Update on Histology and Biology of LPP and FFA

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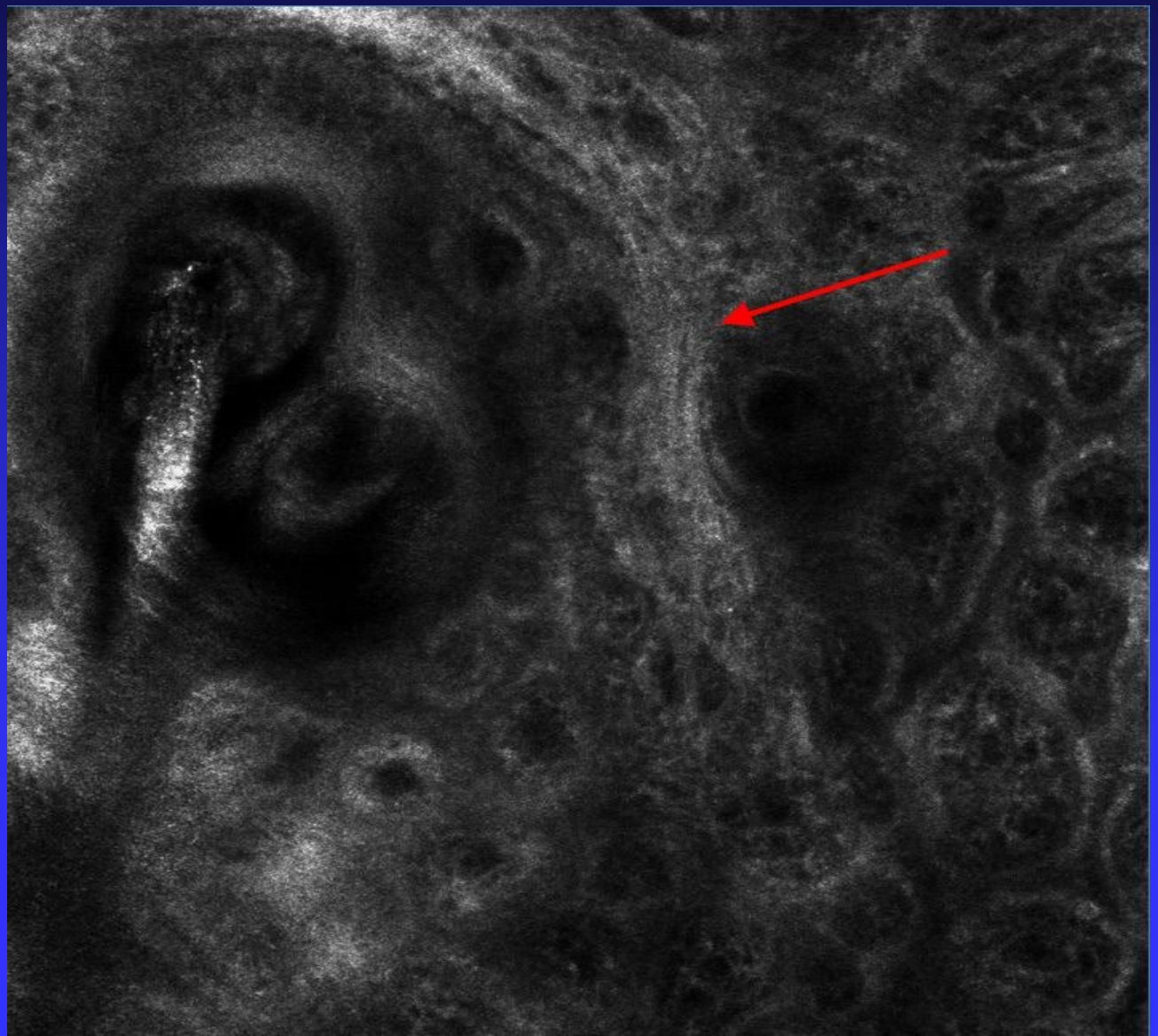
Case Reports > JAAD Case Rep. 2022 Mar 11;23:46-48. doi: 10.1016/j.jdcr.2022.02.036. eCollection 2022 May.

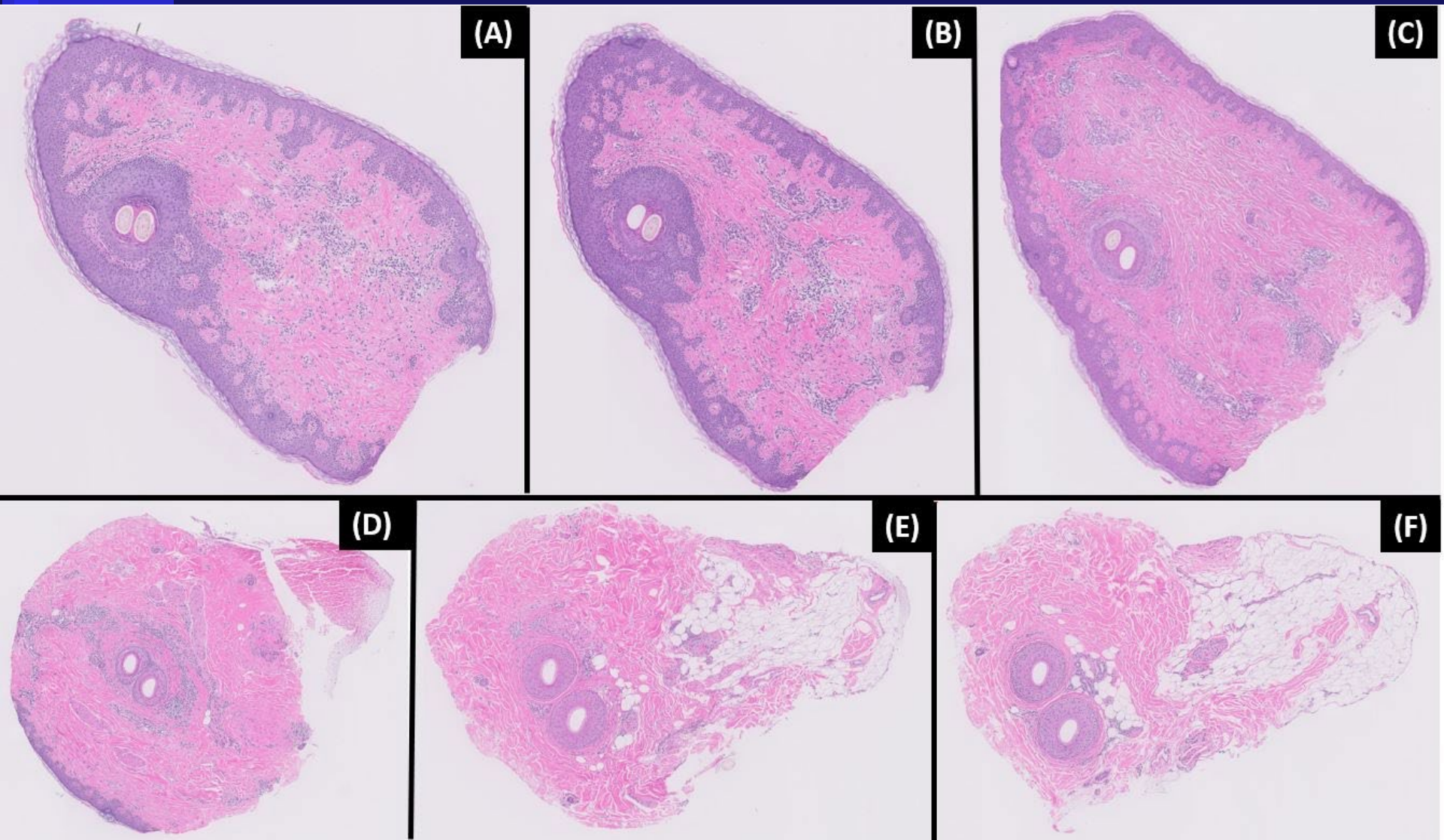
Three-dimensional imaging of a peripilar cast and compound follicle in frontal fibrosing alopecia

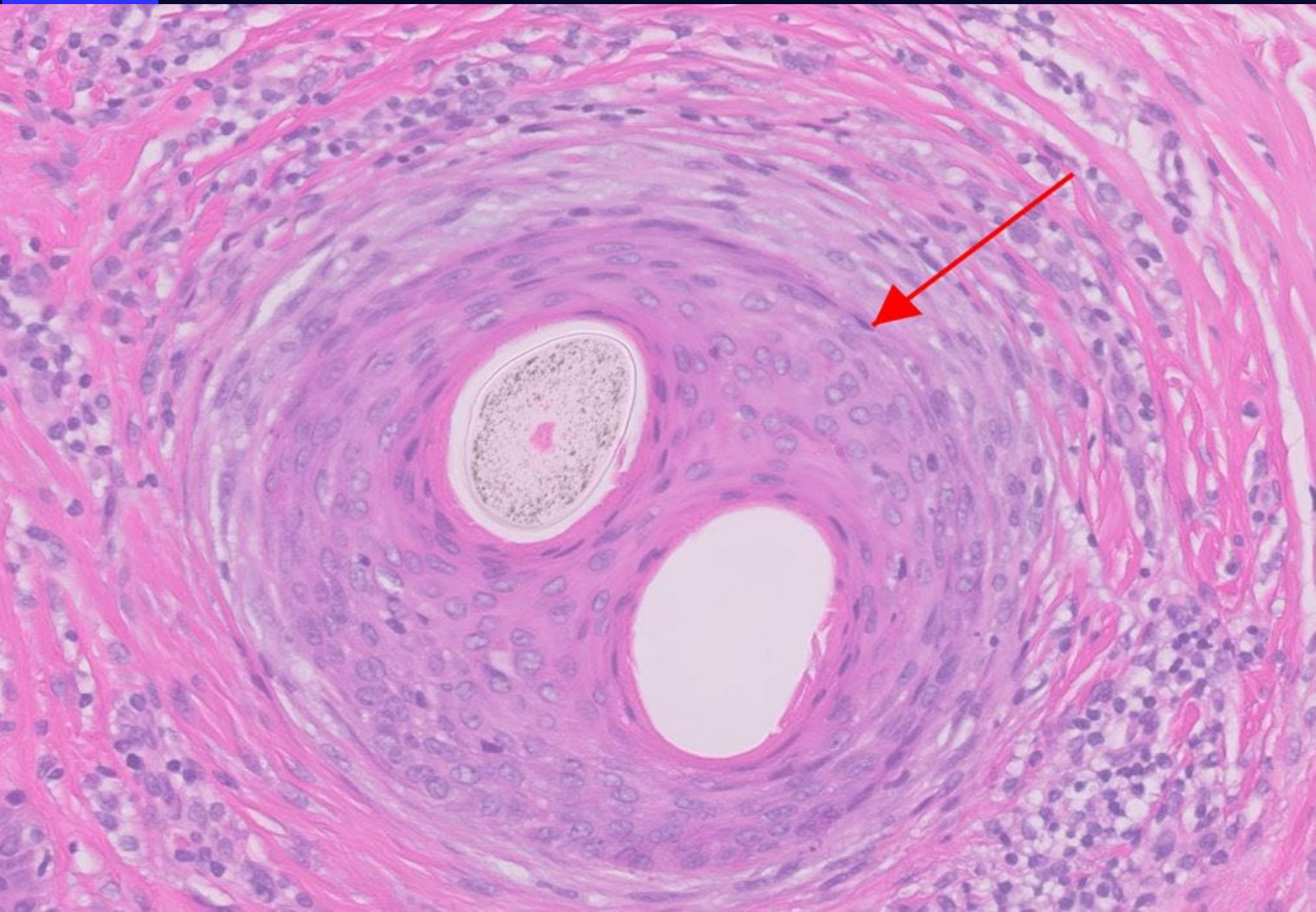
Curtis T Thompson [1 2], Maria Abril Martinez Velasco [3], Antonella Tosti [4]

In vivo confocal microscopy



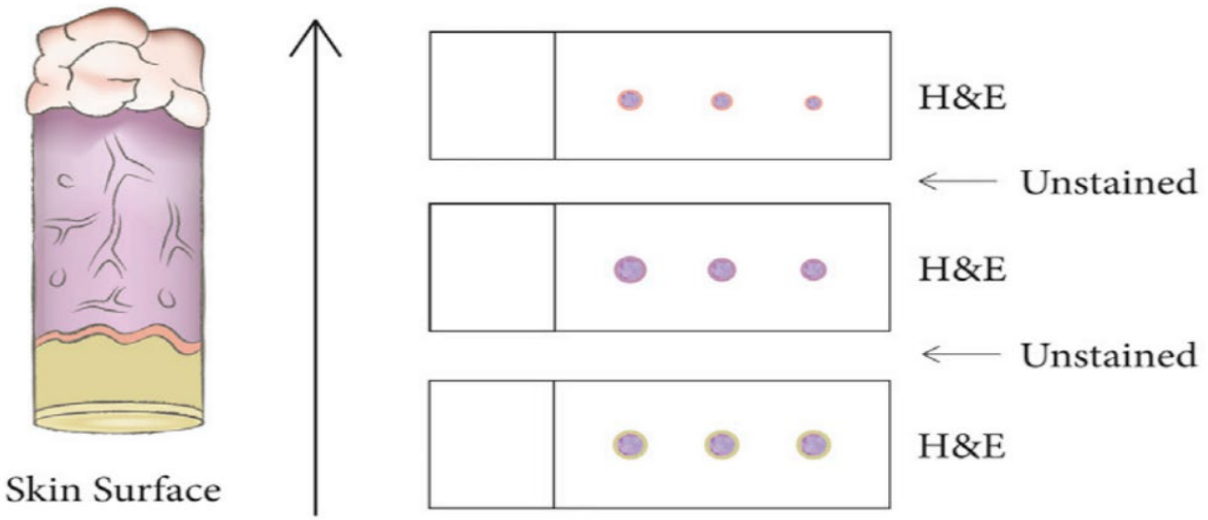
2mm Transverse H&E sections





A method for more precise sampling of the scalp and eyebrows in frontal fibrosing alopecia

Curtis T. Thompson, MD,[a,b,c] and Antonella Tosti, MD[d]
Portland, Oregon, and Miami, Florida



3 slides total with 9 cross sections; 3 sections per slide

1. Tissue is embedded epidermis-down
2. Step through entire block on initial H&E stains
3. Obtain unstained slides

Premature desquamation of the inner root sheath

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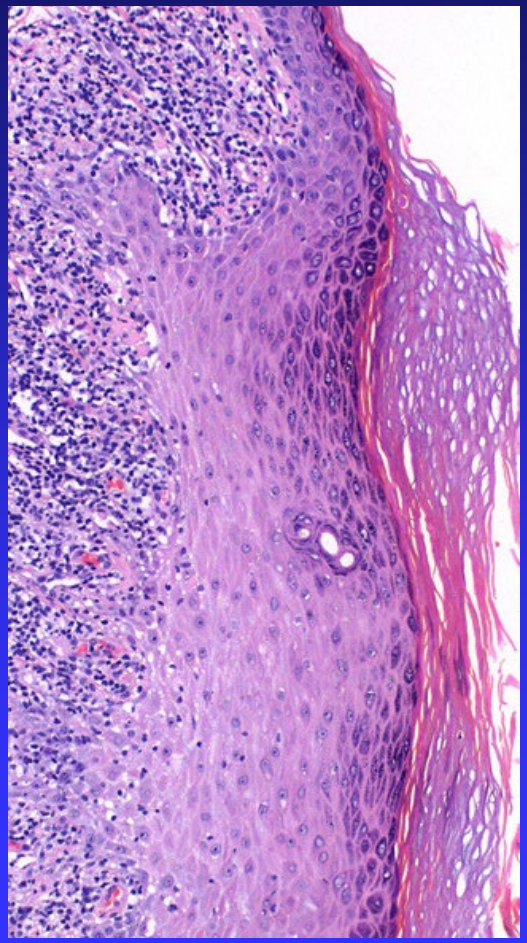
Squamotization of follicular epithelium



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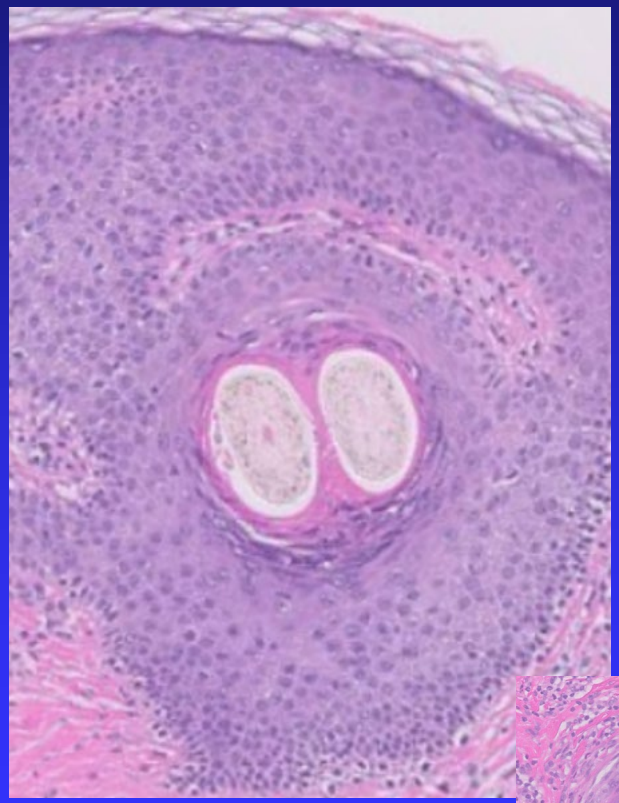

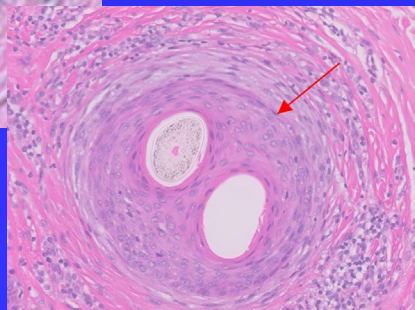

https://dermnetnz.org/topics/lichen-planus-pathology

CTA PATHOLOGY
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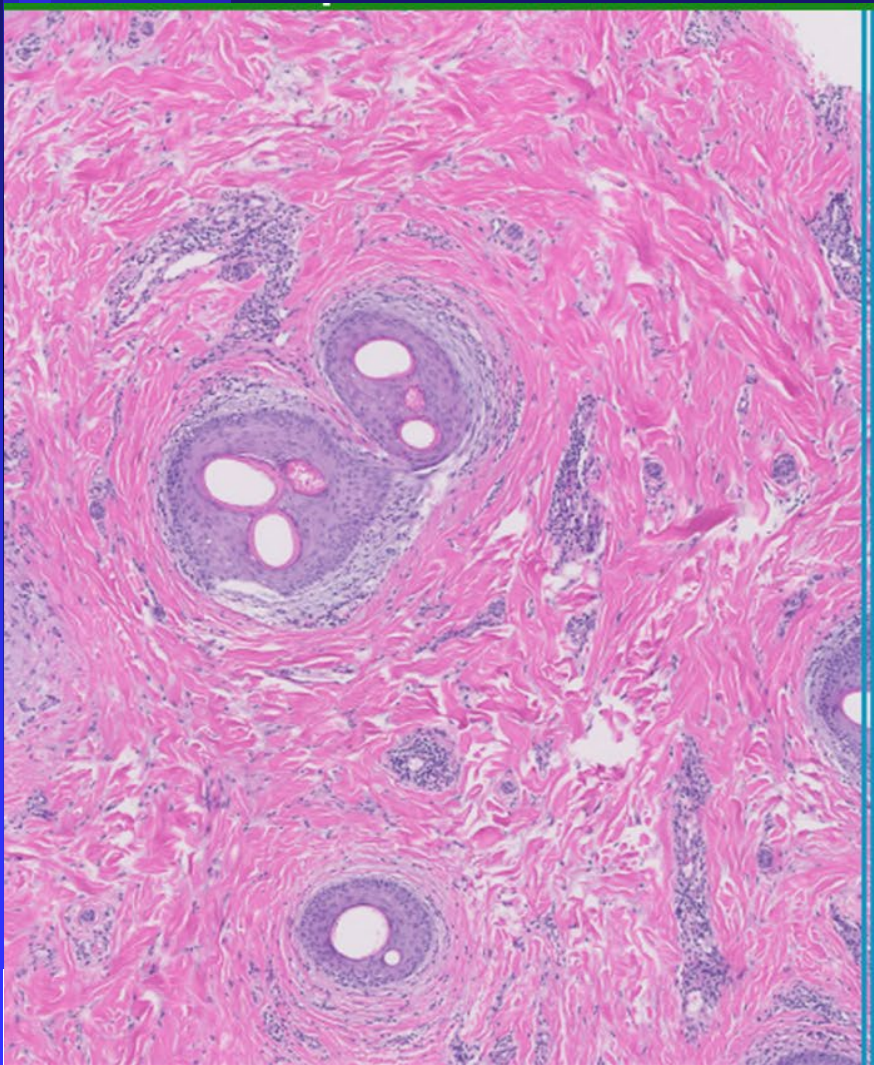
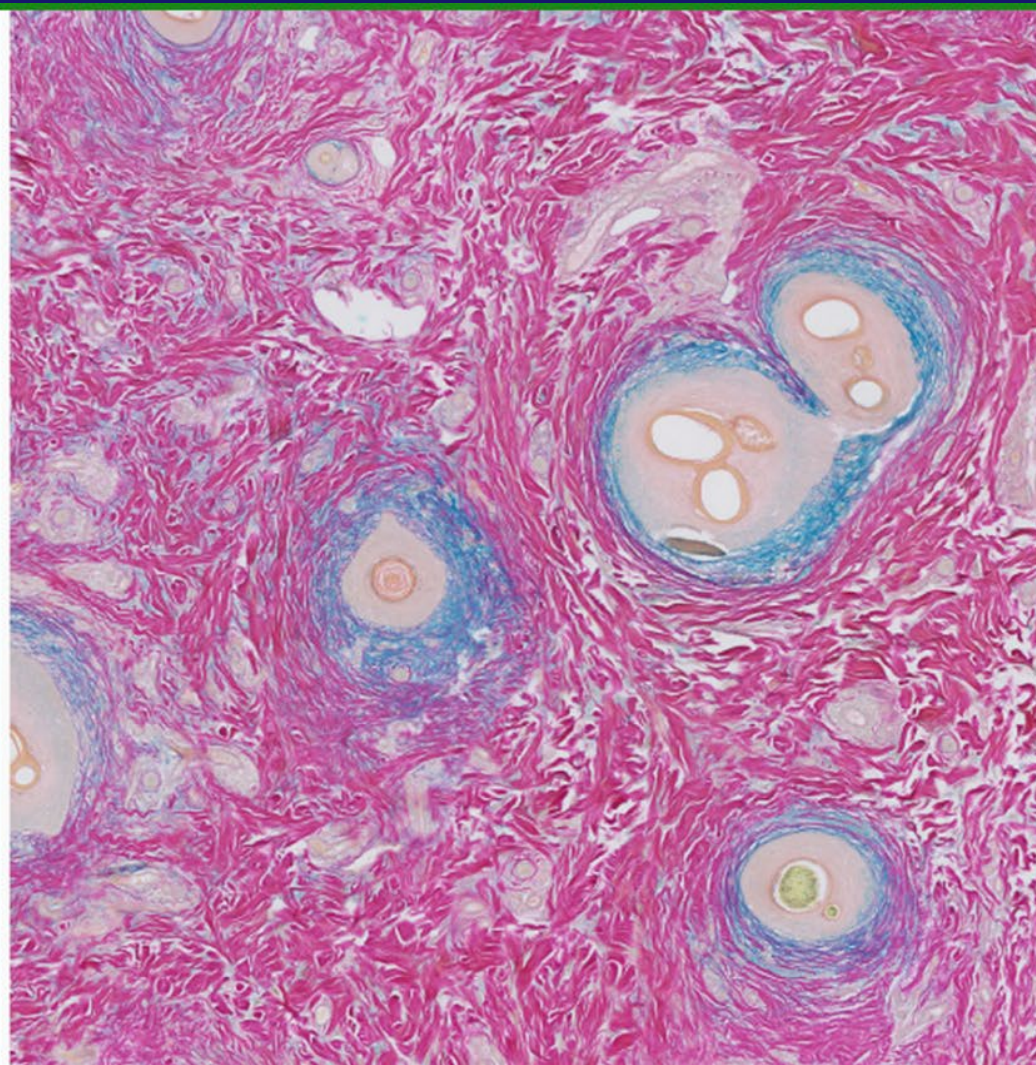
SKIN, HAIR AND NAIL EXPERTS

Perifollicular (concentric lamellar) mucinous fibroplasia





Normal ostium vs Compound follicle

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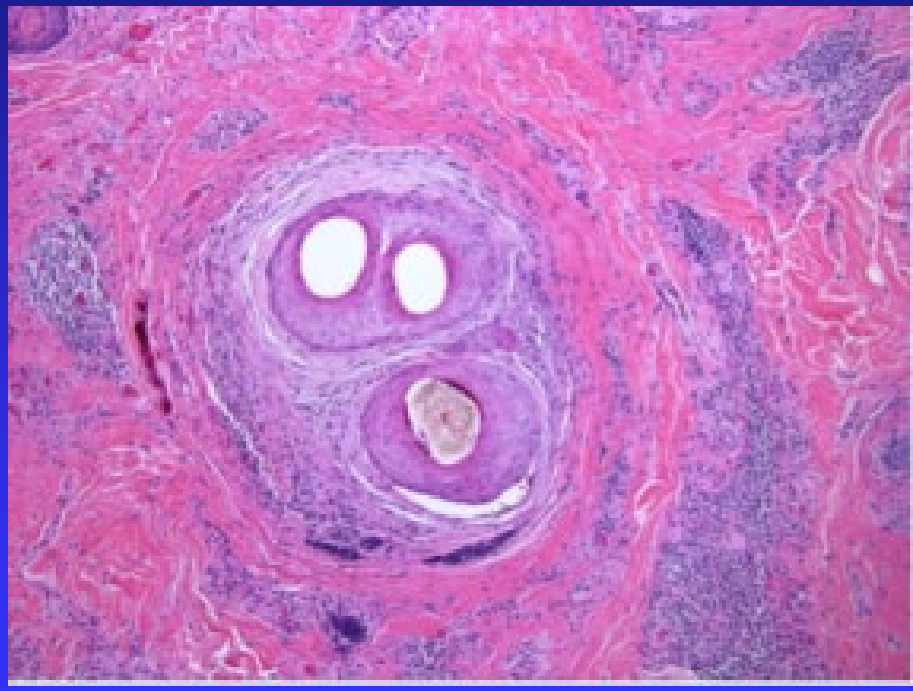
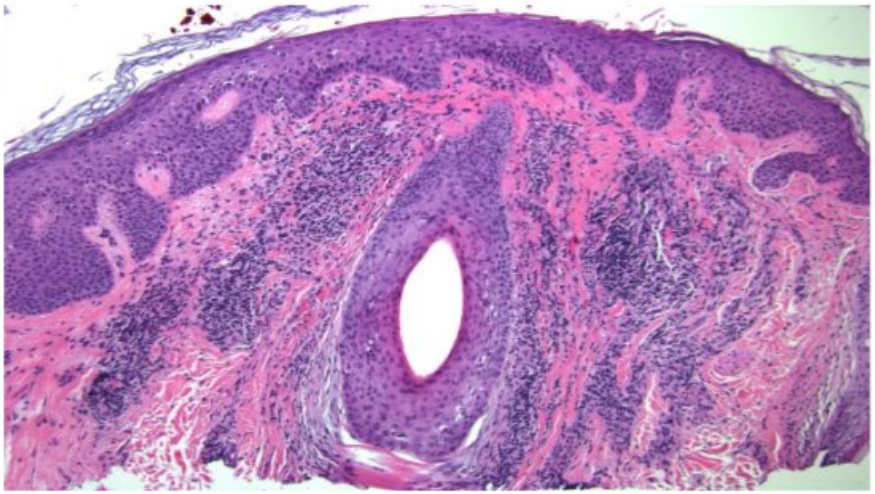
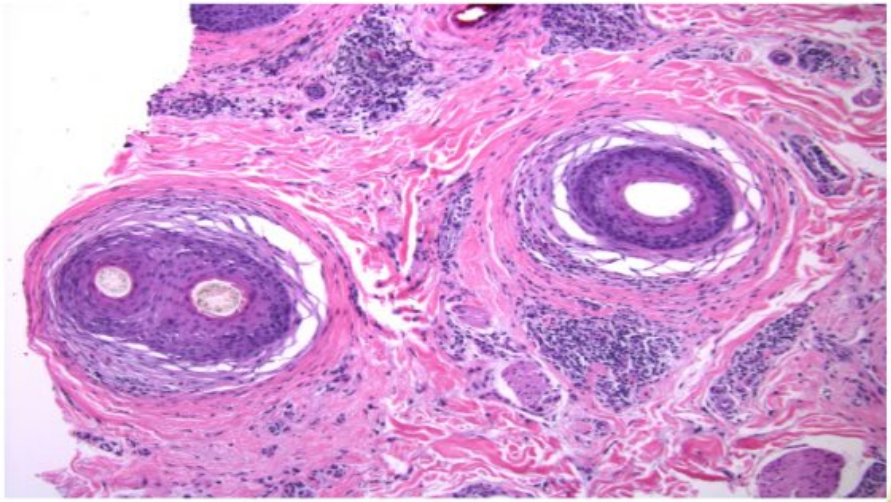


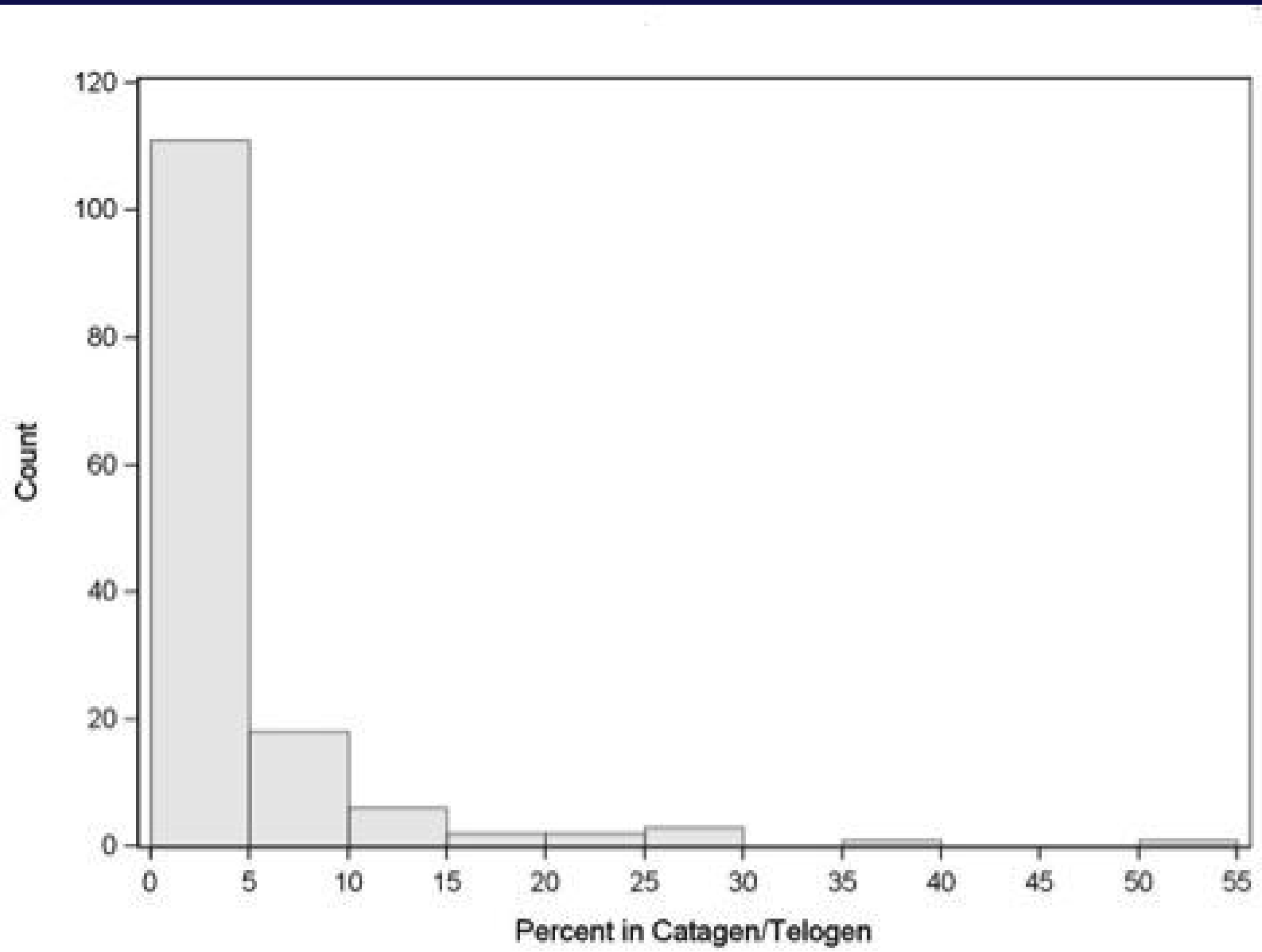
Lichen Planopilaris (LPP)



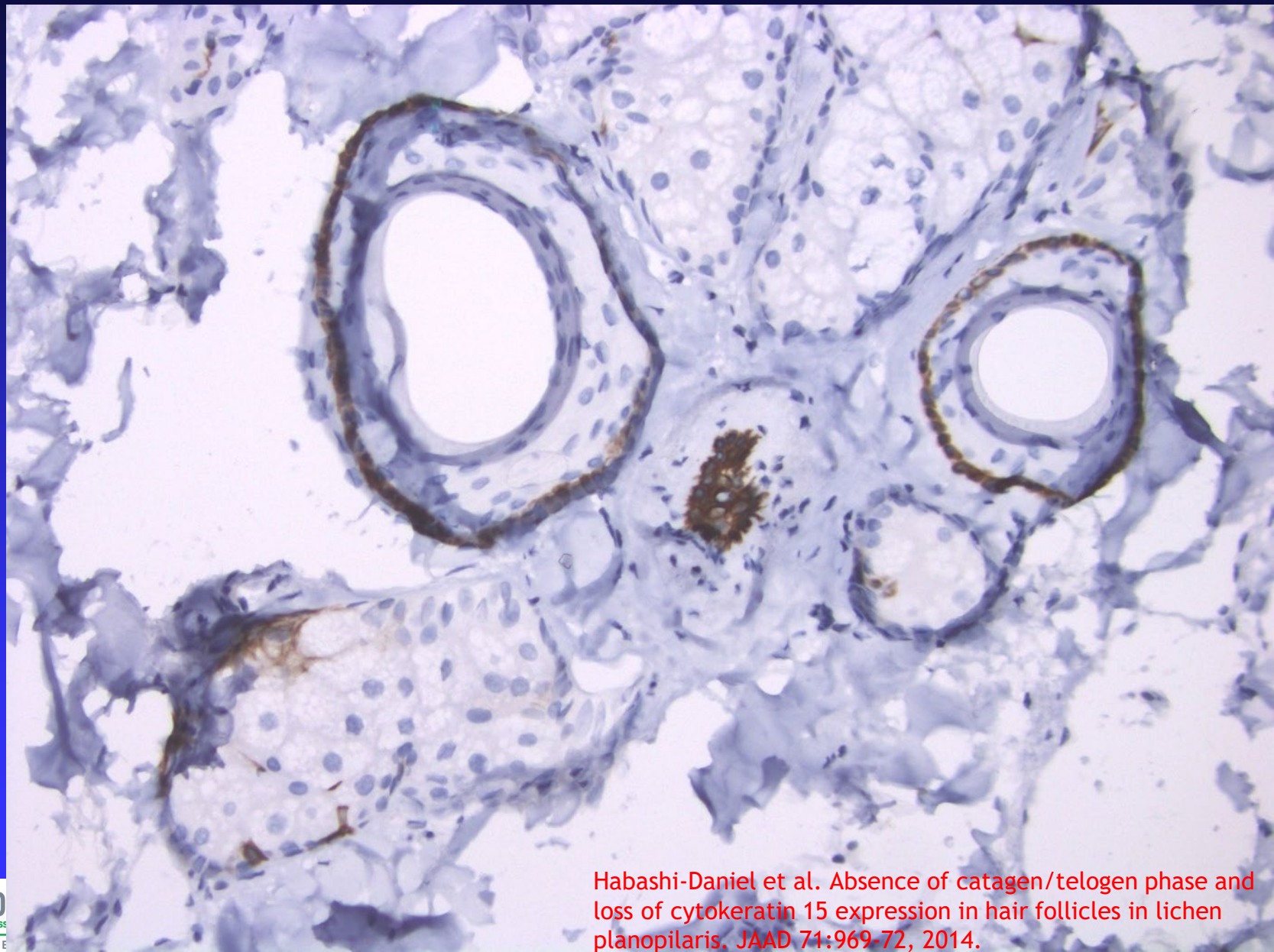


Loss of catagen/telogen phase follicles

Near absence of catagen/telogen in LPP

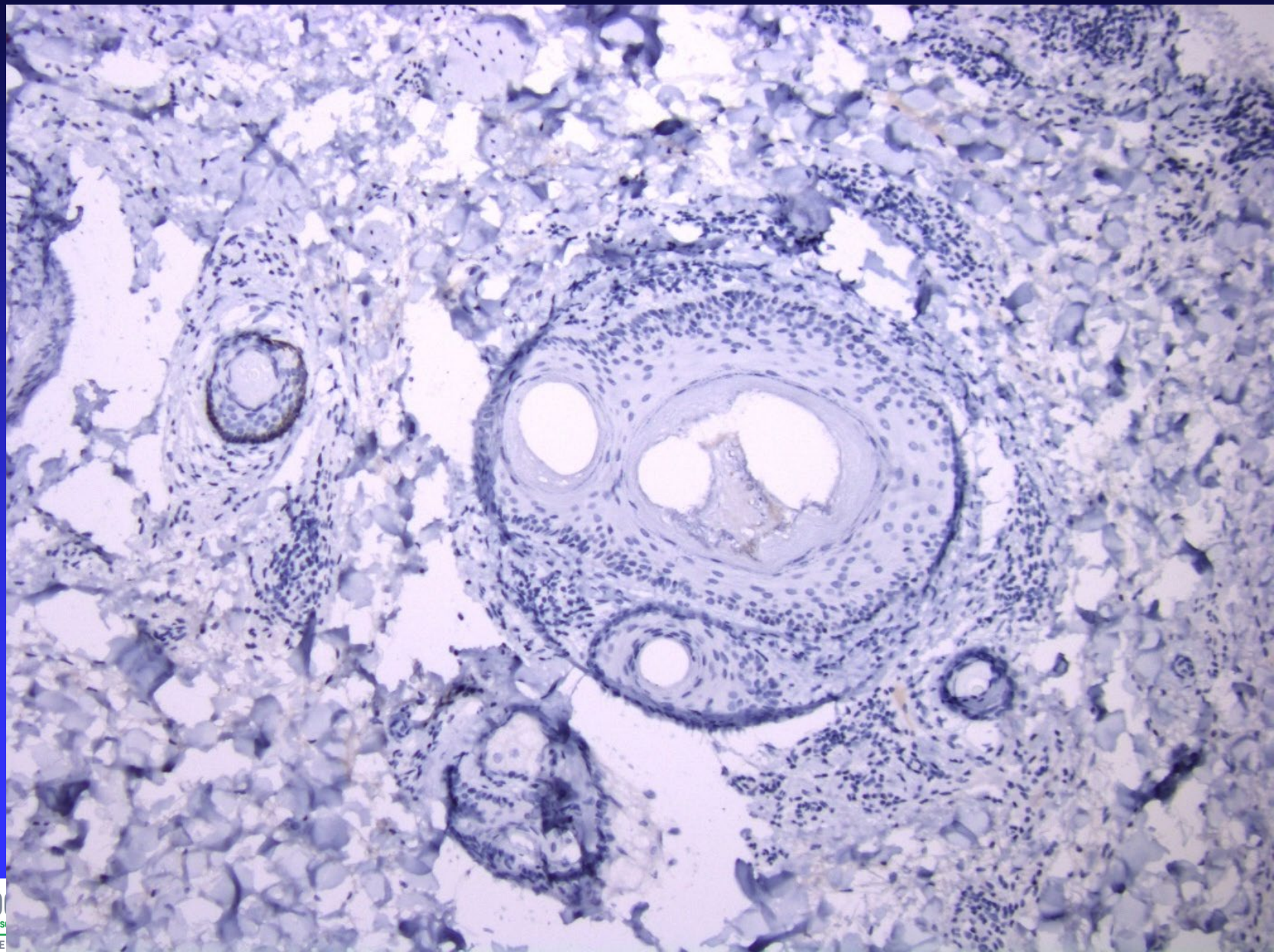


Cytokeratin 15



Habashi-Daniel et al. Absence of catagen/telogen phase and loss of cytokeratin 15 expression in hair follicles in lichen planopilaris. JAAD 71:969-72, 2014.

Loss of Cytokeratin 15 in LPP

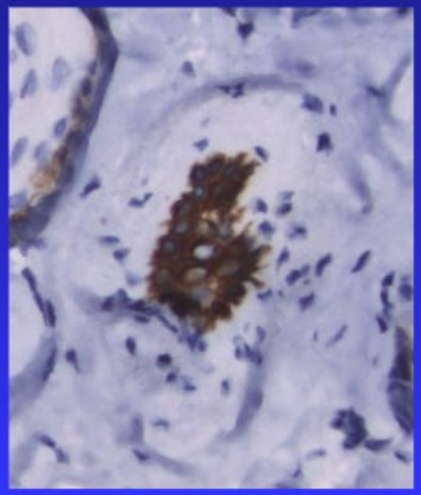


Lichen Planopilaris Progression

Loss of CK15+ stem cells

↓

Disappearance of follicle when cycle into catagen



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Clinical progression despite immunosuppressive treatment

Arch Dermatol. 1994 Jun;130(6):770-4.

Postmenopausal frontal fibrosing alopecia. Scarring alopecia in a pattern distribution.

Kossard S[1].

Author information Papers

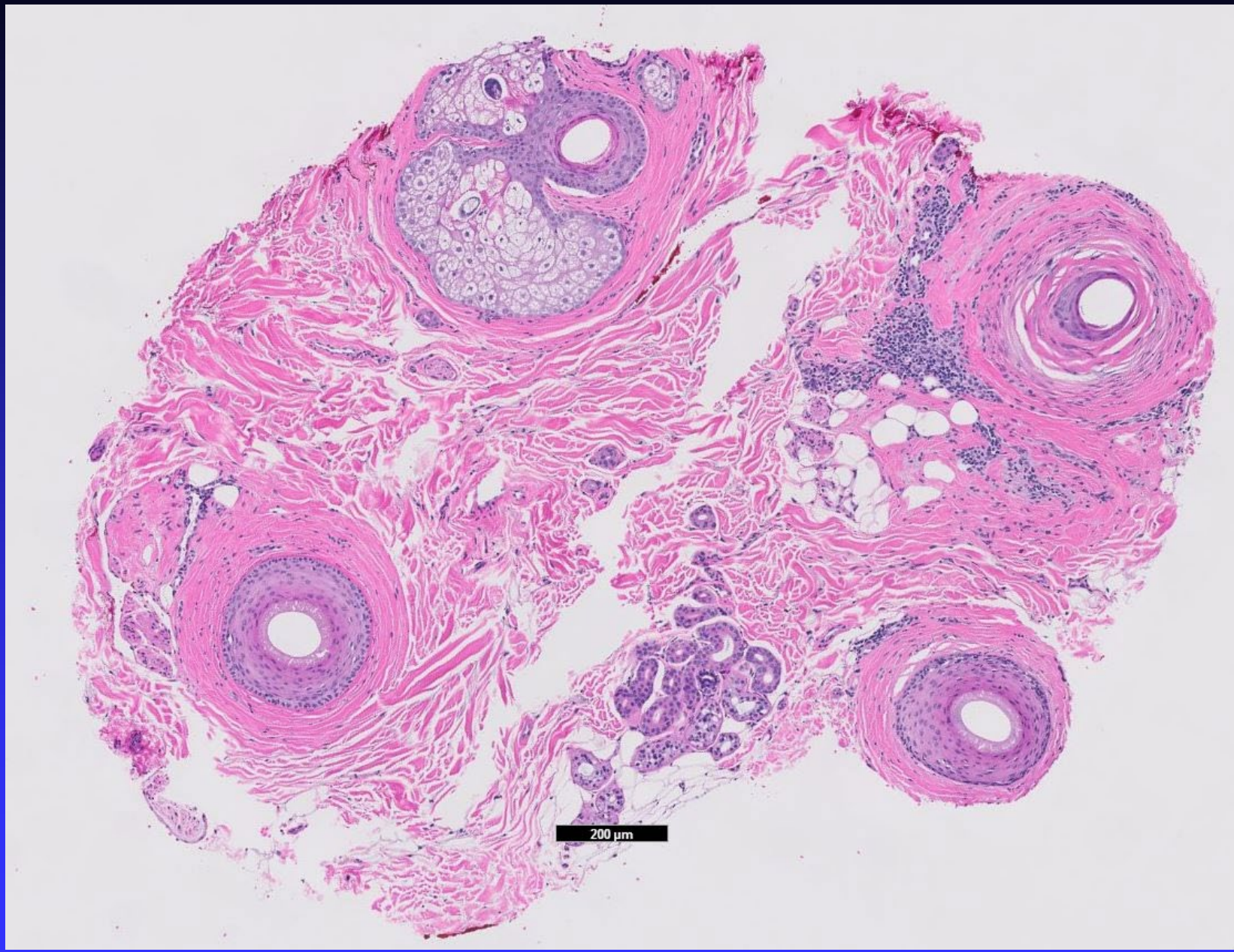
Erratum in
Arch Dermatol 1994 Nov;130(11):1407.

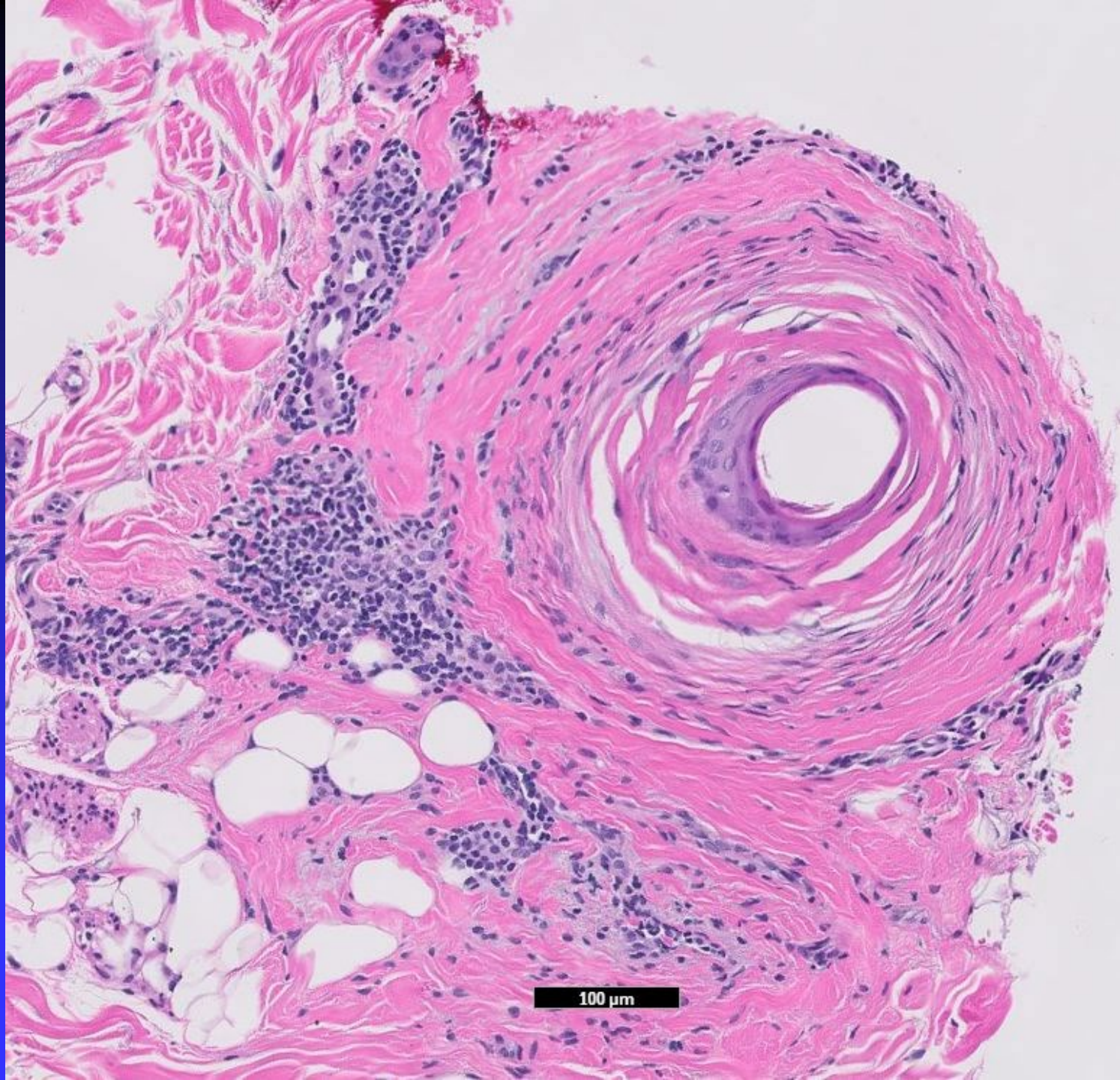
Abstract

BACKGROUND: Recession of the frontal hairline is a common event in postmenopausal women. This has been shown not to be a marker of gross androgenization, and is usually a progressive nonscarring alopecia. Six postmenopausal women, who developed a progressive frontal scarring alopecia, were studied and their clinical and laboratory data, as well as the results of scalp biopsy specimens in all six patients, were analyzed and compared with recognized forms of scarring alopecia and recently described findings in androgenetic alopecia.

OBSERVATIONS: The six postmenopausal women developed a progressive frontal hairline recession that was associated with perifollicular erythema within the marginal hairline, producing a frontal fibrosing alopecia extending to the temporal and parietal hair margins. Scalp biopsy specimens from the frontal hair margin showed perifollicular fibrosis and lymphocytic inflammation concentrated around the isthmus and infundibular areas of the follicles. Immunophenotyping of the lymphocytes showed a dominance of activated T-helper cells. Clinical review of all six cases showed a progressive marginal alopecia without the typical multifocal areas of involvement seen in lichen planopilaris or pseudopelade. None of the patients had mucous membrane or skin lesions typical of lichen planus. Hormonal studies, in five patients, showed no elevated androgen abnormalities.

CONCLUSIONS: Progressive frontal recession in postmenopausal women may show clinical features of a fibrosing alopecia. The histologic findings are indistinguishable from those seen in lichen planopilaris. However, the absence of associated lesions of lichen planus in all six women raises the possibility that this mode of follicular destruction represents a reaction pattern triggered by the events underlying postmenopausal frontal hairline recession.





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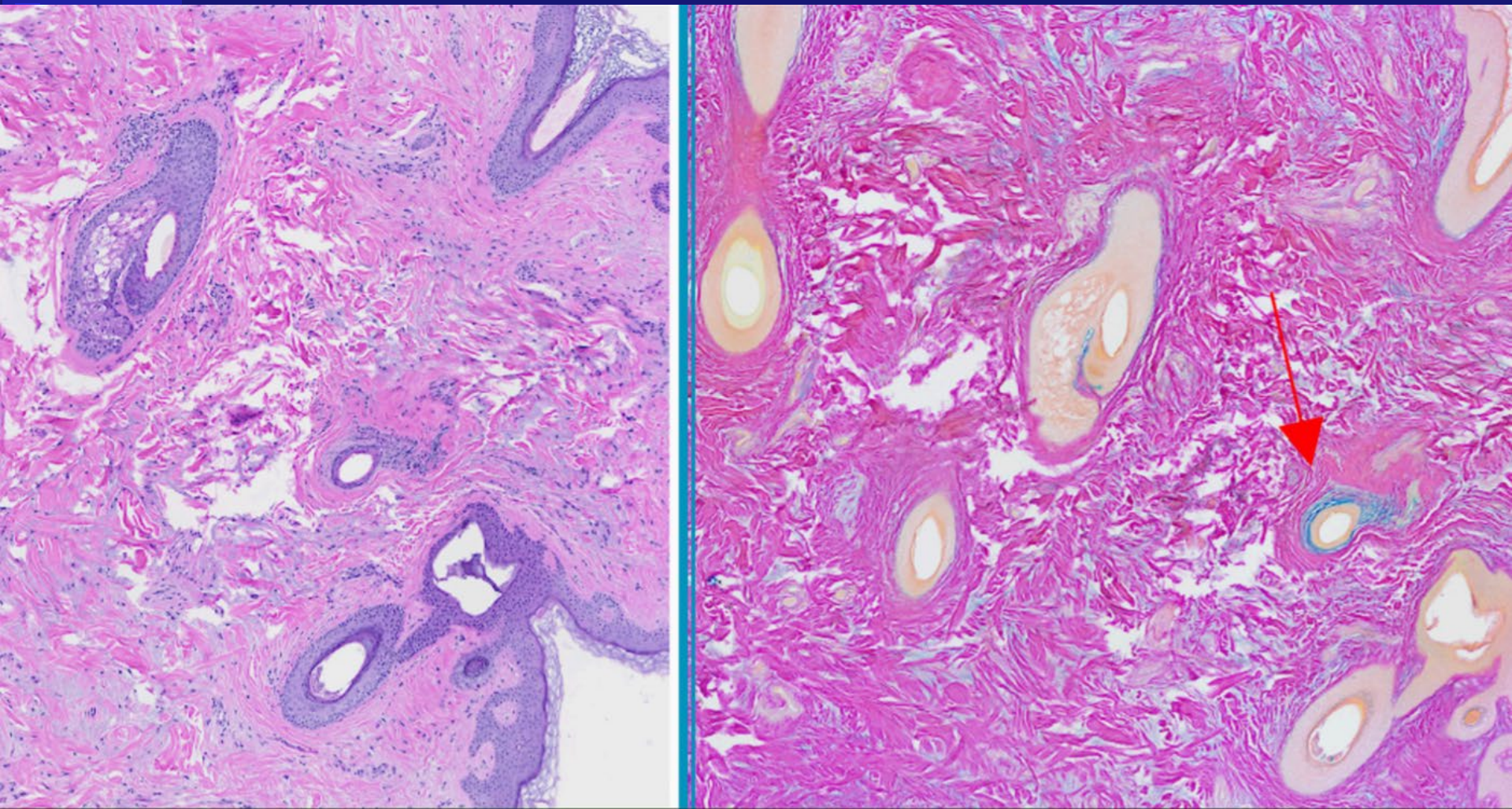
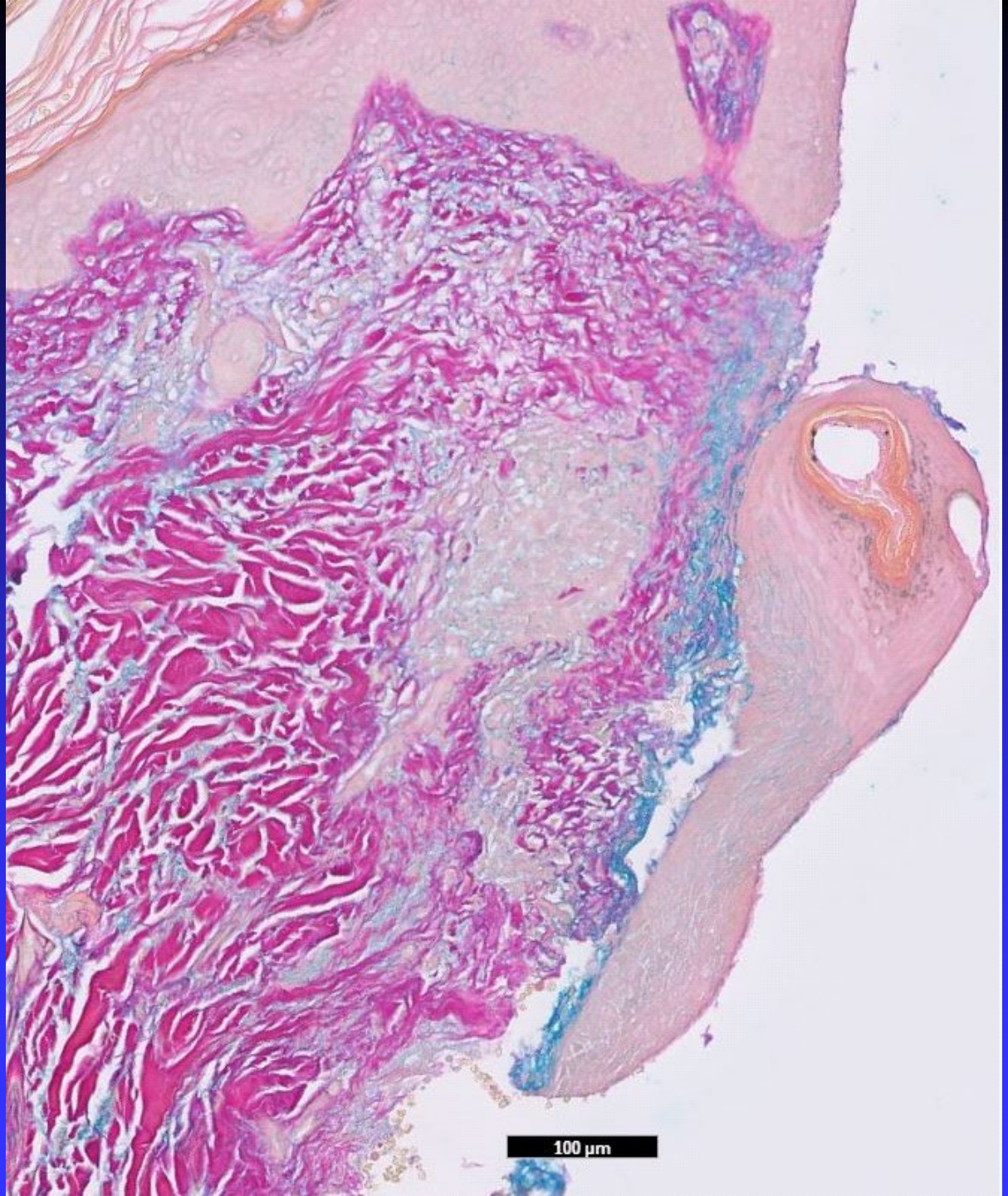
SKIN, HAIR AND NAIL EXPERTS

Subtle perifollicular (concentric lamellar) mucinous fibroplasia in FFA





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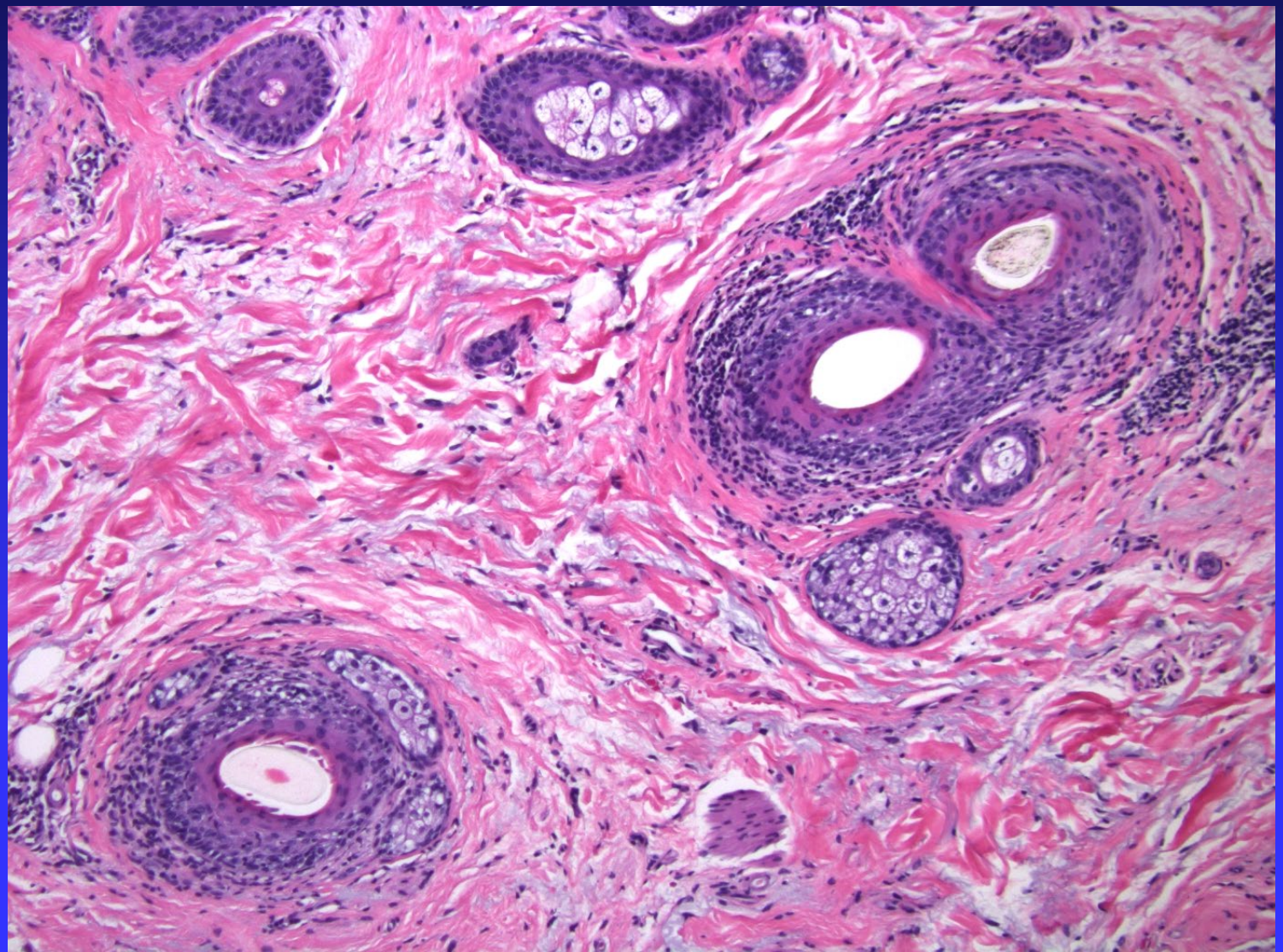
SKIN, HAIR AND NAIL EXPERTS

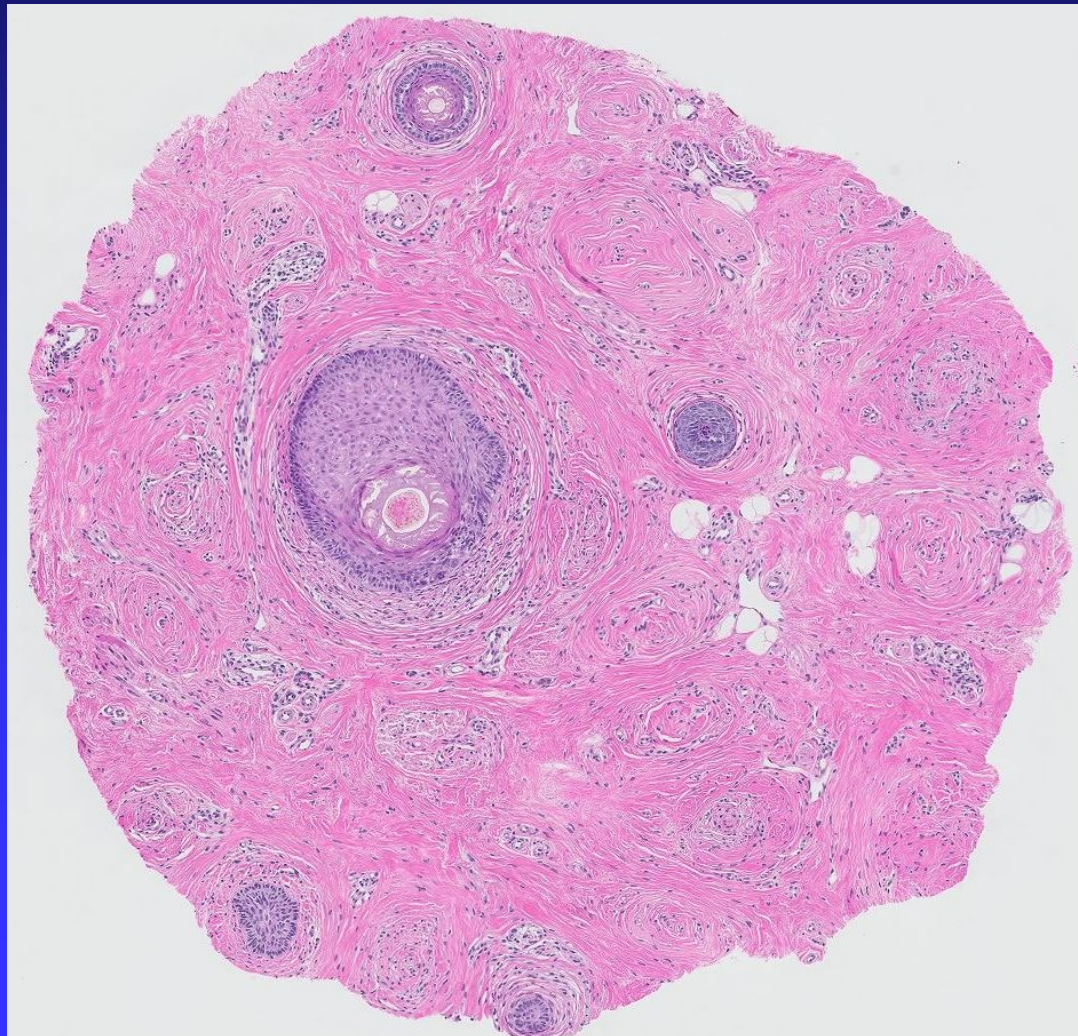
Frontal Fibrosing Alopecia
Minimal perifollicular scarring



Frontal Fibrosing Alopecia

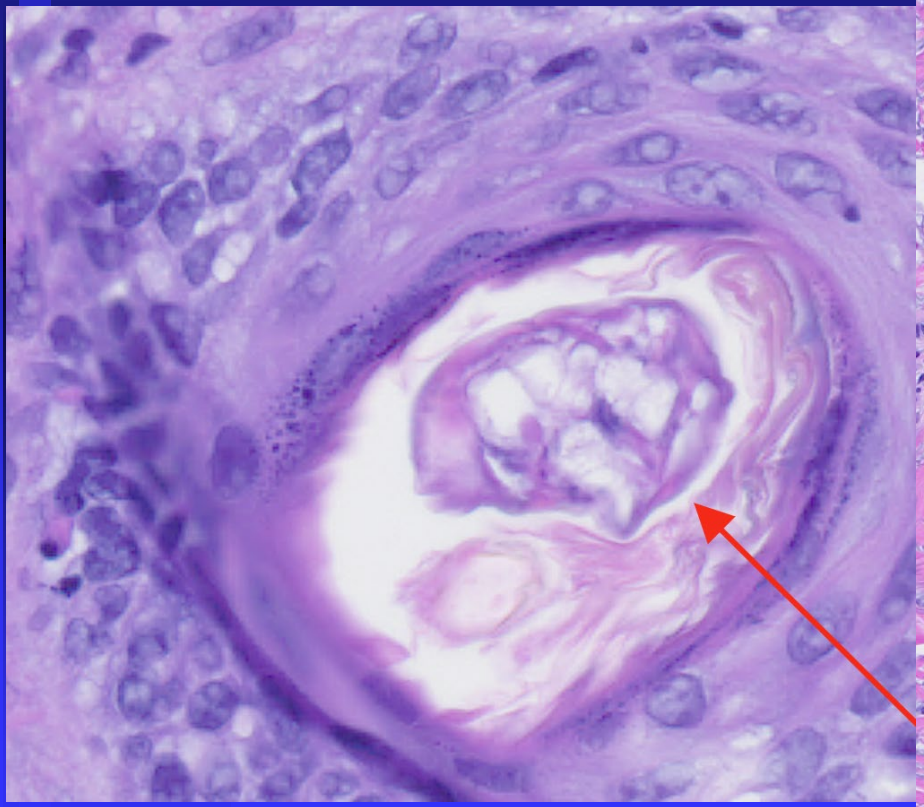
- Target smaller follicles of the skin
  - Frontal hairline
  - Eyebrows
  - Facial hair
  - Body hair

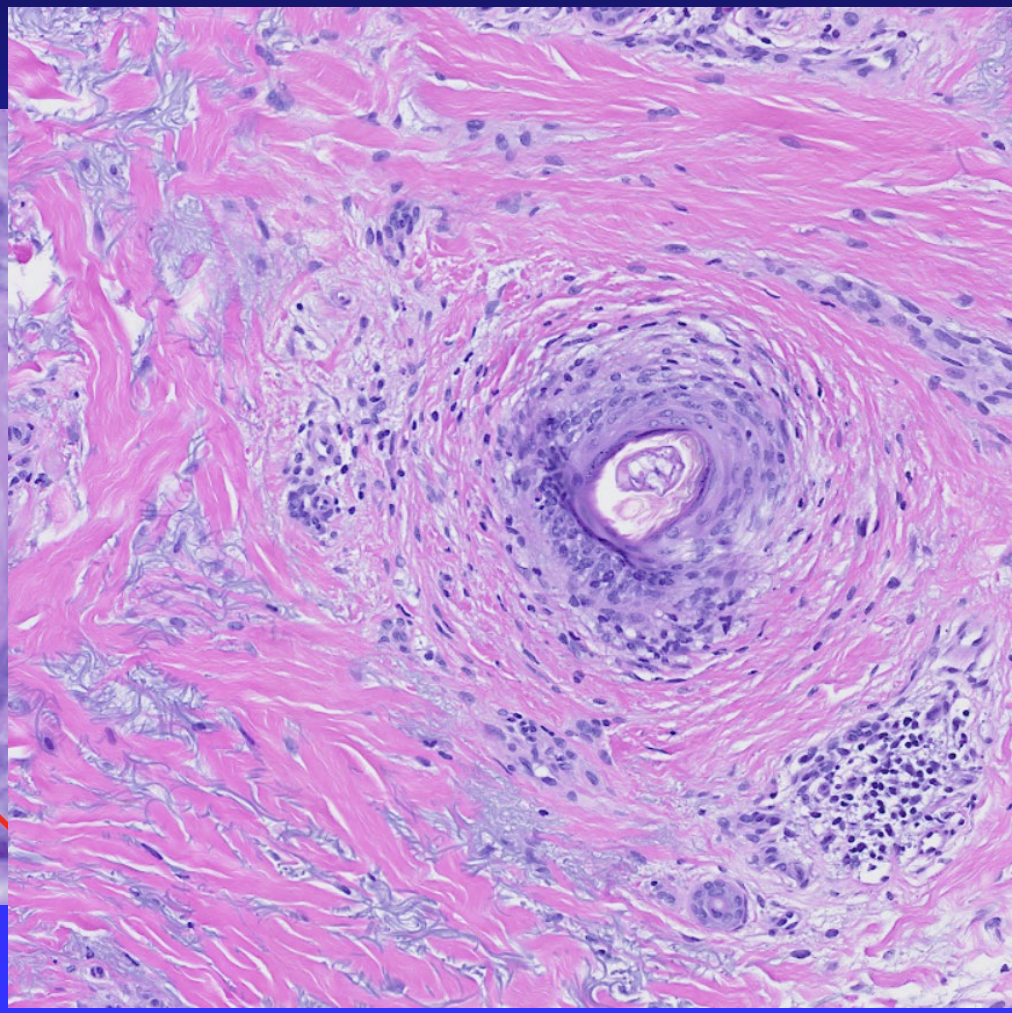
FFA—Eyebrow Involvement



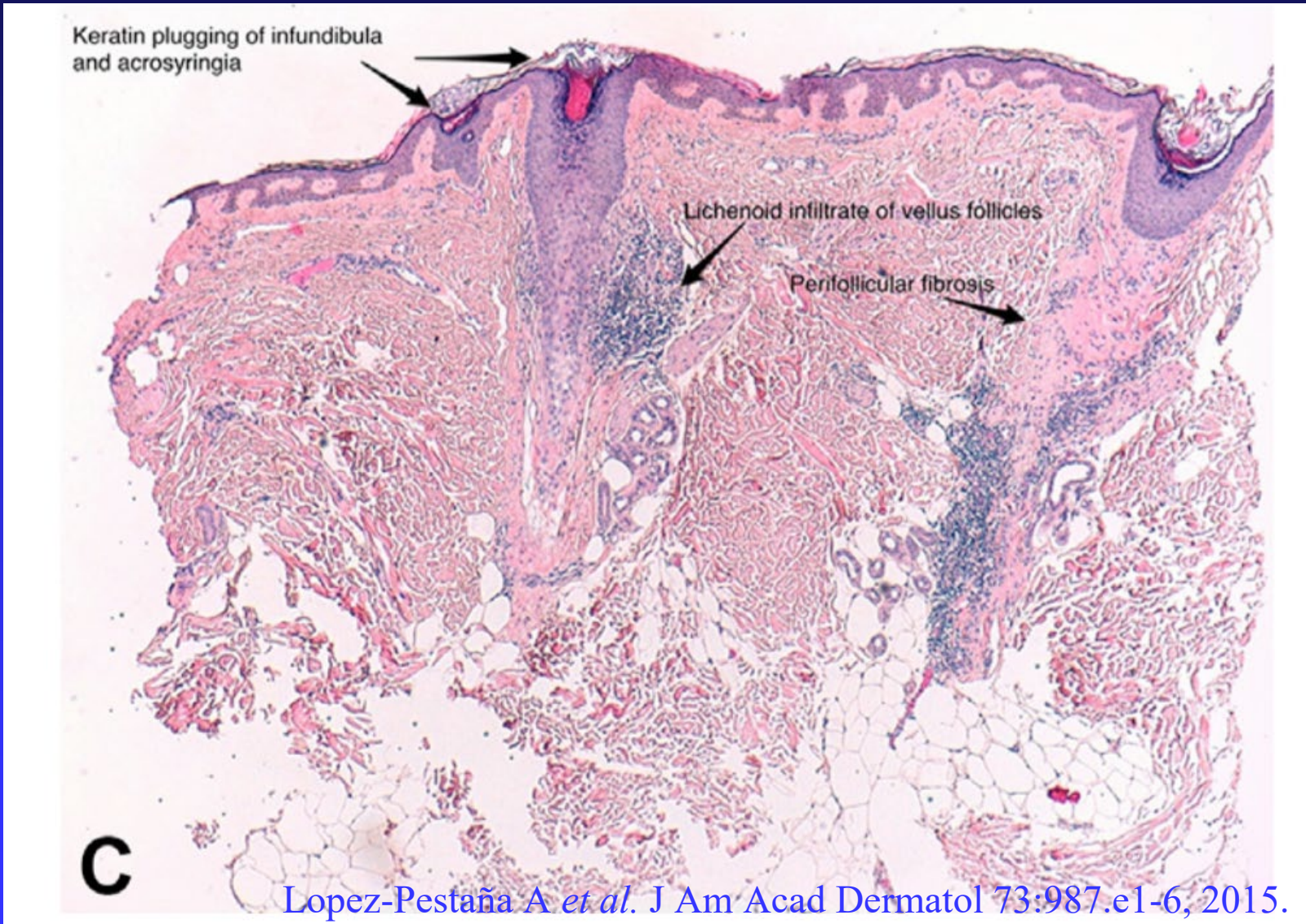
Facial papules: FFA or rosacea?

Demodex
Cause of inflammation and pruritus



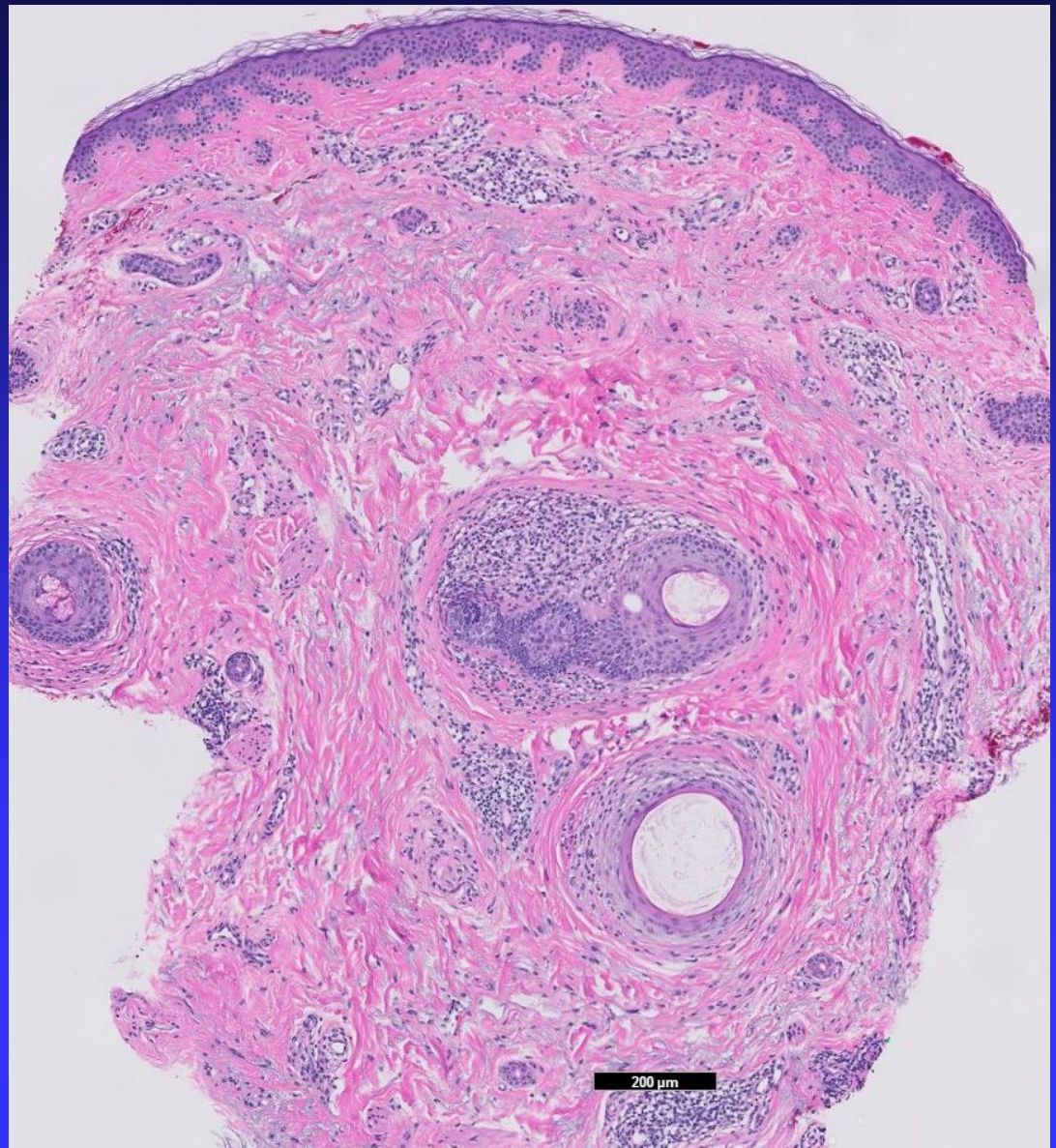


Facial papules in FFA

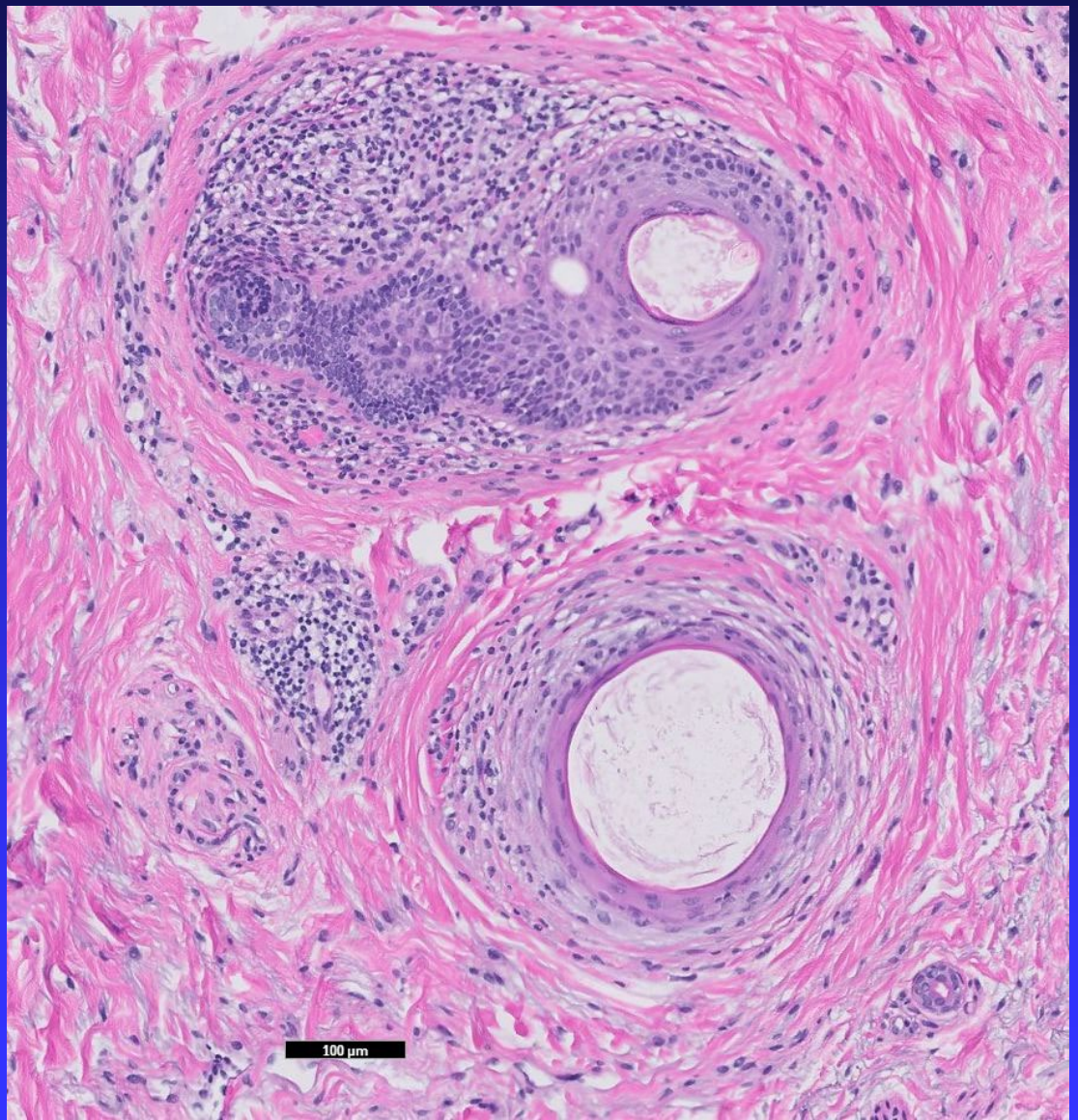


Lopez-Pestaña A *et al.* J Am Acad Dermatol 73:987.e1-6, 2015.

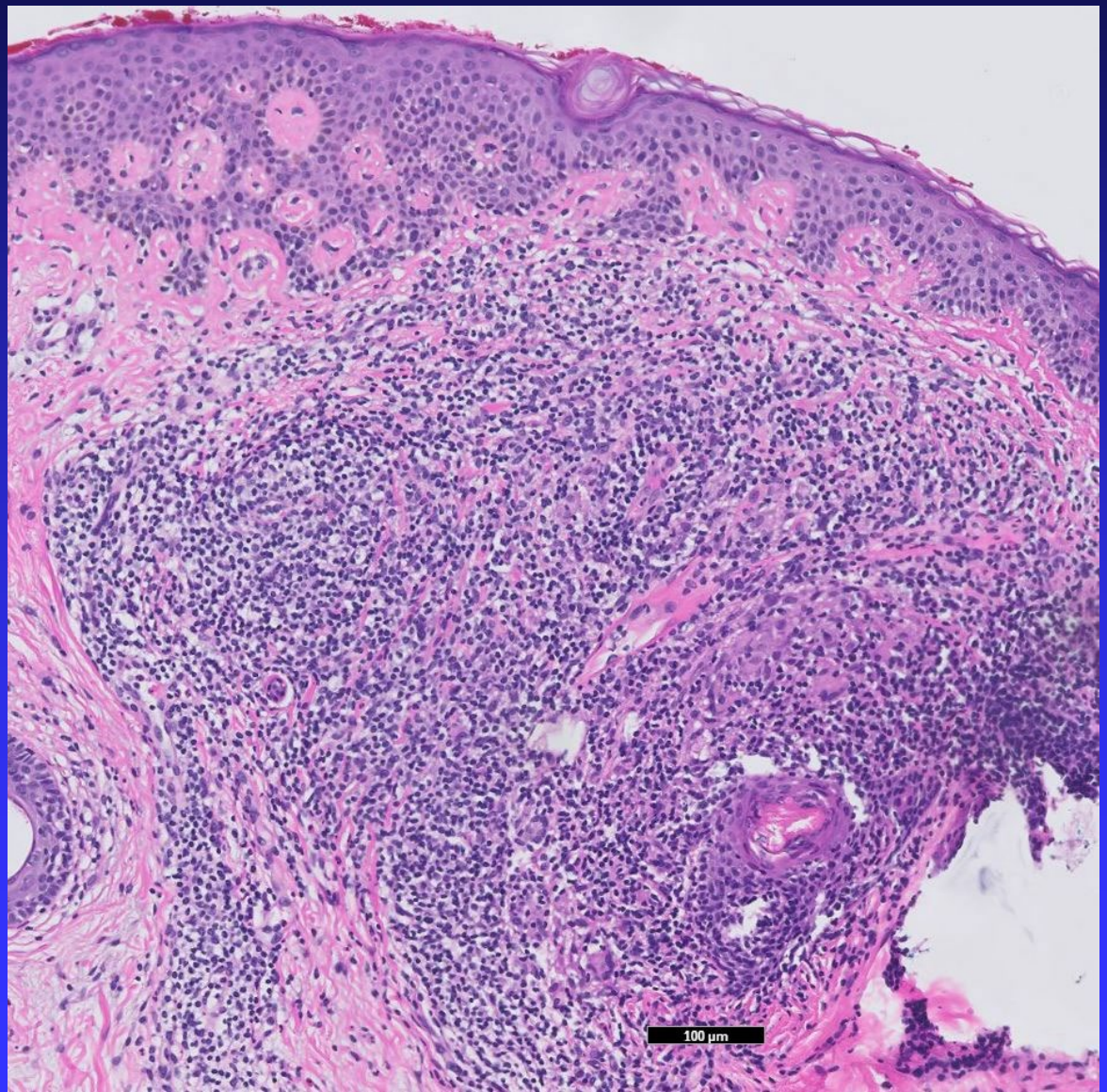
Facial papules in FFA



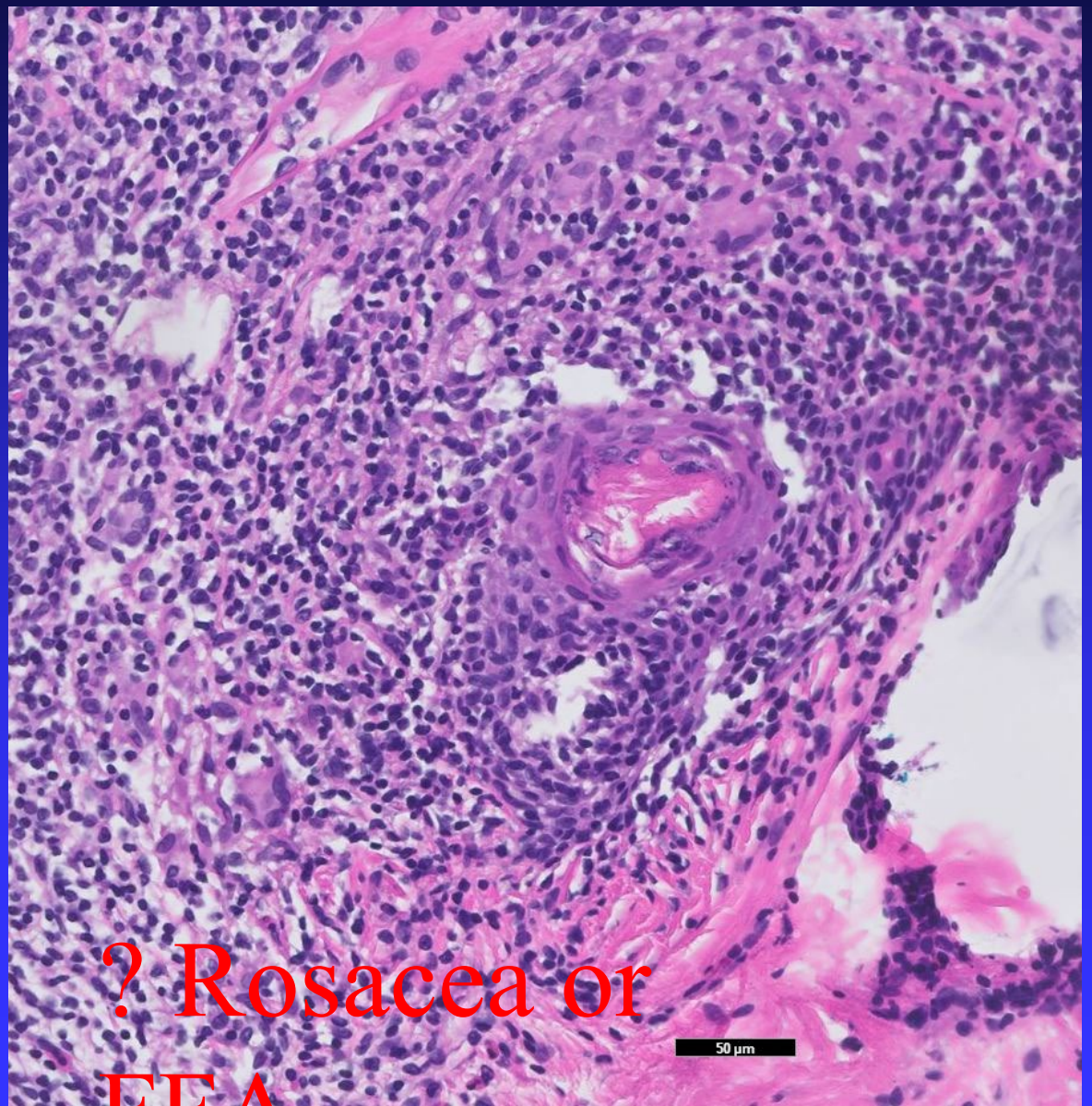
Facial papules in FFA



Facial papules in FFA



Facial papules in FFA



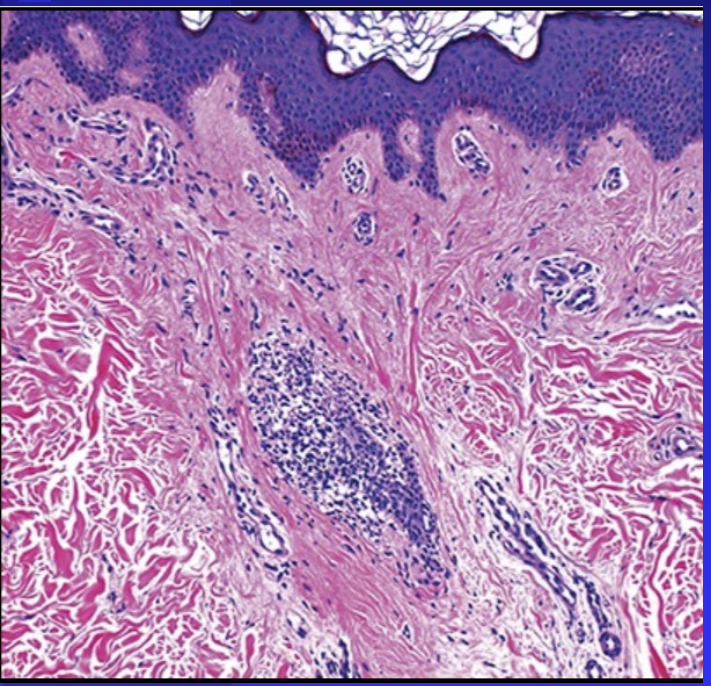
? Rosacea or FFA

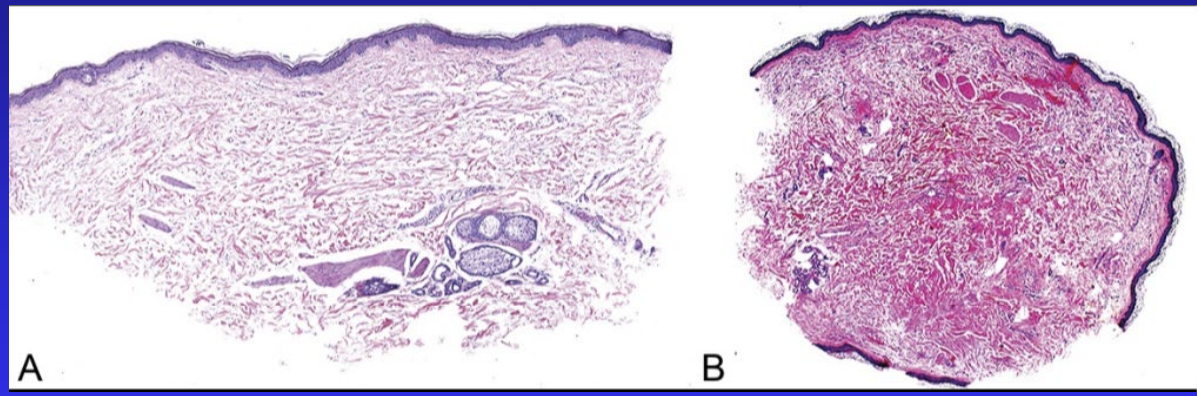
Facial Papules: FFA or rosacea?

Facial papules in FFA

- Confusing reports to on exact histopathology
- Biopsy generally not needed unless FFA has not yet been diagnosed

Frontal Fibrosing Alopecia--Limbs





Frontal Fibrosing Alopecia Involving the Limbs Shows Inflammatory Pattern on Histology: A Review of 13 Cases

Miteva, Mariya MD **Author Information**

The American Journal of Dermatopathology: March 2020 - Volume 42 - Issue 3 - p 226-229
doi: 10.1097/DAD.0000000000001500

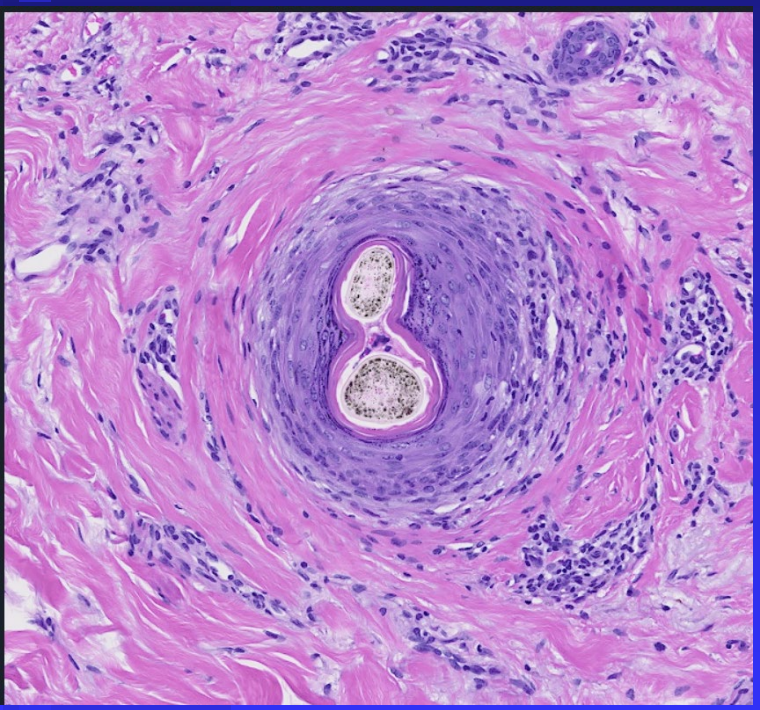
Histologic absence of yeast as a clue for classic lichen planopilaris, fibrosing alopecia in a pattern distribution, and frontal fibrosing alopecia: A cross-sectional observational study

Kimberly Williams, BS [a] · Antonella Tosti, MD [a] · Curtis T. Thompson, MD [b,c]

JAAD International, Volume 19, 10 - 11

There was a distinct difference between the absence and presence of yeast between cases of LPP/FAPD/FFA and FPHL. In LPP/FAPD/FFA, 98.5% (68/69) of cases had no identifiable yeast. In contrast, in FPHL 50% (34/68) of cases had identifiable yeast ($P < .001$).

Absence of yeast clue LPP/FFA



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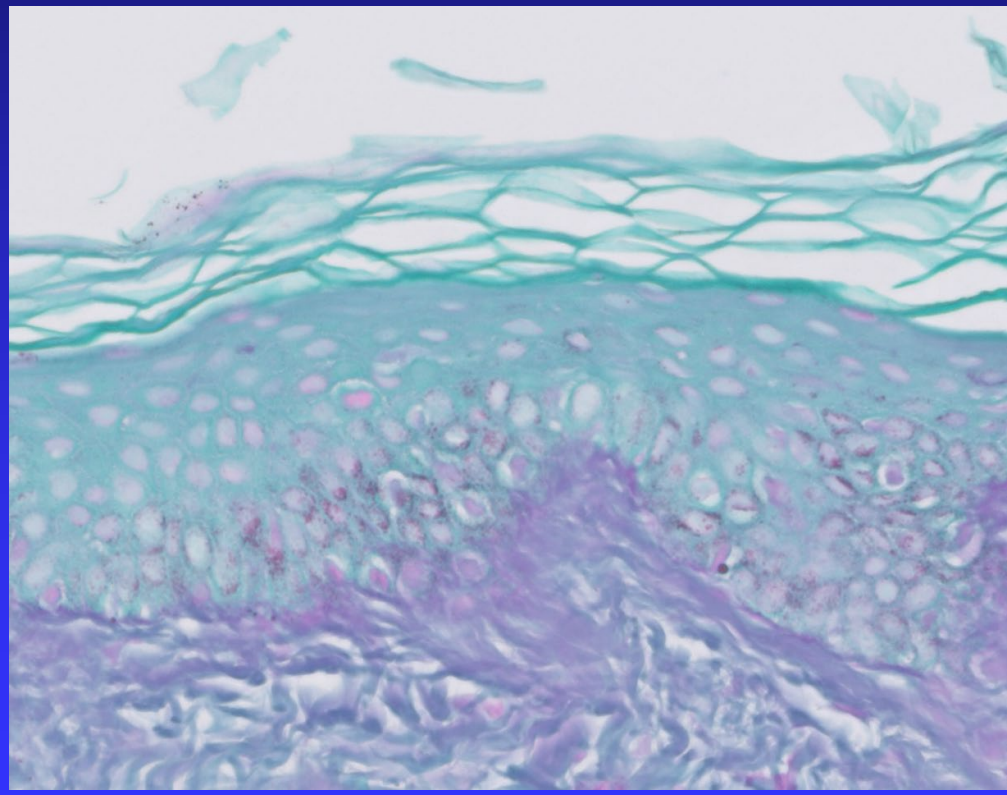
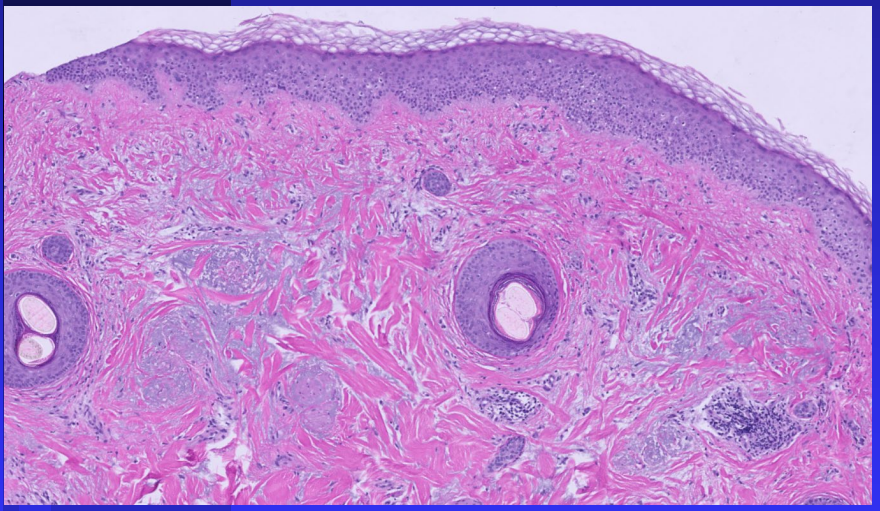


No sebaceous = No yeast



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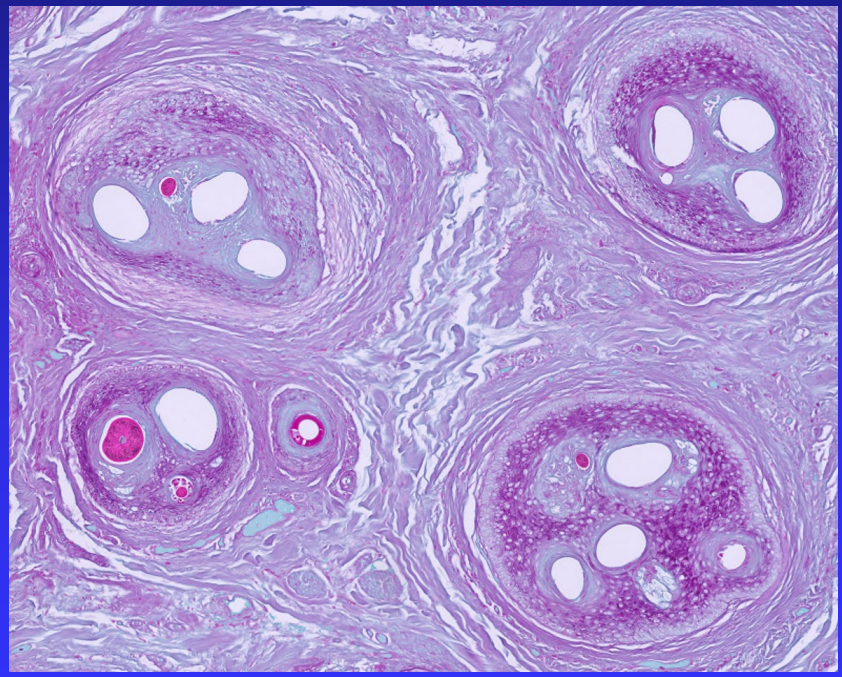
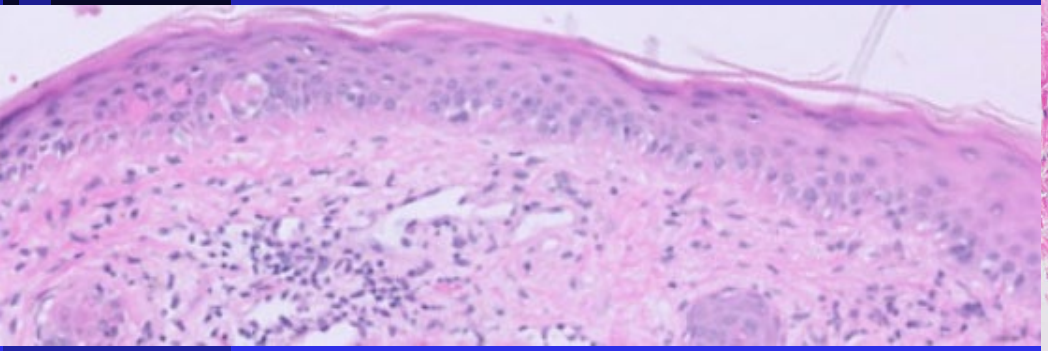
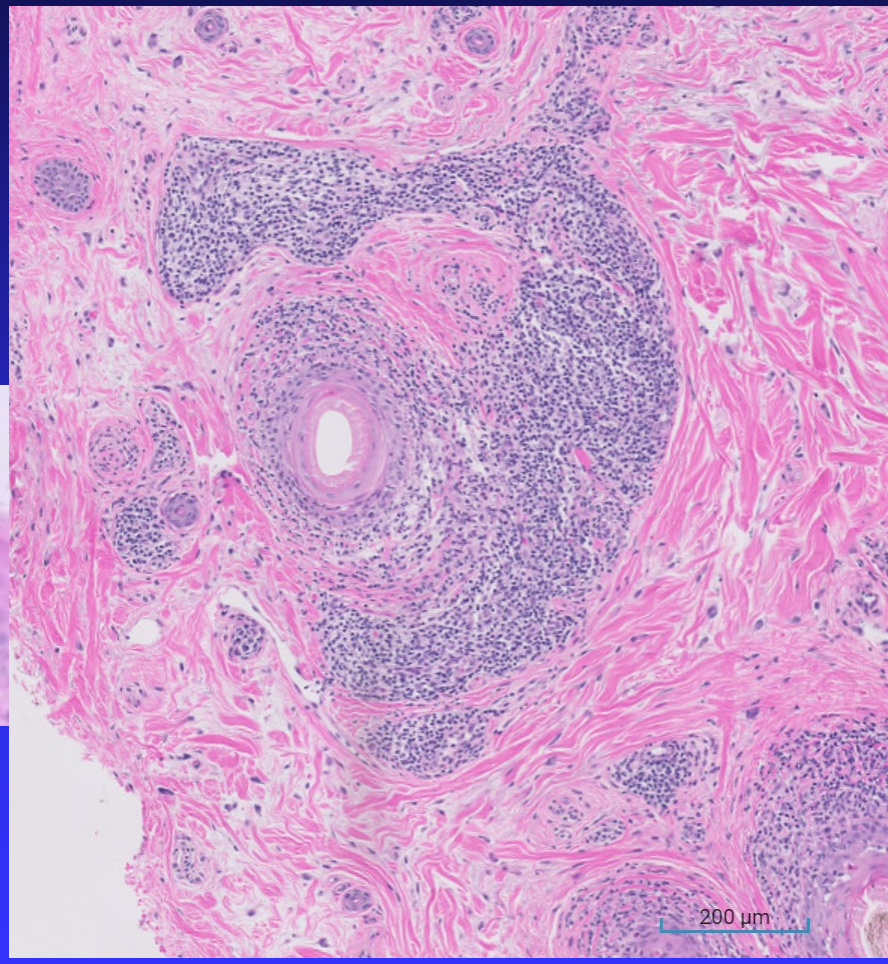


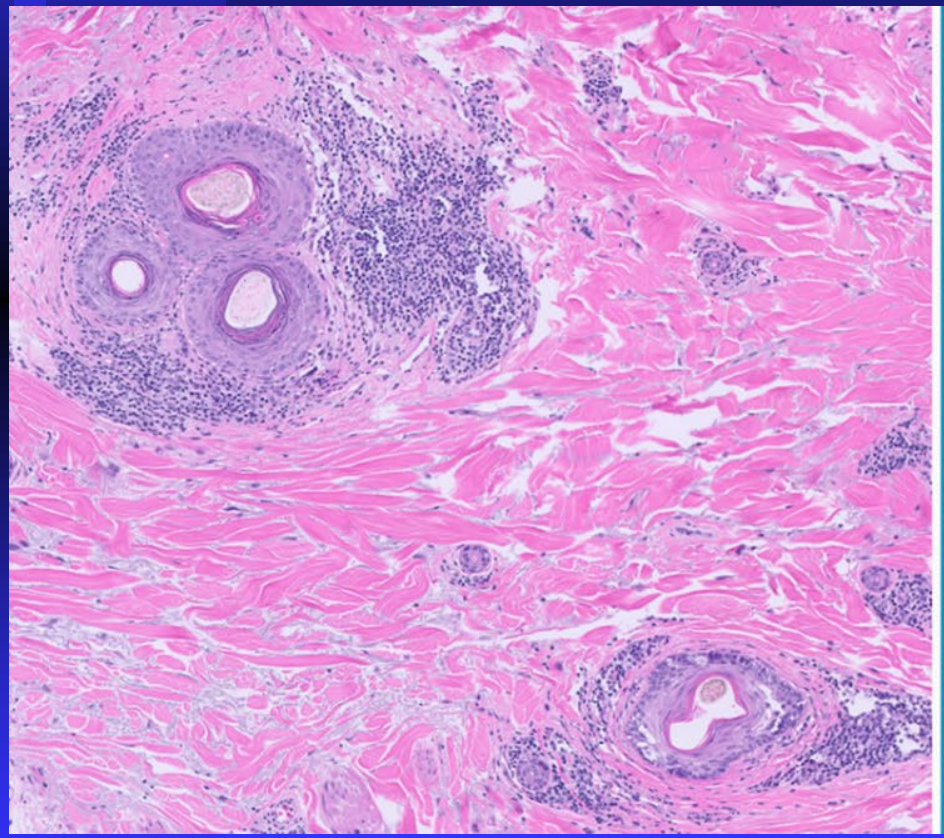
Chronic cutaneous (discoid) lupus erythematosus presenting as FFA

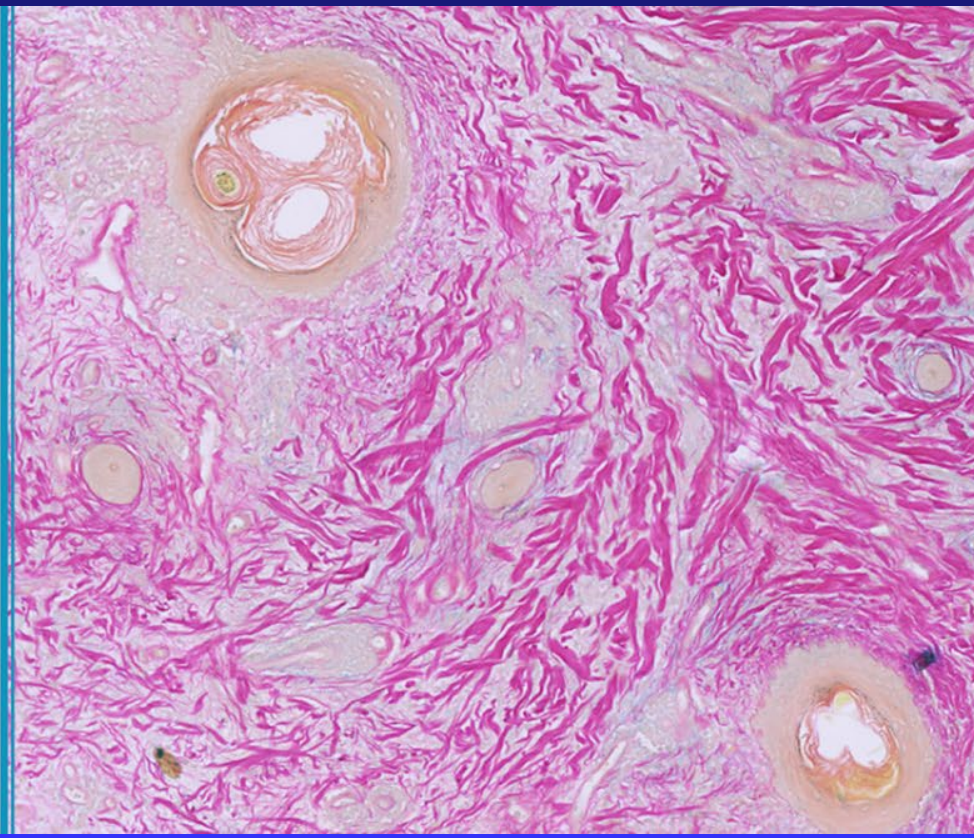
CCLE presenting like FFA





Lupus ≠ LPP/FFA





Arch Dermatol. 1994 Jun;130(6):770-4.

Postmenopausal frontal fibrosing alopecia. Scarring alopecia in a pattern distribution.

Kossard S[1].

Author information Papers

Erratum in
Arch Dermatol 1994 Nov;130(11):1407.

Fibrosing Alopecia in a Pattern Distribution
FAPD

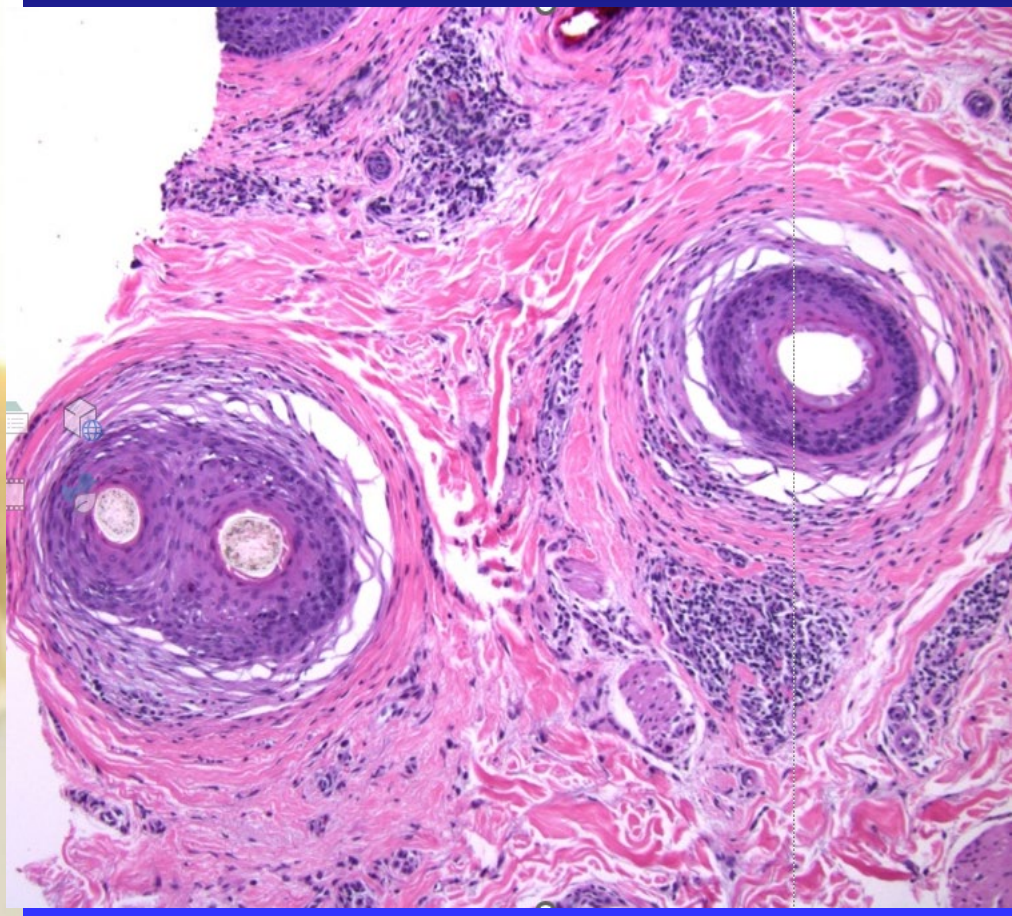
associated with perifollicular erythema within the marginal hairline, producing a frontal fibrosing alopecia extending to the temporal and parietal hair margins. Scalp biopsy specimens from the frontal hair margin showed perifollicular fibrosis and lymphocytic inflammation concentrated around the isthmus and infundibular areas of the follicles. Immunophenotyping of the lymphocytes showed a dominance of activated T-helper cells. Clinical review of all six cases showed a progressive marginal alopecia without the typical multifocal areas of involvement seen in lichen planopilaris or pseudopelade. None of the patients had mucous membrane or skin lesions typical of lichen planus. Hormonal studies, in five patients, showed no elevated androgen abnormalities.

CONCLUSIONS: Progressive frontal recession in postmenopausal women may show clinical features of a fibrosing alopecia. The histologic findings are indistinguishable from those seen in lichen planopilaris. However, the absence of associated lesions of lichen planus in all six women raises the possibility that this mode of follicular destruction represents a reaction pattern triggered by the events underlying postmenopausal frontal hairline recession.

J Eur Acad Dermatol Venereol. 2018 Jun;32(6):e218-e220. doi: 10.1111/jdv.14748. Epub 2018 Jan 15.

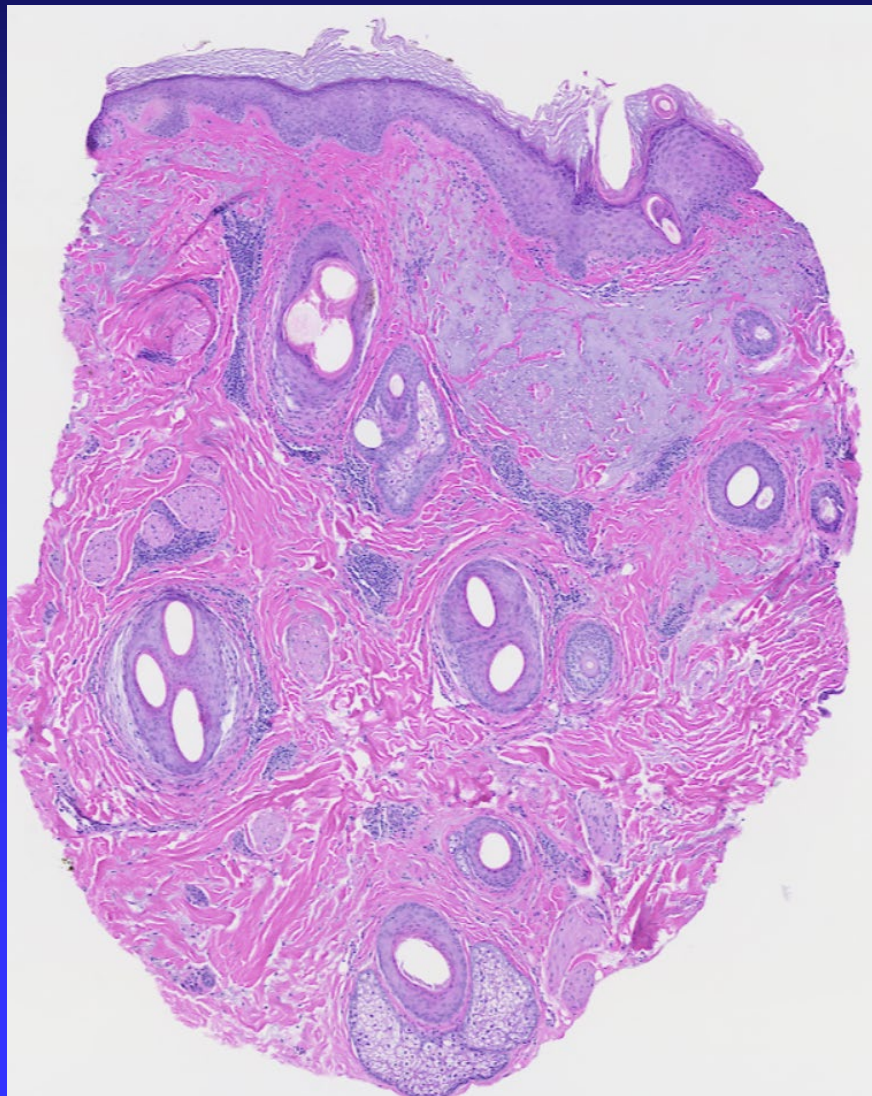
Is there a pathogenetic link between frontal fibrosing alopecia, androgenetic alopecia and fibrosing alopecia in a pattern distribution?

A C Katoulis [1], K Diamanti [1], D Sgouros [1], A I Liakou [1], E Bozi [1], G Avgerinou [2], I Panayiotides [3], D Rigopoulos [2]



Fibrosing alopecia in a pattern distribution (FAPD)

- FPHL
- LPP (diffuse)



Lichen Planopilaris (LPP)

- Mini-Epidemic?
  - Hair loss clinicians observing increased incidence.
  - Traditionally West Coast > East Coast

Lichen Planopilaris Increasing Incidence

- ?Nanoparticle?
  - Sunscreen?
  - Lichen planus—Metals, especially dental implicated
    - Gold, mercury—dental*
    - Nail LP associated with +metal patch test**

*Sasaki G et al. J Dermatol 23:890, 1996.
**Nishizawa A et al. J Eur Acad Dermatol Venerol 27:e231, 2013.

Br J Dermatol. 2016 Oct;175(4):762-7. doi: 10.1111/bjd.14535. Epub 2016 Jun 30.

Frontal fibrosing alopecia: possible association with leave-on facial skin care products and sunscreens; a questionnaire study.

Aldoori N[1], Dobson K[1], Holden CR[1], McDonagh AJ[1], Harries M[2], Messenger AG[3].

Author information

Abstract

BACKGROUND: Since its first description in 1994, frontal fibrosing alopecia (FFA) has become increasingly common, suggesting that environmental factors are involved in the aetiology.

OBJECTIVES: To identify possible causative environmental factors in FFA.

METHODS: A questionnaire enquiring about exposure to a wide range of lifestyle, social and medical factors was completed by 105 women with FFA and 100 age- and sex-matched control subjects. A subcohort of women with FFA was patch tested to an extended British standard series of allergens.

RESULTS: The use of sunscreens was significantly greater in the FFA group compared with controls. Subjects with FFA also showed a trend towards more frequent use of facial moisturizers and foundations but, compared with controls, the difference in frequencies just failed to reach statistical significance. The frequency of hair shampooing, oral contraceptive use, hair colouring and facial hair removal were significantly lower in the FFA group than in controls. Thyroid disease was more common in subjects with FFA than controls and there was a high frequency of positive patch tests in women with FFA, mainly to fragrances.

CONCLUSIONS: Our findings suggest an association between FFA and the use of facial skin care products. The high frequency of sunscreen use in patients with FFA, and the fact that many facial skin care products now contain sunscreens, raises the possibility of a causative role for sunscreen chemicals. The high frequency of positive patch tests in women with FFA and the association with thyroid disease may indicate a predisposition to immune-mediated disease.

Frontal fibrosing alopecia in men: an association with facial moisturizers and sunscreens

DOI: 10.1111/bjd.15311

Dear Editor, Frontal fibrosing alopecia (FFA) was first described by Kossard in 1994 in six postmenopausal women.[1] FFA remained rare during the 1990s, but in the last 10–15 years it has become increasingly common, a phenomenon observed worldwide. The recent onset and apparently rising incidence of FFA suggest involvement of environmental factors in the aetiology. We previously reported a questionnaire study in women with FFA that asked about a wide range of medical, social and environmental exposures. The results suggested an association between FFA and leave-on facial products, including moisturizers and sunscreens.[2] However, although the regular use of moisturizers was greater in women with FFA, these products are used by most women and we were unable to show a significant difference in their use between women with FFA and similarly aged controls. The use of primary sunscreens was significantly greater among women with FFA than in controls, but we were not able to assess whether patients were also exposed to sunscreens from other sources.

We have therefore repeated our questionnaire study in men with FFA, as we anticipated that their use of leave-on facial skincare products would be lower than in women.

As FFA is rare in men, patients were recruited from across the U.K. and one case was recruited from Belgium. In all cases the diagnosis was made by a clinician with special expertise in hair disease, and it was supported by histology in most cases. The clinical diagnosis was based on scarring alopecia affecting the frontal hairline causing recession of the hairline. Additional features included loss of eyebrows, follicular erythema of the frontal hairline and loss of sideburn and beard hair. Male controls aged 35–80 years were recruited from three sites (Sheffield, Salford and Glasgow). The patients completed a questionnaire similar to that used in our female study, but inviting more detailed information on the use of facial skincare and hair care products. Male patients with FFA were asked about the timing and distribution of hair loss, but otherwise the questionnaires completed by both groups were identical.

Seventeen men with FFA and 73 controls were recruited. The mean age of onset of hair loss in the patients with FFA was 54·5 years (range 35–77). All had loss of hair from the frontal hairline, and 16 (94%) had lost eyebrows. Twelve men (71%) reported loss of hair from the beard and 13 (76%) reported loss of hair from the limbs. All men with FFA reported using facial moisturizers, compared with 40% in the control group. Facial moisturizers were used at least twice a week by 94% of patients with FFA, but by only 32% of controls ($P < 0·001$) (Table 1). Sixteen patients reported using moisturizers for a period consistent with their use prior to the onset of FFA. The use of primary sunscreens by men with FFA was significantly more common than by controls. Overall 35% of men with FFA reported using a sunscreen at least twice a week all year round, compared with 4% of controls ($P = 0·0012$).

When moisturizers containing sunscreen chemicals were included in the analysis, at least 71% of men with FFA applied a product containing a sunscreen at least twice a week all year

Table 1 Reported use of skincare and hair care products by patients with frontal fibrosing alopecia (FFA) and controls

	Patients with FFA	Controls	P-value
Number of patients	17	73	
Age (years), mean (range)	63·1 (42–80)	59·1 (37–79)	
Age at onset of hair loss (years), mean (range)	54·5 (35–77)		
Facial moisturizer[a]	16 (94)	23 (32)	< 0·001
Primary sunscreen[b]	6 (35)	3 (4)	0·0012
Sunscreen[b]	12 (71)	8 (11)	< 0·001
Facial cleanser[a]	4 (24)	5 (7)	0·066
Facial scrub[a]	0	0	
Facial mask[a]	0	0	
Aftershave[a]	7 (41)	28 (39)	1·00
Shampoo[a]	13 (76)	62 (85)	0·27
Conditioner[a]	4 (24)	13 (18)	0·73
Hair spray[a]	1 (6)	2 (3)	0·48
Hair mousse[a]	0	0	
Hair gel[a]	2 (12)	10 (14)	1·00
Hair dye[c]	2 (12)	3 (4)	0·26

Values are n (%) unless stated otherwise. [a]Twice a week or more frequently. [b]Twice a week or more frequently all year round. [c]At least once a year. Sunscreen includes exposure to sunscreen chemicals in primary sunscreens and moisturizers. Analyses were performed after excluding subjects who failed to answer the question. Frequencies in the FFA and control groups were compared using Fisher's exact test.

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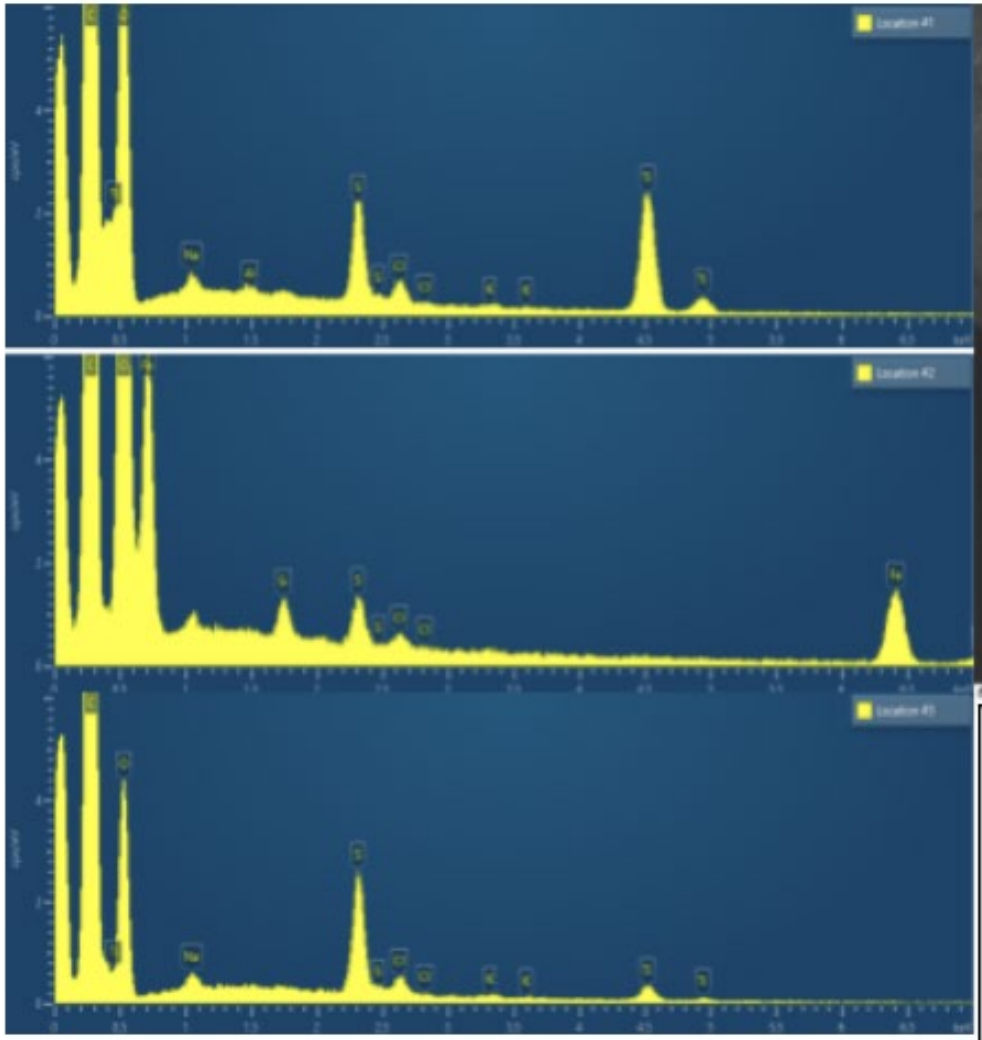
Debroy Kidambi A *et al.* Br J Dermatol 177:260-1, 2017.



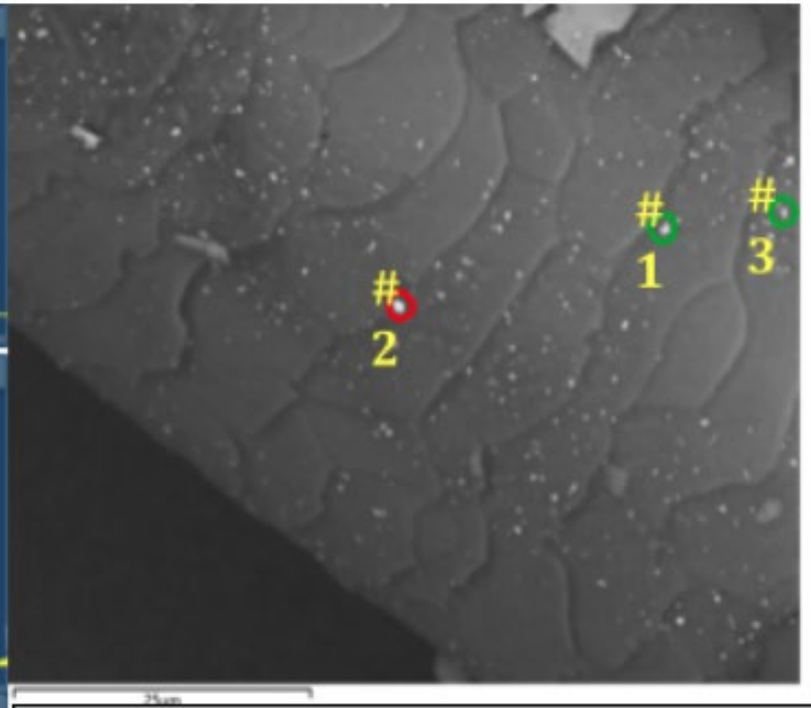


Fig. 1 Right: a backscattered electron image taken from one of typical hair shafts with SEM showing the presence of particles with brighter contrast on a hair shaft; Left: EDX spectra collected from particle 1-3 showing the presence of Ti species on particle 1 and 3.

Sunscreen

- Avobenzone, Homosalate, Octinoxate, Octisalate, Octocrylene, Oxybenzone
- Sd Alcohol 40, C12-15 Alkyl Benzoate, Acrylates Octylacrylamide Copolymer, Caprylyl Glycol, Dimethyl Capramide, Aloe Barbadensis (**Aloe Vera**) Leaf Extract, Retinyl Palmitate, Tocopherol, Fragrance.

Present in 96% of the U.S. population

Sur

Mirmirani, P., & Vanderweil, S. G. (2020). Frontal fibrosing alopecia with involvement of the central hair part: distribution of hair loss corresponding to areas of sunscreen application. *Dermatology Online Journal*, 26(11).

Fibrosing Alopecia in a Pattern Distribution

Hair root touch-up dye?

5A/MEDIUM ASH BROWN

WATER, C12-15 PARETH-3, AMMONIUM HYDROXIDE, OLETH-10, DILINOLEIC ACID, COCAMIDE MEA, LINOLEAMIDOPROPYL DIMETHYLAMINE DIMER DILINOLEATE, STEARETH-21, BEHENTRIMONIUM CHLORIDE, POLYQUATERNIUM-22, SODIUM SULFATE, FRAGRANCE, RESORCINOL, ERYTHORBIC ACID, p-PHENYLENEDIAMINE, CARAMEL, p-AMINOPHENOL, m-AMINOPHENOL, IRON OXIDES, MICA, SODIUM SULFITE, N,N-BIS(2-HYDROXYETHYL)-p-PHENYLENEDIAMINE SULFATE, 1-NAPHTHOL, SODIUM METASILICATE, EDTA, SARGASSUM FILIPENDULA EXTRACT, HYPNEA MUSCIFORMIS EXTRACT, GELLIDIELA ACEROSA EXTRACT, TITANIUM DIOXIDE.

African people with FFA

Dlova NC *et al.* BRJ 169:939-41, 2013.

FFA Causation

Meta-Analysis > Arch Dermatol Res. 2023 Oct;315(8):2313-2331.
doi: 10.1007/s00403-023-02604-7. Epub 2023 Apr 4.

Frontal fibrosing alopecia and personal care product use: a systematic review and meta-analysis

Olivia Kam [1], Sean Na [2], William Guo [3], Christina I Tejeda [3], Tara Kaufmann [3]

Nine studies
1,248 FFA patients
1,459 controls.

FFA Causation (9 studies)

- Sunscreen OR 3.02
  - 4.61 (men)
  - 2.74 (women)
- Facial moisturizer
  - 5.07 (men)
  - 1.58 (women)

Kam O, Na S, Guo W, Tejeda CI, Kaufmann T. Frontal fibrosing alopecia and personal care product use: a systematic review and meta-analysis. Arch Dermatol Res. 2023 Oct;315(8):2313-2331.

No FFA association (9 studies)

- Facial cleanser, toner, aftershave
- Foundation
- Shampoo, conditioner, mousse, gel, dye, straightening/rebonding, perming

Kam O, Na S, Guo W, Tejeda CI, Kaufmann T. Frontal fibrosing alopecia and personal care product use: a systematic review and meta-analysis. Arch Dermatol Res. 2023 Oct;315(8):2313-2331.

Meta-Analysis > JAMA Dermatol. 2025 Mar 1;161(3):310-314.
doi: 10.1001/jamadermatol.2024.6434.

Epistasis of ERAP1 With 4 Major Histocompatibility Complex Class I Alleles in Frontal Fibrosing Alopecia: A Genome-Wide Association Study Meta-Analysis

- 6668 included patients
  - 1585 FFA (European female)
  - 5083 controls.

FFA Genomic Associations

- Genome-wide significant associations at 4 genomic loci
  - HLA-A*11:01, HLA-A*33:01, HLA-B*07:02, and HLA-B*35:01.
  - ERAP1 gene mutation at 5q15

Rayinda T, Dand N, McSweeney SM, Christou E, Ung CY, Stefanato CM, Fenton DA, Harries M, Palamaras I, Tidman A, Holmes S, Koutalopoulou A, Ardern-Jones M, Kaur M, Papanikou S, Chasapi V, Vañó-Galvan S, Saceda-Corralo D, Melián-Olivera A, Azcarraga-Llobet C, Lobato-Berezo A, Bustamante M, Sunyer J, Starace MVR, Piraccini BM, Wiss IP, Senna MM, Singh R, Hillmann K, Kanti-Schmidt V, Blume-Peytavi U, McGrath JA, Simpson MA, Tziotzios C. Epistasis of ERAP1 With 4 Major Histocompatibility Complex Class I Alleles in Frontal Fibrosing Alopecia: A Genome-Wide Association Study Meta-Analysis. JAMA Dermatol. 2025 Mar 1;161(3):310-314.

FFA Causation (Summary)

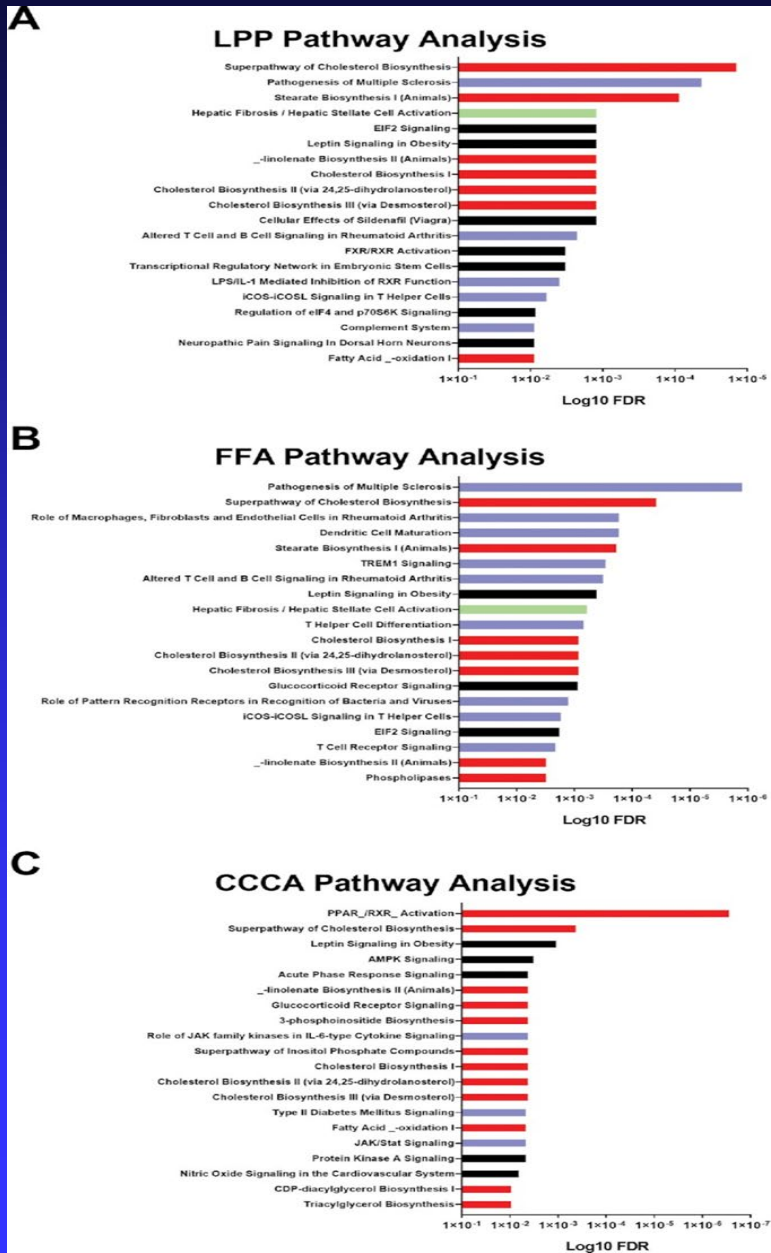
- Sunscreen (men and women) and Facial moisturizer (men)

- Genetic predisposition
  - (40% with association with 4 genomic loci)
    - HLA-A*11:01, HLA-A*33:01, HLA-B*07:02, and HLA-B*35:01.
    - ERAP1 gene mutation at 5q15

Hypothesis:
All caused by same chemical?

- Lichen planopilaris
- Frontal fibrosing alopecia
- Fibrosing alopecia in a pattern distribution
- Central centrifugal cicatricial alopecia
- Lichen planus pigmentosus

Shared dysregulated pathways in cholesterol biosynthesis and ...



Eddy H C Wang, Isha Monga, Brigitte N Sallee, James C Chen, Alexa R Abdelaziz, Rolando Perez-Lorenzo, Lindsey A Bordone, Angela M Christiano, Primary cicatricial alopecias are characterized by dysregulation of shared gene expression pathways, *PNAS Nexus*, Volume 1, Issue 3, July 2022, pgac111.

Hypothesis

- Does sun protection allow chronic inflammation to occur?
- If so, then different sunscreen products could promote LPP and FFA, especially in genetically-susceptible people.

Australas J Dermatol. 2018 Jun 12. doi: 10.1111/ajd.12833. [Epub ahead of print]

Frontal fibrosing alopecia: Regrowth following cessation of sunscreen on the forehead.

Cranwell WC[1,2,3,4], Sinclair R[1,5,6].

36 months after cessation

Thank you very much!

- University of Miami
  - Antonella Tosti, Betty Nguyen and Kimberly Williams
- California
  - Paradi Mirmirani and Vera Price
- Belgium
  - Athanassios Kolivras
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  - Anna Lyakhovitsky
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Mahalo!

¡Gracias!

Merci beaucoup!

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