Dermatology Practical & Conceptual

Peripilar Sign in Androgenetic Alopecia: Does It Really Indicate Peripilar Infiltrate?

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ABSTRACT

Introduction: Peripilar sign (PPS) is a trichoscopic sign that was first described in androgenetic alopecia (AGA) and is thought to reflect the presence of perifollicular infiltrate (PFI) in histopathology.

Objectives: To study PPS in a cohort of patients with AGA and to assess its validity as a sign indicative of PFI.

Methods: One hundred patients with AGA (confirmed by trichoscopic examination) were recruited in this cross-sectional study. From those patients, frontal scalp biopsy was done for two subgroups, 22 patients with PPS and 23 patients without PPS. Both groups were compared as regards the presence of PFI.

Results: Peripilar sign was present in 50% of the 100 studied cases. No significant difference existed between those with and those without PPS as regards PFI. Peripilar sign was significantly more encountered in patients with skin type III ($p=0.001$). Its absence was significantly associated with lower interpretability of yellow dots ($p<0.001$) and their scores were significantly positively correlated ($r=0.498$, $p<0.001$). Peripilar sign was significantly associated with absent melanophages histopathologically ($p=0.011$).

Conclusion: Peripilar sign as a trichoscopic sign in AGA does not reflect PFI. It represents a dark color more encountered in patients with lighter skin types. This can be explained by the increased contrast between the dark PPS and the lighter surrounding skin in lighter skin types. Further studies using melanocyte markers and Masson Fontana's stain are needed to further verify the cause of this peri-follicular dark color.

Introduction

Androgenetic alopecia (AGA) is a very common type of hair loss. It is characterized by progressive miniaturization of hair follicles with shortening of the anagen phase, leading to gradual conversion of terminal hairs into vellus hairs [1]. Diagnosis is usually based on clinical examination, and trichoscopy is usually enough to confirm the diagnosis [2]. Only rarely, a biopsy may be required [3].

The main trichoscopic findings of AGA are: hair shaft diameter diversity more than 20% with an increased number of miniaturized vellus hairs, especially in the frontoparietal region, the predominance of single hair pilosebaceous units, the brown and white peripilar signs (PPSs), and the yellow dots [4].

The typical histopathological findings of AGA are a total number of follicles within the normal range, a decrease in the ratio of terminal to vellus hair, and noticeable variation of shaft diameter. A mild peri-infundibular lymphocytic infiltrate and perifollicular fibroplasia are present in some cases [5].

The PPS which is defined as the presence of a brown halo, roughly 1 mm in diameter, at the follicular ostium was first described by Deloche et al. in 2004 [6] in 90% of males and 86% of females with AGA. The authors reported that PPS significantly correlated with the perifollicular infiltrate (PFI) seen in the papillary dermis around the infundibulum and/or the sebaceous glands. However, they did not compare those with and those without PPS as regards the presence of PFI. They suggested that both PPS and PFI are early signs of AGA [6].

Since the initial explanation of PPS as a sign of PFI in AGA, no further studies were performed to validate this finding. Accordingly, the aim of the current study was to study PPS in a cohort of Egyptian patients with AGA and to assess its validity as a sign indicative of PFI by comparing AGA cases with and without PPS as regards the presence of PFI.

Methods

Patients

This cross-sectional study conformed to the ethical standards of Helsinki Declaration and was approved by the Department's Ethical Committee. An informed consent was signed by the patients for participation in the study, photography, and biopsy.

One hundred patients (of either gender) with any grade or duration of AGA who are above the age of 16 years with any Fitzpatrick's skin type were recruited from the Outpatient Clinic of the Dermatology Department, Cairo University. The diagnosis of AGA was established based on classic clinical and trichoscopic criteria [7,8]. Excluded from the study were patients with patchy hair loss, diffuse alopecia areata, cicatricial alopecia, associated inflammatory scalp disorders or collagen vascular disorders, as well as AGA patients using scalp topical steroids in the previous 2 weeks or systemic steroids in the previous month.

All hundred patients were subjected to detailed history taking including: occupation, special habits of medical importance, duration of hair loss, presence of trichodynia, application of topical minoxidil or topical steroids, hair dying, routine use of oils and creams, hair heating or straightening procedures, habitual head covering and UVR exposure. Disease severity was clinically assessed according to Hamilton and Norwood classification[9] or male pattern AGA and according to Sinclair Hair Density Scale for female pattern AGA [10].

Trichoscopic features analyzed at 20 x magnification of images were:

- Peripilar (PPS) sign: The color of PPS was graded as follows: - = absent; += yellow, ++= light brown; +++=brown.
- Pigment pattern: The honeycomb pattern was graded as follows: - =absent, += scattered in light brown color; ++=more condensed with brown color.
- Yellow dots: The color of the yellow dots was graded as follows: - = absent, += yellow, ++= light brown.
- Pinpoint white dots; evaluated as present or absent.
- White patches (localized areas of shiny fibrosis); evaluated as present or absent.
- Focal atrichia (absence of follicular openings); evaluated as present or absent.

A 4-mm punch skin biopsy was carried out for 45 patients (who consented for biopsy taking), 22 (subgroup A) with PPS in the frontal region and 23 (subgroup B) without PPS in the frontal region. The biopsy site was standardized in both groups (from the frontal area, 4 cm posterior to the anterior hairline and 1 cm lateral to scalp midline). In subgroup A, the biopsy was obtained from an area showing PPS. Biopsies were routinely fixed and processed then embedded for transverse sectioning [11]. Sectioning through the isthmus and infundibulum up to the surface epidermis was ensured. Points assessed in every biopsy were:

- Assessment of perifollicular infiltrates (PFI): The presence of PFI was evaluated in every case. For cases with PFI, the part of the follicular unit involved was documented. The density of PFI was scored as mild, moderate, or severe according to a visual analog scale (Figure 1).
- Assessment of perifollicular fibrosis (PFF): the presence of PFF was evaluated in every case. For cases with PFF, the part of the follicular unit affected by PFF was documented. The PFF was scored as mild, moderate, or severe according to a visual analog scale (Figure 2).

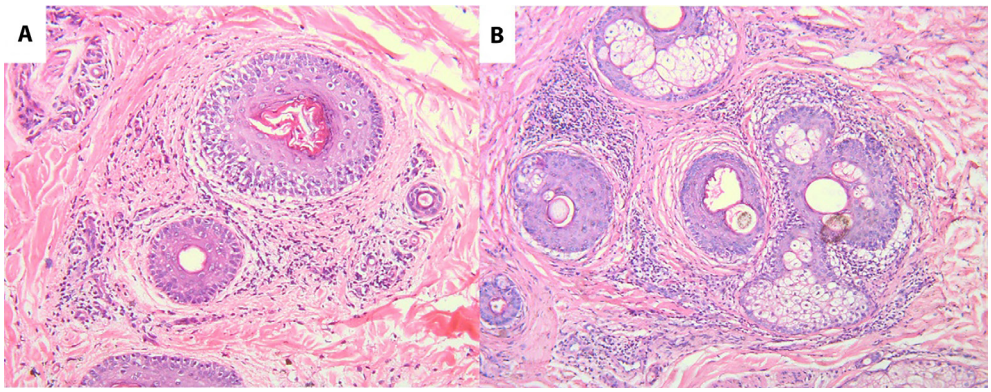

Figure 1. Visual analog scale for scoring perifollicular infiltrate (PFI). a: Mild PFI, b: Moderate PFI (H&E, original magnification X40).

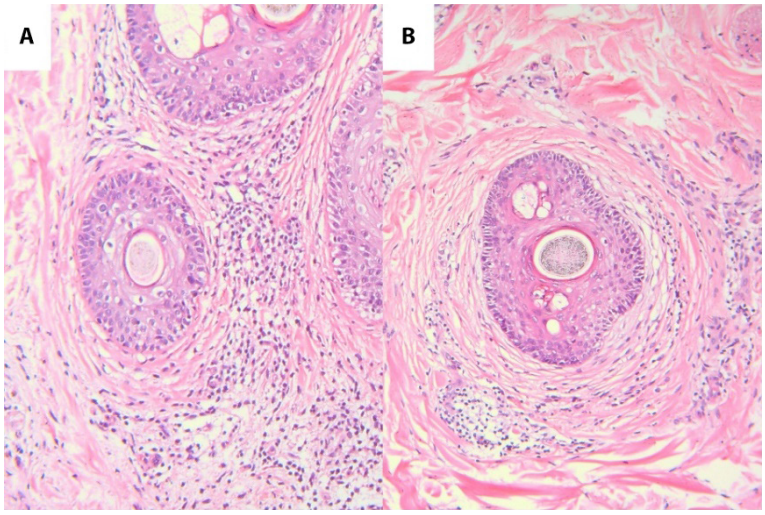

Figure 2. Visual analog scale for scoring perifollicular fibrosis (PFF). a: Mild PFF, b: Moderate PFF with broader zone of concentric fibroplasia (H&E, original magnification X40).

- Assessment of perivascular infiltrate: the presence of perivascular infiltrate was evaluated in every case, as well as its localization in the dermis. It was scored as mild, moderate, or severe according to a visual analog scale (Figure 3).
- Presence of melanophages.

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test [12]. For comparing categorical data, Chi square (χ^2) test was performed. Fisher's exact (F) test was used instead when the expected frequency is less than 5 [13]. Correlations between quantitative variables were done using Spearman correlation coefficient [14]. P-values less than 0.05 were considered as statistically significant.

Results

The studied cohort included 87 (87%) females and 13 (13%) males. Their ages ranged from 16 to 67 years with a mean ±SD of 34±11.55 years and the duration of hair loss ranged from 0.16 to 20 years with a mean ±SD of 5.07±4.73 years. Table 1 summarizes other important demographic and clinical data.

Trichoscopic findings are illustrated in table 2. Peripilar sign was detected both in the frontal and occipital areas in 50 (50%) of cases and in the occipital area only in 7 (7%) of cases (Figure 4).

Perifollicular infiltrate was present in 37 out of 45 biopsies (82.2%), being mild in density in the majority of them (89.2%). It surrounded the infundibulum in 100% of cases.

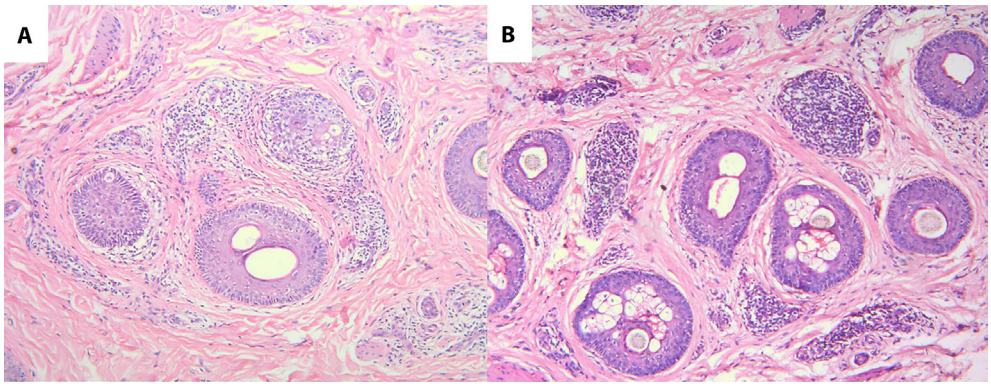

Figure 3. Visual analog scale for scoring perivascular infiltrate. a: Mild perivascular infiltrate, b: Moderate perivascular infiltrate (H&E, original magnification X40).

Table 1. Important Demographic and Clinical Data of the Studied Cohort (N=100).

			Number (%)
Occupation		Indoor worker	97 (97%)
		Outdoor worker	3 (3%)
Special habits of medical importance		Smoker	10 (10%)
		Non-smoker	90 (90%)
Trichodynia			34 (34%)
Application of topical minoxidil			24 (24%)
Application of topical steroids			3 (3%)
Use of hair dyes			15 (15%)
Use of hair straightening procedures			3 (3%)
Use of hair oils/creams			88 (88%)
Use of hot hair styling devices			8 (8%)
Head covering			85 (85%)
Exposure to ultraviolet radiation		Excessive	3 (3%)
		Routine	97 (97%)
Fitzpatrick skin type		III	38 (38%)
		IV	62 (62%)
Grade of hair loss	Females (Sinclair Hair Density Scale)	2	34 (39.1%)
		3	36 (41.4%)
		4	16 (18.4%)
		5	1 (1.1%)
		Total	87 (100%)
	Males (Hamilton and Norwood Classification)	1	1 (7.7%)
		2	2 (15.4%)
		3	3 (23.1%)
		3 vertex	3 (23.1%)
		4	2 (15.4)
		5	1 (7.7%)
		6	1 (7.7%)
		Total	13 (100%)

Table 2. Trichoscopic Findings Encountered in the Studied Cohort (n=100).

Trichoscopic Finding	Number (%)	Score	Number (%)
PPS (Frontal and occipital)	50 (50%)	Light	25(50%)
		Moderate	18 (36%)
		Dark	7 (14%)
PPS (Occipital only)	7 (7%)	Light	5 (71.4%)
		Moderate	2 (28.6%)
		Dark	0 (0%)
Pigment (honeycomb) pattern	35 (35%)	Scattered (light brown)	23 (65.7%
		Condensed (brown)	12 (34.3%)
Yellow dots	33 (33%)	Yellow	27 (81.8%)
		Light brown	6 (18.2%)
Pin-point white dots	24 (24%)		
White patches	4 (4%)		
Focal atrichia	26 (26%)		

PPS: Peripilar sign

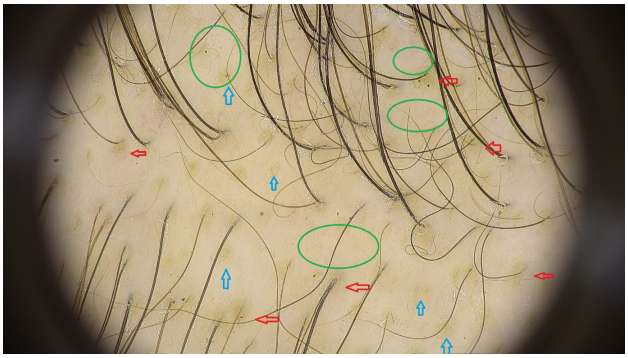

Figure 4. Trichoscopy showing PPS (red arrows); yellow dots (blue arrows) and areas of focal atrichia (green circles) (x20).

Extension around the isthmus was seen in 1 case (2.7%). Table 3 illustrates details of histopathological findings.

PPS was significantly encountered in cases with skin type III (p=0.001) and in females with Sinclair grade 3 (p=0.031). Its absence was significantly associated with the absence of yellow dots (p <0.001) and the PPS score significantly positively correlated with the yellow dots score (r=0.498, p<0.001). PPS was not significantly associated with PFI, PFF, perivascular infiltrate but it was significantly associated with the absence of melanophages (p=0.011) (Table 4, Figures 5 , 6).

Conclusion

In the studied cohort, PFI was present in 82.2% of all studied biopsies with no significant difference between those with and those without PPS indicating that PPS is not a reflection of the presence of PFI.

Although PPS has been frequently reported in AGA with frequencies ranging from 31% to 90% [6,15–17], it has also been reported in other types of hair loss not associated with PFI such as telogen effluvium [4,16–18], anagen effluvium [19] as well as in normal people [20] indicating that there must be an explanation other than PFI for PPS.

In an attempt to identify the relationship between PPS and other variables in AGA cases, we compared those with PPS and those without PPS as regards the demographic, clinical, trichoscopic and histopathological features studied in our cohort. Fitzpatrick's skin type and the presence of yellow dots significantly influenced the presence of PPS. It was significantly encountered in skin type III compared to skin type IV, as was previously reported by Kibar et al. [20]. This can be explained by the increased contrast between the dark PPS and the lighter surrounding skin in skin type III. This is compatible with the observation of Inui et al. [21] on

Table 3. Histopathological Findings in the Studied Biopsies (n=45).

Histopathological Finding	Number (%)	Density/Grade	Number (%)
Perifollicular infiltrate (PFI)	37 (82.2%)	Mild	33 (89.2%)
		Moderate	4 (10.8%)
Perifollicular (peri-infundibuar) fibrosis (PFF)	28 (62.2%)	Mild	25 (89.3%)
		Moderate	3 (10.7%)
Perivascular infiltrate	42 (93.3%)	Mild	37 (88.1%)
		Moderate	5 (11.9%)
		Upper dermis only	38 (90.5%)
		Upper and mid-dermis	4 (9.5%)
Melanophages	27 (60%)		

Table 4. Comparison Between Cases With and Cases Without Peripilar Sign (PPS)

		PPS Present (50 cases)	PPS Absent (50 cases)	P-Value
Age		36.24 ± 12.68	31.76 ± 9.92	0.106 (MW)
Gender	Female	45 (90.0%)	42 (84.0%)	0.372 (χ2)
	Male	5 (10.0%)	8 (16.0%)	
Occupation	Indoor	50 (100.0%)	47 (94.0%)	0.242(F)
	Outdoor	0 (0%)	3 (6%)	
Special habits of medical importance	Smoker	3 (6%)	7 (14%)	0.182(χ2)
	Non-smoker	47 (94%)	43 (86%)	
Fitzpatrick skin type	III	27 (54%)	11 (22%)	0.001(χ2)*
	IV	23 (46%)	39 (78%)	
Duration of hair loss		5.78 ± 5.33	4.36 ± 3.96	0.288 (MW)
Trichodynia	Present	17 (34%)	17 (34%)	1(χ2)
	Absent	33 (66%)	33 (66%)	
Application of topical minoxidil	Present	11 (22%)	13 (26%)	0.640(χ2)
	Absent	39 (78%)	37 (74%)	
Application of topical steroids	Present	2 (4%)	1 (2%)	1(F)
	Absent	48 (96%)	49 (98%)	
Use of hair dyes	Present	5 (10%)	10 (20%)	0.161(χ2)
	Absent	45 (90%)	40 (80%)	
Use of hair straightening procedures	Present	1 (2%)	2 (4%)	1(F)
	Absent	49 (98%)	48 (96%)	
Use of hair oils/creams	Present	46 (92%)	42 (84%)	0.218(χ2)
	Absent	4 (8%)	8 (16%)	
Use of hot hair styling devices	Present	4 (8%)	4 (8%)	1(F)
	Absent	46 (92%)	46 (92%)	
Head covering	Yes	44 (88%)	41 (82%)	0.401(χ2)
	No	6 (12%)	9 (18%)	
UVR exposure	Routine	50 (100%)	47 (94%)	0.242(F)
	Excessive	0 (0%)	3 (6%)	
Females grade (Sinclair Scale)	2	12 (26.7%)	22 (52.4%)	0.031(F)*
	3	24 (53.3%)	12 (28.6%)	
	4	8 (17.8%)	8 (19%)	
	5	1 (2.2%)	0 (0%)	
Males grade (Hamilton and Norwood Classification)	1	1 (20.0%)	0 (0%)	0.322(F)
	2	0 (0%)	2 (25%)	
	3/ 3 vertex	3 (60%)	3 (37.5%)	
	4	0 (0%)	2 (25%)	
	5	0 (0%)	1 (12.5%)	
	6	1 (20%)	0 (0%)	
Yellow dots	**Present**	26 (52%)	7 (14%)	<0.001 (χ2)*
	Absent	24 (48%)	43 (86%)	
		PPS Present (Subgroup A, n=22)	**PPS Absent (Subgroup B, n=23)**	**p-value**
PFI	Present	17 (77.3%)	20 (87.0%)	0.459 (F)
	Absent	5 (22.7%)	3 (13.0%)	
PFF	Present	12 (54.5%)	16 (69.6%)	0.299 (χ2)
	Absent	10 (45.5%)	7 (30.4%)	

		PPS Present (Subgroup A, n=22)	PPS Absent (Subgroup B, n=23)	p-value
Perivascular infiltrate	Present	20 (90.9%)	22 (95.7%)	0.608 (F)
	Absent	2 (9.1%)	1 (4.3%)	
Melanophages	Present	9 (40.9%)	18 (78.3%)	0.011 (χ2)*
	Absent	13 (59.1%)	5 (21.7%)	

Chi square (χ2) test or Fisher's Exact (F) test or non-parametric Mann-Whitney test (MW).
P-value is significant if <0.05*
Data is presented as mean ± SD or as number (%)
PPS: Peripilar sign PFI: Perifollicular infiltrate

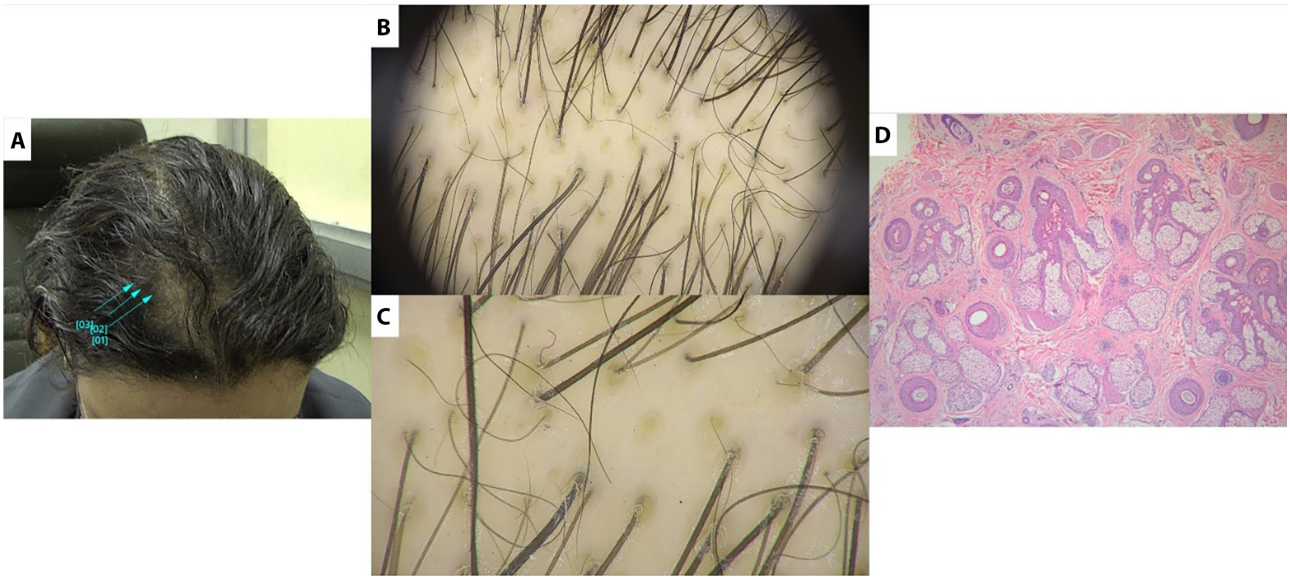

Figure 5. AGA case with peripilar sign (PPS) and no perifollicular infiltrate (PFI). (a) Clinical picture: Sinclair hair density (grade 3). (b) Trichoscopic examination (X20): hair shaft diameter diversity, PPS, and yellow dots. (c) Trichoscopic examination (X50): PPS (+++) and yellow dots (+). (d) Photomicrograph showing no PFI in relation to upper segments of hair follicles (H&E original magnification X40).

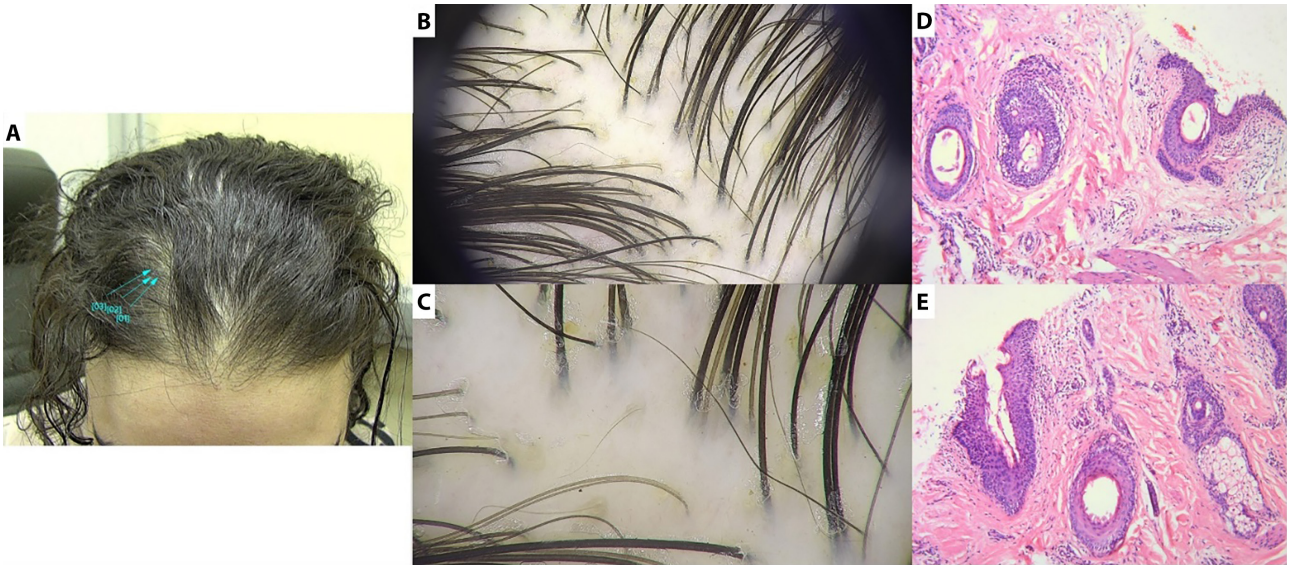

Figure 6. AGA case with peripilar sign (PPS) and perifollicular infiltrate (PFI). (a) Clinical picture: Sinclair hair density (grade 3). (b) Trichoscopic examination (X20): hair shaft diameter diversity, PPS, and yellow dots. (c) Trichoscopic examination (X50): PPS (++) and yellow dots (+). (d & e) Photomicrographs showing mild PFI related to the infundibula of hair follicles (H&E original magnification X100).

Asian population and Chiramel et al. [22] on Indian population, who both reported that darker skin colors concealed the observation of PPS. This can also explain the association between PPS and yellow dots, where PPS was absent in cases with absent yellow dots in a statistically significant manner. Interestingly, the only histopathological finding that was significantly associated with PPS was absent melanophages. This can be explained by the same principle as the presence of melanophages will convey darker skin appearance which will conceal the PPS.

Most Western literature mentions PPS and yellow dots as one of the diagnostic criteria in AGA, however in our population of skin of color (SoC), we speculate that brown or yellow colors on the scalp may not be well visualized and accordingly these two signs are not reliable as diagnostic signs in AGA.

No demographic or clinical features significantly influenced the presence of PPS. The significant association with Sinclair score 3 in female cases mostly reflects the higher percentage of this score among our cohort rather than a true association. In a previous study[20], PPS was found to be related to low severity in male pattern AGA, but not correlated at all to severity of female pattern AGA. Such outcome would indicate that this is not a consistent finding to depend upon.

We hypothesize that PPS is a form of dark color around the follicular openings that appears more obviously in lighter skin types. It is known that ultraviolet rays stimulate inactive melanocytes in the outer root sheath [23] and this may explain PPS in AGA cases due to the increased effect of UVR on the balding skin. Perifollicular infiltrate may stimulate the melanocytes too [21]. Further studies using melanocyte markers and Masson Fontana's stain are needed to further verify the cause of this peri-follicular dark color.

Limitations of the Study

- The lack of comparison with normal healthy controls or patients with other non-scarring hair loss disorders represents a limitation in this study.
- Not all patients consented for scalp biopsy.

PPS in AGA appears to be unrelated to PFI. Skin of color conceals pigmented trichoscopic findings such as PPS and yellow dots which in turn should not be considered as diagnostic criteria for AGA in dark-skinned patients.

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