Patterned cicatricial alopecia in two sisters with lamellar ichthyosis

Dear Editor,

Lamellar ichthyosis (LI) is a non-syndromic, autosomal recessive congenital ichthyosis (ARCI) primarily caused by mutations in the transglutaminase (TGM) 1 gene. It is characterised by plate-like scaling. While LI typically spares hair, nail and teeth development, it can lead to secondary nail dystrophy and scarring alopecia.

Two sisters in their thirties sought a dermatology consultation for the complaints of dryness and scaling all over their bodies since birth, and hair loss over the past four years. Upon examination, they exhibited widespread xerosis with large brown to grey scales, forming a polygonal pattern all over the body. Additionally, there was a noticeable recession of the frontal and retro-auricular hairlines with absent follicular opening and wrinkling, suggestive of scarring alopecia [Figure 1]. Further examination revealed sparse eyebrows, axillary, pubic and body hair. There were no abnormalities in nails or mucous membranes. There was a notable family history of similar lesions in two brothers and they had not received any treatment for their skin condition in the past.

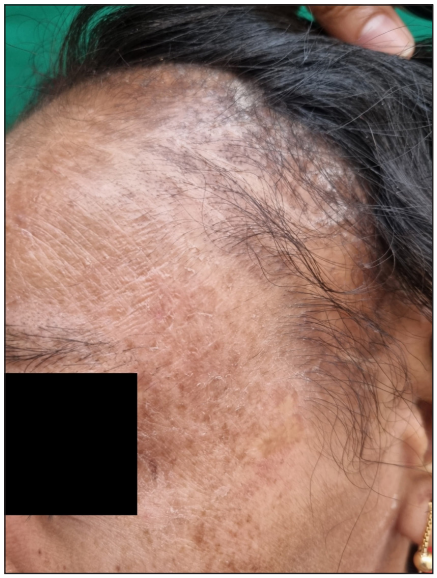

Figure 1: Clinical images of a patient with lamellar ichthyosis showing recession of frontotemporal hairline with large polygonal brown scales.

The trichoscopic examination of the scalp showed loss of follicular ostia. At the progressive edges of alopecia, there was prominent perifollicular scaling, perifollicular pigmentation and interfollicular scaling. Moreover, there were numerous pigtail hairs and sparse vellus hairs [Figure 2a]. The trichoscopic examination of the axilla and pubic area showed a lack of follicular openings. The histopathological examination of the scalp biopsy revealed hyperkeratosis and acanthosis. In the dermis, there were hair follicles in the anagen phase accompanied by perifollicular fibrosis and lymphocytic inflammation [Figure 2b].

Genetic sequencing revealed a mutation in the TGM1 gene, specifically identified as c.2087C>T p.(Thr696Met) missense mutation located in exon 13, classified as a pathogenic variant. Patients were treated with isotretinoin at 0.5 mg/kg/day, along with contraceptive counselling and emollients. After three months, scaling significantly reduced.

A patterned form of alopecia affecting the fronto-temporal scalp is increasingly recognised in LI patients. Many studies have investigated genotype-phenotype correlations in ARCI. TGM1 mutations are linked to alopecia in ARCI patients, with affected individuals over four times more likely to have these mutations.[1,2] Putterman et al. found genotype-influenced hair loss severity, with ABCA12 or TGM1 mutations showing similar alopecia levels, whereas ALOX12B and NIPAL4 mutations were not associated with alopecia.[3] However, these reports did not include a detailed morphological description of LI-associated alopecia. Challamel et al. described distinct alopecia patterns in LI patients, noting frontotemporal and retro-auricular hairline recession with TGM1 mutations.[4] Dias et al. observed frontotemporal cicatricial alopecia in

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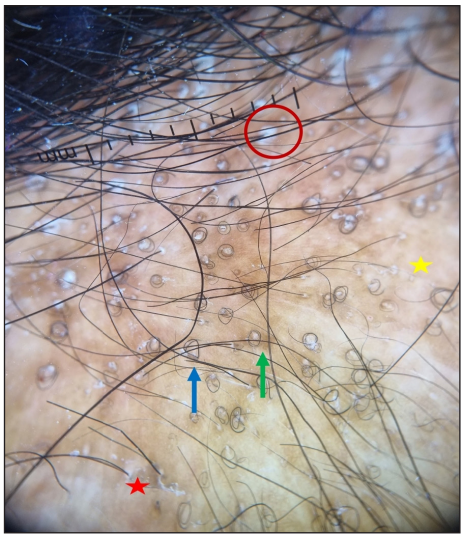

Figure 2a: Trichoscopic image (DermLite DL4, x10) showing perifollicular scale (red circle), coiled hairs (blue arrow), loss of follicular ostia (yellow star), perifollicular pigmentation (green arrow) and interfollicular scaling (red star).

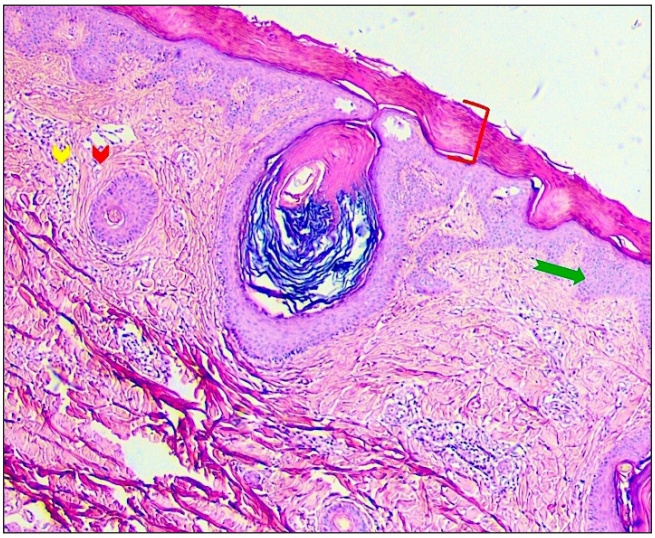

Figure 2b: Histopathological image of scalp biopsy (Haematoxylin and eosin stain, 40x magnification) showing hyperkeratosis (red bracket), acanthosis (green arrow) and spongiosis. Anagen hair follicles in the dermis are accompanied by perifollicular fibrosis (red arrowhead) and inflammation consisting primarily of lymphocytes (yellow arrowhead) with no interface activity.

Table 1: Differences between patterned (frontotemporal) scarring alopecia.

Characteristics	Scarring alopecia secondary to lamellar ichthyosis	Graham-Little Piccardi Lassueur syndrome	Frontal fibrosing alopecia
Type	Secondary scarring alopecia	Primary (variant of LPP)	Primary (variant of LPP)
Age at presentation	1st or 2nd decade of life	30 to 70 years	>Postmenopausal
Gender	Men and women are equally affected	Women are 4 times more affected compared to men (4:1)	Women are affected more than men
Clinical presentation of alopecia	Progressive receding of frontotemporal hairline with large, polygonal brown scales	Patchy scarring alopecia of the scalp	Progressive symmetrical cicatricial alopecia in the frontotemporal area revealing a uniform shiny pale band of skin. Immediate hairline shows perifollicular erythema and scaling
Additional features	Ichthyosis, nail dystrophy	Non-scarring alopecia of axillary and pubic hair and widespread KP-like follicular papules	Thinning of eyebrows or loss may be seen
Dermoscopy	Reduced follicular ostia, perifollicular and interfollicular scaling, pili torti	Trichoscopy is similar to frontal fibrosing alopecia. Dermoscopy of follicular papules- round-to-oval yellowish areas with keratotic follicular plugs with mild erythema	Absence of follicular ostia. Presence of inflammatory signs such as perifollicular erythema, scaling and hyperkeratosis and lonely hairs. In skin of colour perifollicular pigment dots can also be seen
Histopathology	Hyperkeratosis, acanthosis and perifollicular lymphocytic infiltrate with no interface activity	Similar to LPP. Peri-infundibular and peri-isthmic lymphocytic inflammation and fibrosis, interface changes at infundibular-isthmic epithelium, increased hair in catagen and telogen phases, polytrichia	Similar to lichen planopilaris
DIF	Negative	Saggy or patchy deposition of fibrinogen and IgM along follicular BMZ	Non-specific, similar to lichen planopilaris
Pathogenesis	Mutation in TGM1 responsible for encoding TGase-1 enzyme, crucial for forming CCE within keratinocytes, catalysing cross-linking of Nε-(γ-glutamyl)lysine and ω-hydroxyceramides	T cell-mediated autoimmune condition There is a decrease expression of PPAR	A complex interaction between immune-mediated neurogenic inflammation, genetics, hormones, and possible external stimuli (Sunscreens, face soap), lack of PPAR-γ plays a vital role in all stages of disease
Management	Emollients / keratolytic, topical/oral retinoids, Vit D3 derivatives, genetic counselling	Same as frontal fibrosing alopecia	TCS, HCQ, Doxycycline, Finasteride, Pioglitazone, oral steroids, MTX, MMF, retinoids

BMZ: basement membrane zone; CCE: cornified cell envelope; HCQ: hydroxychloroquine; KP: keratosis pilaris; LPP: lichen planopilaris; MTX: methotrexate; MMF: mycophenolate mofetil; PPAR: peroxisome proliferator-activated receptor; TGM1: transglutaminase 1; TCS: topical corticosteroids.

four ichthyosis patients, including three with LI.[5] Our report on LI-associated alopecia explores extra-scalp patterns and histopathological findings. Accurate differentiation from conditions like FFA and Graham-Little Piccardi Lassueur syndrome is vital to avoid unnecessary immunosuppressant treatment [Table 1].[6]

The specific patterned alopecia seen in patients with TGM1 mutations strongly indicates a direct association between the TGM1 gene and hair follicle engagement. TGM1 produces the TGase-1 enzyme, vital for creating the cornified cell envelope in keratinocytes by facilitating the cross-linking of Nε-(γ-glutamyl)lysine and ω-hydroxyceramides. TGase-1 is found in different parts of normal hair follicles including cortex, medulla, outer and inner root sheath cells, aiding hair formation and potentially explaining alopecia in LI cases with TGM1 mutation.

In conclusion, we highlight the significance of recognising LI-associated patterned scarring alopecia, emphasising the importance of genotype-phenotype correlations, particularly concerning TGM1 mutations, in elucidating the pathogenesis of LI-related alopecia and guiding tailored therapeutic strategies.

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