Carcinoma *in situ* Arising in a Case of Hailey-Hailey Disease

Dear Editor,

Hailey-Hailey disease (HHD) is a rare autosomal dominant inherited intraepidermal blistering disorder characterized by painful, pruritic, and often malodorous vesiculobullous eruptions and discrete vegetative plaques in flexural regions or other sites of friction. Its complications include secondary bacterial (streptococcal and staphylococcal) infection, candidal infection, unrecognized tinea, and herpes simplex infection. Though squamous cell carcinoma (SCC) has been described in association with HHD, its incidence is quite low.

A 40-year-old male presented to us with history of recurrent itchy raised lesions over the scrotum and groin folds since 6 years. He also complained of asymptomatic growth over the scrotum of 8 months duration associated with foul-smelling pus discharge and intermittent bleeding. History of application of Beclomethasone propionate, Neomycin, and Clotrimazole combination on and off since last 5 years was noted. Detailed enquiry also revealed a history of similar complaints of itchy red raised and raw areas in flexural distribution in mother, elder and younger sisters, and niece. There were recurrences of these lesions in summers and on excessive sweating. Cutaneous examination revealed diffuse erythema on scrotum, multiple atrophic striae along with diffuse hypopigmentation involving the medial aspect of both thighs [Figure 1a]. A verrucous mass of size 5 x 3 cm present over the lower aspect of scrotum extending to the anal verge along with similar erythematous verrucous papules of varying sizes, ranging from 2 × 1 cm to 0.5 x 0.5 cm were present over the right side of scrotum [Figure 1b] and under the surface of penis [Figure 1c]. Natal cleft area also showed diffuse erythema extending to the buttocks [Figure 2a]. Based on the above findings clinical differentials of genital wart, carcinoma *in situ*, squamous cell carcinoma, and seborrheic dermatitis were considered. Histopathological examination from the growth and verrucous papule revealed similar features of hyperplastic stratified squamous epithelium with full-thickness dysplasia and intact basement membrane. Nuclear atypia involving the full thickness of epidermis with scattered pyknotic cells without any koilocytes were all suggestive of carcinoma *in situ* [Figure 2b]. A wide local excision was performed for the same.

The patient's 49-year-old elder sister presented with white plaques overlying linear erosions in the intertriginous areas of 8-year duration with recurrences in summer season and on excessive sweating [Figure 3a]. A provisional clinical diagnosis of HHD was made. Histopathology showed epidermis with large supra-basal split and villi formation. The cells of detached stratum malpighi had loss of intercellular bridges with acantholysis forming a dilapidated brick wall appearance

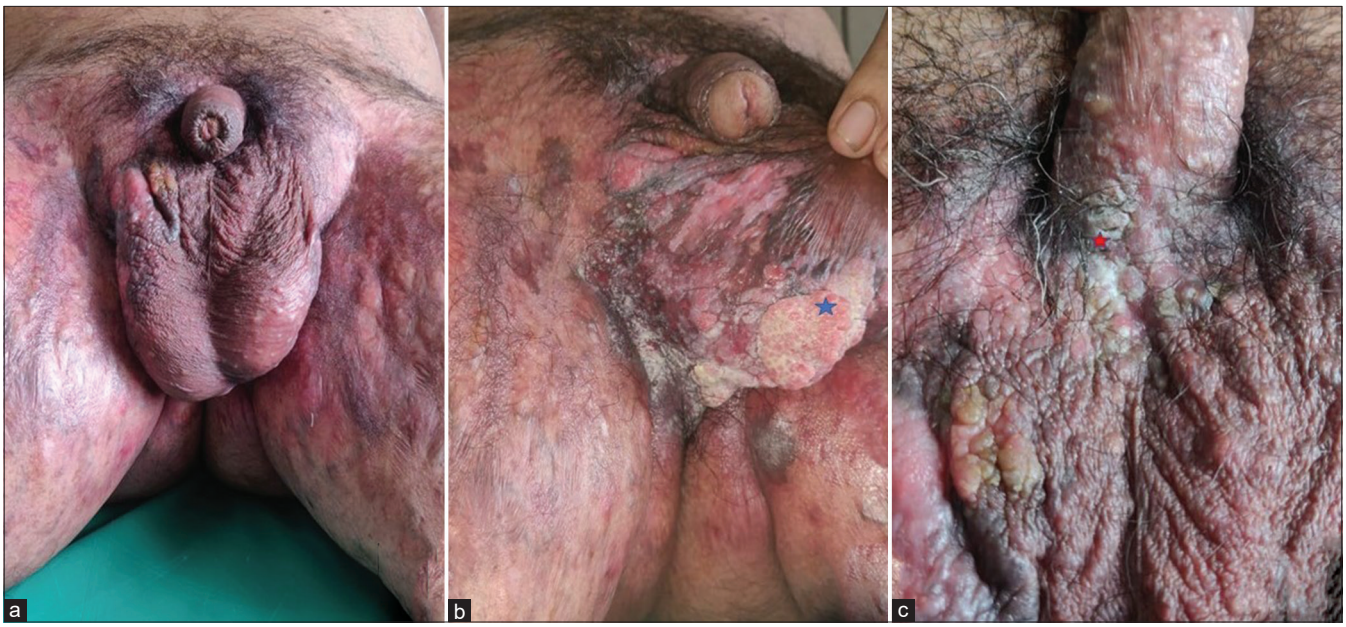

Figure 1: (a) Diffuse erythema on scrotum with multiple atrophic striae present over bilateral groin folds and thighs, diffuse hypopigmentation presents over bilateral thighs (b) A verrucous mass (blue star) of size 5 x 3 cm over the lower aspect of scrotum extending to the anal verge along with similar erythematous verrucous papules of varying sizes, ranging from 2 × 1 cm to 0.5 x 0.5 cm were present over the right side of scrotum (c) Erythematous verrucous papules over under the surface of penis (red star)

confirming our diagnosis of HHD [Figure 3b]. In consequent follow-up, patient developed similar lesions over the neck and axilla. Hence based on positive family history [Figure 3c], recurrent vesiculobullous eruption in flexural distribution in patient and siblings with exacerbation in summer, and characteristic histopathological features we arrived to the diagnosis of HHD with carcinoma *in situ*.

HHD occurs due to mutations in ATP2C1, a gene at chromosome 3q21□24, which encodes human secretory pathway Ca2+/Mn2+ ATPase isoform 1 (SPCA1). It was first described by the Hailey brothers in 1939.[1] Intraepidermal neoplasms are conditions which result from dysplasia of the intraepithelial portion of skin or mucosal surface.[2] The predisposing factors for the development of intraepidermal neoplasia include arsenic consumption, ionizing radiation, skin injury following chronic inflammation such as lupus vulgaris and lupus erythematosus.[2] On reviewing the literature, we could come across eight cases of cutaneous premalignant and malignant conditions in HHD as depicted in Table 1. The exact pathogenesis of the development of cutaneous malignancies in HHD is not known. Cockayne *et al.* implicated role of chronic vulvar disease secondary to human papilloma virus (HPV) infection[3] Ochiai T *et al.* demonstrated the presence of HPV 16 and 39 in vulvar carcinoma in their reported case.[4] Chun *et al.* implicated the use of arsphenamine (Salvarsan 606) in the past for the development of SCC in their patient.[5] However, Holst *et al.* reported de novo development of SCC as no predisposing risk factors could be identified.[6]

Though we could not conduct HPV identification studies from the local skin tissue, the histology of the widely excised tissue did not show koilocytes and hence ruled out genital warts. Similar to Holst *et al.* and unlike other cases no predisposing factors apart from the presence of HHD were present in our case, and hence, we implicate and think this occurrence of carcinoma *in situ* is due to Hailey-Hailey disease *per se*.

This write-up is aimed to highlight the occurrence of inguinoscrotal carcinoma *in situ* in HHD as we could not come across such reports in Indian literature.

Abbreviations

VIN = Vulvar intraepithelial neoplasia

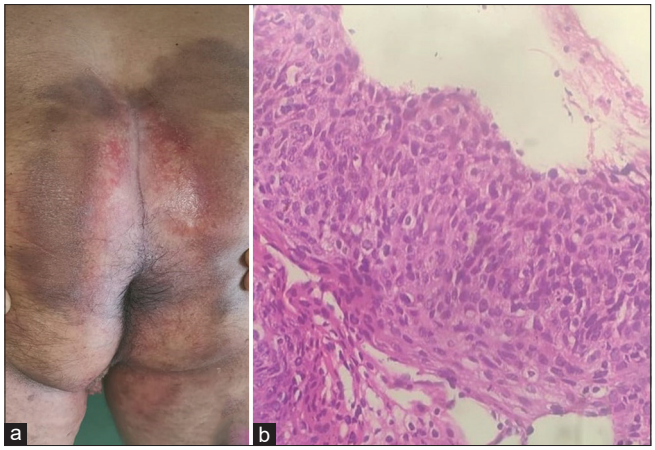

Figure 2: (a) Natal cleft area also showed diffuse erythema extending to the buttocks (b) Nuclear atypia involving the full thickness of epidermis with scattered pyknotic cells without koilocytes suggestive of carcinoma *in situ* (H and E, 40X)

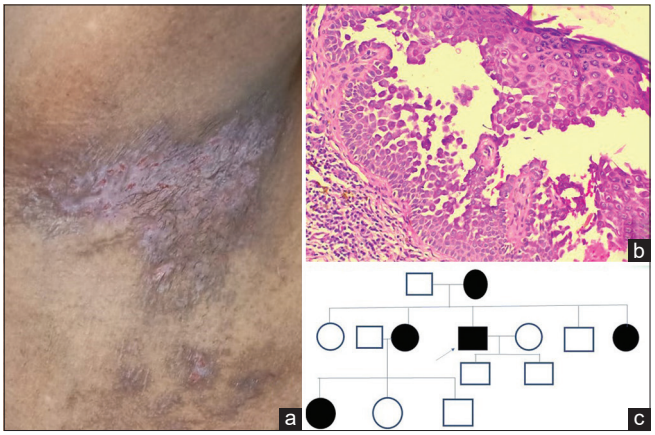

Figure 3: (a) Whitish plaques with linear erosions were present over axilla (b) Supra-basal split with dilapidated brick wall appearance characteristic of Hailey-Hailey Disease (H and E, 10x) (c) Pedigree chart of patient suggestive of autosomal dominant inheritance

Table 1: Review of few reported cases of cutaneous malignancies in Hailey-Hailey Disease[3-10]

Publication	Country	Age/sex	Presentation	Location	History of HHD and other significant past history
Cockayne *et al.*[3]	United Kingdom	61-year-old female	VIN III	Vulva	History of disease control on clobetasone butyrate 0.05%, nystatin, and oxytetracycline application of unknown duration
Ochiai *et al.*[4]	Japan	70-year-old female	VIN III	Vulva	History of Bowen's disease
Chun *et al.*[5]	Korea	65-year-old male	SCC	Penoscrotal	Arsphenamine (Salvarsan 606) used for treatment
Holst *et al.*[6]	Virginia	51-year-old female	SCC	Vulva	De novo
Hirai *et al.*[7]	Japan	-	SCC	-	-
Inaba *et al.*[8]	Japan	-	SCC	-	-
Bitar *et al.*[9]	Canada	51-year-old male	Basal cell carcinoma	Anal margin	9 years after radiation therapy
Furue *et al.*[10]	Japan	60-year-old male	Basal cell carcinoma	Buttock	

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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