Recalcitrant Hailey-Hailey Disease Responds to Oral Tacrolimus and Botulinum Toxin Type A

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To the Editor:

Hailey-Hailey disease, also known as familial benign pemphigus, is a chronic blistering skin disorder that typically presents as a recurrent vesicular or bullous dermatitis found predominantly in the intertriginous regions of the body. Because current treatment regimens for Hailey-Hailey disease are fairly limited, novel treatments may be explored in intractable cases.

A 71-year-old woman presented with well-demarcated erythematous plaques with erosions and white verrucous regions in the perivulvar, vaginal, and perianal areas of 1 month's duration (Figure 1). The lesions were excruciatingly pruritic and excoriated. The patient reported no personal or family history of similar lesions.

Histopathologic examination of multiple biopsies from the periphery of the plaques showed acantholysis of the epidermis and surface necrosis with negative direct immunofluorescence. A diagnosis of Hailey-Hailey disease was made. Over several months following the initial presentation, the patient was treated with regimens of corticosteroids, antibiotics, antifungals, acitretin, and topical tacrolimus (which showed minimal response), but the condition continued to progress and thus warranted a more aggressive approach. After a 4-week course of oral cyclosporine 1.25 mg/kg twice daily, some healthy granulation tissue had formed, but new erosions continued to develop on the vulva, labia, and intergluteal cleft (Figure 2). Subsequently,

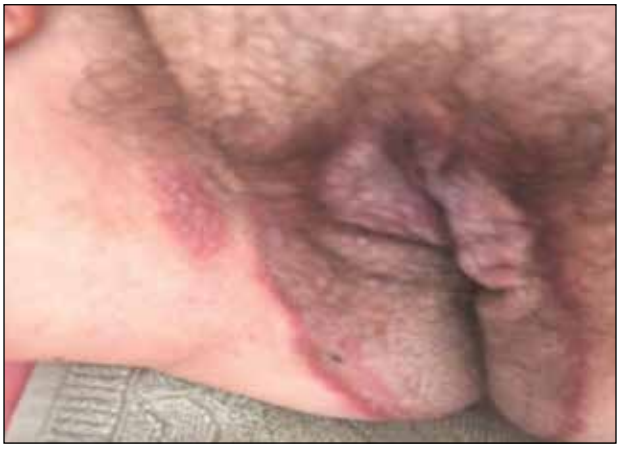

Figure 1. Well-demarcated erythematous plaques with erosions and white verrucous regions in the perivulvar, vaginal, and perianal areas in a 71-year-old woman.

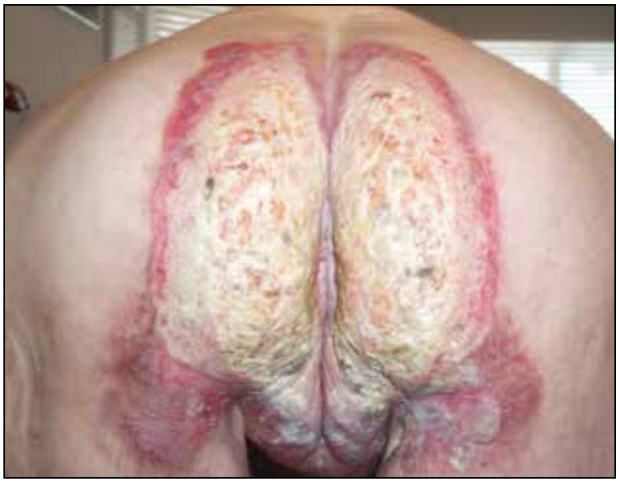

Figure 2. After 4 weeks of oral cyclosporine therapy (1.25 mg/kg twice daily), healthy granulation tissue was seen in the perianal region, but new erosions had developed on the vulva, labia, and superior intergluteal cleft.

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a 2-month course of methotrexate yielded similar results with minimal healing and new necrotic areas (Figure 3).

Following methotrexate therapy, treatment with several other oral agents was considered such as azathioprine, mycophenolate mofetil, and oral tacrolimus. Since the patient had previously shown minimal response to topical tacrolimus, a course of oral treatment (0.05 mg/kg twice daily) was initiated. At 4 weeks' follow-up, extensive healing of the lesions was noted (Figure 4) and the patient reported that the painful pruritus had improved.

After 6 weeks of treatment, there still were a few small lesions in the intergluteal cleft, which were treated with botulinum toxin type A (100 U diluted with 5 cc of bacteriostatic saline per cm^2). After 3 separate injections with botulinum toxin type A and oral tacrolimus for 9 months, complete resolution of the lesions was obtained (Figure 5). After more than 6 months of remission, oral tacrolimus slowly was decreased by 1 mg every 6 weeks until treatment was stopped completely. She has remained in remission without oral treatment. After tapering the tacrolimus, botulinum toxin A injections were continued every 6 months for maintenance with the use of topical tacrolimus 3 to 4 times weekly (Figure 6).

The inheritance of Hailey-Hailey disease is autosomal dominant with incomplete penetrance, although spontaneous mutations are implicated in up to 30% of patients.[1,2] The pathogenesis of Hailey-Hailey disease involves a mutation in the ATPase, Ca++ transporting, type 2C, member 1 gene (*ATP2C1*), which encodes for the hSPCA1 protein.[1-2] The malfunction of this ATPase leads to inadequacy of the keratinocyte adhesive barrier resulting in acantholysis and intraepidermal vesicle formation. Macerated plaques also may be found instead of intact vesicles.[3]

Initial presentation of lesions in Hailey-Hailey disease typically occurs in the third or fourth decades

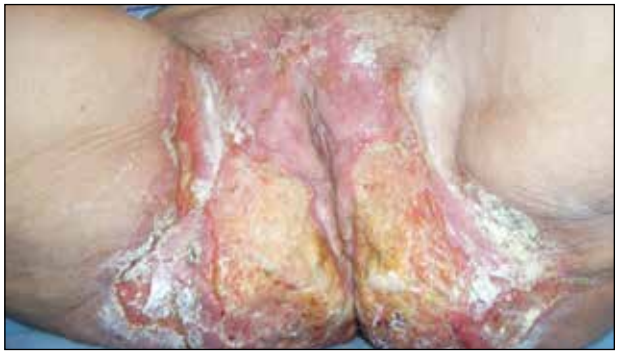

Figure 4. The lesions showed notable healing after 4 weeks of treatment with oral tacrolimus 0.05 mg/kg twice daily.

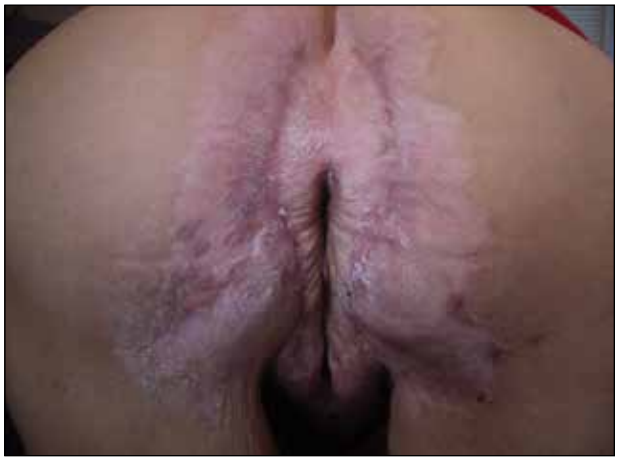

Figure 5. Healing lesions 9 months after initiation of oral tacrolimus with botulinum toxin A injections every 6 months.

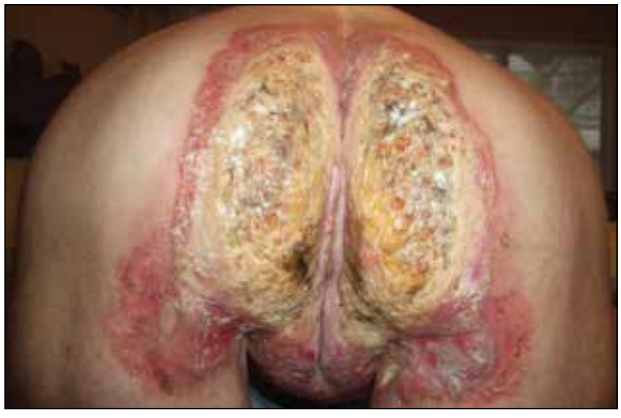

Figure 3. After 2 months of methotrexate therapy (15 mg weekly), granulation tissue was seen with some new areas of necrosis in the perianal region.

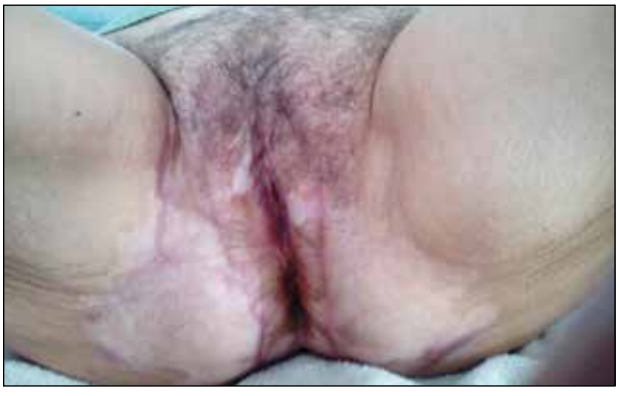

Figure 6. Healed lesions were maintained with botulinum toxin A injections every 6 months along with topical tacrolimus 3 to 4 times weekly.

of life but may present at any age.[4] Areas exposed to increased amounts of friction (eg, axillae, groin, neck, perineum) commonly are involved.[5] Lesions may occur in a relapsing and remitting course and usually are more prominent in summer months because they are exacerbated by sunburn and frictional trauma. Secondary bacterial or fungal infections are common and antibiotics and antifungals often are necessary to prevent progression of the lesions.[5,6]

Various treatment regimens for Hailey-Hailey disease include topical and oral corticosteroids and antibiotics.[5] Topical and oral retinoids, calcitriol, topical tacrolimus, cyclosporin, methotrexate, and even botulinum toxin A have been reported to be effective for refractory cases.[7-12] Our case describes a novel regimen of oral tacrolimus in conjunction with botulinum toxin A used in the successful treatment of recalcitrant Hailey-Hailey disease.

Tacrolimus binds to the immunophilin FK506 binding protein, which inhibits calcineurin. Calcineurin, a protein phosphatase, is necessary for T-cell activation through the nuclear factor of activated T cells. This inhibition of calcineurin blocks the expression of several cytokines.[13] The efficacy of oral tacrolimus demonstrates that cellular immunity could play a role in the pathogenic mechanism of Hailey-Hailey disease.

Contraindications to oral tacrolimus therapy include renal or hepatic impairment, breast-feeding, pregnancy, and certain neoplastic diseases. There also is an increased risk of patients developing malignancies such as lymphoma or skin cancer due to immunosuppression. Use of oral tacrolimus also requires routine laboratory monitoring of renal and hepatic function, potassium, and blood glucose levels.[13]

Botulinum toxin A injections augmented the therapeutic approach in our patient possibly by controlling secretions of sweat and mucous, which may cause maceration and lead to exacerbation of Hailey-Hailey disease. Control of secretions may help in creating an environment that is less prone to exacerbation of lesions and secondary infection.[14] The combination of oral tacrolimus and botulinum toxin A injections provided a safe therapeutic option for recalcitrant Hailey-Hailey disease in our patient.

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