

Perifollicular Inflammation and Fibrosis in Androgenetic Alopecia: Implications for Diagnosis and Treatment - A Comparative Histopathologic and Clinical Study with Normal-Appearing Scalp

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Introduction: Androgenetic alopecia (AGA) is traditionally regarded as a noninflammatory, androgen-driven condition. Yet clinical and histologic evidence identifies a subset of patients with perifollicular infundibulo-isthmic lymphocytic infiltrates and fibrosis (PIILIF), a histopathologic pattern resembling early primary cicatricial alopecia (PCA). This study evaluates the clinical, histologic, and immunophenotypic features of PIILIF and their diagnostic and therapeutic implications.

Methods: This retrospective study of 129 AGA patients drawn from a referral center, obtained trichoscopy-guided biopsies from balding and clinically non-alopecic scalp (cNAS). Histopathologic and immunohistochemical findings were correlated with clinical features and treatment outcomes. Patients with PIILIF received multimodal therapy targeting androgenic and inflammatory pathways. The cohort, from a specialty clinic, included both typical and treatment-resistant AGA.

Results: PIILIF was identified in the cNAS of 81% of patients, particularly in those aged 44 or older, with Norwood stage ≥ 5 , or with prior poor response to therapy. Histology showed CD117+ mast cells, perifollicular CD4-predominant lymphocytes and fibrosis in the infundibulo-isthmic unit. Combination therapy using dihydrotestosterone blockade plus anti-inflammatory agents modeled after PCA therapies, including tetracyclines, topical calcineurin inhibitors, and select phytoactive botanicals, yielded greater improvement than standard AGA treatment regimens alone. Overall, 67% improved, and 2% had suboptimal outcomes ($p < 0.0001$). These findings support an AGA-PIILIF continuum that may include fibrosing alopecia in a pattern distribution.

Conclusion: PIILIF represents an under-recognized inflammatory endotype within AGA that may account for treatment resistance in some patients. Early biopsy can confirm the diagnosis, and therapy targeting hormonal and immune pathways may improve outcomes. Routine trichoscopy with a low threshold to biopsy perifollicularly abnormal units showing mild erythema, scale, or hyperpigmented collars can guide care, particularly in treatment resistant or equivocal cases. The broader systemic implications of this inflammatory signature merit further investigation.

Plain Language Summary: Pattern hair loss is usually linked to hormones. Yet some people do not improve with standard treatment. We asked whether an immune type of inflammation, similar to what doctors see in scarring alopecias, might be present in these patients.

We studied 129 adults with pattern hair loss. Using a magnified scalp exam, we took tiny skin samples from thinning areas and from nearby skin that looked normal.

Most patients, 81%, had immune inflammation around the upper part of follicles with early scarring, even where the scalp looked normal. This differs from the mild, nonspecific inflammation sometimes seen in long-standing baldness. It was more common after age 44 and with advanced thinning. On magnified exam, a reddish ring, a darker ring in skin of color, or fine scale was common but not predictive, and redness faded with pressure.

People did better when treatment targeted both hormones and this immune inflammation. The anti-inflammatory medicines were the same types used for scarring alopecias, such as tetracyclines, topical calcineurin inhibitors, and selected botanical agents, together with blockers of dihydrotestosterone. Overall, 67% improved, and 2% had a poor result.

What this means is that an immune, scarring-type process can coexist with hormone-driven hair loss and may help explain treatment resistance in some patients. It also supports that, when treatment is not working or the exam is unclear, a biopsy can confirm the diagnosis and guide care. Early targeted therapy may improve outcomes.

Keywords: androgenetic alopecia, hair loss treatment, hair transplant failure, scarring alopecia, primary cicatricial alopecia, dihydrotestosterone, male pattern baldness, female pattern hair loss

Introduction

Androgenetic alopecia (AGA) is the most common progressive hair loss disorder, affecting up to 50% of men and women by age 50. Its visible impact and chronic course often cause psychosocial distress. Finasteride in men and minoxidil remain the only FDA approved treatments, with regrowth in 38.6 to 48% of patients and benefits that often plateau or diminish over time.^{1–5} Hair transplantation can improve density, yet long term thinning or graft loss is not unusual, and in some patients, procedures have preceded primary cicatricial alopecias (PCA) including lichen planopilaris (LPP), frontal fibrosing alopecia (FFA), and dissecting cellulitis of the scalp (DCS).^{6–11} These outcomes raise concern about a latent inflammatory process that may be triggered or unmasked by surgical trauma.

Histologic evaluations of AGA have described follicular inflammation and dermal fibrosis. Earlier work, including Whiting, regarded these as mild or nonspecific sequelae of miniaturization such as fibrous streamers.¹² More recent studies document organized lymphocytic inflammation around the upper follicle in both balding and clinically normal scalp.^{13–15} Quantitative and ultrastructural work localized infiltrates to the lower infundibulum and isthmus in transitional vertex skin and also found increased inflammation in non-alopecic occipital scalp compared with controls.¹³ The same series reported abundant mast cells in widened fibrous tracts and lichenoid epithelial injury near the bulge, suggesting a regulated inflammatory and early fibrotic response rather than incidental change. Donor-area analyses during transplantation likewise revealed moderate to dense perifollicular lymphocytes and quantifiable fibrosis at the lower infundibulo-isthmus level, discriminating cases from controls and supporting histologic assessment during surgical planning.¹⁴ A contemporary dermatopathology series confirmed the infundibulum and isthmus as the dominant sites of inflammation, with follicular spongiosis favoring the upper follicle, consistent with an upper-unit process that can coexist with miniaturization.¹⁵

Despite these observations, prior work did not define a reproducible histopathologic entity, use standardized biopsy protocols, or relate histology to treatment outcomes or features of PCA. Perifollicular infundibulo-isthmus lymphocytic infiltrates and fibrosis (PIILIF) describes a pattern with lymphocytes encircling the infundibulum and isthmus of intact follicles and early perifollicular fibrosis that may be subtle; a CD4-predominant infiltrate and increased CD117-positive mast cells are typical.¹⁵ Studying this pattern as a potentially coexisting process within AGA may clarify its role in treatment resistance, disease progression, and post-transplant failure.

This study evaluates whether PIILIF represents a reproducible pattern in a subset of patients with AGA and assesses its clinical, diagnostic, and therapeutic relevance. To address gaps in prior work, we used trichoscopy-guided biopsies from both balding and clinically non-alopecic scalp (cNAS), with vertical and transverse sections and immunophenotyping, and correlated these findings with outcomes. We also examined overlap with early lesions of other scarring alopecias, including acne keloidalis nuchae (AKN), folliculitis decalvans (FD), central centrifugal cicatricial alopecia (CCCA), LPP, and FFA.^{16–21} Here, cNAS denotes scalp that appears unaffected on inspection, recognizing that AGA can affect permanent hair zones despite normal-looking caliber and density.²²

Materials and Methods

Study Design and Population

This retrospective study included patients who presented with AGA between June 2022 and June 2023. The Western Institutional Review Board (WIRB) Copernicus Group granted exemption from full review because the analysis used deidentified data from routine clinical care with no intent to re-identify or contact participants. All patients provided written informed consent, including permission to use and publish anonymized clinical photographs. The study followed the Declaration of Helsinki (1964) and its later amendments.

Biopsies were obtained during routine evaluation and were trichoscopy-guided when perifollicular abnormalities were present. Analyses were performed retrospectively on deidentified clinical and histopathology data from standard care. Endpoints and follow-up intervals were not prespecified, and no procedures were performed prospectively.

Patients were included if their medical records revealed clinical and photographic evidence of AGA. Exclusion criteria were refusal to undergo biopsy, patchy or asymmetric hair loss, known scarring alopecia, alopecia areata, autoimmune disease, immunocompromised status, current systemic immunosuppressant use, or childhood onset hair loss.

Patients are further qualified if their medical records confirm contemporaneous scalp evaluation using trichoscopy. Biopsies were taken from cNAS, usually in the parietal zone. A subset underwent paired cNAS and balding biopsies at the same visit. Site selection was guided by perifollicular scale, erythema, or hyperpigmented collars in darker phototypes (Figure 1). Scalp regions previously treated with hair transplantation were excluded. All patients underwent at least one 4 mm punch biopsy from cNAS; a subset also had a second 4 mm biopsy from the leading edge of AGA thinning zones. All specimens were sectioned in both vertical and horizontal planes.

Histopathology and Immunohistochemistry

Histologic evaluation focused on features consistent with PIIIF. Diagnostic criteria included lymphocytic infiltrates around the infundibulum and/or isthmus (upper follicle above the arrector pili insertion) of intact follicles; fibrosis confined to the upper third of the follicle, often subtle and manifesting as peripilar stromal thickening supported by α smooth muscle actin (α -SMA) staining; and assessment of sebaceous gland preservation or loss. Concentric lamellar scarring was not required for diagnosis.

All follicular counts (anagen, telogen, catagen, and vellus) were derived from horizontal (transverse) sections. Because absolute counts vary by section level and scalp site, standardized reference ranges are not available.

Features suggestive of PCA (for example, interface change, basal vacuolization, or plasma cells) were noted when present but were not the primary focus. Additional observations included hair cycle stage and follicular morphology, including the terminal to vellus (T:V) ratio, to support the diagnosis of AGA.

Two board-certified dermatopathologists independently reviewed all slides while blinded to clinical data. Discrepancies were resolved by consensus, and the consensus designation was used for statistical comparisons.

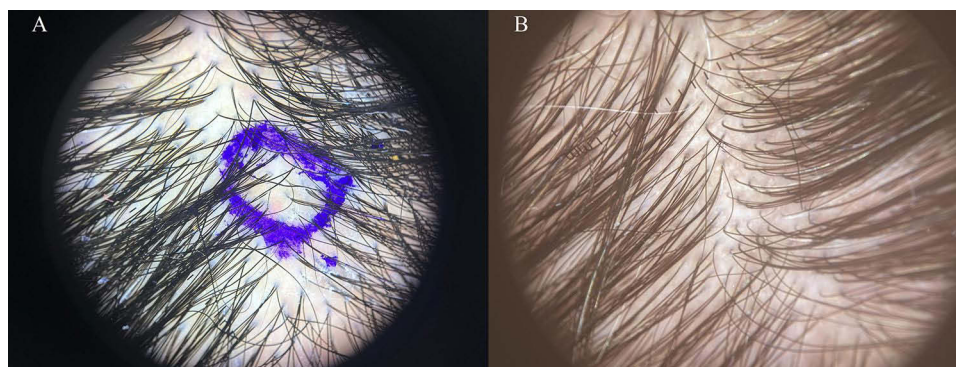


Figure 1 Trichoscopy finding in the cNAS of a patient with AGA-PIIIF showing mild perifollicular scales and mild erythema (A). The blue ink mark indicates the biopsy site, perifollicular erythema, and minimal scaling (B).

Abbreviations: cNAS, Clinically non-alopecic scalp; AGA, Androgenetic alopecia; PIIIF, Perifollicular Infundibulo-isthmic lymphocytic infiltrates and fibrosis.

Clinical Data Collection

Variables included age, sex, race or ethnicity, AGA severity, and symptoms such as pruritus, tenderness, or flaking. History of seborrheic dermatitis, grooming practices (chemical relaxers, hot combs, braiding), and prior hair transplantation were recorded. Treatment history with finasteride, minoxidil, or other agents and use of anti-dandruff products were also documented and examined for association with trichoscopy and histology.

Treatment resistance was defined as suboptimal response to standard AGA therapy (topical minoxidil or oral finasteride), diminished graft survival after transplantation, or progressive thinning in transplanted zones.

Outcomes and Endpoints

Primary outcomes were (i) prevalence of PIILIF in clinically cNAS and, when available, in balding zones and (ii) histologic and immunohistochemical features of PIILIF, including CD4 predominant lymphocytes, increased CD117 positive mast cells, and α -SMA positivity.

Secondary outcomes included (i) concordance of PIILIF between paired cNAS and balding biopsies; (ii) associations with age category, Norwood stage, treatment resistance, and ethnicity; (iii) association of trichoscopic features with histologic PIILIF; (iv) clinical response to multimodal therapy in AGA PIILIF; and (v) frequency of histologic seborrheic dermatitis.

Exploratory analyses evaluated associations between individual treatment components and improvement. Results are presented under the prespecified subheadings: Patient Demographics and Trichoscopic Findings; Histologic and Immunohistochemical Findings; Biopsy Concordance Between cNAS and Balding Zones; Demographic and Clinical Correlates; Treatment Response; and Nape Lesions and Scarring Alopecia Overlap.

Treatment and Response Evaluation

Patients with histologic PIILIF received a combination regimen adapted from PCA protocols. Therapy included topical calcineurin inhibitors (tacrolimus or pimecrolimus),^{23,24} oral tetracyclines (doxycycline or minocycline, 100 mg twice daily for up to six months),^{25,26} and topical or oral phytoactive anti inflammatory agents (Gashee[®], FineTouch Laboratories Inc., California).^{27,28} Hormonal therapy included oral finasteride (1 mg/day) or dutasteride (0.5 mg/day)^{29,30} and oral minoxidil (2.5 mg/day for men, 1.25 mg/day for women).³¹ Therapeutic analysis included only patients with at least 6 months of continuous treatment and photographic follow up; those with less than 6 months were excluded. The primary outcome, global clinical improvement, was assessed at the first visit at least 6 months after regimen initiation; if multiple eligible visits were available, the latest was used.

Follow up duration was recorded in months from treatment initiation to the last on treatment visit for each evaluable patient.

Topical or systemic corticosteroids were discontinued in patients previously misdiagnosed with seborrheic dermatitis. Outcomes were assessed through standardized photographic comparison and global clinical evaluation. A “good” response was recorded when visible regrowth was present, including in patients with prior treatment failure.

Statistical Analysis

Comparative analyses of histologic and immunophenotypic findings between scalp zones used Fisher’s exact test. Multiple comparisons were adjusted using the step-up Hochberg method. Analyses were conducted in R. Two-tailed *p* values less than 0.05 were considered statistically significant.

Results

Patient Demographics and Trichoscopic Findings

We analyzed 129 patients with AGA; 91% were men, and the mean age was 43 years (Standard deviation 13) (Table 1). Trichoscopy showed perifollicular erythema and/or scale in 66.9% of PIILIF cases, most commonly together (44%). Findings were indeterminate in 34% and unavailable in 3.8%. Erythema typically blanched under light dermoscopic pressure (Supplementary Video 1). Prior labeling as seborrheic dermatitis differed between groups (Table 1, *p* = 0.039), but trichoscopic redness or scale did not predict histologic PIILIF (overall *p* = 0.6). Representative cNAS trichoscopy perifollicular erythema and fine scale is shown in Figure 1. Groups were defined histologically as AGA-PIILIF and AGA-only.

Table 1 Demographic and Clinical Characteristics Stratified by Histology Group

Parameter	*All cNAS Biopsies (n =129)	*AGA-PIILIF (n=106)	*AGA-only (n=23)	**P value comparing AGA-PIILIF to AGA-only
Patient characteristics				
Mean Age (SD)	43 (13)	44 (12)	39 (15)	0.044
Sex (n, %)				
Men	117 (91%)	96 (91%)	21 (91%)	>0.9
Women	12 (9.2%)	10 (9.4%)	2 (8.7%)	>0.9
Ethnicity (n, %)				
Ethnicity				
African-descent	16 (12%)	13 (12%)	3 (13%)	0.2
Asian (East Asian/Indian Subcontinent)	17 (13.2%)	10 (9.4%)	7 (30%)	0.004
White	67 (52%)	57 (54%)	10 (43%)	0.2
Hispanic	17 (13%)	15 (14%)	2 (8.7%)	0.4
Middle Eastern	12 (9.3%)	11 (10%)	1 (4.3%)	0.053
Clinical history				
Traumatic grooming practices [†]	12 (9.4%)	7 (6.7%)	5 (22%)	0.04
Hair Loss Level:				
NW 2-4	36	24 (23%)	12 (52%)	0.004
NW 5-7	82	73 (69%)	9 (39%)	0.007
Prior Surgical Events (Poor Regrowth)				0.038
Yes		57 (54%)	7 (30%)	
Unknown		0	1	
Misdiagnosed Seborrheic Dermatitis				0.039
No		70 (67%)	11 (48%)	
Unsure		0	1 (4.3%)	
Yes		35 (33%)	11 (48%)	
Unknown ^{††}		0	0	
Trichoscopy (Perifollicular)				0.6
Erythema		19 (19%)	5 (23%)	
Scales		3 (2.9%)	1 (4.3%)	
Erythema + Scales		45 (44%)	11 (50%)	
Non-Specific		35 (34%)	5 (23%)	
Unknown ^{††}		4 (3.8%)	1 (4.3%)	

Notes: Results are presented as n (%) unless otherwise stated. *Mean (SD); n (%) **P values for continuous variables were calculated using the Wilcoxon rank-sum test; p values for categorical variables were obtained using Pearson's chi-square test. Raw p-values were adjusted for type I error using the step-up Hochberg procedure for expected low frequencies. [†]Traumatic grooming practices include braids, chemical relaxers, permanent dyes, and hot combs. ^{††}Unknown" = Missing/Unknown categories are displayed descriptively and excluded from hypothesis testing.

Abbreviations: AGA, Androgenetic alopecia; cNAS, Clinically non-alopecic scalp; PIILIF, Perifollicular Infundibulo-isthmic lymphocytic infiltrates and fibrosis; SD, Standard deviation.

Histologic Findings

PIILIF was present in cNAS in 81% of patients (95% CI, 74.9–87.1). Fibrosis, when present, was usually subtle as mild peripilar collagen thickening confirmed by α -SMA; Overt concentric lamellar scarring was uncommon. Most diagnoses were established with a single biopsy; two patients required a second sample. Twenty-three patients (18%) showed no histologic PIILIF. PIILIF occurred in 23% of Norwood 2–4 cases (Table 1), supporting its presence in earlier AGA stages rather than a feature limited to advanced stages. Representative paired histologic micrographs from cNAS and balding zones demonstrating infundibulo-isthmic lymphocytes and early perifollicular fibrosis are shown in Figures 2 and 3.

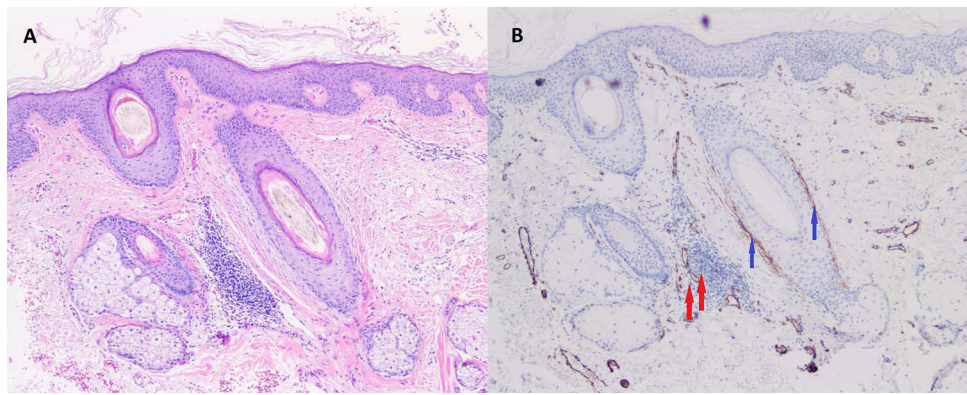


Figure 2 Hematoxylin and eosin staining (A) and α -SMA staining (B) of the vertical section taken from the cNAS biopsy specimen of an AGA-PIILIF patient, showing perfollicular lymphocytic infiltrates involving the infundibulo-isthmic zone (Red arrows). There is perfollicular fibrosis (Blue arrows). Magnification 4x.
Abbreviations: SMA, Smooth muscle actin; cNAS, Clinically non-alopecic scalp; AGA, Androgenetic alopecia; PIILIF, Perifollicular Infundibulo-isthmic lymphocytic infiltrates and fibrosis.

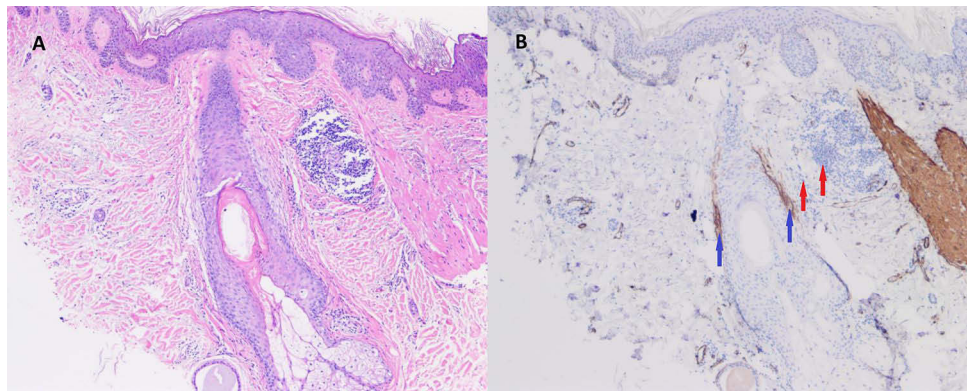


Figure 3 Hematoxylin and eosin staining (A) and α -SMA staining (B) of the vertical section of a balding zone biopsy specimen from the AGA-PIILIF patient of Figure 2A and B showing perfollicular lymphocytic infiltrates involving the infundibulo-isthmic zone (Red arrows). There is perfollicular fibrosis (Blue arrows). Magnification 4x.
Abbreviations: SMA, Smooth muscle actin; cNAS, Clinically non-alopecic scalp; AGA, Androgenetic alopecia; PIILIF, Perifollicular Infundibulo-isthmic lymphocytic infiltrates and fibrosis.

Among 21 patients with paired biopsies, findings were concordant in all cases (Figures 2–3, Table 2, [Supplementary Table S1](#) and [S2](#)). In those with paired PIILIF biopsies, upper-perifollicular lymphocytes and fibrosis appeared in both zones, and non-lymphocytic patterns were not seen. Among continuous measures in the paired-biopsy cohort, only the anagen:telogen–catagen ratio differed significantly between cNAS and balding sites (mean $\pm$ SD 6 ± 9 vs 12 ± 10 ; paired signed-rank $p = 0.03$). The continuity-corrected T:V ratio was lower in balding zones (6.2 ± 3.4 vs 10.5 ± 8.0) but did not

Table 2 Key Histologic Concordance Between cNAS and Balding Sites in AGA–PIILIF (n = 18 Pairs)

Feature	cNAS n/N (%)	Balding n/N (%)	**p value
Infundibulo-isthmic perfollicular lymphocytes (upper follicle above arrector pili insertion)	17/18 (94)	18/18 (100)	>0.9
Infundibulo-isthmic perfollicular fibrosis (upper follicle above arrector pili insertion)	18/18 (100)	18/18 (100)	>0.9
Peribulbar lymphocytes (lower follicle, hair bulb region)	6/18 (33)	6/18 (33)	>0.9

(Continued)

Table 2 (Continued).

Feature	cNAS n/N (%)	Balding n/N (%)	**p value
Complete sebaceous gland loss	3/18 (17)	2/18 (11)	>0.9
**Anagen: telogen-catagen ratio, mean (SD)	6 (9)	12 (10)	0.03
***Terminal hair: Vellus hair Ratio (SD)	6.3 (3.4)	10.5 (8.0)	0.051

Notes: Infundibulum/isthmus defined as the upper follicle from the ostium to the arrector pili insertion. Bulbar region defined as the lower follicle including the suprabulbar segment and hair bulb. *Mean (SD); n (%). ** P values for continuous variables were calculated using the Wilcoxon signed-rank test; p values for categorical variables were obtained using exact paired test. Raw p-values were adjusted for type I error using the step-up Hochberg procedure for multiple comparisons. Values are paired observations from the same patients. Exact tests were applied as prespecified in Statistical Analysis. Full variable list and detailed descriptors are provided in [Supplementary Table S1](#).

Abbreviations: cNAS, clinically non-alopecic scalp; AGA, androgenetic alopecia; PIILIF, perifollicular infundibulo-isthmus lymphocytic infiltrates and fibrosis; SD, Standard deviation.

reach statistical significance (paired Wilcoxon $p = 0.051$; Hochberg-adjusted $p > 0.05$). This directional difference reflects greater follicular miniaturization in the balding area but did not reach statistical significance after adjustment for multiple testing. Detailed features for the 18 paired AGA-PIILIF cohorts appear in [Supplementary Table S1](#). The remaining 3 of the 21 patients, PIILIF was absent in the cNAS or balding zones and are designated AGA-Only ([Supplementary Table S2](#)). Overall, 106 were AGA-PIILIF, and 23 AGA-only.

Compared with PIILIF in cNAS of patients with AKN, PIILIF in the cNAS of AGA showed a higher rate of peribulbar lymphocytosis (20% vs 0%, $p = 0.013$; [Supplementary Table S3](#)).

Seborrheic dermatitis was confirmed histologically in only 1 of 129 cNAS biopsies, and anti-dandruff shampoo use showed no association with trichoscopic findings or PIILIF on biopsy, arguing against seborrheic dermatitis as a confounder.

Demographic and Clinical Correlates

AGA-PIILIF was more common in patients aged 44 years or older, in Norwood stage 5 or greater, and in those with prior poor response to standard therapy or transplant failure. AGA-only predominated in younger patients (≤ 39 years) and Norwood 2–4. East Asian and South Asian patients were less likely to show AGA-PIILIF ($p = 0.004$). Traumatic grooming practices were uncommon ($<10\%$) and not associated with AGA-PIILIF ([Table 1](#)).

Treatment Response

Patients with less than six months of therapy (5%) were excluded from response analyses. Among evaluable patients, mean follow-up was 9.7 months (SD 3.0). Of 106 AGA-PIILIF patients treated with combined hormonal and anti-inflammatory therapy, 67% improved and 2% had suboptimal outcomes ($p < 0.0001$) ([Figures 4](#) and [5](#)). After accounting for 16% loss to follow-up and 5% with insufficient duration, the benefit remained statistically significant. Among patients with prior treatment failure, 64% improved ($p = 0.009$). Improvement was associated with topical phytoactives ($p = 0.001$), oral phytoactives ($p = 0.009$), topical calcineurin inhibitors ($p = 0.022$), minocycline ($p = 0.041$), and dutasteride ($p = 0.043$).

Nape Lesions and Scarring Alopecia Overlap

Nine patients with subtle nuchal erythema ([Figure 6](#)) underwent targeted biopsy: five had AKN (all white men of European descent), two showed PIILIF features, and two had no diagnostic abnormality. All five AKN patients had Norwood stage 4 or higher and attributed their nuchal symptoms of occasional flakes to dandruff.

Immunohistochemistry

PIILIF-positive sites showed CD4-predominant T cells, increased CD117-positive mast cells, and α -SMA expression indicative of early fibrotic remodeling. This immunoprofile was consistent across cNAS, balding scalp, subtle nape zones

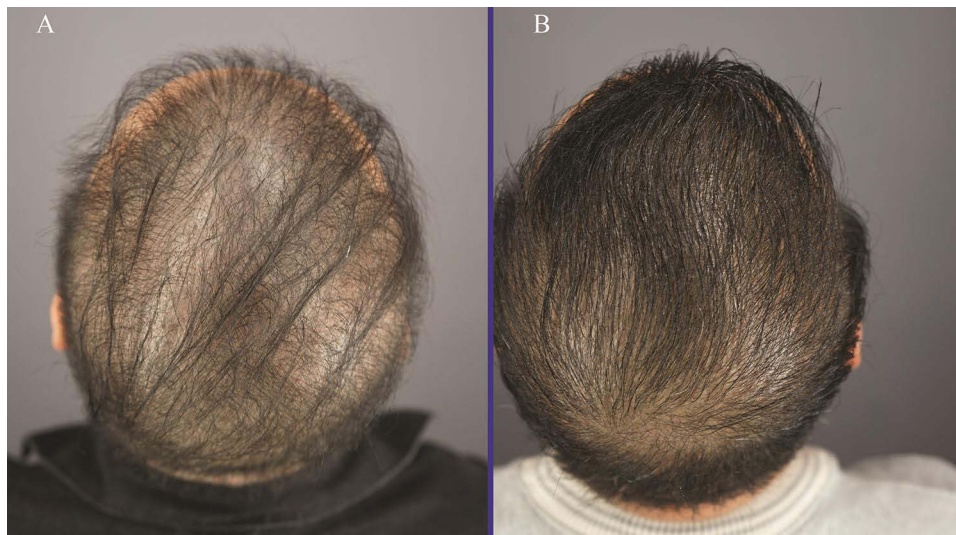


Figure 4 AGA-PIILIF Patient with NW 6 zone of thinning: 1 year after multiple hair transplant surgeries with suboptimal yields and several years of topical minoxidil, oral finasteride, and ketoconazole shampoo (**A**); Six months after switching to multimodal AGA-PIILIF therapy with oral and topical phytoactives, topical tacrolimus, oral minoxidil, and oral dutasteride (**B**).

Abbreviations: AGA, Androgenetic alopecia; PIILIF, Perifollicular Infundibulo-isthmic lymphocytic infiltrates and fibrosis.



Figure 5 Patient with Norwood 6 zone of thinning who presented requesting a hair transplant after failed attempts to restore hair using platelet-rich plasma injections. Before multimodal AGA-PIILIF treatment (**A**); Six months after using oral and topical phytoactive, topical tacrolimus, oral dutasteride, oral minoxidil, and minocycline (**B**).

Abbreviations: AGA, Androgenetic alopecia; PIILIF, Perifollicular Infundibulo-isthmic lymphocytic infiltrates, and fibrosis.

with AKN on biopsy (Figure 7; [Supplementary Tables S4](#) and [S5](#)), and beard regions. Representative CD4, CD8, and CD117 stains are shown in Figure 7. Demodex and Pityrosporum prevalence did not differ between groups.

Discussion

This study identifies a reproducible and clinically meaningful histopathologic endotype within AGA, defined by PIILIF. It occurred most often in patients aged 44 years or older, at Norwood stage 5 or higher, and in those with treatment resistance or post-transplant failure. The pattern is anatomically confined to the perifollicular infundibulo-isthmic unit and immunologically active, distinguishing it from the nonspecific changes associated with follicular miniaturization seen in AGA.

PIILIF Differential Diagnosis

Nonspecific AGA-Associated Changes

PIILIF in AGA should be distinguished from the nonspecific histologic findings of typical AGA, such as fibrous streamers or mild perivascular lymphocytic infiltrates.¹² These changes are often interpreted as sequelae of follicular regression rather than true perifollicular disease. In contrast, PIILIF localizes to the perifollicular infundibulo-isthmic

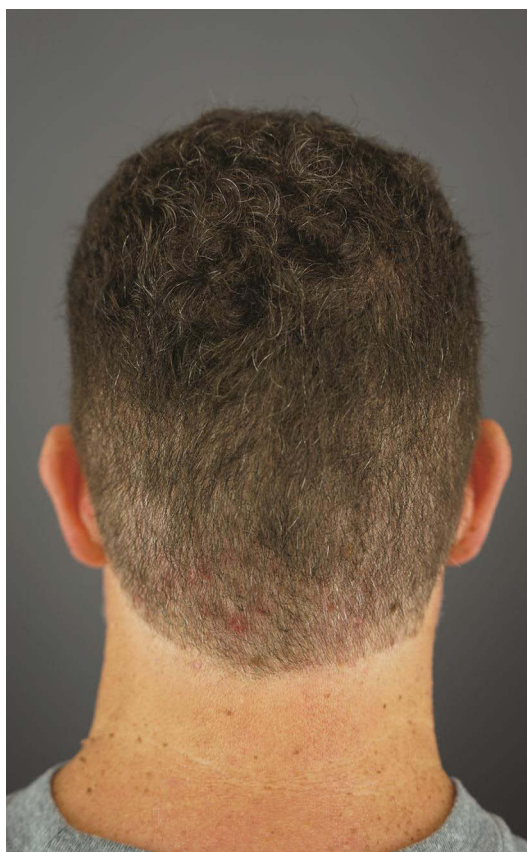


Figure 6 European-descended white men with AGA-PIILIF presenting with mild erythematous papules in the nape zone and Norwood 5-pattern hair thinning. Biopsy of the nuchal area revealed histologic features diagnostic of acne keloidalis nuchae (AKN), illustrating a subclinical AGA-PIILIF-AKN overlap phenotype. Image adapted from: Umar S, Ton D, Carter MJ, Shitabata P. Unveiling a shared precursor condition for acne keloidalis nuchae and primary cicatricial alopecias. *Clin Cosmet Investig Dermatol*. 2023;16:2315–2327. <https://doi.org/10.2147/CCID.S424135>. Licensed under CC BY-NC (Creative Commons Attribution-NonCommercial 4.0 International License).¹⁶

Abbreviations: AGA, androgenetic alopecia; PIILIF, perifollicular infundibulo-isthmic lymphocytic infiltrates and fibrosis; AKN, acne keloidalis nuchae.

unit of intact follicles and can precede miniaturization. Prior studies documented dense perifollicular lymphocytic and mast cell aggregates at this level with ultrastructural epithelial injury near the bulge.¹³ Donor-area analyses during transplantation likewise revealed moderate to dense perifollicular lymphocytes and fibrosis around the infundibulo-isthmic region in the occiput, a pattern linked to reduced graft survival when anti-inflammatory therapy was not used.¹⁴ Contemporary dermatopathology series reaffirm this anatomic signature, with inflammation clustering at the infundibulum and isthmus rather than around the bulb, and spongiosis, when present, confined to the upper follicle.¹⁵ Collectively, these findings define PIILIF as a CD4-predominant perifollicular infundibulo-isthmic inflammatory endotype detectable in cNAS and sharing features with early PCAs.^{16–21}

PIILIF as a Parallel Inflammatory Endotype Within AGA

The T:V ratio, traditionally used to gauge miniaturization in AGA, confirmed the expected gradient between balding and cNAS in our cohort. The modest reduction in balding zones indicates that miniaturization coexists with, rather than explains, the perifollicular inflammation and early fibrosis that define PIILIF. Perifollicular inflammatory signatures were also present where the ratio remained within non-balding ranges, supporting PIILIF as a subclinical perifollicular inflammatory endotype that can precede visible AGA miniaturization.

Distinguishing PIILIF from Classic PCAs

PIILIF differs from classic PCA entities, such as lichen planopilaris (LPP), both clinically and histologically. In this study, cNAS biopsies were taken from scalp without visible alopecia, whereas classic PCAs like LPP present with clinically evident lesional hair loss and overt activity.³² Miniaturized hairs and lower T:V ratios in balding compared with

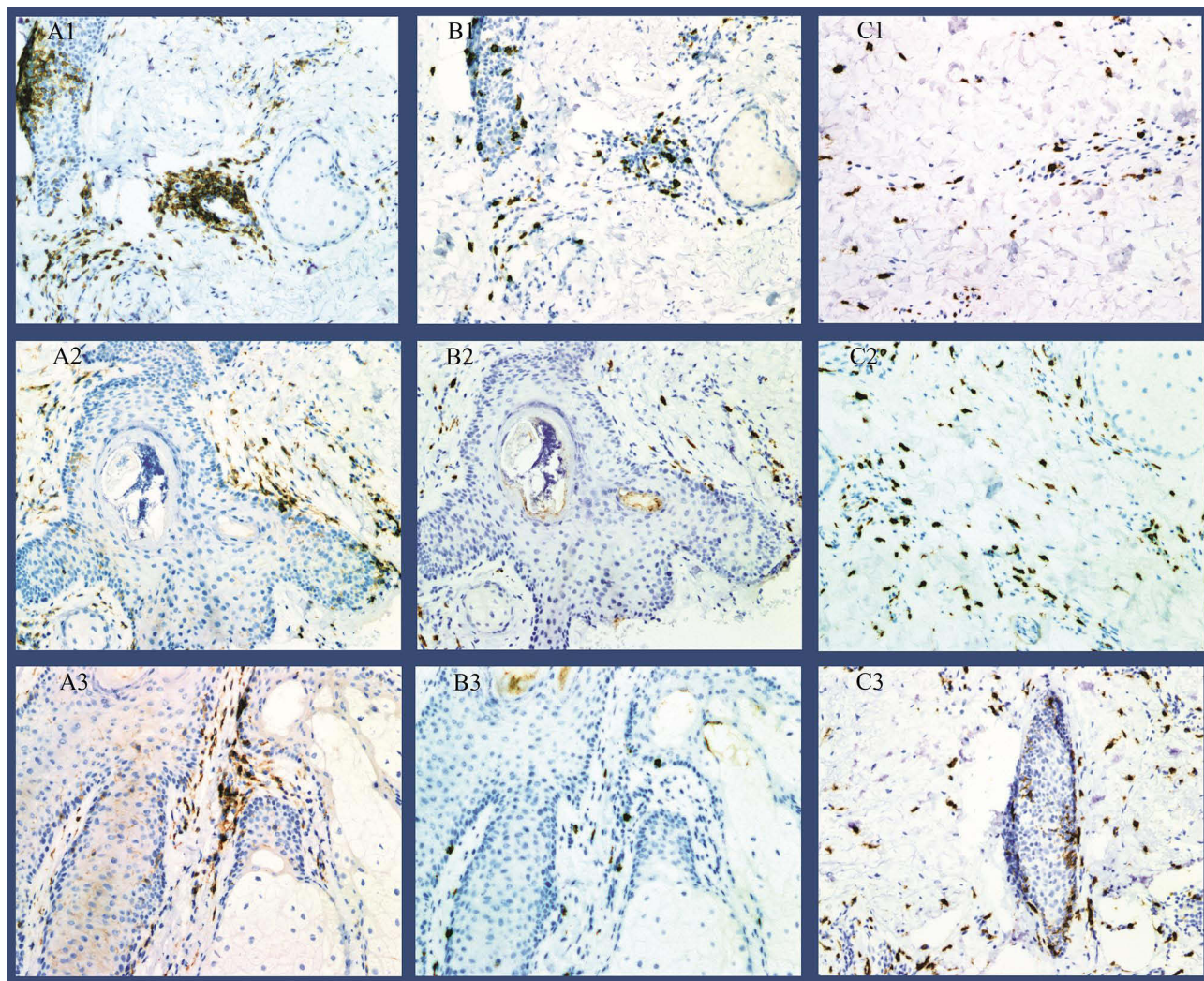


Figure 7 Immunohistochemistry of a single patient with AGA-PIILIF showing CD4 (A columns), CD8 (B columns), and CD117 (C columns) taken from the cNAS PIILIF zone (A1, B1, C1); The Balding zone (A2, B2, C2) and Beard zone (A3, B3, C3).

Abbreviations: AGA, androgenetic alopecia; PIILIF, perifollicular infundibulo-isthmic lymphocytic infiltrates and fibrosis; cNAS; clinically non-allopecic scalp.

cNAS among PIILIF-positive cohorts confirm concurrent AGA in the balding zones (Table 2) and support PIILIF as a subclinical perifollicular inflammatory process that accompanies rather than replaces AGA. In cNAS, inflammation was low-grade and confined to the perifollicular infundibulo-isthmic unit, which explains its clinical silence until field-level miniaturization crosses the threshold for visible thinning. Sebaceous gland loss, typical of established PCA, was uncommon at 11 to 17%, which supports an early or subclinical stage.³³ The combination of upper-unit restriction and preserved sebaceous units mirrors the incipient zones described in LPP and FFA, whereas gland loss together with concentric lamellar fibroplasia has been linked to clinically scarred and less reversible disease.³³

Distinguishing PIILIF from Seborrheic Dermatitis

Misclassification of PIILIF as seborrheic dermatitis is common. Many patients presented with flaking or scale, yet true seborrheic dermatitis was confirmed histologically in only 0.8% of our cohort, while PIILIF was present in 81%, as shown in Table 1. Both conditions can show a similar pattern of redness and scale. While anti-dandruff shampoos may briefly reduce surface erythema or scale through antimicrobial or anti-inflammatory effects,^{34–36} they do not treat the perifollicular lymphocytic inflammation and early fibrosis that define PIILIF. In several patients, PIILIF progressed while

the surface appeared calmer. Lasting improvement occurred only after a diagnostic biopsy confirmed PIILIF and therapy was redirected to target both inflammation and androgens.

In our series, neither perifollicular erythema nor scale predicted histologic PIILIF, which supports routine biopsy of perifollicularly abnormal units in resistant or ambiguous cases.

AKN Overlap and Site-Specific Expression

PIILIF was also identified in nuchal biopsies where subtle erythema had been labeled seborrheic dermatitis. Several of these cases proved to be AKN or showed overlap with PIILIF, particularly among white men of European descent.¹⁶ CD4-predominant perifollicular lymphocytes and CD117-positive mast cells in these lesions support an immunopathologic continuum that links PIILIF, AGA, and AKN, as shown in [Figures 6 and 7](#) and in [Supplementary Tables S4 and S5](#). These findings suggest that anatomic site, host background, and immune reactivity can shape clinical expression and point to a shared perifollicular inflammatory substrate across PCAs.

Fibrosing Alopecia of Patterned Distribution (FAPD) as a Later Stage Within the AGA-PIILIF Continuum

FAPD was first described from retrospective review of archived balding-zone specimens without standardized histologic criteria or paired sampling of non-balding scalp.^{37,38} That series reported lichenoid lymphocytic inflammation at the infundibulum and isthmus with perifollicular lamellar fibrosis in nearly all cases and miniaturization consistent with AGA. In our cohort, AGA-PIILIF was identified through standardized paired biopsies from balding and cNAS, showing a consistent perifollicular infundibulo-isthmic immune pattern and resistance to standard AGA therapy. Histology across AGA-PIILIF formed a continuum from mild perifollicular collagen thickening, confirmed by α -SMA staining, to concentric lamellar fibrosis in both balding and cNAS sites. When seen only in a balding-zone specimen, this advanced perifollicular fibrosis matches the original description of FAPD and represents a later stage within the AGA-PIILIF spectrum rather than a separate disorder. Recognizing this relationship supports a unified diagnostic framework. For clinical clarity, we recommend replacing FAPD with AGA-PIILIF, staged by the degree of perifollicular fibrosis from early collagen thickening to concentric lamellar scarring. Diagnosing AGA-PIILIF before concentric lamellar fibrosis, which signals a less reversible stage,³³ may allow earlier and more effective intervention.

Immunophenotype

PIILIF in AGA shows a CD4 predominant perifollicular lymphocytic infiltrate with increased CD117 positive mast cells and early α -SMA positivity. This immunoprofile is documented in LPP, CCCA, and FFA^{39–41} and was replicated in our AKN series.¹⁶ Within AGA, the same perifollicular signature supports PIILIF as a regulated inflammatory endotype that is more aligned with PCAs than with long standing AGA related miniaturization or aging, as detailed in [Supplementary Tables S3–S5](#).

Diagnostic Pitfalls

Lack of Standardization in Earlier AGA Studies

Earlier AGA studies rarely combined standardized trichoscopy-guided site selection, paired sampling from balding and cNAS, and both vertical and transverse sections.^{13–15} This methodological gap likely under-detected the upper-unit signal that becomes more apparent with our protocol.^{42,43}

Recognizing a Subtle Perifollicular Signal

AGA-PIILIF can be clinically quiet. Erythema often blanches with gentle dermoscopy pressure and fine perifollicular scale may be minimal, as illustrated in the Supplemental Video.¹⁶ In our cohort, perifollicular erythema and/or scale were present in 66.9% of AGA-PIILIF cases, yet no single trichoscopic feature predicted histologic PIILIF ($p = 0.6$; [Table 1](#)). This justifies a low threshold to biopsy perifollicularly abnormal units in resistant or ambiguous cases.

Sectioning Strategy and Sampling Plane

Because the change occupies a thin rim around the infundibulo-isthmic unit, detection is plane-dependent. Using combined vertical and transverse sections improves visualization but does not eliminate sampling limitations.^{42,43}

This is a frequent reason for false-negative reads when only one plane is used or the wrong transverse level is sectioned.

When H&E is Equivocal, Use α -SMA

When fibrosis is not readily appreciable on H&E, α -SMA highlights early perifollicular myofibroblast activity, epithelial-mesenchymal transition and incipient fibrosis.⁴⁴ Applying α -SMA in perifollicularly abnormal units reduces, but does not eliminate, the risk of under-calling early disease,⁴⁴ which may be missed if the section plane passes above or below the peripilar collar.

Equivocal Collagen Change: Prioritize Clinicopathologic Correlation

If the characteristic perifollicular lymphocytic pattern is present but collagen change is subtle, treat the clinicopathologic picture as a whole. In AGA with treatment resistance or recurrent transplant failure, suspicion for PIILIF is appropriate and steroid-sparing anti-inflammatory measures alongside Dihydrotestosterone (DHT) blockade can be started with close follow-up.³⁹ Early recognition matters because reversibility diminishes once lamellar fibrosis and clinically evident scarring develop.³⁹

Value of Repeat Biopsy

AGA-PIILIF was occasionally detected only on repeat biopsy. In our series, inflammation in cNAS tended to be low-grade and smoldering, and symptoms such as pruritus or dandruff-like scale were not associated with histologic PIILIF ($p = 0.6$; [Table 1](#)). Persisting clinical suspicion should prompt re-sampling of a perifollicularly abnormal unit.

Procedure-Triggered Expression

A primed perifollicular immune milieu may declare itself after procedural trauma. Reports of post-transplant emergence of classical PCA alopecias in susceptible individuals support this risk and underscore the value of pre-procedural biopsy when trichoscopy shows perifollicular abnormality.^{8–11}

Unassessed Confounders in Trichoscopy Appearance

The potential impact of prior or ongoing topical treatments on trichoscopy appearance was not evaluated in this study. This limitation should be acknowledged when interpreting a visually quiet scalp in patients with compatible histology.^{13–15}

Mechanistic Framework

AGA-PIILIF appears to arise from a hormonal-immune-fibrotic axis centered on DHT, interleukin (IL)-6, and transforming growth factor (TGF) β . As part of canonical AGA biology, DHT upregulates IL-6 in dermal papilla cells, which contributes to follicular miniaturization and, in a subset of patients, supplies the upstream signal that recruits CD4+ T cells and CD117+ mast cells to the infundibulo isthmic unit⁴⁵ evident in both balding and cNAS ([Supplementary Table S4](#)). IL-6 then signals through its receptor complex, including IL 6R, soluble IL 6R, and gp130 expressed widely on follicular epithelium,⁴⁵ amplifying early myofibroblast activity and a thin rim of subtle perifollicular fibrosis. This pattern localizes to the upper follicle and provides the immunologic context in which PIILIF can coexist with AGA.

The dermal papilla locus offers a biologic rationale for the higher rate of peribulbar lymphocytosis we observed in AGA-PIILIF compared with cNAS PIILIF within AKN (20% versus 0%, $p = 0.013$; [Supplementary Table S3](#)).

Downstream, tumor necrosis factor- α , interferon- γ , and profibrotic mediators including TGF- β and components of the JAK-STAT pathway⁴⁶ promote myofibroblast differentiation and early perifollicular fibrosis confined to the infundibulo-isthmic unit. This upper-unit restriction contrasts with the deeper injury profile of AKN, which shows greater root sheath desquamation ($p = 0.03$) and more frequent sebaceous gland loss ($p < 0.001$).¹⁶

Therapeutically, because DHT drives IL-6 expression in dermal papilla cells, reduction of DHT can plausibly attenuate IL-6-mediated recruitment of CD4 T cells and mast cells at the infundibulo-isthmic unit and is consistent with clinical benefit from dutasteride in our cohort. Once established, however, PIILIF may persist independently of DHT, which helps explain plateaus or regression on finasteride or minoxidil monotherapy over time.^{1,3–5}

Our data do not support a linear progression among alopecia types. Rather, PIILIF behaves as a parallel, subclinical perifollicular inflammatory endotype that can coexist with AGA. Procedural trauma, including hair transplantation, may amplify this primed state, contributing to graft failure or the emergence of overt PCA phenotypes such as LPP, FFA, or DCS.^{6–8,11} These observations support a dual-pathway strategy that addresses both hormonal drivers that are DHT-dependent and immune-fibrotic drivers that involve IL-6, TGF- β , and JAK–STAT.

Therapeutic Implications

Within AGA, PIILIF represents a PCA-like inflammatory substrate characterized by CD4-predominant lymphocytes, increased CD117 mast cells, and early α -SMA-positive stromal change (Figures 2–3; Table 2; [Supplementary Table S4](#)). Standard AGA regimens do not address this biology. In our cohort, adding PCA-style anti-inflammatory and anti-fibrotic measures (tetracyclines, topical calcineurin inhibitors, selected botanicals) to DHT blockade was associated with better outcomes, including after prior treatment failure.^{23–31} Representative responses are shown in Figures 4 and 5. Chronic topical corticosteroids were avoided to favor long-term, steroid sparing control of a low grade, persistent perifollicular process.

Dutasteride outperformed finasteride,^{30,47} likely through more complete DHT suppression and secondary IL-6 attenuation. Persistence of fibrosis despite DHT reduction supports direct treatment of the inflammatory axis.^{23–31,48} Clinically, the T:V ratio captures field miniaturization, whereas PIILIF marks the perifollicular inflammatory substrate that can hasten this process; early recognition enables earlier, targeted therapy and better durability. Pre-transplant control of PIILIF and biopsy-informed planning are advisable.

Systemic and Demographic Considerations

AGA-PIILIF also involved beard and eyebrow in some patients, supporting a broader perifollicular inflammatory phenotype and a unifying lichenoid folliculitis concept.⁴⁹

Given IL-6 links to systemic inflammation, the PIILIF signature could plausibly relate to cardiometabolic risk, consistent with early-onset AGA associations,^{50,51} although this remains hypothesis-generating.

AGA-PIILIF was more frequent after age 44, overlapping typical onset windows for LPP and FFA and aligning with PCA-adjacent biology.^{52,53} Environmental factors, including chronic photoexposure and cosmetic chemicals, may contribute but were not measured here. Traumatic grooming was uncommon and not associated with PIILIF in this dataset.

East and South Asian patients were less likely to exhibit AGA-PIILIF (Table 1), which may reflect population structure and environmental context, including dietary polyphenols and isoflavones.^{54–59} These observations warrant targeted study, not inference.

Limitations

Single-center, retrospective design and a cohort drawn from a referral center, thus enriched for advanced or treatment-resistant AGA limit generalizability; mean follow-up was mid-term. Paired biopsies were obtained in a subset only (n = 21), constraining precision for zone-concordance. There was no non-AGA control group, although prior studies have not identified PIILIF in healthy scalp.^{13,14} Histories of telogen effluvium were not ascertained, and no serial biopsies were performed, so temporal sequences or histologic reversibility cannot be inferred. These features should temper prevalence and response estimates and motivate larger prospective studies.

Conclusions

PIILIF is a reproducible inflammatory endotype within AGA, defined by CD4-predominant lymphocytes, increased CD117 mast cells, and early perifollicular fibrosis limited to the infundibulo-isthmic unit. It is enriched in older patients, advanced loss, and treatment resistance or post-transplant failure. Collectively, the topography, immune phenotype, and early fibrotic remodeling indicate that PIILIF may represent an early or mild, subclinical PCA phenotype that can coexist with AGA in a subset of patients. Routine trichoscopy with a low threshold for biopsy in resistant or equivocal cases is advisable, with sampling of both cNAS and balding zones using vertical and transverse sections, and use of α -SMA when

fibrosis is subtle. When PHLIF is present in AGA, outcomes appear to improve with a dual-pathway strategy that treats androgen signaling and inflammation; pre-transplant control is advisable. Prospective, longitudinal work should define durability and any systemic correlates.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article and its supplementary materials. Additional de-identified datasets are available from the corresponding author upon reasonable request.

Ethical Approval

This study was granted exemption from full review by the Western Institutional Review Board (WIRB) Copernicus Group, as it involved retrospective analysis of deidentified data from routine clinical procedures, with no plans for re-identification or patient contact. All patients provided written informed consent, including consent for the use and publication of anonymized clinical photographs. The study was conducted in accordance with the Declaration of Helsinki (1964) and its later amendments.

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