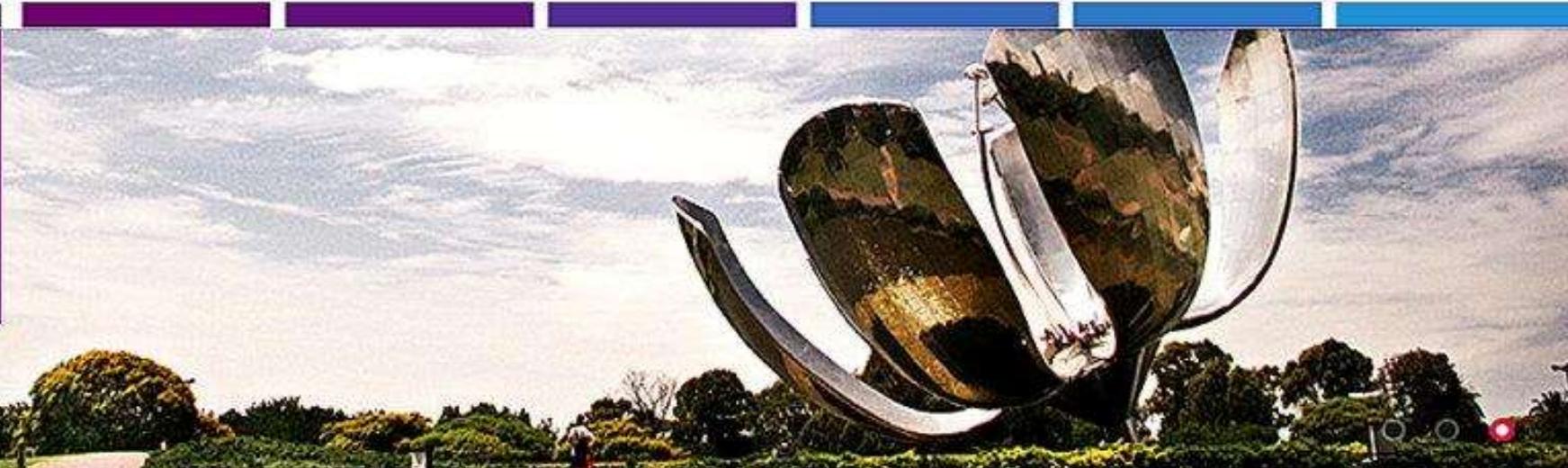




25 al 29 Octubre de 2016



LO NUEVO, LO IMPORTANTE, PARA INTERPRETAR UNA BIOPSIA POR ALOPECIA.

Rodrigo Restrepo
Jefe Dermatopatología Universidad CES
Profesor Dermatopatología UPB
Medellín. Colombia.

**Doctor, llego una biopsia de pelo por efluvium telógeno.
¿Y, cómo la corto?.....**



SIN EMBARGO HA HABIDO GRANDES AVANCES EN LA CARACTERIZACIÓN DE LAS ENFERMEDADES DEL PELO.

- Algunos procedimientos diagnósticos nuevos han aparecido y otros se han consolidado definitivamente.
- Igualmente la comprensión de las enfermedades del pelo ha mejorado y es probable que aparezcan nuevos tratamientos.

Revisaremos algunas de estas ideas.

- Dermatoscopia
- Proceso de biopsia más adecuado
- Parámetros normales en población sana
- Estelas foliculares Vs. Cicatrices foliculares
- Alopecia cicatricial linfocítica Vs Neutrofílica
- Folículo compuestos -Normales-
- Alopecia areata. Fisiopatología

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DERMATOSCOPIA

- Método no invasivo que permite reconocer estructuras típicas en las enfermedades del cuero cabelludo.



Guía la toma de la biopsia a las áreas más significativas.



Alopecias no cicatriciales	Características dermatoscópicas ¹⁻⁴
Alopecia androgenética	Heterogeneidad en el grosor del tallo mayor del 20% Puntos amarillos Incremento en la proporción de vellos Halo café perifolicular Unidades foliculares con solo un folículo piloso emergiendo
Efluvium telógeno	Múltiples pelos cortos en recrecimiento Unidades foliculares con solo un folículo piloso emergiendo o vacías
Alopecia areata	Puntos amarillos y puntos negros Pelos en signo de admiración, pelos rotos, vellos Sugieren actividad: puntos negros, pelos en signo admiración, pelos rotos Sugieren severidad: puntos amarillos, vellos
Tiña capititis	Pelos en espiral, coma y/o sacacorcho Puntos negros
Tricotilomanía	Múltiples anormalidades del tallo en ausencia de cambios perifoliculares Pelos rotos a diferentes longitudes, pelos cortos con tricopilosis, pelos en espiral, pelos en signo de admiración Puntos negros
Alopecia triangular congénita	Aperturas foliculares normales con vellos rodeados por pelos terminales

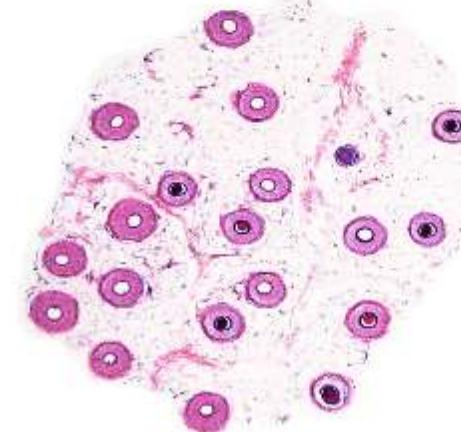
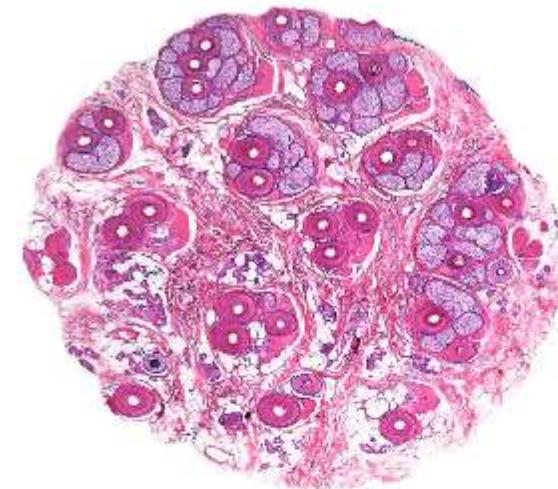
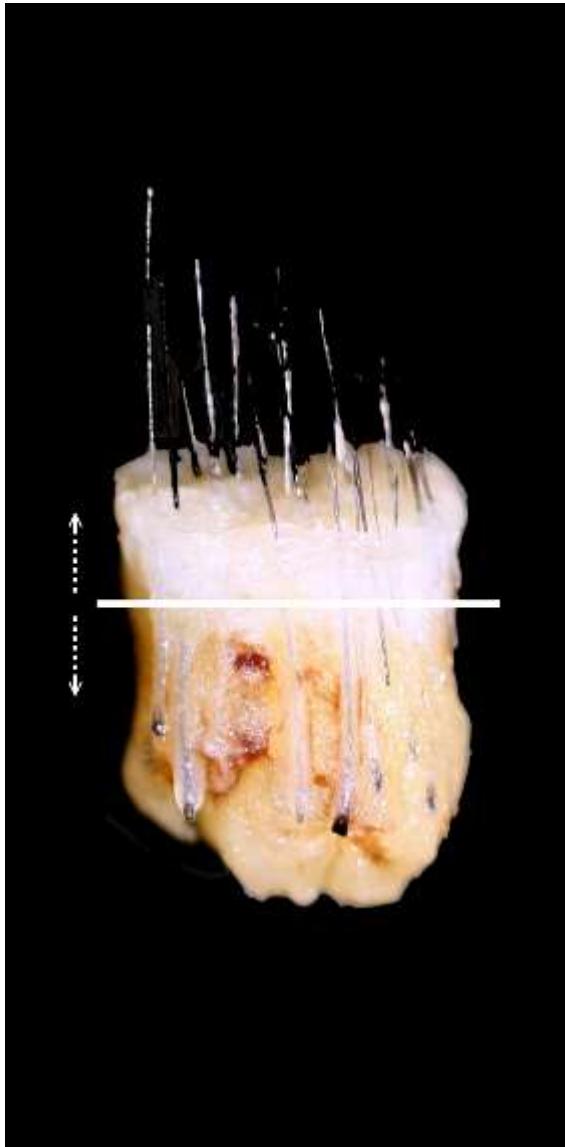
1. Mubki T, Rudnicka L, Olszewska M, Shapiro J. Evaluation and diagnosis of the hair loss patient: part II. Trichoscopic and laboratory evaluations. *J Am Acad Dermatol.* 71, 2014;431.e1-431.e11.
2. Jain N, Doshi B, Khopkar U. Trichoscopy in alopecias: diagnosis simplified. *Int J Trichology.* 5, 2013;170-8.
3. Tosti A, Torres F. Dermoscopy in the diagnosis of hair and scalp disorders. *Actas Dermosifiliogr.* 2009;100 Suppl 1:114-9.
4. Ferrández L, Moreno D, Peral F, Camacho FM. Tricoscopia. *Piel.* 26, 2011;323-29

Alopecias cicatriciales	Características dermatoscópicas¹⁻³
Característica general de alopecias cicatriciales	Ausencia de puntos negros o amarillos Áreas rojo lechosas
Liquen plano	Descamación peri-folicular tubular Puntos gris- azul en diana Sugieren actividad: vasos sanguíneos elongados en distribución concéntrica y áreas violáceas inter-foliculares Sugieren enfermedad avanzada: áreas blancas irregulares con ausencia de aperturas foliculares
Alopecia frontal fibrosante	Pelos individuales rodeados de áreas fibróticas Ausencia de orificios foliculares Eritema y descamación peri-folicular leve
Lupus discoide	Puntos amarillo-cafe grandes Enfermedad avanzada: vasos arboriformes Sugieren buen pronóstico: puntos rojos
Foliculitis decalvans	Orificios foliculares con 5 a más de 20 tallos pilosos Descamación amarilla peri-folicular tubular Pústulas foliculares
Celulitis disecante	Estadios tempranos: puntos negros y amarillos. Aparecen como estructuras tridimensionales sobre pelos distróficos Áreas sin estructura amarillas

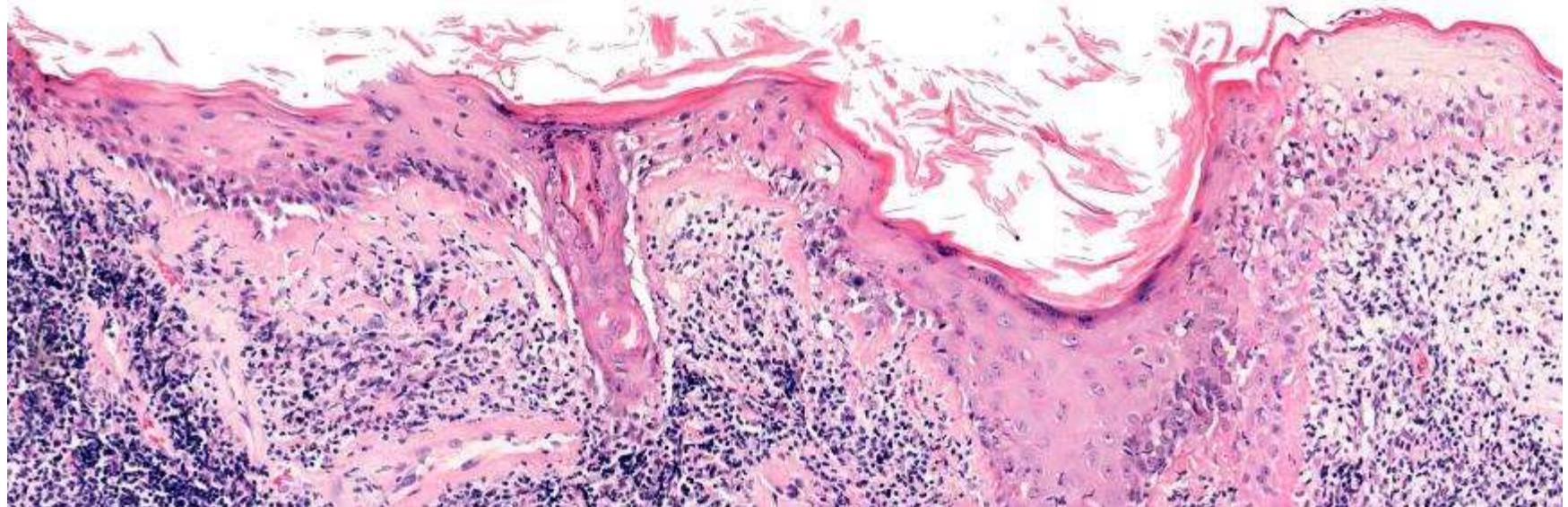
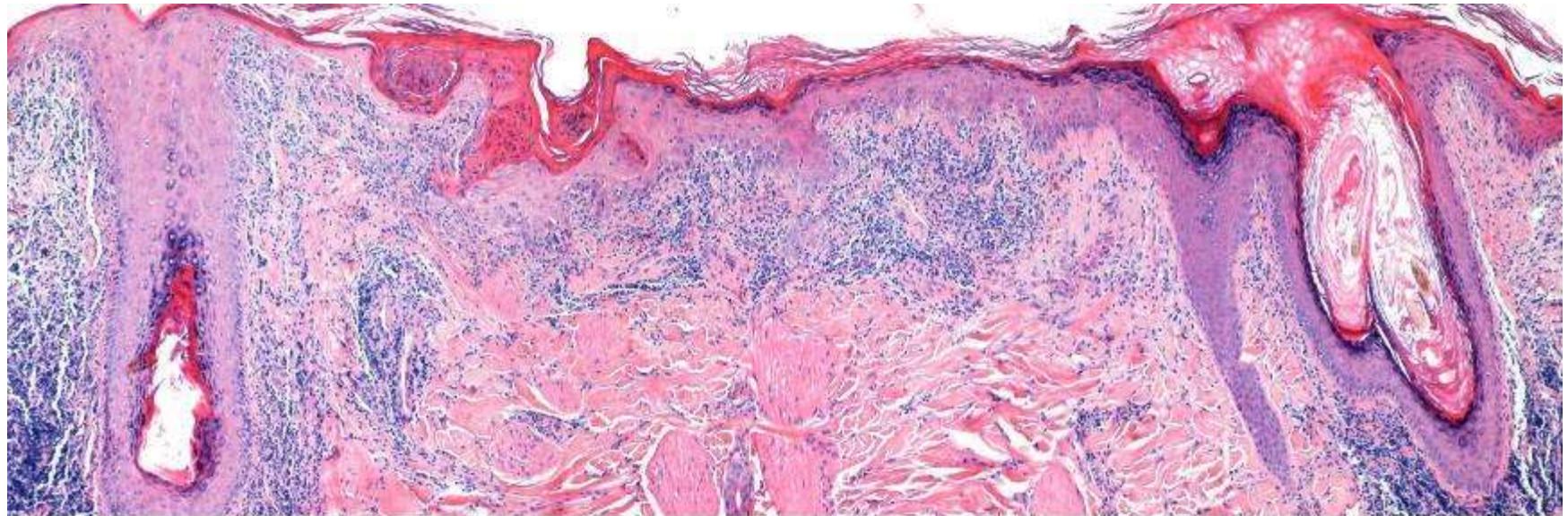
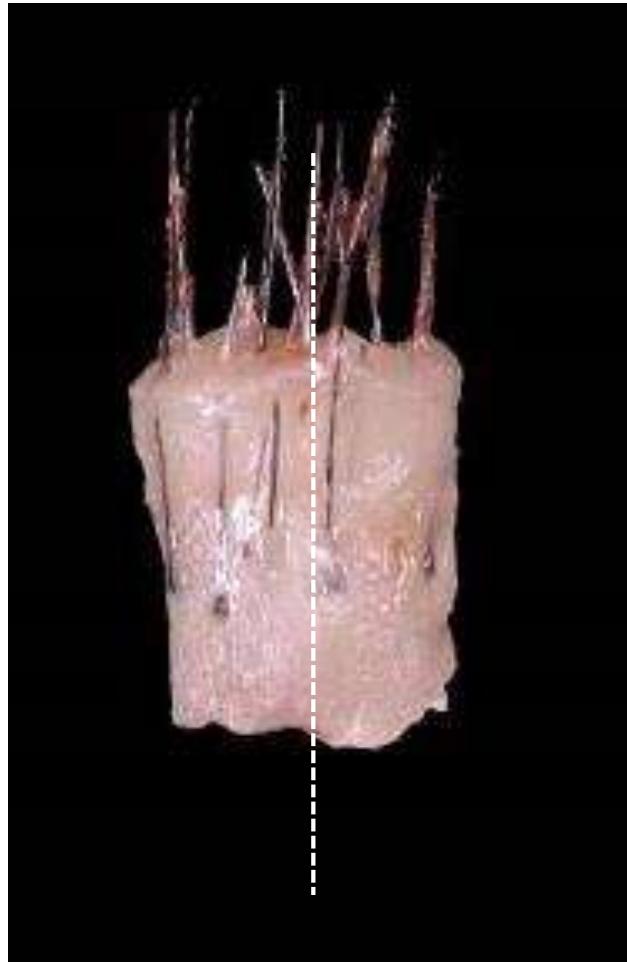
1. Mubki T, Rudnicka L, Olszewska M, Shapiro J. Evaluation and diagnosis of the hair loss patient: part II. Trichoscopic and laboratory evaluations. *J Am Acad Dermatol.* 2014;71(3):431.e1-431.e11.
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PROCESO DE BIOPSIA MÁS ADECUADO



PROCESO DE BIOPSIA MÁS ADECUADO



HA APARECIDO OTROS MÉTODOS PARA PROCESAR BIOPSIAS DE CUERO CABELLUDO

J Cutan Pathol. 2012; 39: 506–508
doi: 10.1111/j.1600-0536.2011.01620.x
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Journal of
Cutaneous Pathology

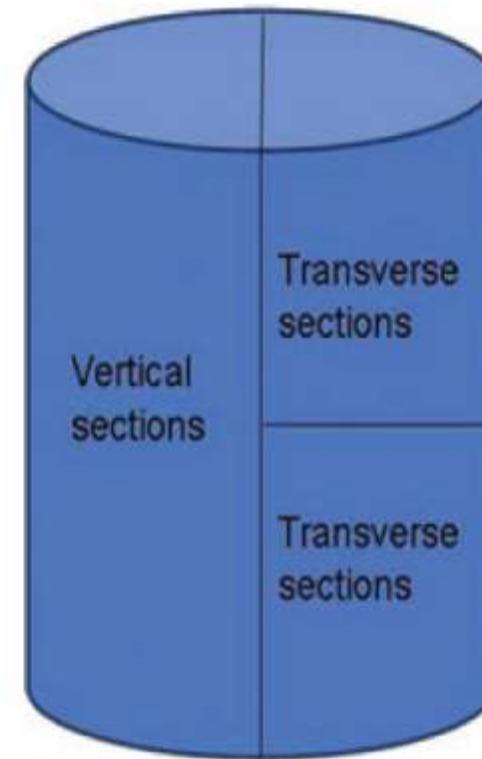
Letter to the Editor

The ‘Tyler technique’ for alopecia biopsies

Keywords: alopecia, dermatologist, dermatology, dermatopathology

Técnica de Tyler

- El punch es seccionado verticalmente.
- Una mitad se usa para cortes verticales y la otra para cortes horizontales.



Técnica de HoVert (Horizontal & Vertical).

- El punch es cortado transversalmente a 1 mm de la superficie.
- La mitad inferior se usa para cortes transversales y el disco epidérmico superior para cortes verticales.

J Cutan Pathol 2011; 38: 401–406
doi: 10.1111/j.1600-0560.2010.01669.x
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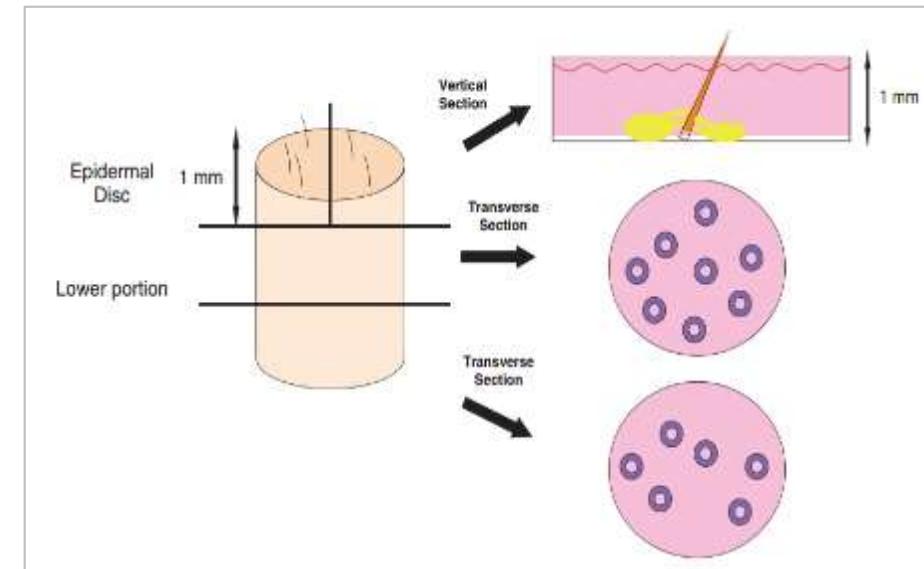
**Journal of
Cutaneous Pathology**

The HoVert technique: a novel method for the sectioning of alopecia biopsies

Background: Cicatricial forms of alopecia, including lichen planopilaris (LPP) and discoid lupus erythematosus (DLE), may present with overlapping clinical features. In such cases, histopathological examination may provide key information for resolving the differential diagnosis. Optimally, microscopical analysis for alopecia requires both vertical and horizontal sections, and this may necessitate multiple samples. Here, we present what we term the "HoVert" technique,

Jennifer V. Nguyen, Kristin Hudacek, Joseph A. Whitten, Adam I. Rubin and John T. Seykora

Department of Dermatology, University of Pennsylvania Medical School, Philadelphia, PA, USA



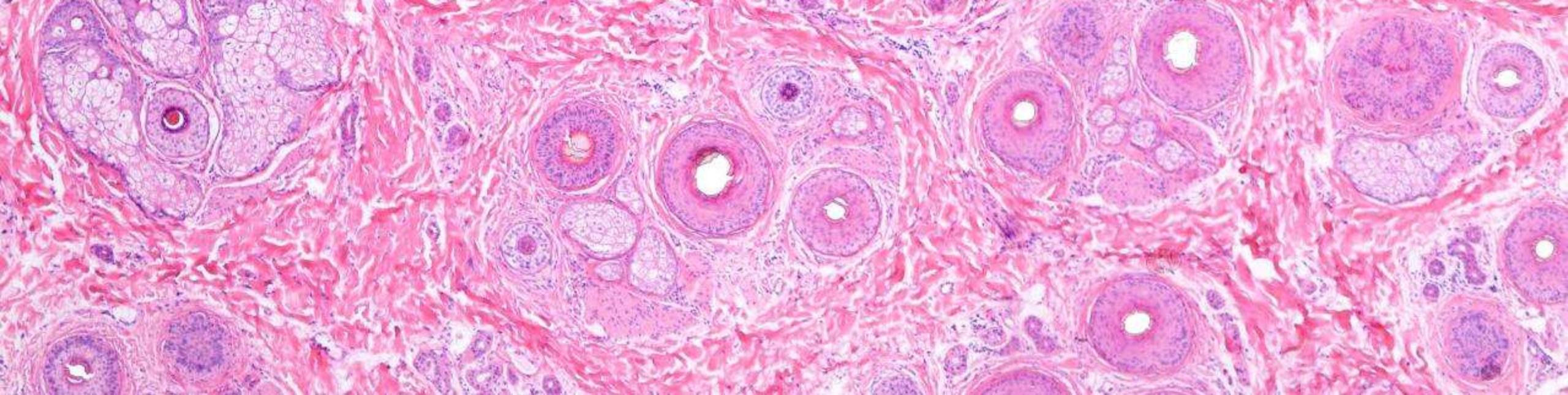
Definitivamente usar cortes horizontales en :

- Alopecia androgénica
- Efluvium telógeno crónico
- Alopecia areata crónica e incógnita

Definitivamente usar cortes verticales en:

- Foliculitis disecante
- Foliculitis decalvans
- Alopecia psoriásica

En los otros casos use el corte con el que se sienta más cómodo.



Cuando se toman biopsias por alopecia, debería quedar claro para el patólogo cual es el diagnóstico principal y los diagnósticos diferenciales

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PARÁMETROS NORMALES EN POBLACIÓN SANA

MD,^{*†} Yu-HUEI HUANG, MD,^{*†} AND TSENG-TONG KUO, MD, PHD^{‡†}

Horizontal scalp biopsy is a better method to use when evaluating hair loss requires quantitative data regarding normal hair counts to be used as a guide only for Caucasians, African Americans, Koreans, and Iranians.

evaluate scalp hair counts in the Taiwanese population.

4-mm punch biopsies were taken from clinically normal-looking scalp skin during scalp surgery for non-hair-loss disorders. Punch biopsy specimens were taken at the sebaceous gland level and the number of follicular units, terminal hairs, and vellus hairs were counted and compared with other published data. Data were compared between the sexes, different age groups, and different anatomic sites.

Average counts of total hairs, terminal hairs, vellus hairs, and follicular units were 11.3, 20.5, 0.8, and 9.4, respectively. The mean ratio of anagen hair to telogen hair to vellus hair was 25.3:1. The average density of hair follicles was 1.6 hairs/mm². Total hairs, follicular units, and hair follicles/mm² were significantly higher in men than in women. Total hairs, terminal hairs, and hair follicles/mm² increased with age in both sexes. There was no significant difference in hair counts between the two sides of the head in either sex. The mean number of hairs per follicular unit was 2.3. The mean ratio of terminal hair to vellus hair was 25.3:1. The mean ratio of anagen hair to telogen hair was 3.6:1. The mean density of hair follicles was 1.6 hairs/mm².

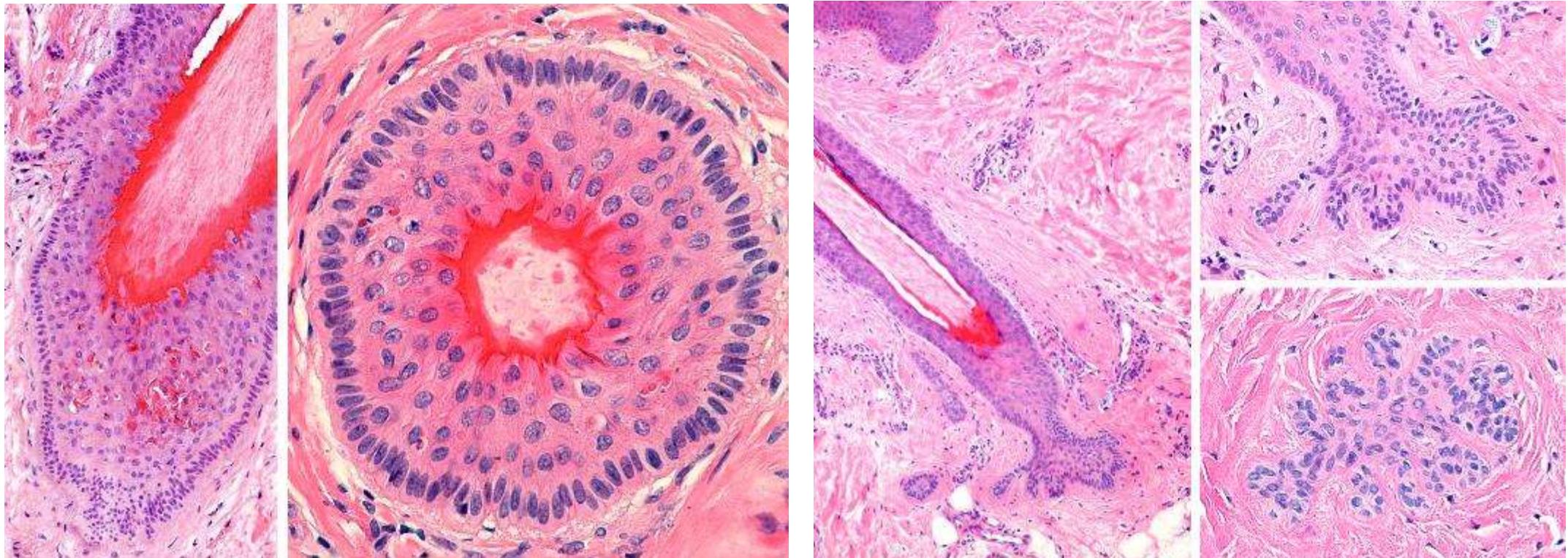
1. Whiting DA. **Diagnostic and predictive value of horizontal sections of scalp biopsy specimens in male pattern androgenetic alopecia.** J Am Acad Dermatol 1993;28:755–63.
2. Sperling LC. **Hair density in African Americans.** Arch Dermatol 1999;135:656–8.
3. Lee HJ, et al. **Hair counts from scalp biopsy specimens in Asians.** J Am Acad Dermatol 2002;46:218– 21.
4. Aslani FS, et al. **Hair counts in scalp biopsy of males and females with androgenetic alopecia compared with normal subjects.** J Cutan Pathol 2009;36:734–9.

	Taiwanese, n = 31 <i>Present study</i>	Korean, n = 35 <i>Lee et al</i> ⁵	Iranian, n = 30 <i>Aslani</i> ⁸	Caucasian, n = 22 <i>Whiting</i> ²	African American, n = 10 <i>Spektor</i> ⁹
terminal hairs,	37.0 ± 15.3	33.1 ± 10.0	35.5 ± 14.7	43 ± 3.5	31.7 ± 10.0
terminal hairs,	20.5 ± 4.6	14.9 ± 3.2	34 ± 6.4	35 ± 2.1	18.4 ± 4.0
terminal hairs,	0.8 ± 1.0	1.1 ± 1.3	2.4 ± 1.2	5 ± 0.6	3.0 ± 1.0
terminal hairs,	21.3 ± 4.8	16.1 ± 3.6	36.3 ± 7.2	40 ± 2.2	21.5 ± 4.0
terminal hair units,	9.4 ± 1.9	7.8 ± 1.7	ND	14 ± 0.5	ND
terminal hair ratio,%	91.6:8.4	93.6:6.4	93.7:6.3	93.5:6.5	93.9:6.1
terminal hair ratio	25.3:1	13.5:1	17.4:1	7:1	6.1:1
terminal hair density	1.69 ± 0.4	1.2 ± 0.3	2.89 ± 0.6	3.1 ± 0.8	1.65 ± 0.4

terminal hairs,	20.5 ± 4.6	14.9 ± 3.2	34 ± 6.4	35 ± 2.1	18
sebaceous hairs,	0.8 ± 1.0	1.1 ± 1.3	2.4 ± 1.2	5 ± 0.6	3
→ terminal hairs,	21.3 ± 4.8	16.1 ± 3.6	36.3 ± 7.2	40 ± 2.2	2
→ sebaceous units,	9.4 ± 1.9	7.8 ± 1.7	ND	14 ± 0.5	N
ratio, %	91.6:8.4	93.6:6.4	93.7:6.3	93.5:6.5	9:
ratio	25.3:1	13.5:1	17.4:1	7:1	6:
	1.69 ± 0.4	1.2 ± 0.3	2.89 ± 0.6	3.1 ± 0.8	1:
larger	0.75 ± 0.2	0.62 ± 0.1	ND	1.11 ± 0.04	N

La variación puede ser debido a la no estandarización de las variables :

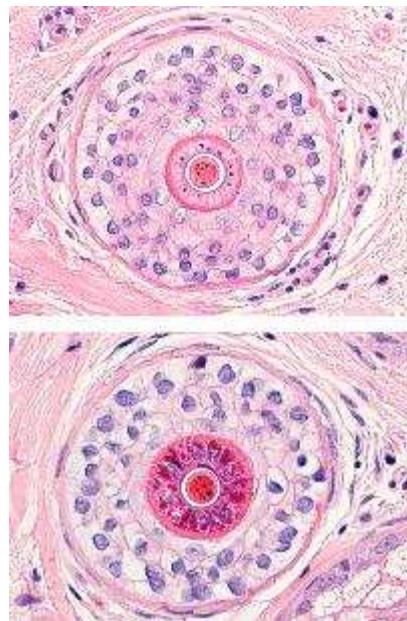
- **¿Se incluyeron pelos en catagen en el conteo de telogen?**



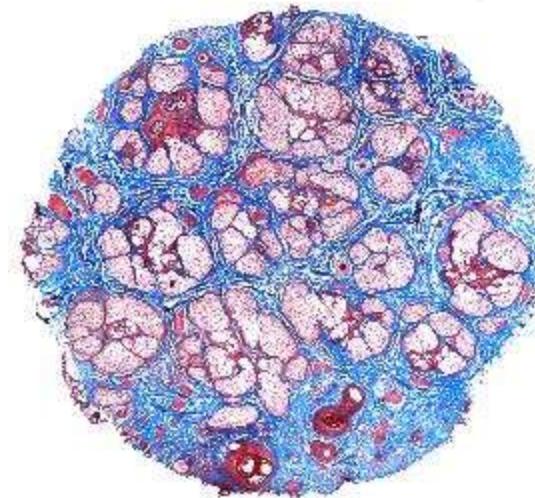
La variación puede ser debido a la no estandarización de las variables :

- **¿Como se contabilizaron los folículos intermedios (FI)?**

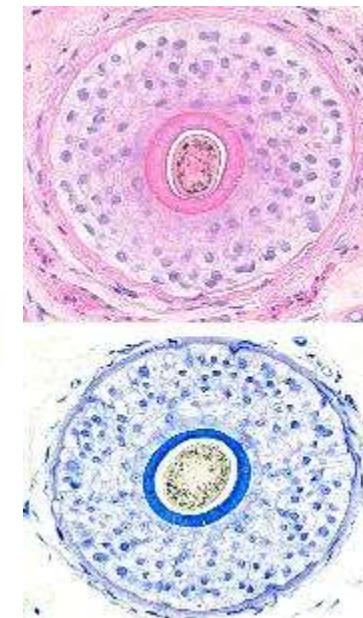
No hay un consenso acerca de a que grupo (Terminales/Vellos) asignar los FI.
Actualmente se recomienda agregarlos equitativamente a ambos.



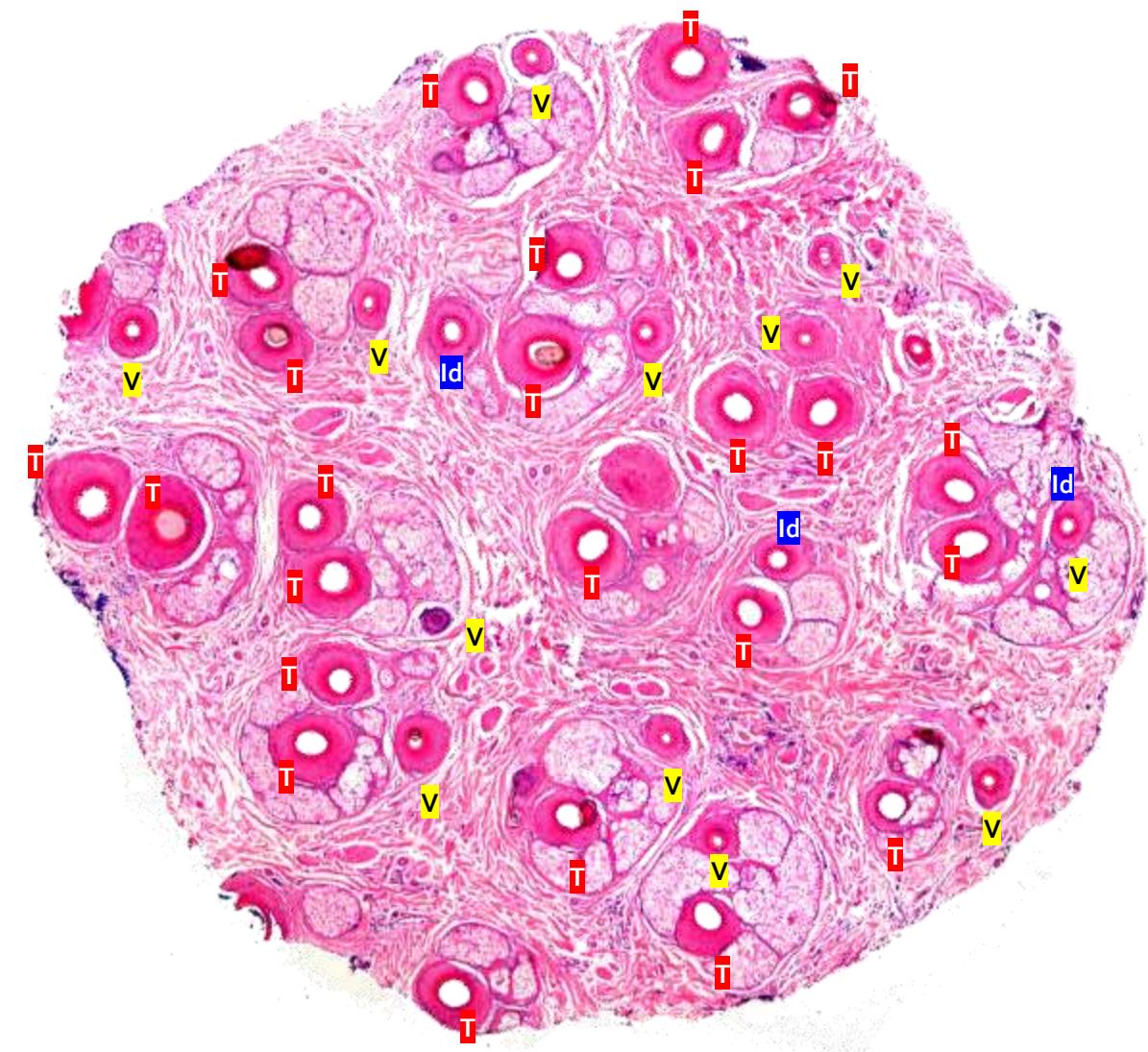
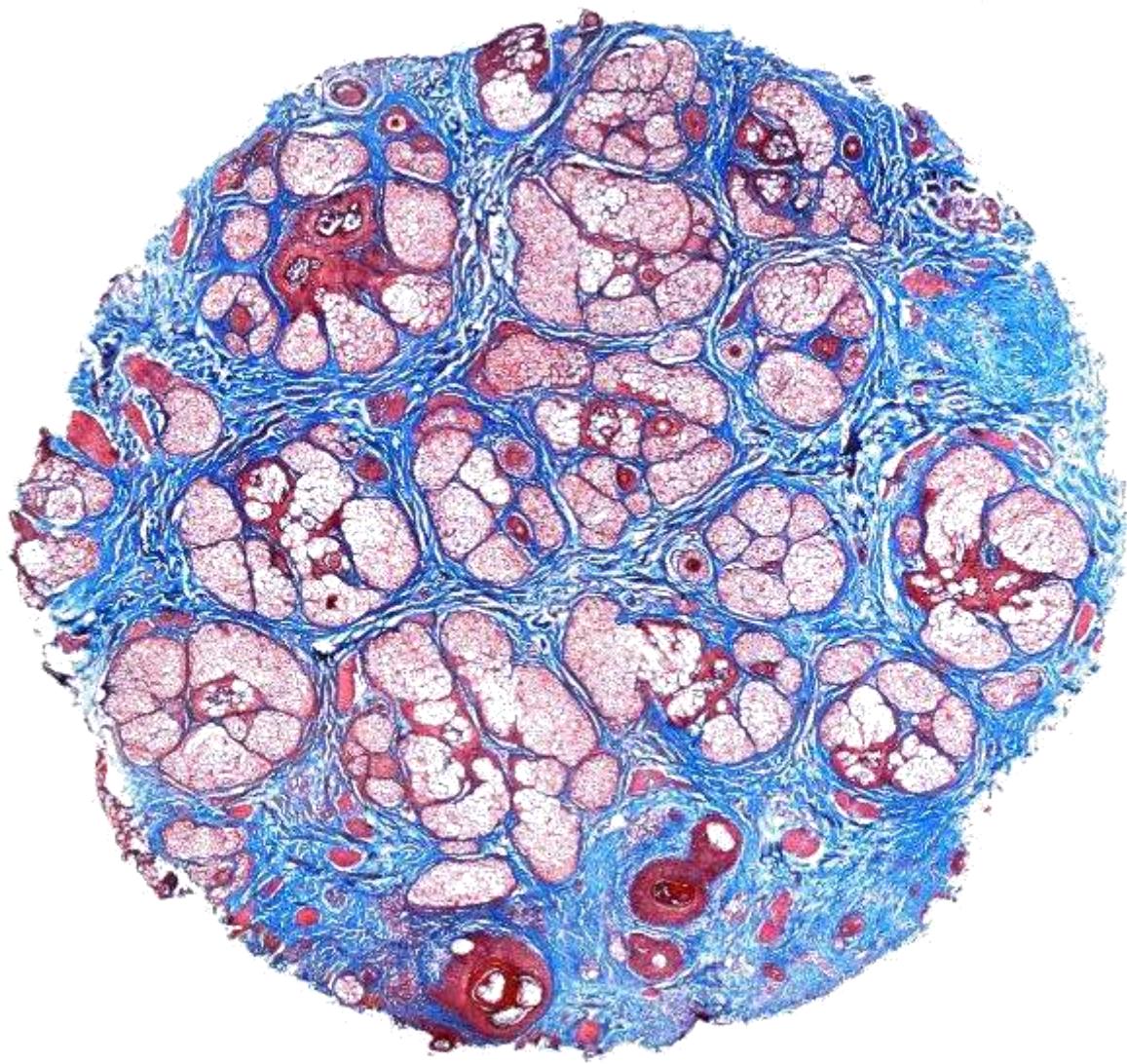
VELLOS



0.03 - 0.06 mm



TERMINALES



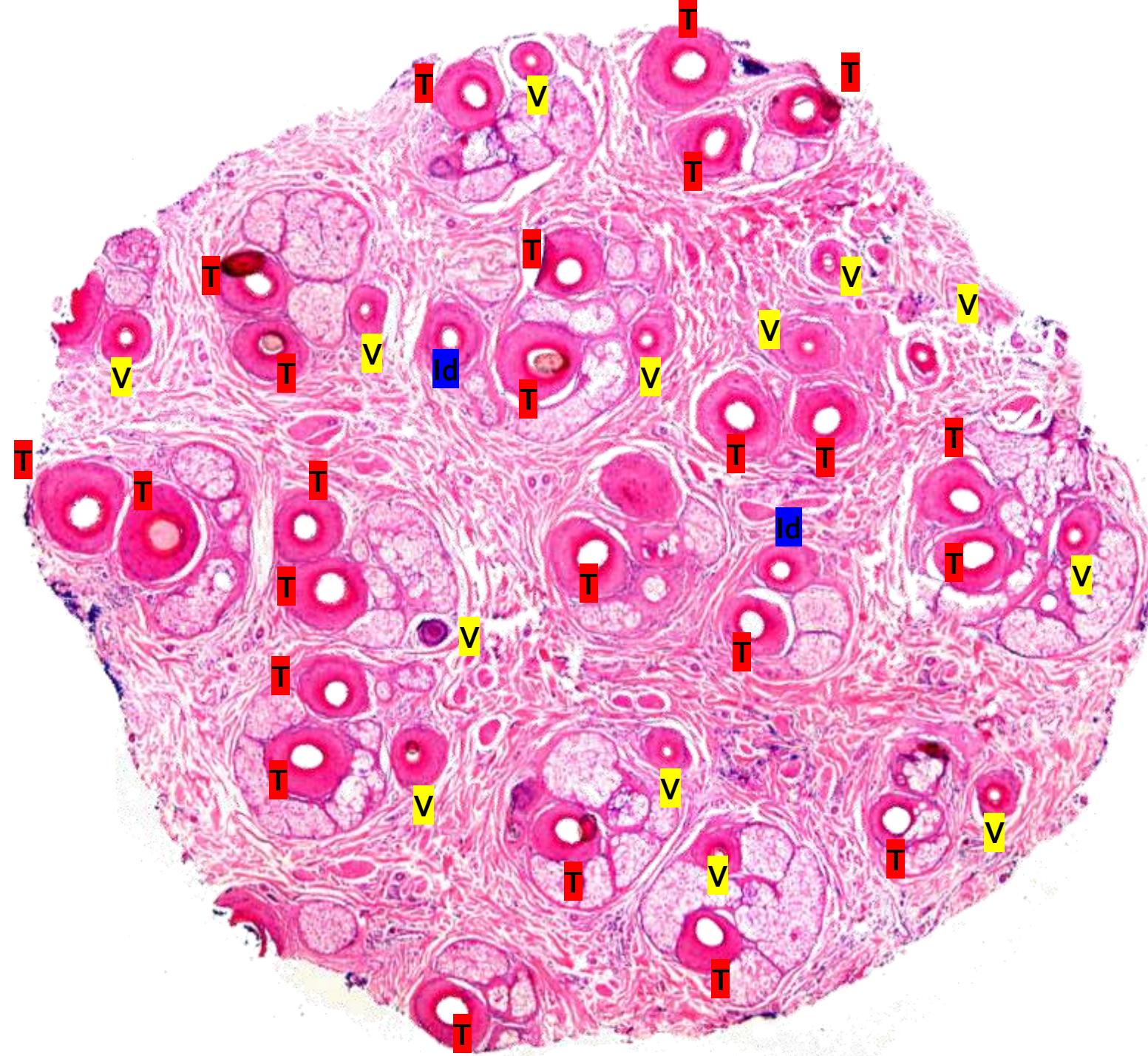
Terminales 24

Vellos 13

Indetrd 2

$$24 \div 13 = 1,85$$

$$25 \div 14 = 1,78$$



- Dermatoscopia
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ESTELAS FOLICULARES VS. CICATRICES FOLICULARES

OBSERVATION

Polarized Microscopy as a Helpful Tool to Distinguish Chronic Nonscarring Alopecia From Scarring Alopecia

Mariya Miteva, MD; Antonella Tosti, MD



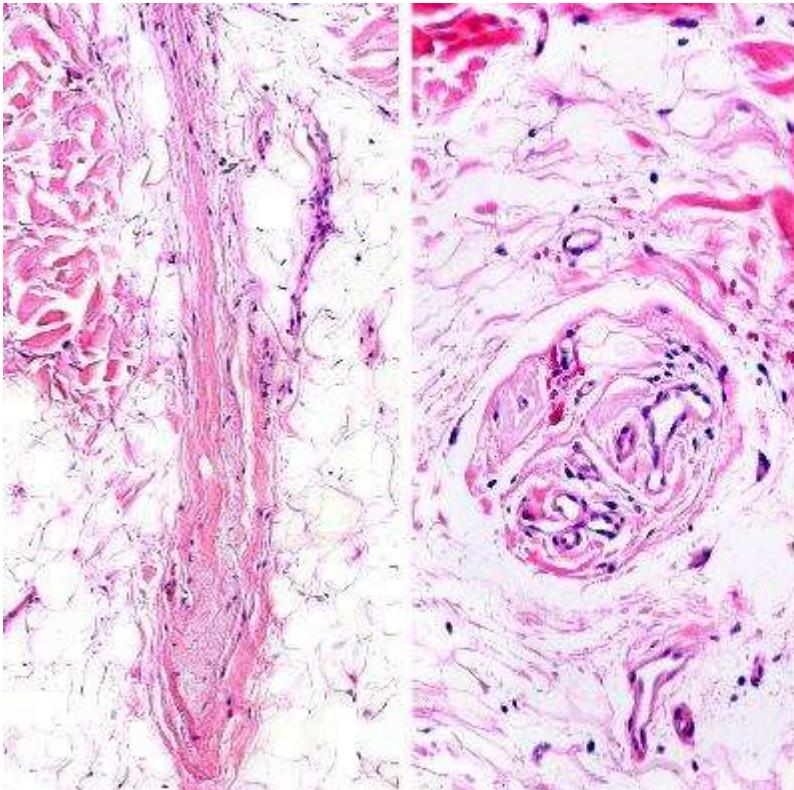
Las estelas foliculares (EF) son el residuo de los folículos miniaturizado y en telogen.

Las cicatrices foliculares (CF) son la cicatriz de un folículo previo que sea perdido en el curso de una alopecia cicatricial.

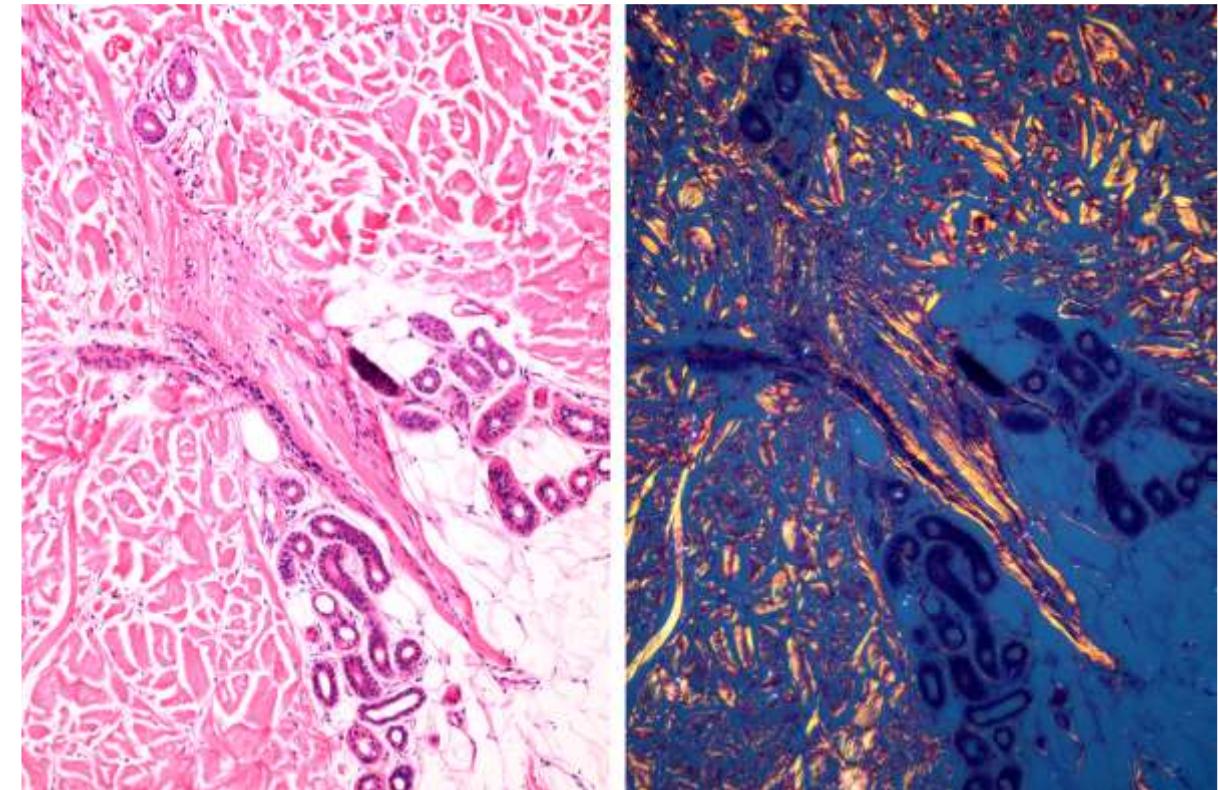
- **Su diferenciación es importante pues ayuda a definir el tipo de alopecia como cicatricial o no cicatricial.**

Las EF, a diferencia de las CF de las alopecias cicatriciales, no son refrigentes con la luz polarizada.

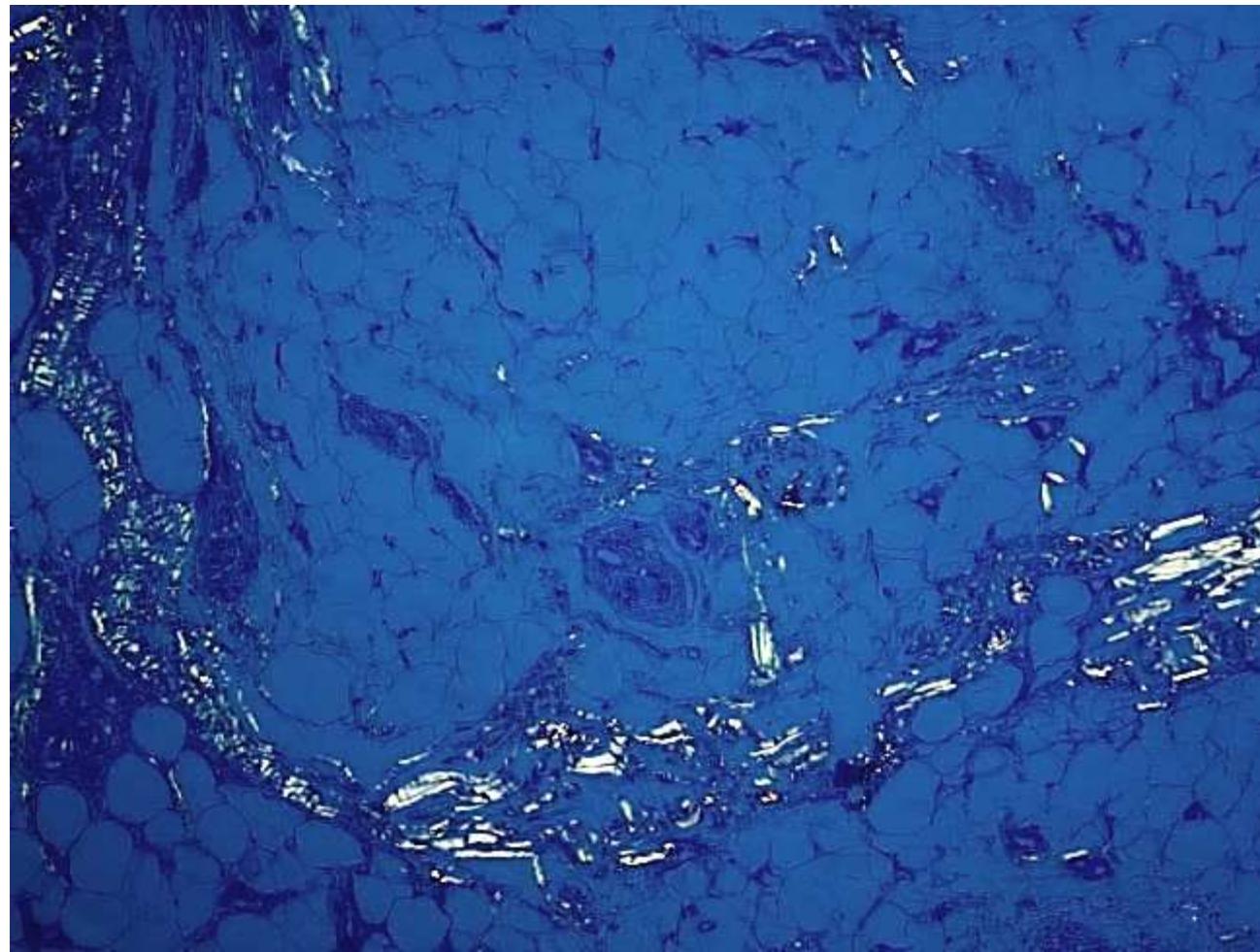
ESTELAS FOLICULARES



CICATRICES FOLICULARES



ESTELAS FOLICULARES

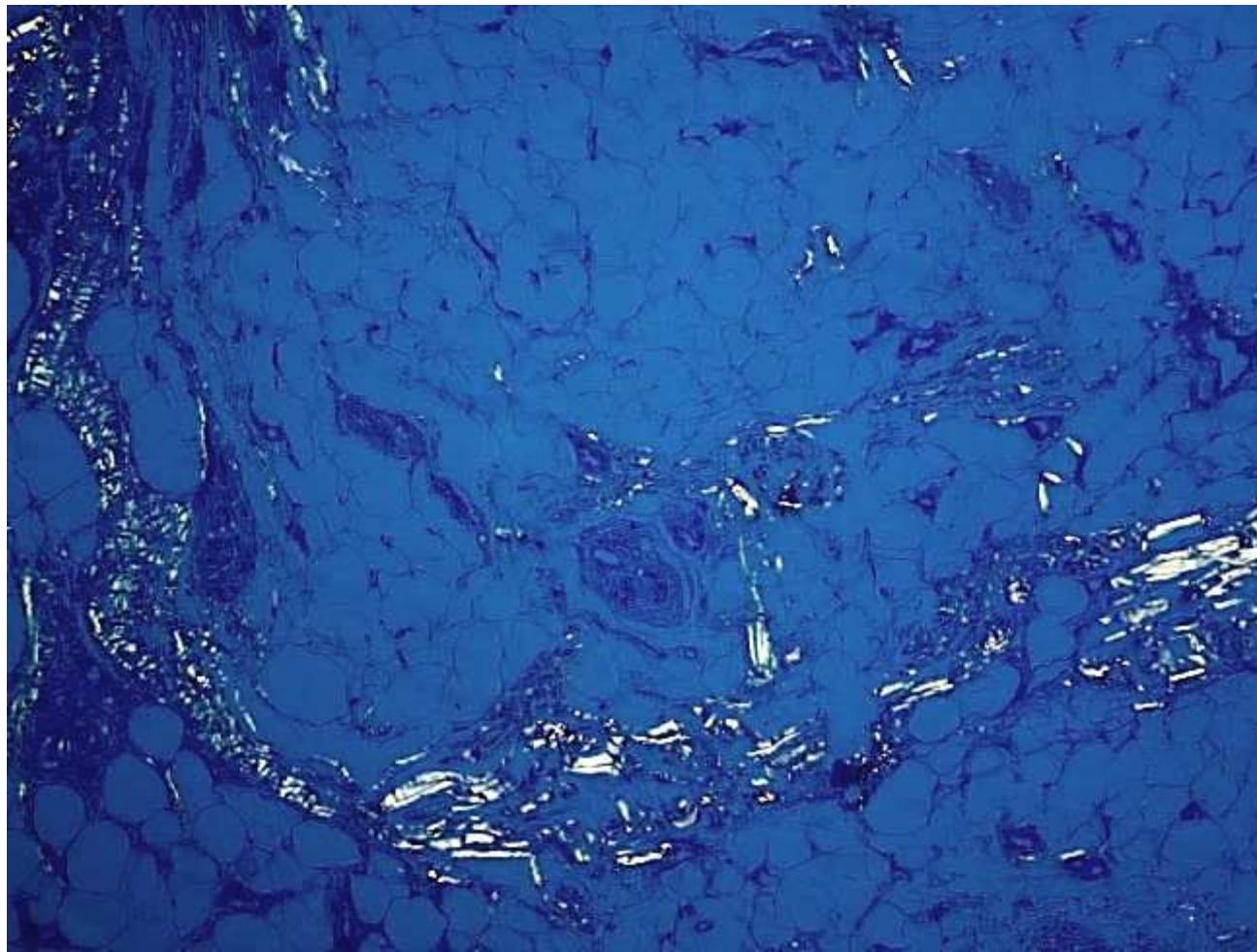


CICATRICES FOLICULARES



Miteva M., Tosti A. Polarized microscopy as a helpful tool to distinguish chronic nonscarring alopecia from scarring alopecia. *Arch Dermatol.* 148. 2012;91-4.

ESTELAS FOLICULARES



CICATRICES FOLICULARES



Miteva M., Tosti A. Polarized microscopy as a helpful tool to distinguish chronic nonscarring alopecia from scarring alopecia. *Arch Dermatol.* 148. 2012;91-4.

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ALOPECIA CICATRICIAL LINFOCÍTICA VS NEUTROFÍLICA

The Amount Counts: Distinguishing Neutrophil-Mediated and Lymphocyte-Mediated Cicatricial Alopecia By Compound Follicles

Laura B. Pincus, Vera H. Price and Timothy H. McCalmont

University of California, San Francisco

e-mail: Tim.McCalmont@ucsf.edu

Keywords: alopecia, cicatricial alopecia, compound follicle

Accepted for publication October 13, 2010

Pincus LB, Price VH, McCalmont TH. The amount counts: distinguishing neutrophil-mediated and lymphocyte-mediated cicatricial alopecia by compound follicles. *J Cutan Pathol.* 2011;38:1–4

LAS ALOPECIAS CICATRICIALES PRIMARIAS SE COMPORTAN DE MANERA DIFERENTE SEGÚN EL INFILTRADO INFLAMATORIO PREDOMINANTE:

- LAS LINFOCÍTICAS MUESTRAN POCA FUSIÓN DE LOS FOLÍCULOS Y TALLOS PILOSOS (2-3).
- LAS NEUTROFÍLICAS Y MIXTAS MUESTRAN EXTENSA FUSIÓN DE FOLÍCULOS Y TALLOS (5-15).

CLASIFICACIÓN DE LAS ALOPECIAS CICATRICIALES

Proposed working classification of primary cicatricial alopecia

Lymphocytic

- Chronic cutaneous lupus erythematosus
- Lichen planopilaris (LPP)⁴
 - Classic LPP
 - Frontal fibrosing alopecia⁵
 - Graham-Little syndrome³
 - Classic pseudopelade (Brocq)^{6,7}
 - Central centrifugal cicatricial alopecia⁸
 - Alopecia mucinosa³
 - Keratosis follicularis spinulosa decalvans⁹

Neutrophilic

- Folliculitis decalvans³
- Dissecting cellulitis/folliculitis³ (*perifolliculitis abscedens et suffodiens*)

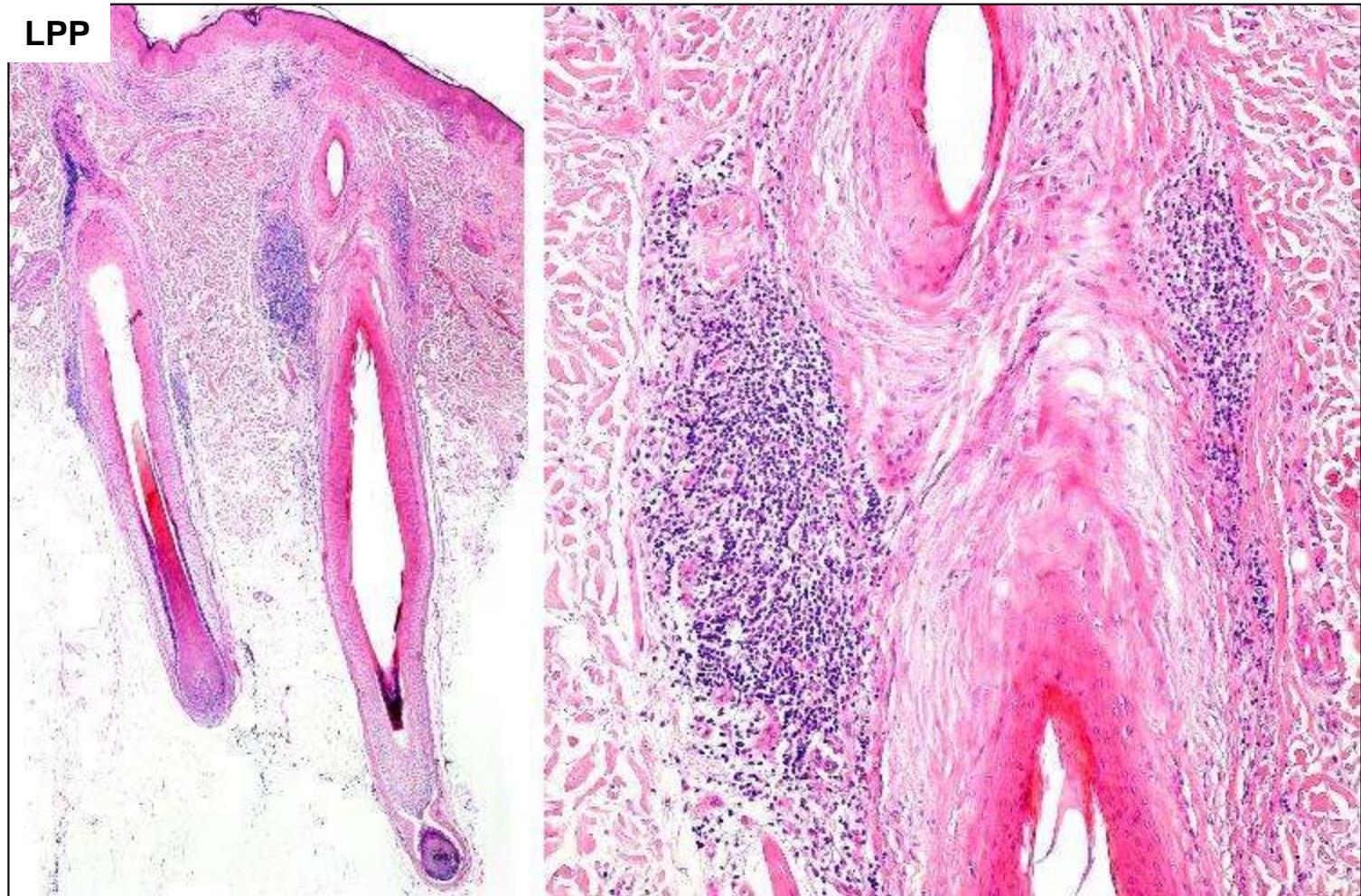
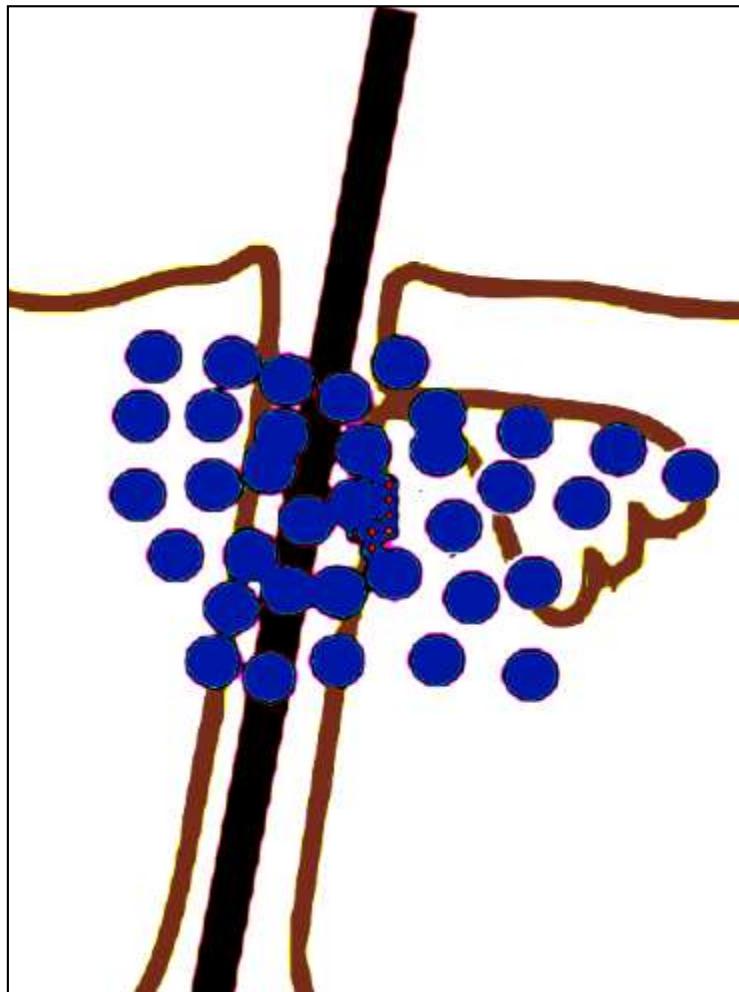
Mixed

- Folliculitis (acne) keloidalis⁹
- Folliculitis (acne) necrotica³
- Erosive pustular dermatosis¹⁰

Nonspecific

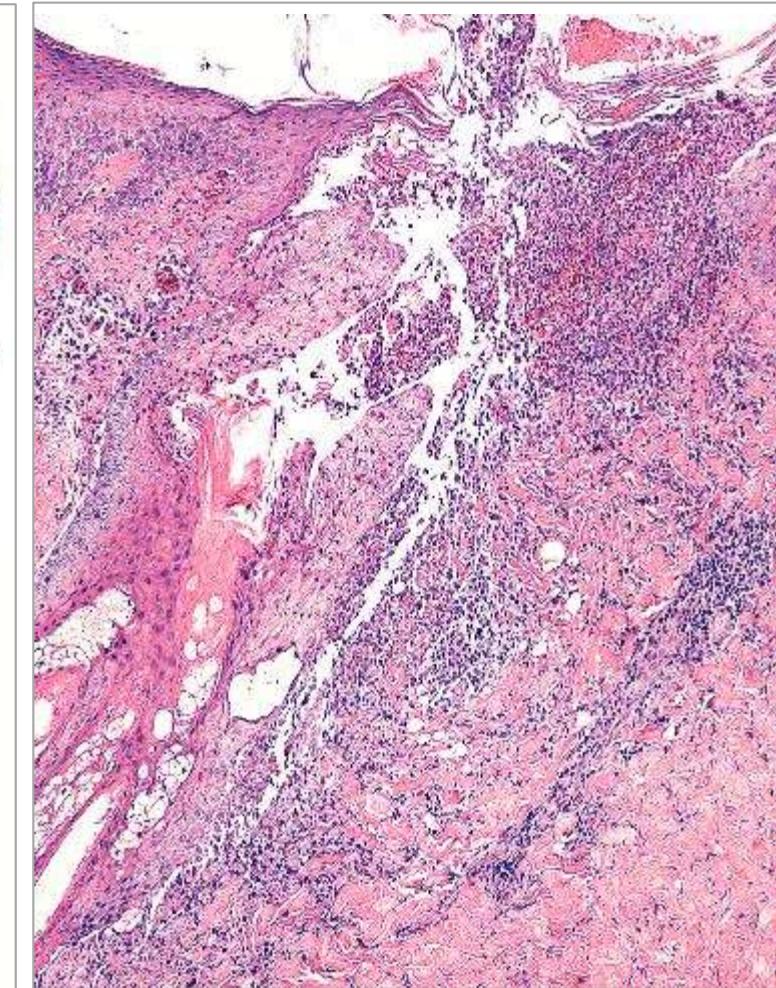
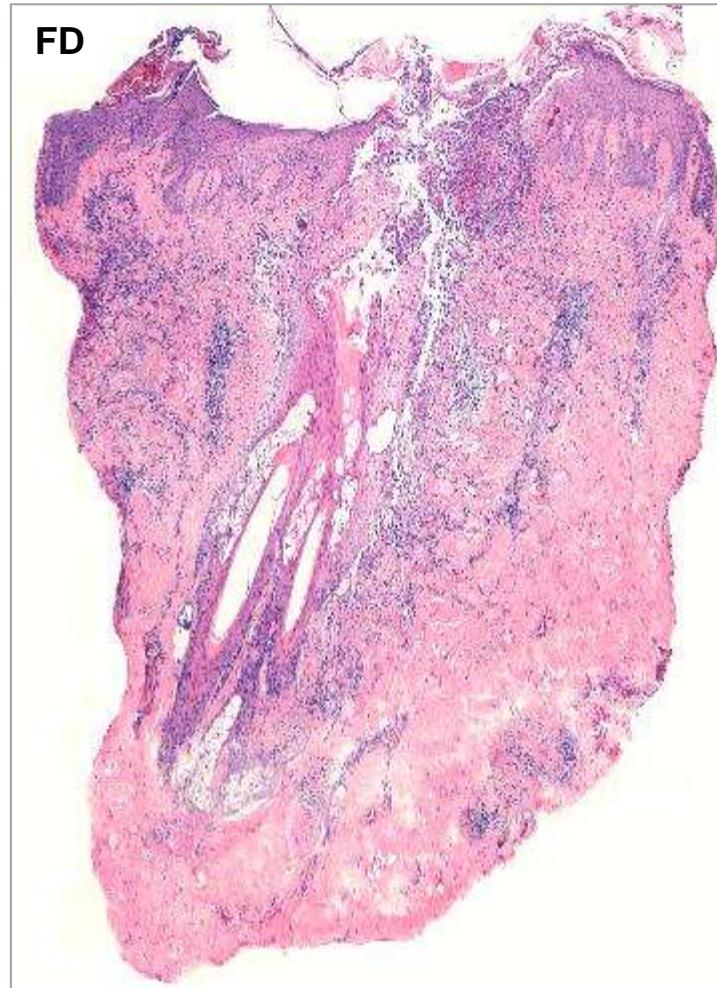
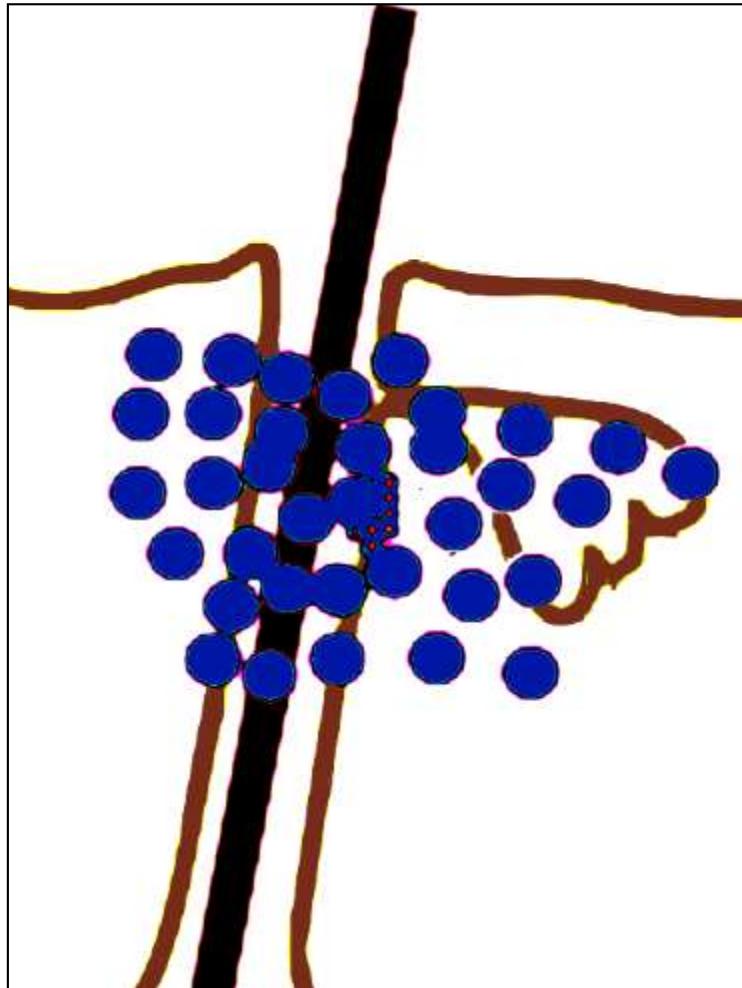
FUSIÓN DE ESTRUCTURAS FOLICULARES

ALOPECIAS CICATRICIALES PRIMARIAS MEDIADAS POR LINFOCITOS

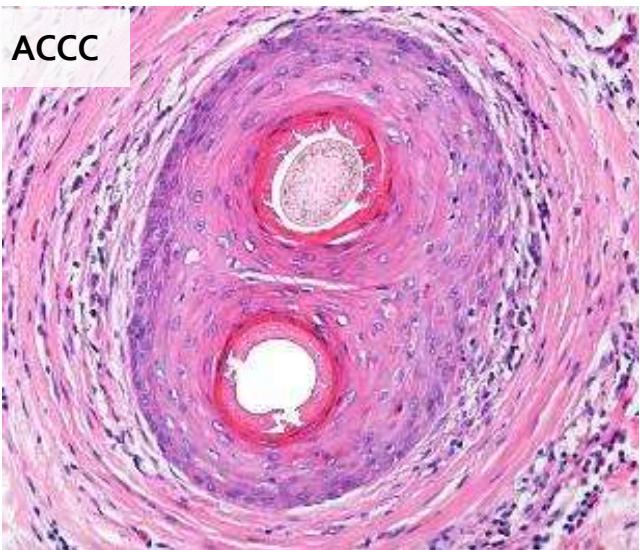


FUSIÓN DE ESTRUCTURAS FOLICULARES

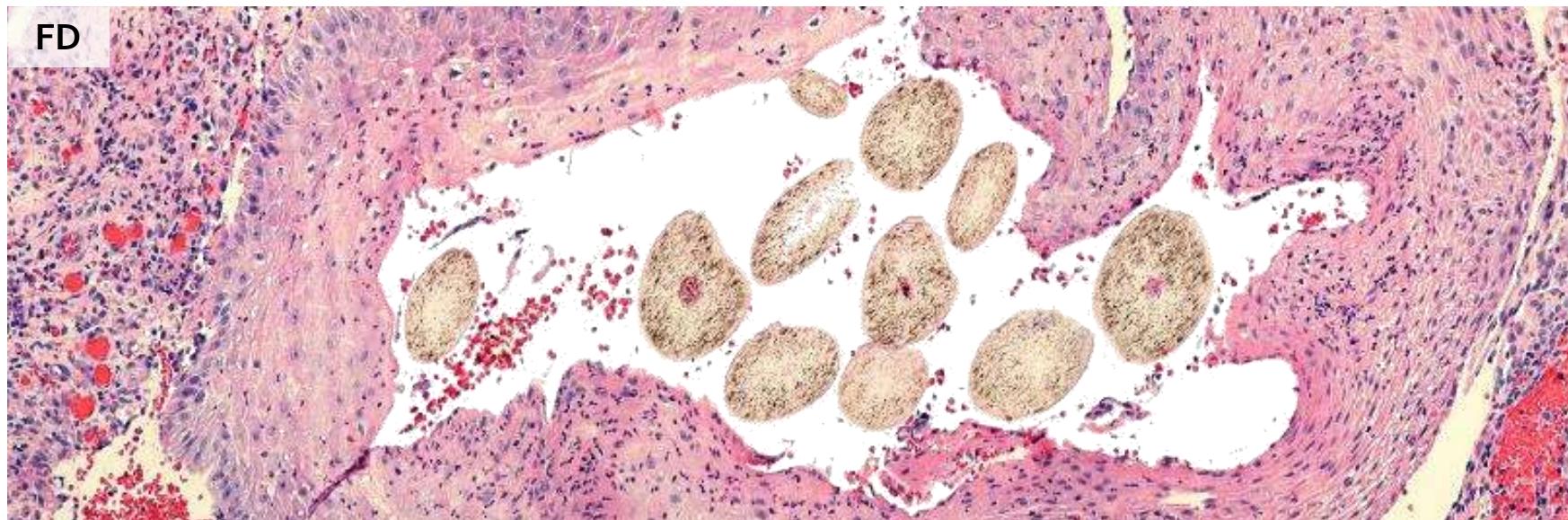
ALOPECIAS CICATRICIALES PRIMARIAS MEDIADAS POR NEUTRÓFILOS



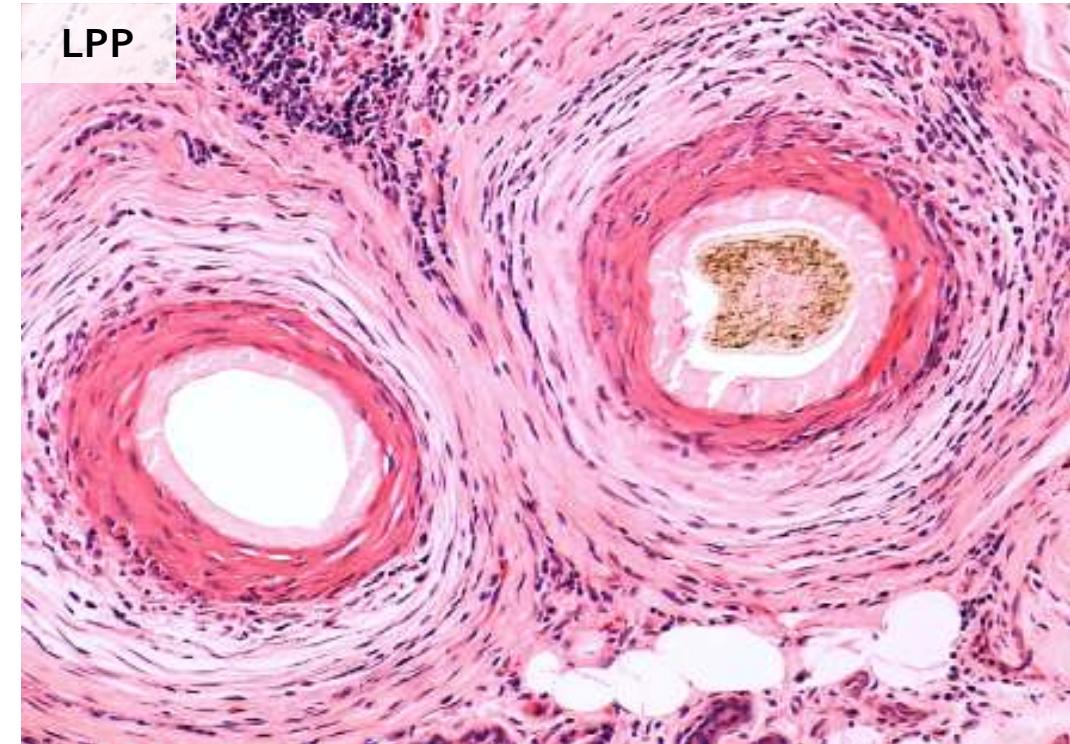
ALOPECIAS CICATRICIALES PRIMARIAS MEDIADAS POR LINFOCITOS



ALOPECIAS CICATRICIALES PRIMARIAS MEDIADAS POR NEUTRÓFILOS



FUSIÓN DE ESTRUCTURAS FOLICULARES ALOPECIAS CICATRICIALES PRIMARIAS MEDIADAS POR LINFOCITOS



- 'Gafas' en ACCC
- 'Ojos de búho' in LPP/AFF

- Dermatoscopia
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FOLÍCULO COMPUESTOS NORMALES

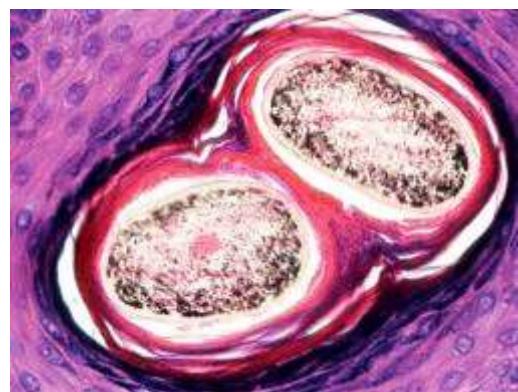
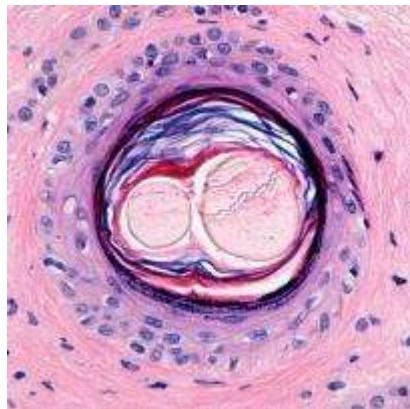
CME ARTICLE

Pathologic Diagnosis of Central Centrifugal Cicatricial Alopecia on Horizontal Sections

Mariya Miteva, MD and Antonella Tosti, MD

Miteva M, Tosti A. Pathologic diagnosis of central centrifugal cicatricial alopecia on horizontal sections. Am J Dermatopathol. 2014 Nov;36(11):859-64; quiz 865-7.

Miteva M, Tosti A. 'A detective look' at hair biopsies from African-American patients. Br J Dermatol. 2012 Jun;166(6):1289-94.
Miteva. A comprehensive approach to hair pathology of horizontal sections. Am J Dermatopathol. 35, 2013;529-40.



FOLÍCULOS COMPUESTOS NORMALES

Siempre tener en mente que los folículos a nivel del infundíbulo se fusionan en 2-3 tallos pilosos.

A veces hay infiltrado mononuclear y fibrosis, particularmente en individuos de raza negra.

A este nivel siempre hay capa granulosa.

Los folículos fusionados patológicos se evalúan a nivel del istmo, donde NO hay capa granulosa.

Miteva M, Tosti A. Pathologic diagnosis of central centrifugal cicatricial alopecia on horizontal sections. Am J Dermatopathol. 2014 Nov;36(11):859-64; quiz 865-7.

INFUNDIBULO

ALOPECIA CICATRICIAL CENTRAL CENTRÍFUGA



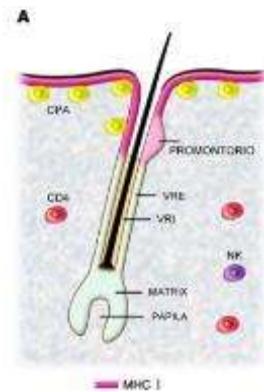
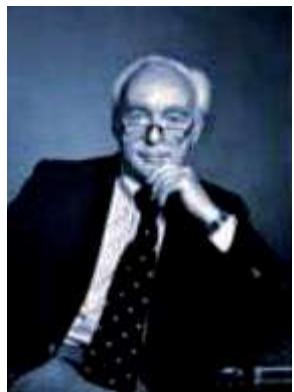
FOLÍCULO COMPUESTO NORMAL



- Dermatoscopia
- Proceso de biopsia más adecuado
- Parámetros normales en población sana
- Estelas foliculares Vs. Cicatrices foliculares
- Alopecia cicatricial linfocítica Vs Neutrofílica
- Folículo compuestos -Normales-
- Alopecia areata. Fisiopatología

ALOPECIA AREATA

NUEVOS HALLAZGOS EN FISIOPATOLOGÍA



Billingham, R.E., and Silvers, W.K. A biologist's reflections on dermatology. *J. Invest. Dermatol.* 1971;57:217–240.



Petukhova L, Duvic M, Hordinsky M, Norris D, Price V, Shimomura Y, Kim H, Singh P, Lee A, Chen WV, Meyer KC, Paus R, Jahoda CA, Amos CI, Gregersen PK, Christiano AM. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature*. 2010;466(7302):113–117.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921172/pdf/nihms226472.pdf>

EL ESTADO DE INMUNOPRIVILEGIO

SPECIAL ARTICLE

A BIOLOGIST'S REFLECTIONS ON DERMATOLOGY*

R. E. BILLINGHAM, D.Sc. AND WILLYS K. SILVERS, PH.D.[†]

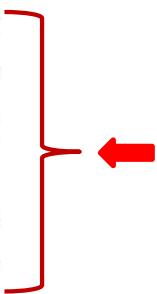


Photo by Karsh

Rupert Billingham

Billingham, R.E., and Silvers, W.K.
A biologist's reflections on dermatology.
J. Invest. Dermatol. 1971;57:227-40.

When *homografts* of black skin epidermis are transplanted to white skin beds, pigmentation of the superficial epidermis never proceeds very far. Blanching or bleaching out usually overtakes the darkening graft area by about the 13th day. This is interpreted as the survival endpoint of the alien donor melanocytes in the superficial epidermis. Despite this, an appreciable number of *black* hairs subsequently pierce the surface of the grafted area and continue to grow for upwards of 50 to 100 days before they gradually become depigmented. This observation indicates that the milieu of the hair follicle, or at least that of its bulb, is immunologically privileged, being capable of protecting the alien pigment cells incorporated within it from an extant level of sensitivity. It is possible, therefore, that the immunological surveillance mechanisms believed to be responsible for destroying potentially malignant cells at an early stage may be inoperative within the follicles. Possibly the fibrous exoskeleton of the follicle inhibits penetration of



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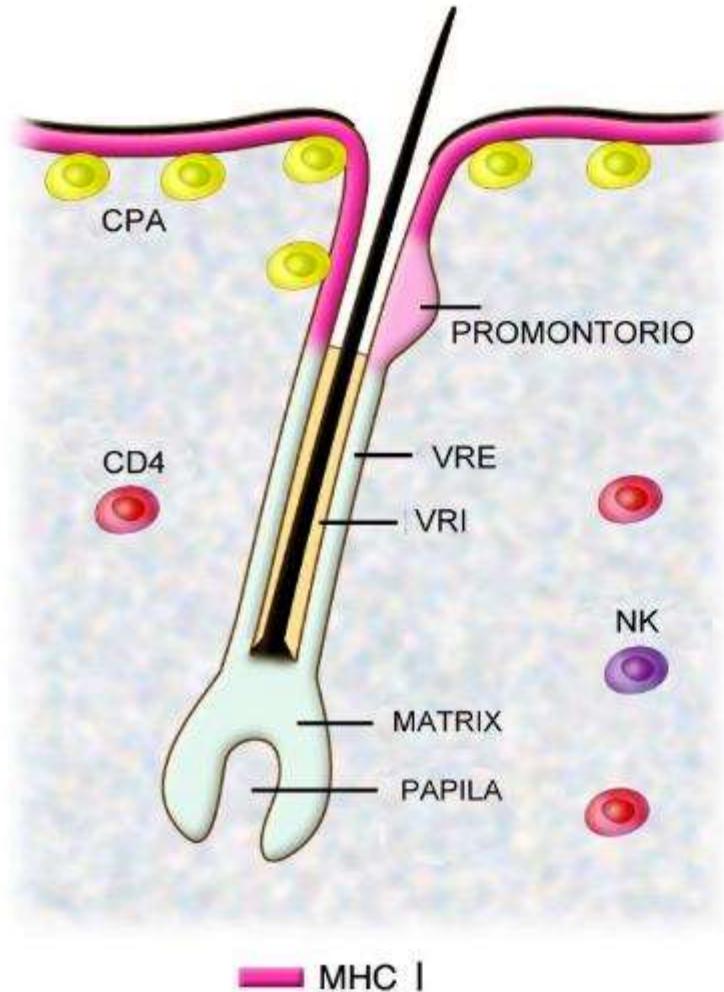
Billingham, R.E., and Silvers, W.K.
A biologist's reflections on dermatology.
J. Invest. Dermatol. 1971;57:227-40.

Sorprendentemente, tomó más de 20 años para que los conceptos revolucionarios de Bilingham fueron aplicados a la patogénesis de la alopecia areata.

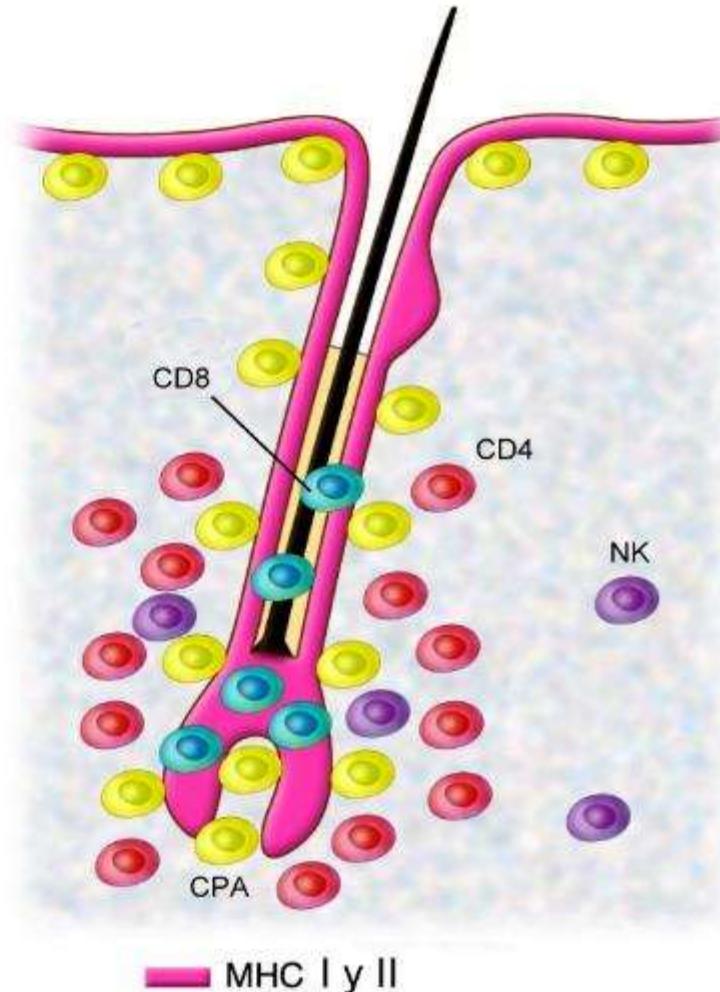
Se acepto entonces que el área de inmunoprivilegio del folículo piloso servía para secuestrar melanocitos y otros antígenos expresados en anagen del reconocimiento inmune, o también induciendo una tolerancia periférica contra tales antígenos.

2. NUEVOS HALLAZGOS EN FISIOPATOLOGÍA

EL ESTADO DE INMUNOPRIVILEGIO



NORMAL
ESTADO DE INMUNOPRIVILEGIO EN ANAGEN



ALOPECIA AREATA
PERDIDA DEL ESTADO DE INMUNOPRIVILEGIO

Modificado con autorización de American Society of Clinical Investigation

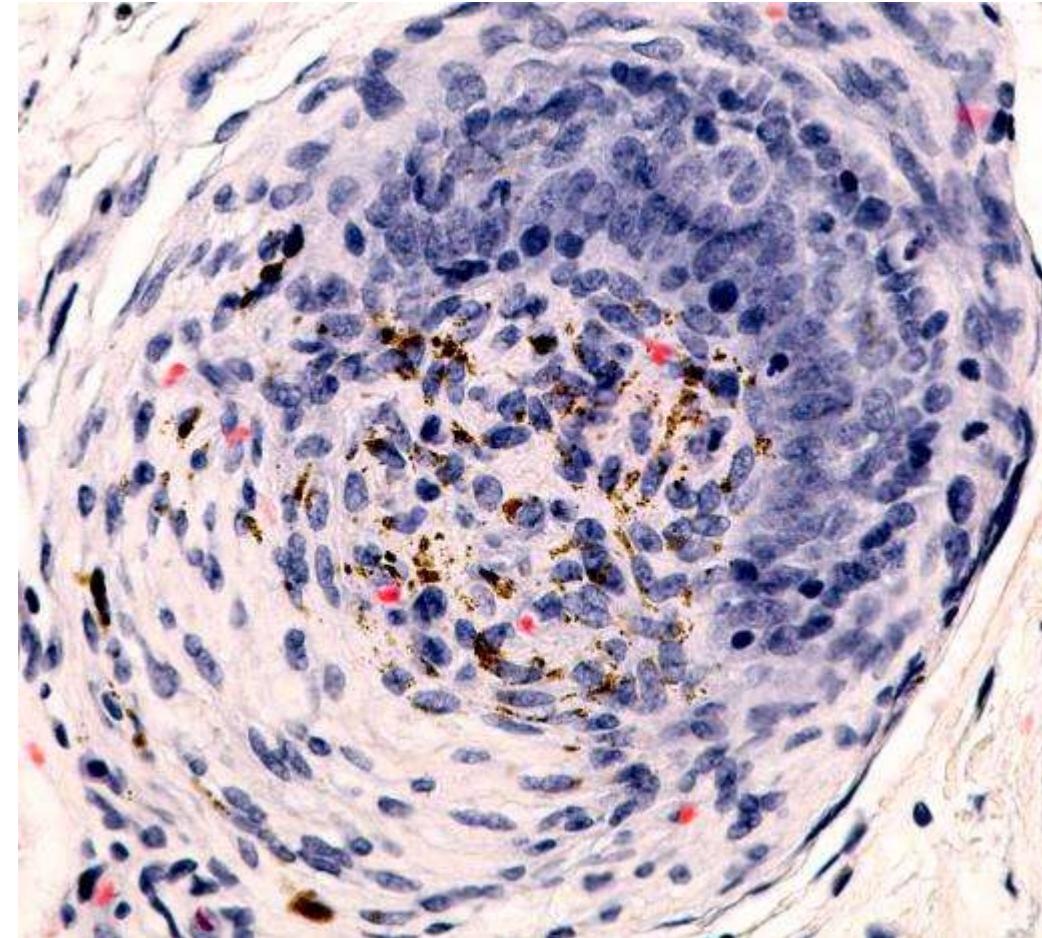
Gilhar A. Paus R. Kalish R.S. Lymphocytes, neuropeptides, and genes involved in alopecia areata. J Clin Invest. 2007;117(7):2019-27.

<http://www.jci.org/articles/view/31942/pdf>

NUEVOS HALLAZGOS EN FISIOPATOLOGÍA

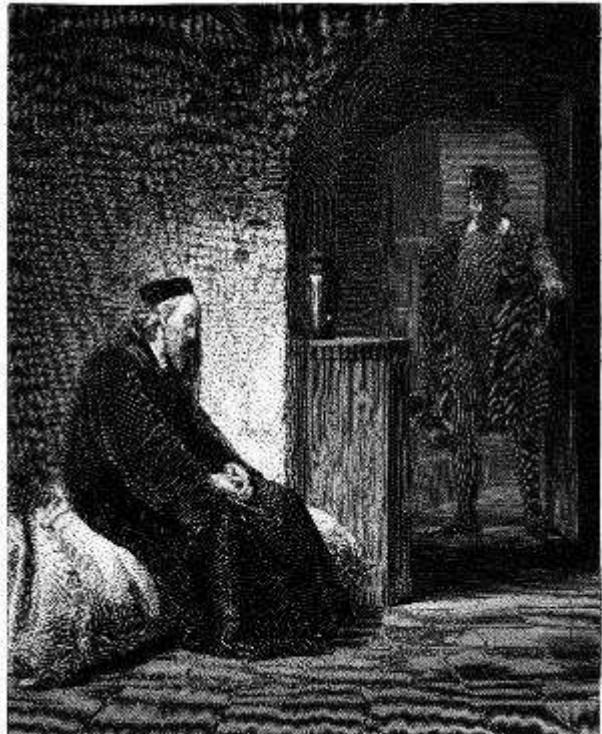
ESTADO DE INMUNOPRIVILEGIO

ANTÍGENO (S) ?

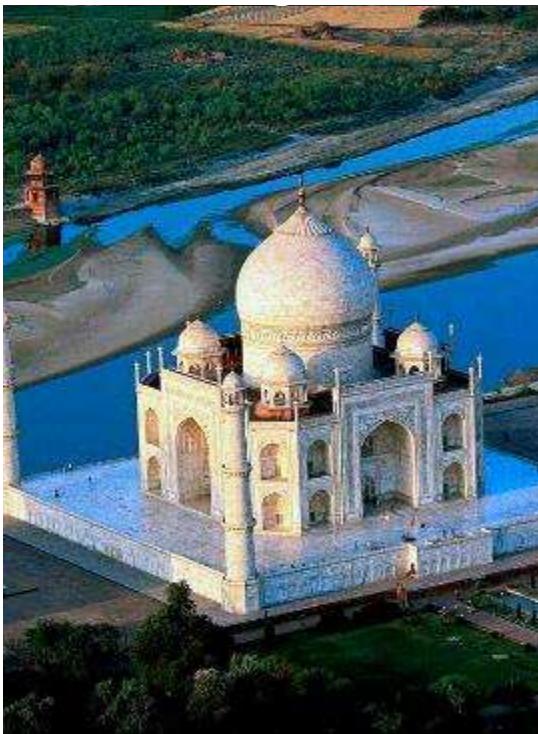


NUEVOS HALLAZGOS EN FISIOPATOLOGÍA

ANTÍGENO (S) ?



Sir Thomas More (1535)



Shah Jahan (1631)

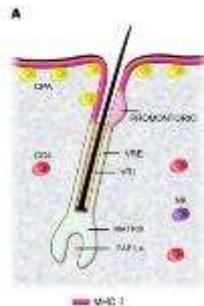
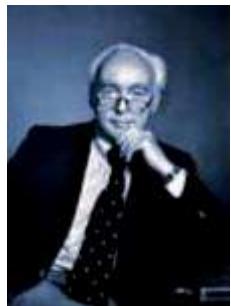


María Antonieta (1793)

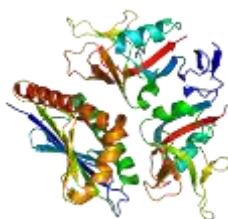
Navarini AA, Nobbe S, Trüeb RM. Marie Antoinette syndrome. Arch Dermatol. 2009;145(6):656.
Jelinek, J.E. Sudden whitening of the hair. Bull N Y Acad Med 48, 1003-13 (1972).

2.

NUEVOS HALLAZGOS EN FISIOPATOLOGÍA

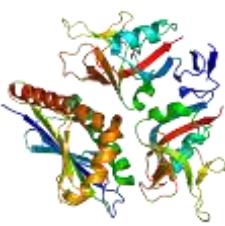


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Genome-wide association study in alopecia areata implicates both innate and adaptive immunity

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Abstract

Alopecia areata (AA) is among the most highly prevalent human autoimmune diseases, leading to progressive hair loss due to the collapse of immune privilege of the hair follicle and subsequent autoimmunity attack^{1,2}. The genetic basis of AA is largely unknown. We undertook a genome-wide association study (GWAS) in a sample of 1,054 cases and 3,778 controls and identified 139 single nucleotide polymorphisms that are significantly associated with AA ($P \leq 5 \times 10^{-7}$). Here we show

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Case-patient and control samples should be submitted to A.M.C. (amosci@jhu.edu).
Supplementary Information is available online at www.nature.com/nature.

Author Contributions L.P., M.D., V.P., Y.S., H.K., P.S., A.L., W.V.C., K.C.M., and P.K.G. provided samples and clinical information; M.D., V.P., H.K., and D.M. performed all GWAS analyses; and A.M.C. provided samples from the National Alopecia Areata Registry. W.V.C. and C.L.A. provided statistical analyses and helped write the manuscript. R.P. and C.L.A. provided additional statistical analyses and helped write the manuscript. C.L.A. and A.M.C. provided oversight and conceptual guidance to the project; and A.M.C. provided the financial support of candidate gene resequencing personnel. Correspondence: resequencing project: A.M.C.; all reporting requirements for grants sponsor: resequencing project: A.M.C.; and additional information is available in www.nature.com/nature.

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Page 2

an association with genomic regions containing several genes controlling the activation and proliferation of regulatory T cells (Treg cells), cytotoxic T lymphocyte-associated antigen 4 (CTLA4), interleukin (IL)-2R β , IL-2 receptor A (IL-2RA, CD137) and FoxJ1 (also known as fibroblast factor cluster 4, FCGR7a), as well as the transmembrane leukocyte antigen (TIA-1) region. We also find associations evidence for regions containing genes expressed in the hair follicle itself (PAX20) and SFTN1. A region of strong association resides within the ULBP3 (cysteine-rich lectin, UL-16-binding protein) gene cluster on chromosome 6q25.1, encoding with string ligands of the natural killer cell receptor NK2R2 that have not previously been implicated in an autoimmune disease. By probing the role of ULBP3 in disease pathogenesis, we also show that its expression in human scalp skin patches with AA is markedly upregulated in the hair follicle dermal papilla during active disease. This study provides evidence for the involvement of both innate and acquired immunity in the pathogenesis of AA. We have defined the genetic underpinnings of AA, placing it within the context of shared pathways among autoimmune diseases, and implicating a novel disease mechanism, the upregulation of ULBP ligands, in triggering autoimmunity.

AA affects about 5.3 million people in the United States alone, including males and females across all ethnic groups, with a lifetime risk of 1.7% (refs 1,2). Autoimmunity develops against the hair follicle, resulting in non-scarring hair loss that may begin as patches that can coalesce and progress to cover the entire scalp (alopecia totalis) or eventually the entire body (alopecia universalis) (Supplementary Fig. 1). The phenomenon of 'bulldog whitening' of the hair³ is ascribed to the active onset of AA at times of profound grief, stress or fear⁴, in which the pigmented hair is selectively shed while the white hair persists. AA spares the stem cell compartment and specifically only the base of the hair follicle, which is surrounded by infiltrating lymphocytes. Despite these marked perturbations in the hair follicle, there is no permanent scarring destruction, and regrowth of the hair remains possible. The concept of an autoimmune mechanism in the basis for AA emerged during the 1960s century from multiple lines of evidence⁵. AA hair follicles are surrounded by an immune infiltrate with activated T-helper cells (Th cells), cytotoxic T cells (Tc cells) and natural killer (NK) cells, characterized as a Th1-type inflammatory response⁶. The action of a collagen of immune privilege is thought to be a key event in triggering AA⁷.

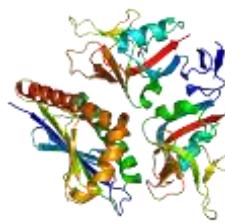
Evidence supporting a genetic basis for AA comes from multiple lines of research, including the observed heritability in first-degree relatives^{8,9}, twin studies¹⁰ and, more recently, from our family-based linkage studies¹¹. Although a number of candidate-gene association studies have been performed over the past two decades, the informativeness of these studies was inherently limited by small sample sizes and protection of candidate genes.

To determine the genetic architecture of AA, we genotyped or used publicly available data for up to 1,054 AA cases and 3,778 controls with a combination of Illumina 610K and 550K arrays. We performed association tests adjusted for residual population stratification ($P = 1.051$) and found 139 single nucleotide polymorphisms (SNPs) significant at 5×10^{-7} (Fig. 1 and Supplementary Table 1).

Our analysis identified several susceptibility loci for AA, most of which clustered into eight genomic regions and fell within disease linkage disgregations (LD) blocks (Fig. 1 and Table 1). These include loci on chromosome 2q32.2 containing CTLA4, chromosome 4q27, containing IL-2R β ; chromosome 11q13.32 containing the HLA, chromosome 6q25.1 harbouring the ULBP genes, chromosome 10q11.51 containing IL-2RA (CD137), and chromosome 13q11 containing IL2RN and ERBB4. One SNP resides on chromosome 9q31.1 within system 17 (SFTN1), and one resides on chromosome 11q13, upstream from peroxiredoxin 5 (PRDX5). Several of these LD blocks coincide with regions of linkage that we reported previously on chromosomes 4p (HLA), 6q (ULBP3), 10p (IL-2RA) and 11p (PRDX5)¹¹. We also identified an additional 165 SNPs that were nominally significant (10^{-6} – 10^{-7}).

[Nature. Author manuscript; available in PMC 2011 January 1.](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921172/pdf/nihms226472.pdf)

NUEVOS HALLAZGOS EN FISIOPATOLOGÍA



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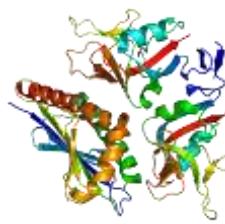
Los estudios que intentan relacionar la AA con otros genes han tenido un gran impulso en los últimos años con la utilización de los nuevos métodos de estudio genómico amplificado, permitiendo a los investigadores hacer rastreos genéticos en el genoma completo de miles de pacientes.

Estos han sido posibles gracias a las base de datos genéticos preexistentes del registro nacional de AA de los Estados Unidos.

En el último estudio genómico ampliado de AA se estudiaron 1054 pacientes y 3278 controles, identificándose 139 nucleótidos únicos con polimorfismo que estaban significativamente asociados con la AA.

En este estudio se probaron aproximadamente 600 mil marcadores, buscando sitios en el genoma entero donde los pacientes tenían alelos diferentes a aquellos de los controles

2. NUEVOS HALLAZGOS EN FISIOPATOLOGÍA



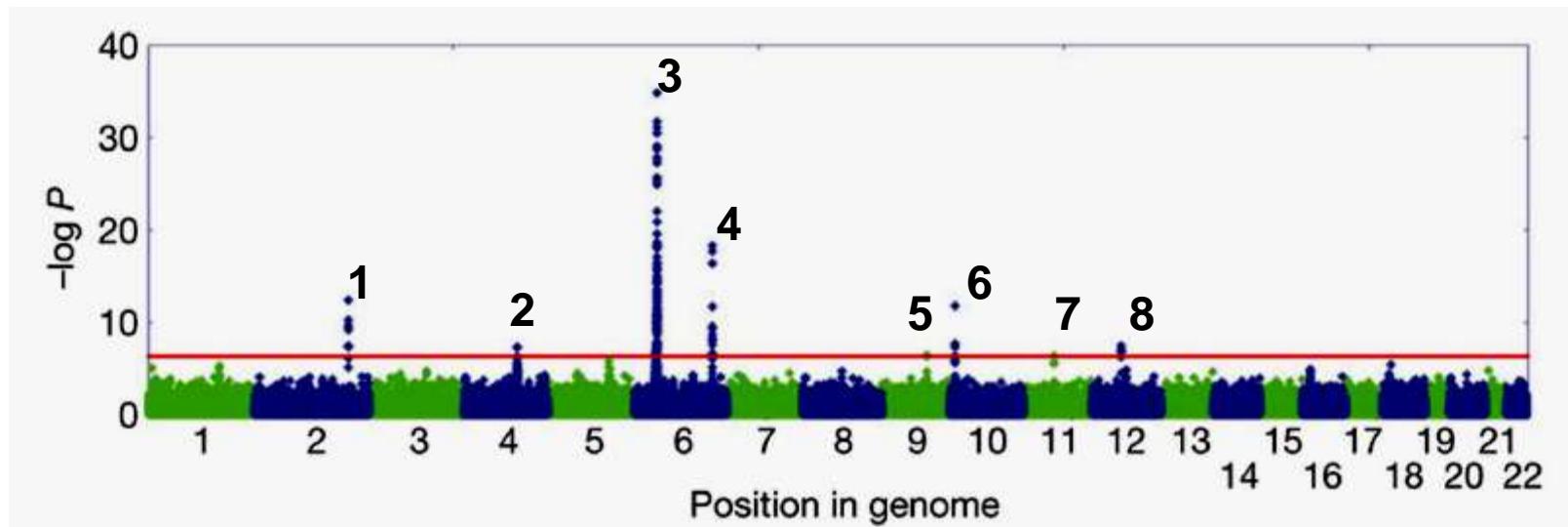
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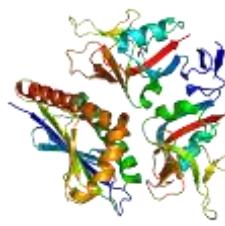
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Se encontraron ocho diferentes regiones asociadas con la AA. Una de esas regiones correspondía al complejo HLA, que confirma entonces lo que ya se sabía desde hace 20 años.

Los investigadores también encontraron otros siete locus genómicos que albergaban interesantes genes candidatos para la AA.

Cinco se expresan en el sistema inmune y otros dos en el folículo piloso.





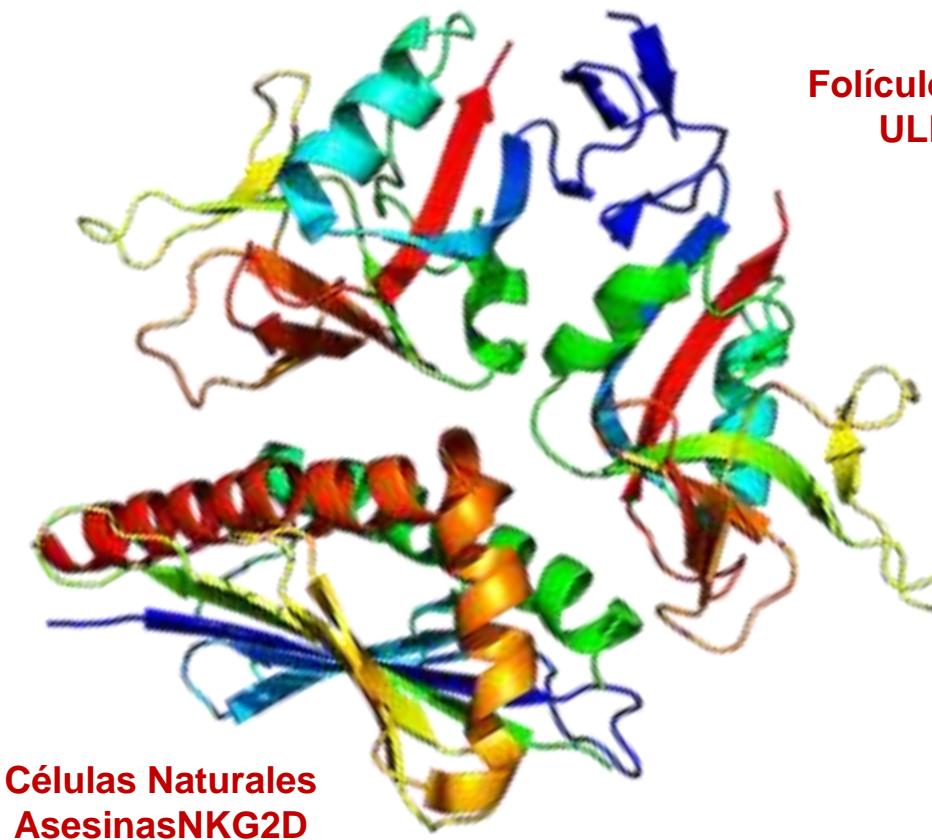
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Una de las grandes sorpresas fue que los genes asociados a la AA encontrados en este estudio se relacionan más con padecimientos del tipo de la diabetes tipo I, esclerosis múltiple, artritis reumatoide y enfermedad celiaca que con las enfermedades que antiguamente se creían relacionadas, como la psoriasis y el vitílico.

Cuando se observan estas nuevas enfermedades se encuentra que hay al menos un mecanismo unificador con la AA y es el aumento en la regulación de una señal de peligro en el órgano blanco.

2. NUEVOS HALLAZGOS EN FISIOPATOLOGÍA



Folículo Piloso
ULBP3

En este estudio se encontró evidencia para una clase de señal de peligro llamada ULBP.

Esta señal de peligro sirve como un rastreador para células inmunes citotóxicas que infiltran el órgano y comienzan a destruirlo. Normalmente ULBP3 no está presente en los folículos pilosos pero es abundante en los folículos enfermos de AA

Estas proteínas atraen a las células, marcadas a su vez por un receptor de células asesinas conocidas como NKG2D.

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- Folículo compuestos -Normales-
- Alopecia areata. Fisiopatología

**LO NUEVO, LO IMPORTANTE, PARA INTERPRETAR
UNA BIOPSIA POR ALOPECIA.**

