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Correlation of clinical and trichoscopy features with the degree of histologic inflammation in lichen planopilaris and frontal fibrosing alopecia in a cross-sectional study

To The Editor: Follow-up assessment of primary cicatricial alopecia inflammatory activity is a major challenge in clinical practice. Symptoms, signs, clinical extent of involvement, and pull tests are used to assess the disease activity of lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA) in different scores such as LPPAI, FFASI, FFASS, and ALODEXFFA.[1-4] However, many of these scoring systems rely on clinical parameters without trichoscopic or histopathologic correlation.

We performed a 5-years observational, cross-sectional study of treatment-naive patients presenting for possible LPP or FFA at a hair loss clinic.

During the first visit, patients were clinically and trichoscopically assessed by 3 independent examiners who completed a form with findings from the area of greatest clinical inflammation. Scalp 4-mm punch biopsies (horizontal and vertical sections) were performed from this area on the same day. The sections were read blindly and independently by 2 experienced dermatopathologists.

The analysis of the intensity of perifollicular inflammatory infiltrate was performed in 3 ways. Expert dermatopathologist opinion graded as none, mild, moderate, or severe. The assessment per microscopic field of 400× was according to the size that the infiltrate occupied (mild: up to half of the field; moderate: from half to less than the whole field; and severe: whole field or more). The section with the most robust perifollicular infiltrate was photographed with a microscope. The area of the infiltrate was measured with the Image J program in micrometers.[2]

Correlations were tested for the null hypothesis by Spearman's test. The pairs of variables that obtained significance ($P < 5\%$) were tabulated with the significance information and the corresponding correlation coefficient (Spearman's Rho).

A total of 103 patients enrolled in the study, 94 patients had a diagnosis of LPP or FFA confirmed by histology (27 LPP and 67 FFA). The results of demographic, clinical, trichoscopy, and histopathology data are in Tables I and II.

The correlation between subjective and microscopic field assessments had a strong direct correlation with the measurement of inflammatory infiltrate by area (correlation coefficient 0.84; $P = .00$ and correlation coefficient 0.83; $P = .00$, respectively). Therefore, the opinion of an experienced dermatopathologist in hair diseases and microscopic field method are simpler, practical, but still reliable approaches to assess the intensity of the inflammation, facilitating the routine of pathologists.

Comparing the clinical examination and the trichoscopy findings to the degree of histologic inflammation in LPP and FFA groups revealed no positive correlation ($P = .511$ for LPP, and $P = .624$ for FFA). Furthermore, even when the clinical variables were considered in combination, all patients with the most pronounced clinical signs and symptoms had a smaller area of inflammation compared with those of patients without clinical signs and symptoms. In our medical practice, we have observed a lack of correspondence between symptoms, signs, histopathologic inflammation and evolution during follow-up as observed in a previous study, but without histopathology information.[5]

These data are highly relevant for diagnosis, follow-up and therapeutic management, considering that none of these clinical variables translates the histopathologic inflammation at the isthmus level of both diseases, meaning they cannot be considered representative of disease activity.

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Table I. Demographic data, clinical manifestations, and trichoscopy signs of patients with lichen planopilaris and frontal fibrosing alopecia

Demographic data	LPP	FFA
Number of patients, *n* (%)	27 (29)	67 (71)
Mean age*, average (range)	54 ± 10.52 (32-79 y)	60 ± 11.88 (33-88 y)
Number in menopause, *n* (%)*	17 (63)	60 (90)
Age of menopause, average (range)	49.7 ± 3.31 (40-53 y)	45.2 ± 4.36 (36-55 y)
Phototype*	5 (40.7)	4 (38.8)
Clinical manifestations, *n* (%)		
Eyebrows alopecia*	5 (19)	60 (90)
Body hair alopecia*	4 (15)	26 (39)
Facial papules*	0	26 (39)
Lichen planus pigmentosus*	2 (7)	19 (28)
Eyelashes alopecia*	0	9 (13)
Facial erythema	0	4 (6)
Facial hypochromia	0	1 (1)
Vascular evidence on the forehead	0	1 (1)
Symptoms and clinical signs, *n* (%)		
Pruritus	15 (56)	27 (40)
Burning	11 (41)	16 (24)
Pain	7 (26)	8 (12)
Erythema	2 (7)	5 (7)
Peripilar erythema	11 (41)	29 (43)
Telangiectasias	0	2 (3)
Peripilar scaling	21 (78)	54 (81)
Pull test	5 (19)	14 (21)
Peripilar papule	7 (26)	17 (25)
Trichoscopy signs, *n* (%)		
Absence of follicular ostia	27 (100)	67 (100)
Peripilar scaling	26 (96.3)	67 (100)
Fibrotic white patches*	27 (100)	48 (72)
Absence of vellus hairs*	4 (15)	67 (100)
White dots	16 (59)	41 (61)
Peripilar erythema	16 (59.3)	33 (49)
Peripilar white halo	13 (48)	39 (58)
Telangiectasias	7 (26)	28 (42)
Black dots	3 (11)	19 (28)
Blue gray dots*	8 (30)	5 (7)
Erythema*	0	13 (19)
Yellow dots	0	8 (12)

Symptoms and clinical signs were assessed for the absence or presence of each variable and, when possible, graded according to intensity (0 = absent, 1 = mild, 2 = moderate, 3 = intense). Progression of the alopecia (0 = no, 1 = uncertain, 2 = yes). Pull test: 0 = no anagen, 1 = any anagen.

LPP, Lichen planopilaris; *FFA*, frontal fibrosing alopecia; *n*, number of patients; *min*, minimum; *max*, maximum.

*Statistically significant differences for age ($P = .035$); menopause ($P = .002$); phototype ($P = .019$); eyebrows alopecia ($P = .000$); body hair alopecia ($P = .024$); facial papules ($P = .000$); lichen planus pigmentosus ($P = .028$); eyelash alopecia ($P = .046$); absence of vellus ($P = .000$); blue gray dots ($P = .005$); fibrotic white patches ($P = .002$); and erythema ($P = .014$).

Table II. Horizontal section findings in patients with LPP and FFA

Horizontal section	LPP, *n* (%)	FFA, *n* (%)
Inflammatory infiltrate (400×)		
Absent	1 (4)	1 (1)
Mild	19 (70)	38 (57)
Moderate	6 (22)	24 (36)
Severe	1 (4)	4 (6)
Location of infiltrate		
Infundibulum	9 (33)	34 (51)
Isthmus	26 (96)	66 (99)
Lower segment*	7 (26)	7 (10)
Cell type		
Lymphohistiocytic	27 (100)	67 (100)
Plasmocytic	1 (4)	1 (1)
Perifollicular inflammation		
Lichenoid	3 (11)	19 (28)
Displaced by fibrosis	26 (96)	66 (99)
Perivascular inflammation	2 (7)	6 (9)
Follicle		
Lymphocyte exocytosis*	10 (37)	49 (73)
Presence of apoptosis*	3 (11)	33 (49)
Vacuolar degeneration	3 (11)	19 (28)
Periostial hyperkeratosis	5 (19)	5 (7)
Corneal plug	1 (4)	3 (4)
Perifollicular fibrosis		
Concentric eosinophilic	26 (96)	66 (99)
With mucin	15 (56)	47 (70)
Cicatricial tract	18 (67)	45 (67)

LPP, Lichen planopilaris; *FFA*, frontal fibrosing alopecia.

*Statistically significant differences for infiltrate subjective method ($P = .028$); location of infiltrate in the lower segment ($P = .025$); lymphocyte exocytosis ($P = .001$); and presence of apoptosis ($P = .000$).

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Conflicts of Interest

None disclosed.

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Sexual dysfunction with 5-alpha-reductase inhibitor therapy for androgenetic alopecia: A global propensity score matched retrospective cohort study

To the Editor: 5-alpha-reductase inhibitors (5-ARIs) are a therapeutic mainstay for androgenetic alopecia (AGA). Uncertainty exists surrounding sexual dysfunction (SD) associated with 5-ARIs. Meta-analyses examining associations between 5-ARIs and SD demonstrate conflicting results (Supplementary Table I, available via Mendeley at https://doi.org/10.17632/nfsydtdcsm.1).[1-4] Prior analyses involved predominately pooled data from trials. Currently, there is a paucity of population-level data investigating 5-ARI and SD. Here we evaluate potential associations of 5-ARIs with SD in a global population.

A retrospective cohort study was conducted analyzing patients with AGA in TriNetX, a health research network with electronic medical record data from 120 million patients worldwide; 59,473 male patients with AGA were extracted (Supplementary Fig 1, available via Mendeley at https://doi.org/10.17632/nfsydtdcsm.1). Patients with any history of benign prostatic hyperplasia or unclear timeline of 5-ARI prescription were excluded (n = 36,136); 23,337 included patients were split into 2 cohorts, those prescribed 5-ARI within 1 month of AGA diagnosis (n = 10,585), and those with no history of 5-ARI inhibitor (n = 12,572) (Supplementary Table II, available via Mendeley at https://doi.org/10.17632/nfsydtdcsm.1). A risk analysis was undertaken calculating the risk of developing SD up to 1 year after 5-ARI prescription for AGA. Propensity score matching was implemented balancing for confounders.

Of 10,585 5-ARI exposed patients (mean age 39), 289 (3%) experienced SD with an absolute risk increase of 0.97% compared to 5-ARI naïve patients (95% CI 0.528%, 1.413%; $P < .001$) (Table I). On subanalysis by dosage/agent, the only significant risk increase found was patients with AGA on finasteride 5 mg vs no 5-ARI (Table I).

In 5-ARI exposed patients with SD, prevalence of the following comorbidities was significantly elevated compared to those without SD: obesity, nicotine dependence, diabetes mellitus, hypertension, mood, and anxiety disorders ($P < .0001$) (Table II). Patients with these factors were excluded independently and a decrease in absolute risk increase was seen but was still significant (Table I). Once patients with any of these comorbidities were excluded from risk analysis, the absolute risk increase for 5-ARI exposed patients was reduced to 0.43 compared to 5-ARI naïve patients (95% CI −0.02%, 0.885%; $P = .061$).

Data investigating comorbidities in 5-ARI AGA patients are limited. The previous cohort study investigating these factors found hypertension, depression, smoking, obesity, and diabetes mellitus all contributed to risk of SD.[5] Results here align with these prior findings, demonstrating an initial significant increase in risk of SD with 5-ARI which lost significance once patients with any of the 6 previously mentioned comorbidities were excluded. Of note, because many of these chronic comorbidities affect patients after 5-ARIs are stopped, these results may contribute to a working hypothesis for persistent SD after 5-ARI discontinuation, a subject debated in literature and media.

Limitations include the retrospective nature of this study, potential for documentation errors, and underreporting of SD as patients require a follow up visit for documentation. However, this study analyzes over 23,000 real-world patients with robust external validity while controlling for confounders in a way not feasible in other study types of this size.

Ultimately comorbid factors may play a significant role in SD associated with 5-ARIs. The findings of this study emphasize the importance of medical history in determining candidacy for 5-ARIs to reduce SD related adverse events.

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