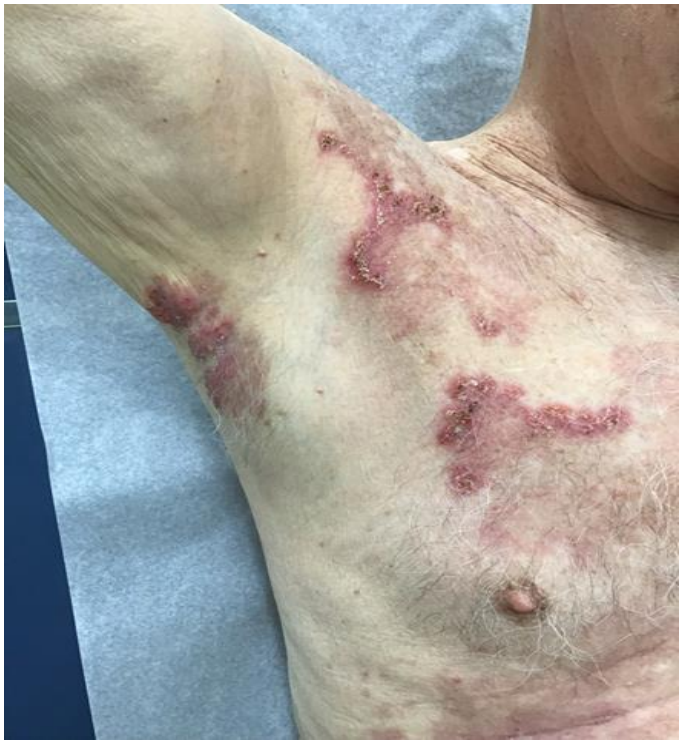

Figure 1: Prior to daily application of topical roflumilast 0.3% cream.

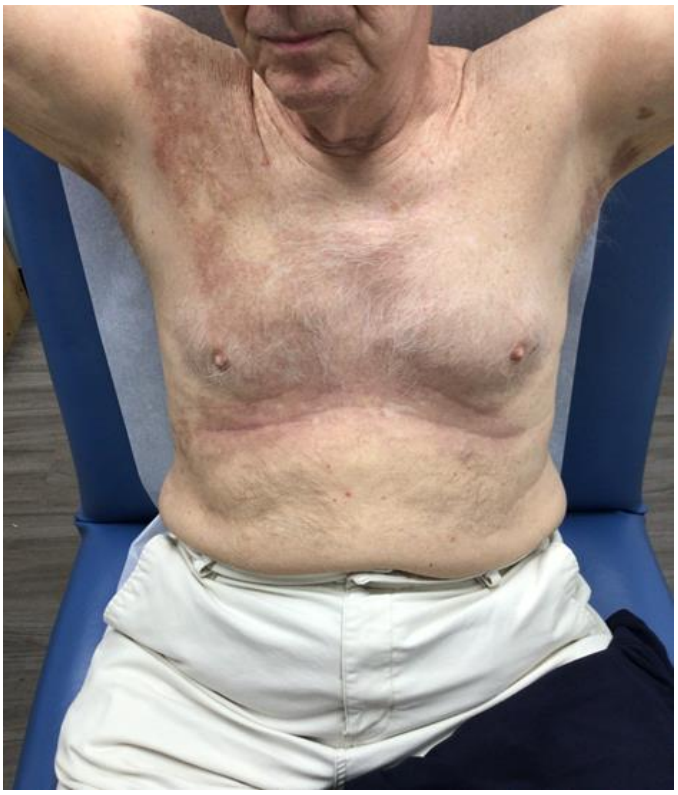

Figure 2: Four weeks after daily application of topical roflumilast 0.3% cream.

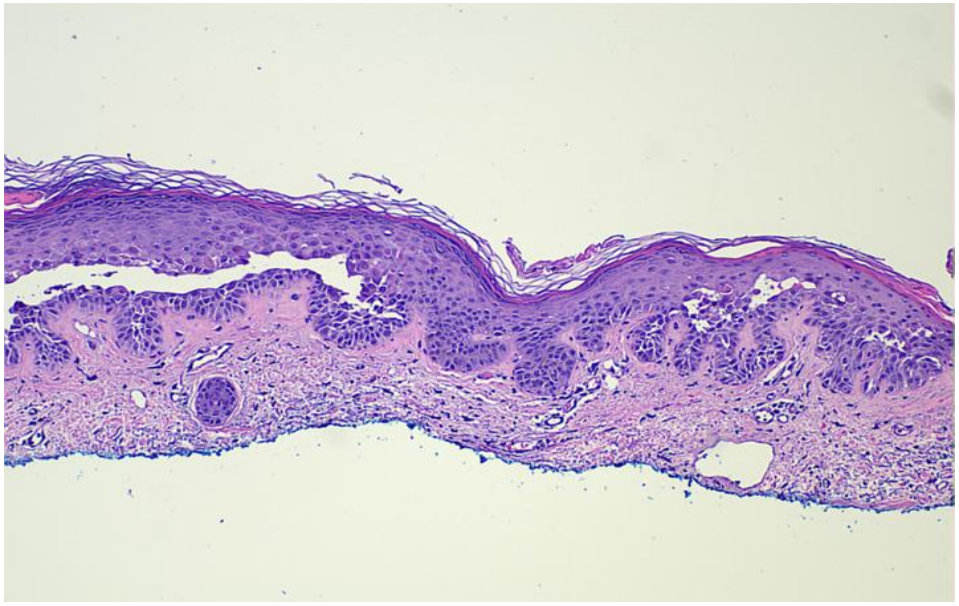

Figure 3: 10x H&E displayed a prominent suprabasilar acantholytic change with associated dyskeratosis, resembling a "dilapidated brick wall." This demonstrated focal erosion and associated impetiginized neutrophilic crusting. Solar elastosis and chronic inflammation were also present.

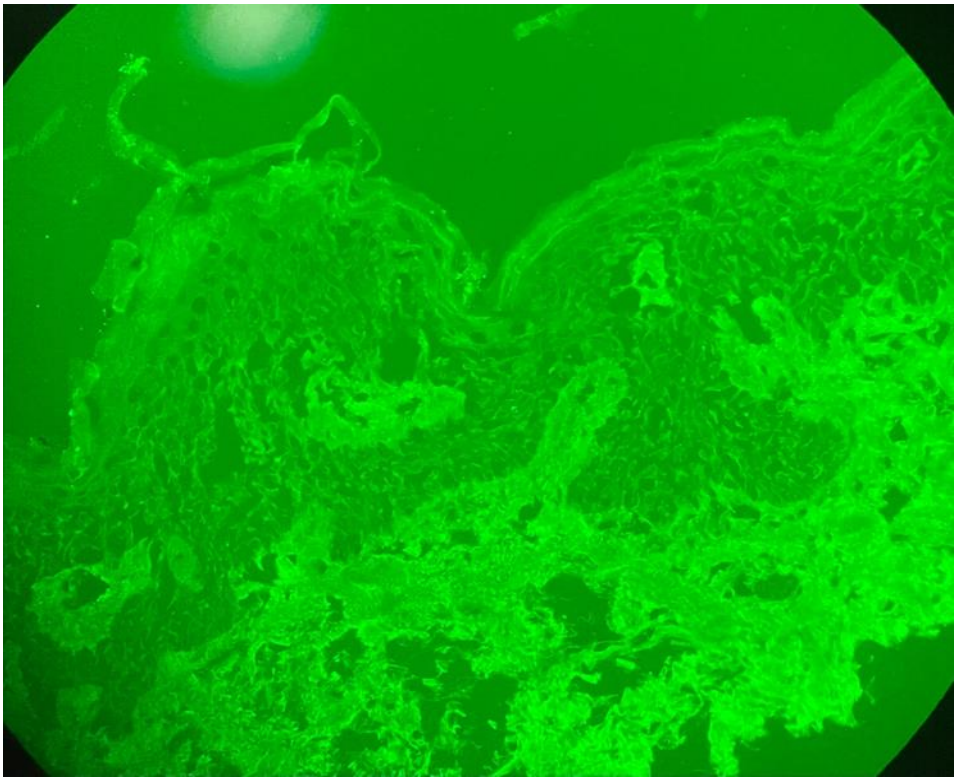

Figure 4: DIF showed no significant immune deposits.

Discussion

Treatments for HHD have been attempted without a known specific mechanism of action. There are multiple theories on why a PDE-4 inhibitor may help with HHD but these authors speculate that due to defects in the $Ca^{2}+/Mn^{2}+$-ATPase secretary pathway, intercellular calcium increases and impairs the formation of desmosomes, therefore, the keratinocytes lose their integrity and are subsequently recognized as a foreign body. This then triggers a cascade of pyroptosis/necroptosis and chemotaxis of inflammatory mediators and neutrophils. Pyroptosis and necroptosis differ from apoptosis in that they induce more

inflammation [8]. This inflammatory response exacerbates and spreads the condition. This inflammation is thought to be driven by recruitment of neutrophils as evidenced by neutrophils being present in the serum crusts of HHD lesions [1]. Oral roflumilast, which was approved for moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD) in 2011, has been shown to decrease neutrophils in the sputum of patients with chronic obstructive pulmonary disease [9]. These authors believe the mechanism of action for COPD further translates to the effectiveness of roflumilast for HHD.

Conclusion

Larger studies will be needed to determine the efficacy of PDE-4 inhibitors, specifically topical roflumilast, for the treatment of HHD. Further studies are needed to elucidate the inflammatory mediators involved with HHD. Limitations include small sample size and the possibility of spontaneous remittance. With the advent of understanding the genetics of HHD, we anticipate that future researchers will be able to correct the genetic defects possibly using CRISPR therapeutics or alternatively, pharmacologic agents that would correct the Ca^{2+}/Mn^{2+}-ATPase secretary pathway rendering the desmosomes more stable.

Acknowledgements

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Conflict of Interest

The authors have no conflict of interest to declare.

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