Benign familial pemphigus (Hailey-Hailey disease) responsive to low dose cyclosporine

Sir,

A 43-year-old Egyptian male was referred to us with eight year history of recurrent painful vesico-pustular eruption followed by painful erosions affecting the groins, axillae and neck. He gave family history of similar disease in six other family members including his younger brother, father, paternal grandfather, paternal uncle, and one paternal cousin. Before coming to us, he had been treated with several treatment modalities including oral and topical antibiotics, topical antifungals, corticosteroids, and dapsone with a partial or temporary improvement. His condition had been steadily deteriorating. On examination, he was observed to have large denuded plaques studded with pus on the erythematous base along with erosions and crustations present on the neck, axillae [Figure 1a and b] and groins. A skin biopsy from the affected skin revealed suprabasal cleft, acantholysis with dilapidated brick wall appearance, and presence of dyskeratotic cells [Figure 2a and b]. In the upper dermis, there was mixed inflammatory cell infiltrate comprising lymphocytes, polymorphs and few eosinophils. A diagnosis of benign familial pemphigus (Hailey-Hailey disease) was done. He was started on acetretin 0.75 mg/kg per day in combination with topical pimecrolimus and topical antibiotics. His situation continued to worsen and a month later he was shifted to cyclosporine 2.5 mg/kg per day. Within a week of cyclosporine treatment, he showed 80% clearance of skin lesions with a complete clearance in three weeks time [Figure 3a and b]. A week after complete clearance, the dose of cyclosporine was slowly tapered off by 0.5 mg/kg every month and was stopped over six months. During cyclosporine treatment, he was observed to have mild hypertension that was effectively controlled with calcium channel blockers. After discontinuing this treatment, his blood pressure reverted back to normal limits. During a follow-up two years later, he continues to be in comfortable condition with only minor recurrences that could be controlled with topical tacrolimus (0.1%), and topical and/or systemic antibiotics.

Benign familial pemphigus (Hailey-Hailey disease) is a rare autosomal dominant disorder characterized by development of recurrent blisters, erosions, and crustations in the intertrigenous areas. Mutations in ATP2C1 gene, which encodes the human secretary pathway Ca^{2+}/Mn^{2+} ATPase protein 1 (HSPCA) have been observed to be responsible for Hailey-Hailey disease.[1] Various treatment options include topical or systemic antibiotics, antifungals, corticosteroids in early stages, and dapsone, PUVA, systemic retinoids, cyclosporine, methotrexate, and photodynamic therapy for the recalcitrant cases.[2] Our patient had used several treatment modalities including antibiotics, antifungals, corticosteroids and dapsone earlier and when presented to us had a severe recalcitrant disease. He failed to show an improvement to acetretin tried for four weeks, Infact while on acetretin, his condition continued to deteriorate. We observed a favorable response to low dose of cyclosporine (2.5 mg/kg/day) with complete clearance in three weeks and a week after the clearance, the dose of cyclosporine could be further reduced and was stopped after six months. Cyclosporine in a dose of 2.8–5 mg/kg per day has been reported to be effective earlier in three patients of Hailey-Hailey disease.[3,4] All patients achieved remissions but a rebound was observed soon after stopping cyclosporine. Adverse effects related to long term use of cyclosporine were described to restrict its use on long term basis. Tacrolimus has been recently used on the same basis to control some cases of Hailey-Hailey disease.[5-7] Due to a severe, progressive, and recalcitrant disease, a systemic therapy was indicated in our patient. Thus, we used cyclosporine A to control the acute activity followed by antibiotics and topical tacrolimus ointment to treat the minor recurrences. He showed improvement with a low dose of cyclosporine and continued to have sustained remission with only minor recurrences for two years even after stopping the cyclosporine. We feel, at least some patients with severe and recalcitrant disease can be controlled with a low dose cyclosporine and can be maintained in prolonged remission by slow tapering and thus avoiding the toxicity related to high dose or long term use of this drug. The exact mechanism of action, how cyclosporine and tacrolimus work in Hailey-Hailey disease, is not clear. The proposed mechanism of action is suppression of inflammation

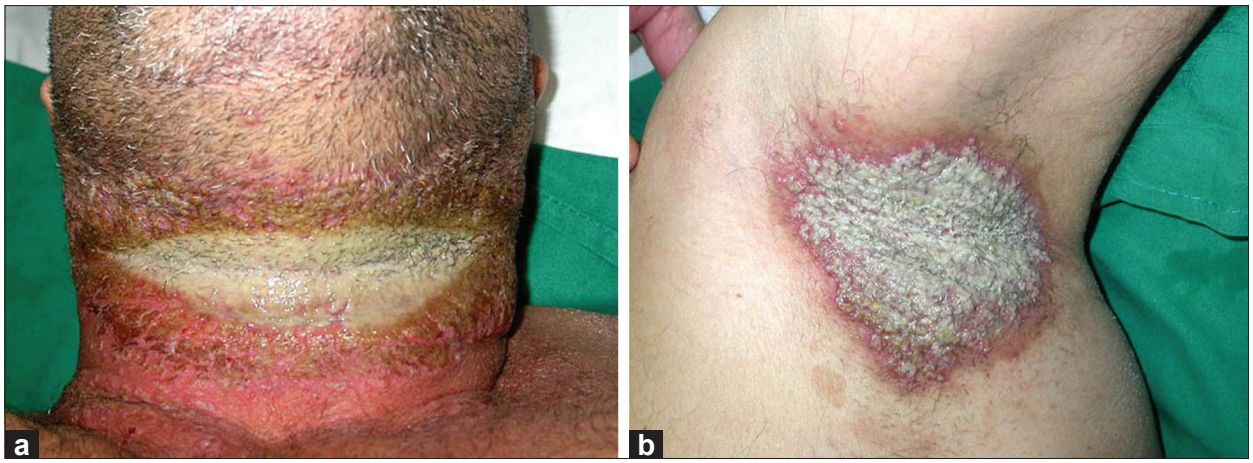

Figure 1: Large denuded plaques studded with pus on erythematous base, with scattered pustules, and crustations present on the (a) neck and (b) left axilla

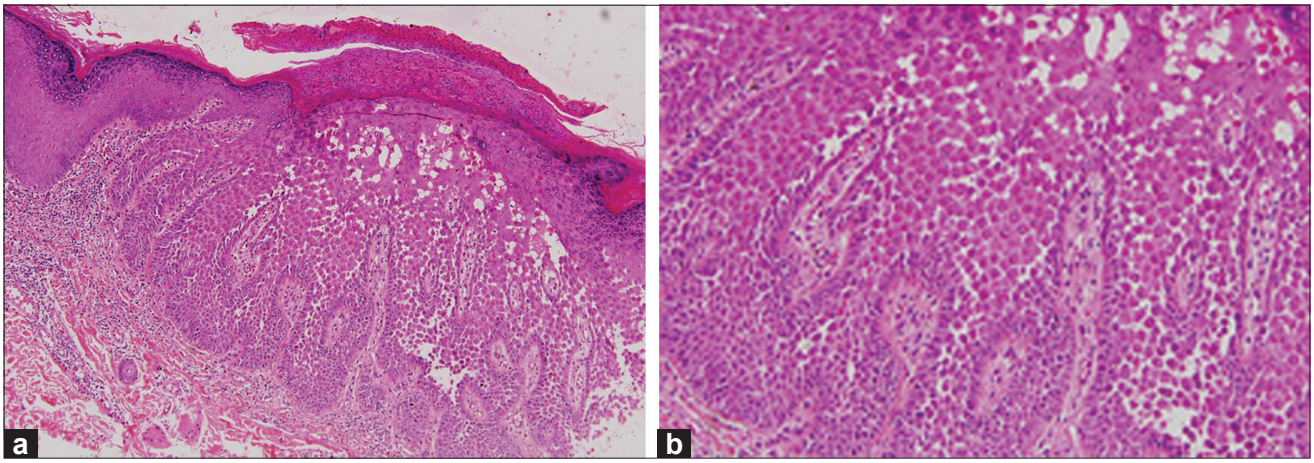

Figure 2: Skin biopsy shows acantholysis with dilapidated brick wall appearance and presence of dyskeratotic cells (H&E stain, (a) ×200; (b) ×400)

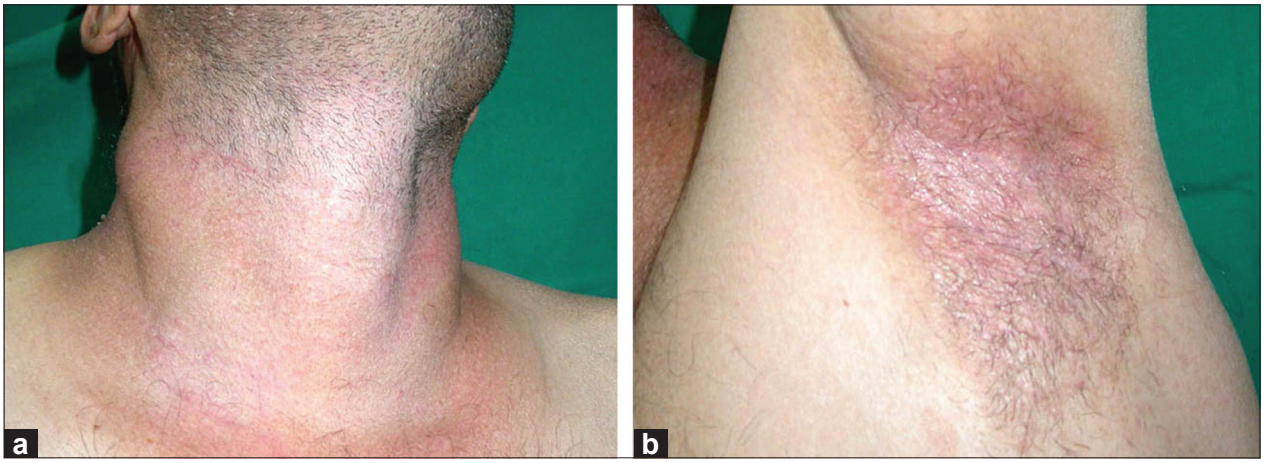

Figure 3: Three weeks after treatment with cyclosporine (a) neck and (b) left axilla

by their immunomodulatory action.[3,6] Presumably various stimuli including heat, friction, UV light, etc are known to precipitate or aggravate the disease in these patients by inducing inflammation.

Arti Nanda, Fatima Khawaja, Rafat Harbi, Mousmee Nanda, Richard Dvorak, Qasem A. Alsaleh

As'ad Al-Hamad Dermatology Center, Al-Sabah Hospital, Kuwait

Address for correspondence: Dr. Arti Nanda, P.O. Box: 6759, Salmiya, 22078, Salmiya, Kuwait.
E-mail: artinanda@hotmail.com

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REFERENCES

1. Hu Z, Bonifas JM, Beech J, Bench G, Shigihara T, Ogawa H, *et al*. Mutations in ATP2C1, encoding a calcium pump, cause Hailey-Hailey disease. Nat Genet 2000;24:61-5.
2. Ruiz-Rodriguez R, Alvarez JG, Jaén P, Acevedo A, Córdoba S. Photodynamic therapy with 5-aminolevulinic acid for recalcitrant familial benign pemphigus (Hailey-Hailey disease). J Am Acad Dermatol 2002;47:740-2.
3. Ormerod AD, Duncan J, Stankler L. Benign familial pemphigus responsive to cyclospoprin, a possible role for cellular immunity in pathogenesis. Br J Dermatol 1991;124:299-305.
4. Berth-Jones J, Smith SG, Graham-Brown RA. Benign familial chronic pemphigus (Hailey-Hailey disease) responds to cyclosporine. Clin Exp Dermatol 1995;20:70-2.
5. Rabeni EJ, Cunningham NM. Effective treatment of Hailey-Hailey disease with topical tacrolimus. J Am Acad Dermatol 2002;47:797-8.
6. Sand C, Thomsen HK. Topical tacrolimus ointment is effective therapy for Hailey-Hailey disease. Arch Dermatol 2003;139:1401-2.
7. Rocha Paris F, Fidalgo A, Baptista J, Caldas LL, Ferreira A. Topical tacrolimus in Hailey-Hailey disease. Int J Tissue React 2005;27:151-4.