Sparing of Nipple and Areola During Keloid Growth

Dear Editor,

Keloids are dermal benign fibroproliferative disorders. It occurs due to excessive pathologic scarring, and the most common sites are the pre-sternal area, shoulder, and suprapubic areas.[1] It spreads beyond the margins of the original wound. We are reporting nine lesions of keloid on the chest area in which the nipple and areola were relatively spared with keloidal tissue extending around the surrounding skin. Multiple theories have been postulated to explain the phenomenon. Our observations and a literature review have given insight into the pathogenesis and identification of new treatment modalities of the keloids.

A 45-year-old male presented to us with hard, red to brown-colored lesions on the chest which were associated with itching. There was no history of prior trauma at the site of lesions. On examination, there was skin-colored to hyperpigmented, firm to hard plaques, present bilaterally over the anterior part of the chest. The diagnosis of keloid was considered. On careful examination, it was observed that keloid tissue was extending up to the margins and sparing the nipple and areola area of both breasts. Histopathological examination was not done as the diagnosis was clinically confirmed. In the following months, the author saw five more clinical cases with a total of nine keloids over the chest area in which keloid tissue was sparing the nipple-areola area [Table 1 and Figures 1 and 2].

The aetiology and pathogenesis of keloid disease are still not clear. In its pathogenesis, there is the role of mast cells, macrophages, lymphocytes, fibroblasts, and myofibroblasts. Fibroblast is the primary cell in keloid pathogenesis. In one study by Ashcroft *et al*.,[1] it was seen that keloid fibroblasts release cytokines and activate the surrounding fibroblasts to proliferate and increase collagen synthesis.

TGF-ß released by different cell groups is the master pro-fibrotic cytokine in keloid pathogenesis. These cell groups activate surrounding fibroblasts to express increased levels of TGF-ß, type I, and VI collagen. Keloid fibroblasts are more sensitive to TGF-ß stimulation and response occurs at lower concentrations as compared to normal. TGF-ß activates fibroblast proliferation and synthesis of extracellular proteins like elastin, fibronectin, and collagen type I and III. It also downregulates collagenase synthesis. Sparing of nipple-areola complex in our patients can be explained by estrogen-regulated action on TGF-ß on nipple-specialized fibroblast.

In humans, nipple skin is the specialized skin site that expresses unique differentiation markers. This specialization is dependent on inductive signals that originate from underlying fibroblasts. John Foley and colleagues identify an estrogen-regulated TGFβ signaling pathway that is crucial for the maintenance of the highly specialized nipple epidermis.[2] TGFβ pathway is shown to be inhibited by estrogen signaling components. The reduced TGFβ pathway activity is essential for maintaining nipple skin and its unique characteristics in the adult. In our patients, this estrogen-regulated TGFβ signaling pathway on nipple fibroblasts may be the reason for the sparing of the

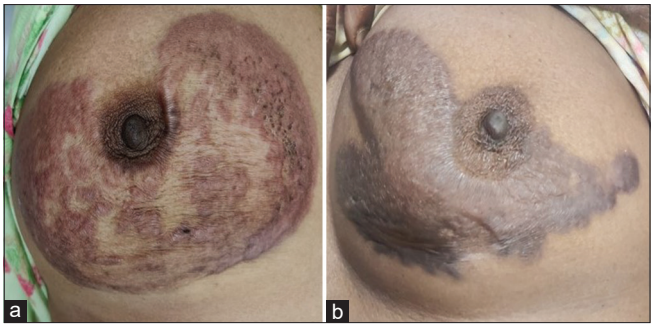

Figure 1: (a) Annular erythematous plaque on the right breast with sparing of nipple and areola (b) Hyperpigmented plaque on left breast with sparing of nipple and areola

Table 1: Demographic and clinical features of patients

Case	Age (in years)/Sex	Location	Clinical findings and spared area	Onset
Case 1	45, male	Bilateral breasts	Erythematous, firm to hard plaques involving the chest area with sparing of nipple-areola	Spontaneous onset
Case 2	39, male	Bilateral breasts	Erythematous hard plaques involving chest area with sparing of nipple and areola	Spontaneous onset
Case 3	42, female	Bilateral breasts	Annular shaped firm to hard plaques not extending to nipple and areola in both breasts	Spontaneous onset
Case 4	35, female	Unilateral, right	Annular erythematous plaque on the right breast with sparing of nipple and areola	Spontaneous onset
Case 5	38, female	Unilateral, left	Hyperpigmented plaque on left breast with sparing of nipple and areola	Spontaneous onset
Case 6	39, female	Unilateral, left	Hyperpigmented to erythematous plaque on left breast with sparing of nipple and areola	Spontaneous onset

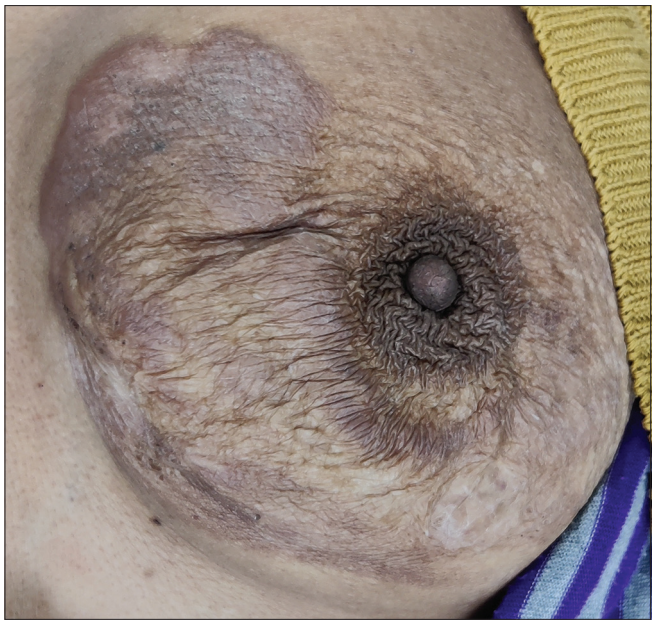

Figure 2: Annular erythematous plaque on the left breast with sparing of nipple and areola

nipple-areola complex. The female predominance present in our case series also supports this theory.

Sparing of nipple-areola complex in our patients can also be explained by the anti-inflammatory and antifibrotic action of α-MSH (alpha-melanocyte stimulating hormone). α-MSH acts via the melanocortin 1 receptor (MC1R) present in melanocytes.[3] The binding of α-MSH to MC1R receptors on dermal fibroblasts gives antifibrotic action while binding to receptors on immune cells gives potent anti-inflammatory and immunosuppressive activities. It has been found that α-MSH/MC1R expression is reduced in keloid fibroblasts.[4] It has also been postulated from studies that estrogen and α-MSH converge on adenylate cyclase to modulate melanin synthesis in areas where melanocytes or UV (Ultraviolet) radiation exposure is highest, including genital and areola regions.[5] Besides cutaneous disease, the antifibrotic effect of α-MSH has also been studied in animal models of hepatic and lung fibrosis.[6,7] Hence we can hypothesize that increased melanocytes in the nipple and areola skin cause increased action of α-MSH in the nipple-areola complex in that area which may consequently lead to sparing of that area in keloid formation due to its anti-inflammatory and antifibrotic actions in our patients. This hypothesis can only be confirmed by future research studies.

Both areas are also regions with relatively lesser skin tension. Nangole *et al*. also proposed that keloids tend to occur in areas of high skin tension.[8] Therefore this can be another hypothesis for sparing of areola in keloid formation.

Another cutaneous condition in which the nipple and areola have been said to be characteristically spared is morphea. Sherber *et al*. described the sparing of the areola and lateral pectoral region in pansclerotic morphea.[9] They believed that spatial boundaries that are first defined during embryonic development make specific areas of skin susceptible to pathologic stimuli. Experimental data also suggest that skin fibroblast populations differ by anatomic site and their biological response to stimuli varies respectively.[9]

It is still not clear what the factors are for sparing of the nipple-areola complex in keloid. Estrogen-regulated TGFβ signaling pathway and α-MSH may be responsible for limiting the formation of keloids by its ant-fibrotic action. However, more studies are required to elucidate the mechanism to pave the way for newer modalities of treatment.

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Conflicts of interest

There are no conflicts of interest.

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