Severe Relapsing Hailey-Hailey Disease Displaying a Durable Complete Response to Hydroxyurea

Dear Editor,

Familial benign chronic pemphigus, also known as Hailey-Hailey disease, was first described by the Hailey brothers in 1939 (1). It represents a chronic autosomal-dominant genetic skin disorder with incomplete penetrance, usually diagnosed in children and young adults. As a result, family history of this disorder can be elicited in only about 66% of patients. We describe herein a patient with Hailey-Hailey disease who received treatment with hydroxyurea for a new diagnosis of polycythemia vera, with a surprising outcome.

A 54-year-old man was diagnosed with Hailey-Hailey disease at age ten when he presented with several erythematous and blistering skin lesions involving the neck, wrist flexure surfaces, and the forearms. The patient underwent regular dermatology follow-up for this condition. His disease followed a relapsing-remitting pattern, with short disease-free intervals. It predominantly involved the neck, torso, and upper extremities (Figure 1), and only rarely buttocks and groin areas. Initially, mild-moderate potency topical steroid creams were tried, with only modest success.

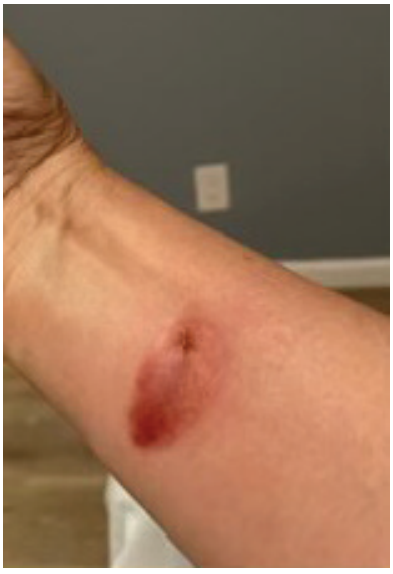

Figure 1. Erythematous and blistering skin lesion involving the wrist area in the index patient.

Topical antibiotics were required on several occasions due to secondary infections. Photodynamic therapy was only minimally helpful, as the disease continued to worsen. In his 40s, the disease became more difficult to manage, and several systemic options were tried, with very little if any success. Thus, the patient failed oral steroids, dapsone and azathioprine. He became anxious, depressed, and socially isolated.

Other past medical history was significant for hypertension. The patient was a never-smoker, and denied alcohol or drug abuse. There was no family history of skin disorders of cancers in his immediate family members.

In May 2019, the patient presented with elevated hemoglobin/hematocrit and moderate thrombocytosis. Further work-up identified JAK-2 V617F kinase mutated polycythemia vera, for which he was started on periodic phlebotomies and low-dose aspirin. Four months later, hydroxyurea was prescribed due to increased phlebotomy needs and worsening thrombocytosis. The hydroxyurea dose was subsequently titrated to 1000 mg orally per day, alternating with 1500 mg orally per day. The patient tolerated this agent well, without significant side-effects. He also achieved excellent control of hematocrit and normalization of platelet count.

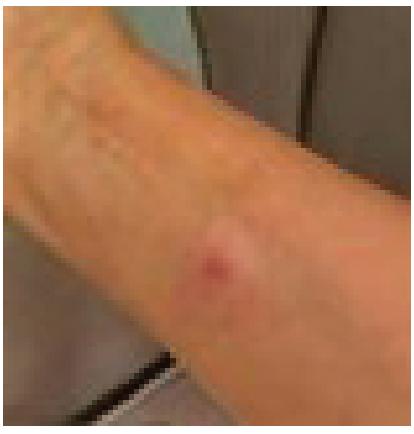

Figure 2. Most Hailey-Hailey disease lesions are transient and leave little or no scars upon healing.

Pleasantly surprised, the patient also realized that he had not experienced any more relapsing Hailey-Hailey skin lesions 8 weeks after the commencement of hydroxyurea. Four years later, his polycythemia remains in excellent control. He also remains without any further evidence of skin lesions.

The hallmark of Hailey-Hailey disease is believed to be the haploinsufficiency of the enzyme ATP2C1 (2). The ATP2C1 gene is located on chromosome 3 and encodes a Ca2+ ATPase protein. A mutation in one copy of the gene causes only half of this necessary protein to be synthesized. Consequently, impaired keratinocyte adhesion ensues, leading to acantholysis, blisters, and rash (2). The initial lesion may be an erythematous area or a fluid-filled blister which subsequently ruptures, leading to a macerated or crusted lesion. The lesions more commonly affect the sides of the neck, armpits, forearms, buttocks and groins, but may expand to a generalized skin eruption. Patients may complain of itching in the affected areas, potentially leading to social distress and isolation (3). Affected areas undergo repeated blistering and inflammation, and may be tender to touch. A pattern of multiple relapses and remissions is characteristic of Hailey-Hailey disease. Nonetheless, most lesions are transient and leave little or no scars (Figure 2).

The differential diagnosis includes intertrigo, contact dermatitis, pemphigus, psoriasis, and cutaneous candidiasis. Skin biopsy and/or family history can confirm the diagnosis of Hailey-Hayley disease. The lack of both mucosal lesions and intercellular antibodies on immunohistochemistry distinguishes this entity from other forms of pemphigus.

Hailey-Hayley disease is currently believed to be incurable, and its complications include secondary bacterial, viral, or fungal infections, which may require antimicrobial agents (4). The patients are advised to avoid friction and sweating by wearing light cotton clothes. Sun avoidance as much as possible and using SPF 50 sunscreen while in the sun are advised. Applying soothing compresses followed by topical corticosteroid cream can offer symptom relief (3,4). Topical antibiotics can be used for localized lesions. Generalized lesions may require systemic steroids and antibiotics.

Topical tacrolimus, laser, and photodynamic therapy have been used with varying degrees of success in the second line (4). Oral dapsone, cyclosporine, azathioprine, thalidomide, etretinate, and intramuscular alefacept were shown to control the mild-moderate disease but not severe chronic or relapsing forms (4). Surgical skin grafting usually represents the last resort in resistant localized disease.

Mestre et al. (5) described a case of chronic Hailey-Hailey disease in a Caucasian woman, whose skin lesions were refractory to topical and oral steroids, tetracyclines, antifungals, and azathioprine. After introduction of weekly oral methotrexate for rheumatoid arthritis treatment, the skin lesions regressed, with significant impact on the patient's quality of life.

Similarly, Hailey-Hailey disease in our patient responded completely to hydroxyurea, without any relapses over a 4-year interval. Hydroxyurea has been used for many decades in hematology and oncology, has a favorable side-effect profile, and is cost-effective. Our case report supports the clinical evidence of hydroxyurea's potential role in Hailey-Hailey disease treatment. There is hope that our findings will be confirmed by larger studies and shift the treatment paradigm in severe chronic or relapsing-remitting forms of Hailey-Hailey disease.

References:

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