Histopathology 2010, **56**, 24–38. DOI: 10.1111/j.1365-2559.2009.03439.x

REVIEW

Histopathology of alopecia: a clinicopathological approach to diagnosis

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(2010) *Histopathology* **56**, 24–38

Histopathology of alopecia: a clinicopathological approach to diagnosis

Interpretation of the histopathological findings of primary scarring and non-scarring alopecias may prove daunting. This is especially true if the biopsy specimen is inadequate, and the clinical history and pattern of the alopecia are not known. Common forms of scarring alopecias discussed here are the lymphocytic (discoid lupus erythematosus, lichen planopilaris, central centrifugal cicatricial alopecia, pseudopelade of Brocq), the neutrophilic (folliculitis decalvans, dissecting folliculitis), and the mixed (acne keloidalis) entities. The non-scarring alopecias reviewed are androgenic alopecia, telogen effluvium, alopecia areata, trichotillomania and traction alopecia. In all cases of primary alopecia, adequate tissue sampling and appropriate laboratory processing, in combination with pertinent clinical information, provide the key to diagnosis.

Keywords: clinicopathological correlation, histopathology, non-scarring alopecia, scarring alopecia

Abbreviations: AA, alopecia areata; CCCA, central centrifugal cicatricial alopecia; H&E, haematoxylin and eosin; LPP, lichen planopilaris; PAS, periodic acid–Schiff; SLE, systemic lupus erythematosus; T, terminal; V, vellus

'The learning and the knowledge that we have, is, at the most, but little compared with that of which we are ignorant'

Plato *(The Republic)*

Introduction

Primary alopecia of the scalp is commonly divided into two groups, namely scarring and non-scarring. The histopathological interpretation of scalp biopsy specimens of patients with alopecia, whether scarring or non-scarring, may represent a challenging task, especially in the absence of a good, definitive clinical history, adequate tissue sampling, and an appropriate grossing technique.

The histopathology of the most commonly encountered varieties of primary scarring (cicatricial) and non-scarring alopecias forms the basis of this review.

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Grossing technique considerations

The current gold-standard for a scalp biopsy specimen is the use of a 4-mm punch; the specimen may be sectioned vertically or transversely.

VERTICAL (LONGITUDINAL) SECTIONS

A 4-mm vertically-sectioned punch biopsy specimen is adequate for assessing alopecias associated with interface changes, lichenoid infiltrates, and subcutaneous pathology.[1] However, only portions of a small number of follicular units (2–3) are seen in a given tissue section,[2] because the hair follicles, which grow at an angle, are cut tangentially and, as such, cannot be visualized in their entirety in conventional vertical sections. Thus, vertical sectioning will show only 10% of the follicles present in the specimen, with the consequent risk of sampling error, as the pathological changes may be present only focally in a few hair follicles. Moreover, obtaining hair follicles' quantitative data in non-scarring hair loss disorders such as

androgenic alopecia, telogen effluvium and alopecia areata, is precluded.[2] On the other hand, a transversely sectioned specimen will include all the hair follicles present in the biopsy, and in the same section.

TRANSVERSE (HORIZONTAL) SECTIONS

Transverse sectioning will allow detection of follicular pathology, even if it is focal. Moreover, it will yield quantitative data of follicular cycling, as well as morphometric evaluation of the hair follicles throughout their entire length, from the bulb to the acroinfundibulum.[3] To achieve this, a 4-mm punch biopsy specimen including subcutaneous tissue is required, as well as special training of the pathology laboratory personnel for appropriate grossing and embedding of the specimen. Since the original description by Headington,[2] who demonstrated that the best area to bisect the biopsy transversely is 1 mm above the dermal–subcutaneous junction, other authors have indicated slightly different areas to section, such as 1–1.5 mm below the epidermal–dermal junction,[4] or 1–2 mm below the epidermal surface.[5]

Frishberg *et al.*[1] proposed a variant of the transverse sectioning technique whereby the 4-mm biopsy specimen is sliced into three or four sections, and all the disks embedded with the cut surface down in the same cassette. Thus, the sampling of the hair follicles at different levels is directly visualized on the same glass slide, and, as a practical consequence, fewer histological sections and slides are required.

Irrespective of whichever level of transverse sectioning of the punch biopsy specimen is chosen, the ultimate goal is to reach the isthmic area. This is the site where the follicular units reside and affords the greatest amount of diagnostic findings, including the opportunity to perform accurate follicular counts and follicular ratios, which are critical, for example, in the assessment of non-scarring alopecia.[6]

The use of transverse sectioning of scalp biopsy specimens has been questioned in the past,[7] the argument being that, although it permits a quantitative approach to diagnosis, it is imperfect, as it does not allow for a qualitative approach based on the repetitive criteria that can be obtained in vertically oriented sections.[7] Clearly, there are limitations with both methods if they are used singly.[8] However, transverse sections are undoubtedly superior to vertical sections in the study of the diameter of the hair follicles and the hair cycle, and allow visualization of virtually all the hair follicles present in the skin biopsy specimen, a feature particularly helpful in the evaluation of non-scarring alopecias.[9] Vertical sections find their importance in assessing the full thickness of the skin in every section, a feature that proves useful in the evaluation of scarring alopecia.[9]

The St John's multiteam clinicopathological approach

The protocol adopted in our dermatopathology laboratory for processing scalp biopsies is based on the evaluation of combined transverse and vertical sections of two 4-mm punch biopsy specimens.[10] This method is derived from that previously described by Elston *et al.*[11] The choice of which combination of biopsies and sectioning to use may vary, based on the clinical data provided (scarring versus non-scarring alopecia). This approach acknowledges the advantage of both methods with the goal of obtaining the 'best of two worlds'.

A newly proposed model to avoid sample bias and to achieve optimal diagnostic yield is the St John's multiteam clinicopathological approach.[12] As biopsy site selection is crucial,[5] this model is based upon strong communication between the dermatologist performing the biopsies in the clinic, the dermatopathology laboratory processing the specimens, and the dermatopathologist trained in hair histopathology. These three elements are individually and collectively important factors required to reach histopathologically the final diagnostic interpretation.[12] Thus, the key factors that will enhance the histopathological diagnosis of alopecia include knowledge of the patient's clinical history and the pattern of the alopecia, adequate choice of sampling 'active' areas, and two 4-mm punch biopsy specimens that include subcutaneous tissue. In addition, numerous haematoxylin and eosin (H&E) serial sections and ancillary studies (direct immunofluorescence, periodic acid–Schiff (PAS), elastic tissue and mucin stains) are carried out.

Modus operandi

SCARRING ALOPECIA

Two 4-mm punch biopsy specimens, both taken at the peripheral edge of the alopecia deemed to be the 'active' area, are more likely to show diagnostic features. A biopsy of the central portion of the scar cannot be of diagnostic help, except for confirming a scarring process. Of the two specimens obtained, one is sectioned transversely (Figure 1A) with the embedding cut surfaces indicated by red ink (Figure 1B), while the second one is sectioned vertically, with 1/2 of it placed in Michel's medium and sent for direct immunofluorescence studies, in accordance with the scarring alopecia

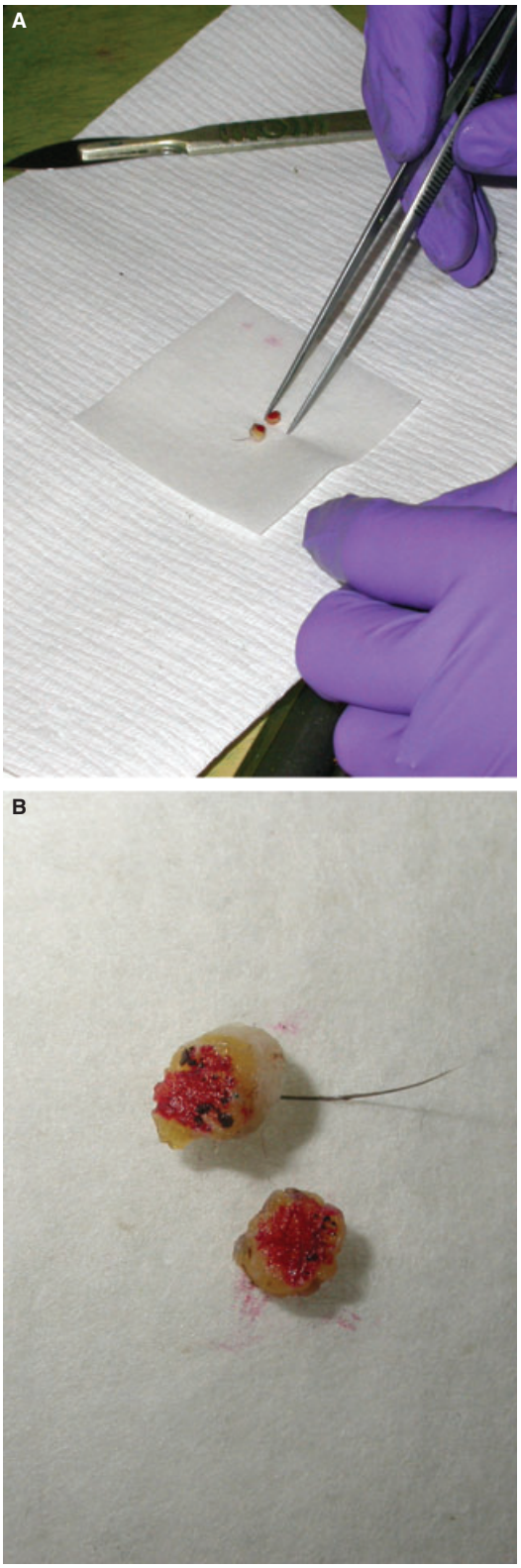


Figure 1. **A**, A 4-mm punch biopsy specimen is sectioned horizontally. **B**, The two cut surfaces are red-inked before laboratory processing.

protocol (Figure 2). The transversely sectioned skin biopsy specimen is placed in a different cassette when grossing, and processed separately from the vertically sectioned one. Finally, in order to obtain a perfect horizontal section, special attention is also given to the final sectioning of the paraffin block at the microtome: the blade should be adjusted horizontally according to the specimen requirements.

NON-SCARRING ALOPECIA

Among the non-scarring alopecias, the most difficult task for the histopathologist is to distinguish early female pattern hair loss (androgenic alopecia) from chronic telogen effluvium. In accord with the non-scarring alopecia protocol (Figure 3), the clinician will have taken one biopsy from the site of clinical involvement, usually the vertex, and the second from an uninvolved area of the scalp, commonly the occiput. Hair growth in the latter area is non-androgen dependent, and serves as the positive control of the patient's normal hair characteristics. In this instance, both specimens are sectioned transversely. In cases of trichotillomania and AA, a single specimen transversely sectioned will suffice.

In both scarring and non-scarring alopecia protocols, the scalp biopsy specimens are processed with multiple H&E serial sections until the histological 'clues' required to make the diagnosis are identified. Ancillary stains, including PAS, elastic tissue and mucin stains, are also performed. If only one specimen is provided for evaluation, the ultimate choice of sectioning (trans-

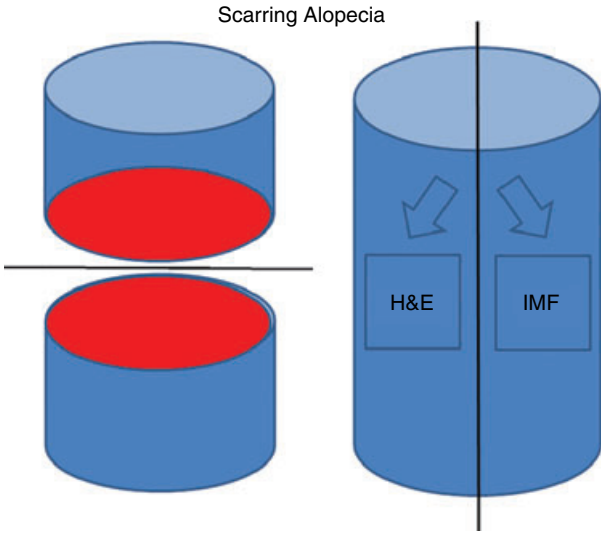


Figure 2. Schematic diagram of the St John's scarring alopecia protocol.

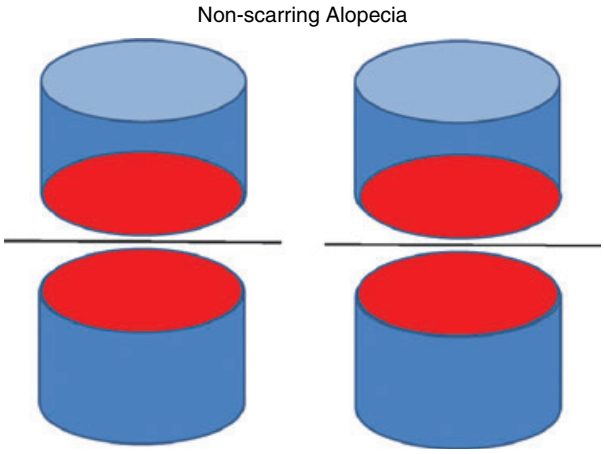


Figure 3. Schematic diagram of the St John's non-scarring alopecia protocol.

Table 1. Secondary scarring alopecia

Aplasia cutis congenita
Cicatricial bullous pemphigoid
Infectious (kerion, staphylococcal)
Neoplastic (primary, metastasis)
Connective tissue disease (morphea)
Trauma (burn)
Metabolic (amyloid, mucin)
Granulomatous (sarcoid)

versely versus vertically) will depend on the clinical query provided.[12]

Histopathology of primary scarring (cicatricial) alopecia

Scarring (cicatricial) alopecia represents a complex group of hair disorders all characterized by having as a common final pathway the destruction of the hair follicle unit. This process may be secondary, and due to numerous aetiologies (Table 1),[13] or primary, where the cause and pathogenesis are largely unknown, but the target is the hair follicle itself.[14–23] Biphasic scarring alopecias comprise another subset of permanent alopecias; in these cases, early non-scarring hair loss is followed by permanent follicle drop-out. This situation occurs in longstanding androgenic alopecia, AA and traction alopecia.[5,21,24,25]

Table 2. Classification of primary cicatricial alopecia*

Lymphocytic
Chronic cutaneous lupus erythematosus
Lichen planopilaris (LPP)
Classic LPP
Frontal fibrosing alopecia
Graham–Little syndrome
Classic pseudopelade (Brocq)
Central centrifugal cicatricial alopecia
Alopecia mucinosa
Keratosis follicularis spinulosa decalvans
Neutrophilic
Folliculitis decalvans
Dissecting cellulitis/folliculitis (*perifolliculitis capitis abscedens et suffodiens*)
Mixed
Folliculitis (acne) keloidalis
Folliculitis (acne) necrotica
Erosive pustular dermatosis

*Adapted from[18].

Histopathologically, primary scarring (cicatricial) alopecia is characterized by the presence of fibrous tissue replacing the hair follicles.[14–23] This corresponds clinically to loss of hair follicle ostia.[18,20] The current working classification of primary cicatricial alopecia is that proposed by the North American Hair Research Society,[18] in which the cicatricial alopecias are divided into several categories, including lymphocytic, neutrophilic and mixed (Table 2).

Lymphocytic scarring alopecias

CHRONIC CUTANEOUS (DISCOID) LUPUS ERYTHEMATOSUS

Clinically, chronic cutaneous lupus erythematosus is characterized by ill-defined patches of alopecia, with decreased follicular orifices, scale, erythema, follicular plugging, depigmentation and atrophy[26] (Figure 4A). Less than 5% of patients progress to systemic lupus erythematosus (SLE), and a few patients may have concomitant lesions of subacute cutaneous lupus erythematosus.[26]

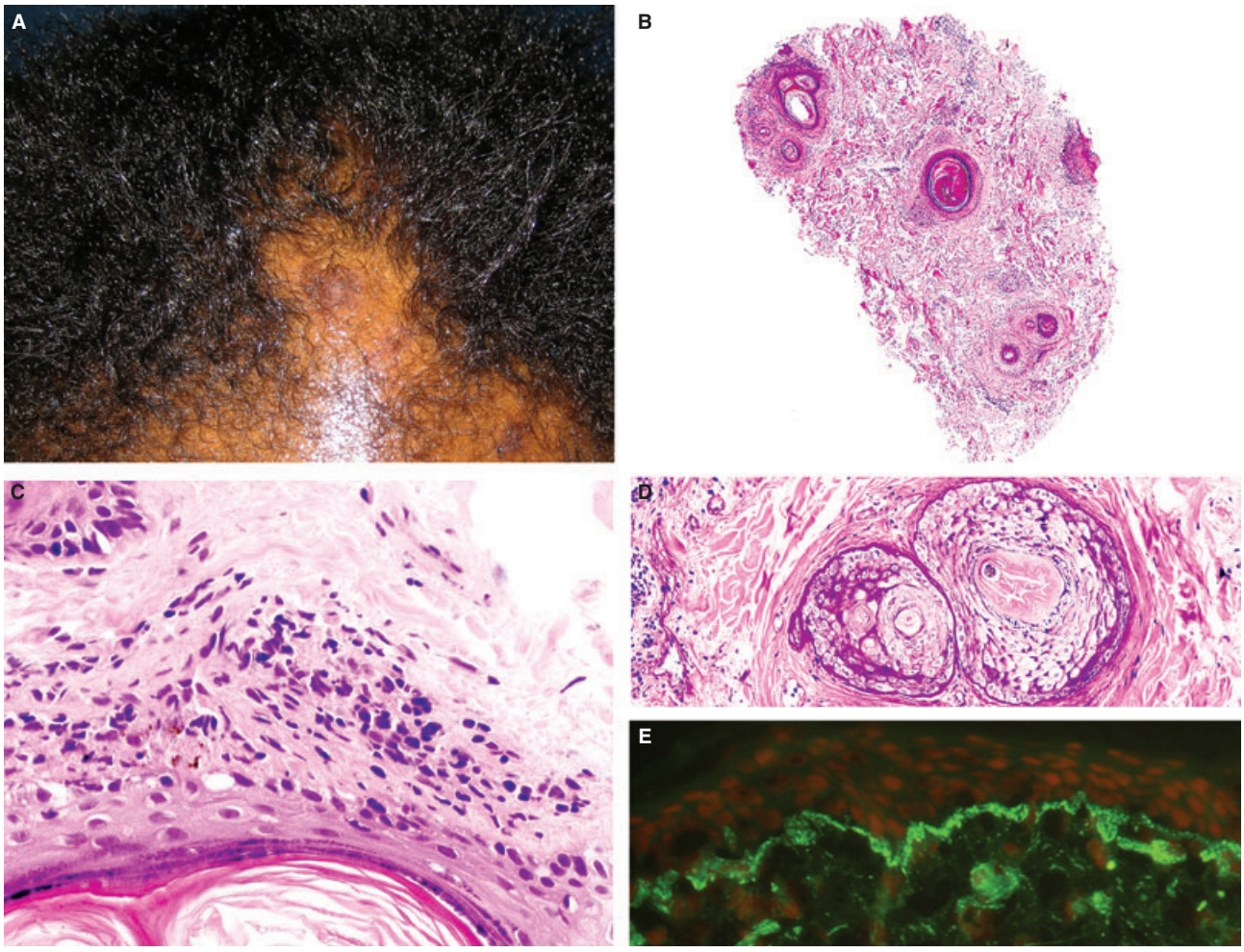


Figure 4. Chronic cutaneous (discoid) lupus erythematosus. **A**, Patch of alopecia involving the anterior vertex. **B**, Transverse section showing only a few hair follicles with follicular hyperkeratosis. **C**, Vacuolar-interface change of the follicular epithelium with mild lymphoid cell infiltrate. **D**, Periodic acid–Schiff highlights the perifollicular basement membrane zone thickening. **E**, Granular deposits of IgG along the basement membrane zone.

Histopathological features include follicular hyperkeratosis (Figure 4B) and a vacuolar-interface folliculitis at the level of the infundibulum (Figure 4C). The interfollicular epidermis may at times also be involved, in association with a perivascular and periappendageal superficial and deep lymphoid cell infiltrate with plasma cells. Late stages are characterized by concentric lamellar perifollicular fibroplasia and by basement membrane zone thickening that is highlighted by PAS (Figure 4D). Suprabasilar dyskeratosis, pigmentary incontinence and dermal mucin may also be seen. On vertical sections the Verhoeff–van Gieson elastic stain shows loss of the elastic fibres throughout the dermis.[24,27] Direct immunofluorescence will confirm the diagnosis with granular deposits of IgG and C3 along the epidermal and follicular basement membrane zone[24] (Figure 4E).

LICHEN PLANOPILARIS

Clinically, typical lesions of lichen planopilaris (LPP) present with atrophic, ill-defined patches of scarring alopecia with decreased follicular orifices. The margins of the alopecia, where the process is still active, will show perifollicular erythema with follicular scale (Figure 5A).[28] Cutaneous lesions of lichen planus may be present in up to 28% of cases,[19] and with keratotic follicular papules on the trunk and extremities, such as in the Graham–Little syndrome (also known as Piccardi–Lassuer–Graham Little syndrome) in which the hair loss not only affects the scalp, but also involves eyebrows, axillae and/or pubic hair.[29, 24] Subsets of patterned variants of LPP have been described in patients presenting with progressive fibrosing alopecia of the central scalp distributed in an

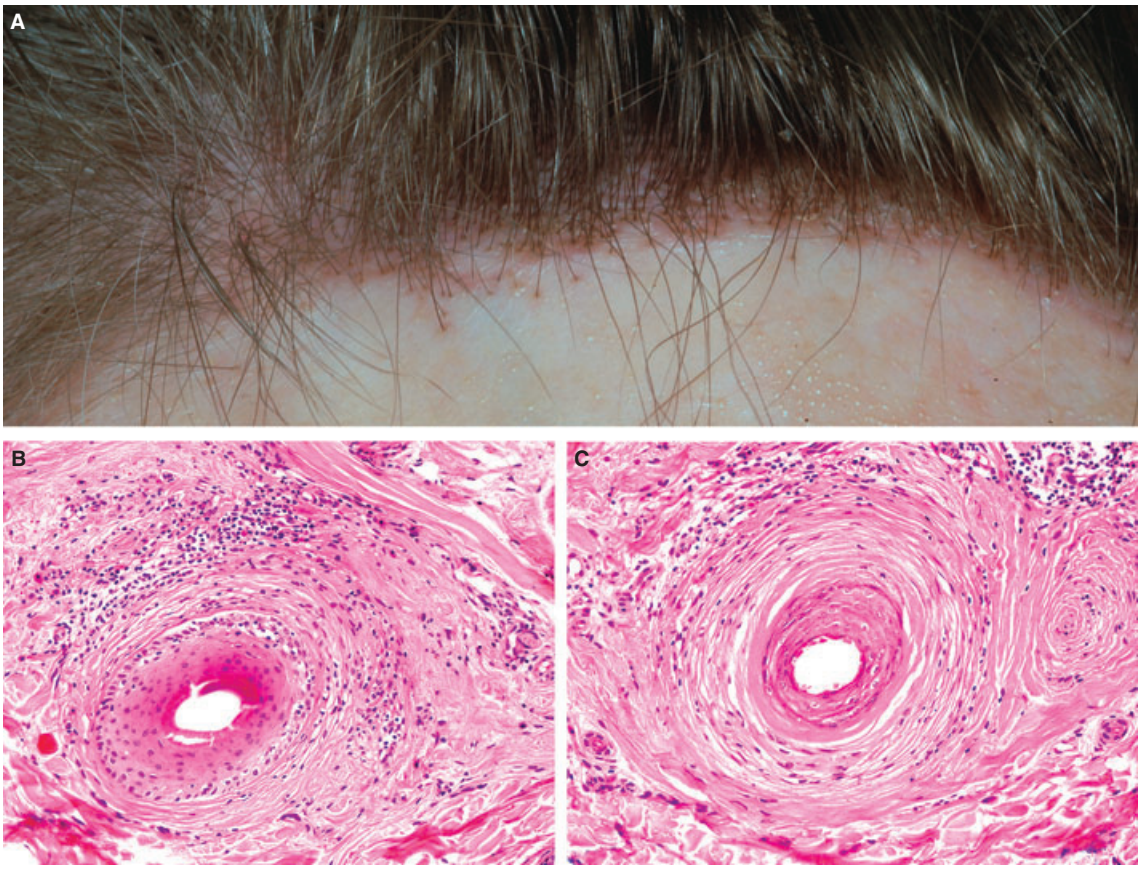


Figure 5. Lichen planopilaris (frontal fibrosing alopecia variant). **A**, Active margin of the alopecia with perifollicular erythema and follicular scale. **B**, Isthmus: a hair follicle showing interface alteration, perifollicular fibrosis and a mild perifollicular lymphoid cell infiltrate. **C**, Another hair follicle with a more advanced perifollicular concentric fibrosis, and with a lymphoid cell infiltrate that 'backs away' from the hair follicle.

androgenic pattern,[30,31] or with progressive frontal recession, as initially reported by Kossard[32,33] in postmenopausal women, and subsequently observed also in premenopausal women.[34,35] In this entity, now designated as frontal fibrosing alopecia, the changes of LPP appear not only to be localized to the scalp, but also to involve the eyebrows[33,36] and the peripheral body hair.[37]

Histopathologically, the features of LPP and its variants are similar, irrespective of clinical presentation. In early lesions there is vacuolar interface change with a moderately dense perifollicular lichenoid lymphocytic cell infiltrate at the level of the infundibulum and isthmus.[21] Occasionally, the interfollicular epidermis may have an associated lichenoid infiltrate. In advanced lesions, concentric lamellar perifollicular fibrosis occurs, and the lichenoid infiltrate 'backs away' from the follicle[21] (Figure 5B,C). Clefting between the follicular epithelium and the stroma may be seen in longstanding lesions.[21] Mucinous perifollicular fibroplasia with absence of the interfollicular dermal mucin in the upper dermis has been described in vertical sections.[38] End-stage LPP will show loss of elastic fibres in a superficial dermal wedge-shaped scar (Figure 6A), which is better demarcated with the Verhoeff–van Gieson elastic stain[24,27] (Figure 6B). Direct immunofluorescence highlights the presence of colloid bodies in the peri-infundibular/isthmic area staining with IgM (less frequently with IgG, IgA and C3).[24] There is a 'shaggy' or linear band of fibrinogen deposition along the basement membrane zone of affected follicles, while the interfollicular epidermis is negative for immunoreactants.[39]

CENTRAL CENTRIFUGAL CICATRICIAL ALOPECIA

Central centrifugal cicatricial alopecia (CCCA), formerly known as 'hot comb alopecia' [40] or 'follicular degeneration syndrome',[41] is a progressive form of scarring alopecia that is most commonly seen in young to middle-aged women of African descent,[41–43] but has been reported also in Black men.[44] The aetiology is

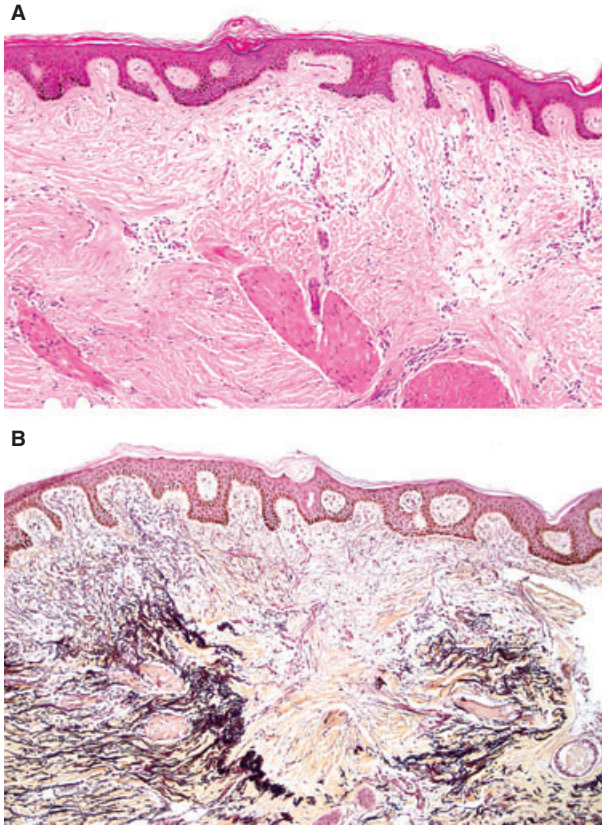


Figure 6. Lichen planopilaris, end-stage (vertical section). **A**, Superficial dermal wedge-shaped scar with loss of hair follicles and residual arrector pili muscle. **B**, Verhoeff–van Gieson elastic stain demarcates the wedge-shaped morphology of the scar with loss of elastic fibres.

unknown, but patients often report a history of traumatic hairstyling involving a combination of hair straighteners and perms, oils, heat, chemicals and traction.[42,45] No history of trauma associated with hairstyling is present in men.[44] The possibility of genetic and autoimmune involvement in the pathogenesis has been postulated.[42] Clinically, CCCA typically starts at the vertex or crown of the scalp, and spreads centrifugally (Figure 7A); it progresses slowly and in time burns itself out.[42] In the early stages, it may show associated features of folliculitis decalvans, with pustules, crusting and erythema with bacterial superinfection.[21]

The histopathology is that of a typical scarring alopecia with perifollicular concentric fibrosis, mild perifollicular and perivascular lymphoid cell infiltrate, destruction of the follicular epithelium, naked hair shafts in giant cells, and, in terminal phases, follicular dropout (Figure 7B). However, the most distinctive finding is found below the isthmus, and is characterized by premature desquamation of the inner root sheath and eccentric thinning of the follicular epithelium[16,21,41] (Figure 7C). Whereas desquamation of the inner root sheath is a feature normally observed at the isthmus, its presence below this level indicates pathology. Premature desquamation of the inner root sheath can be found in other inflammatory conditions of the scalp, including LPP.[6] However, in the latter instance, the follicles are damaged by the inflammatory cell infiltrate, and represent an 'end-stage' follicle.[46] In CCCA premature desquamation of the inner root sheath may be observed also in otherwise normal, unaffected hair follicles, suggesting that it is a characteristic feature of this entity.[21,46] In vertical sections, thickened dermal elastic fibres in a hyalinized dermis have been reported.[27] Numerous end-stage fibrous tracts replaced by amorphous connective tissue, consistent with follicular scars,[47] are seen in the subcutaneous tissue (Figure 7D).

PSEUDOPELADE OF BROCQ

Pseudopelade of Brocq is an idiopathic and slowly progressive form of cicatricial alopecia, clinically presenting with multiple small alopecic patches on the vertex and parietal areas, in a pattern that has been defined as 'footprints in the snow'.[48] While the clinical presentation is characteristic, the histopathology simply shows features of end-stage scarring alopecia.[21] Thus, it is still debated whether this is an entity *per se*, or instead represents the end stage of other scarring alopecias, such as chronic cutaneous lupus erythematosus or LPP.[21,48]

The histopathology shows all features of end-stage scarring alopecia, with concentric perifollicular lamellar fibrosis, loss of sebaceous glands, loss of follicular units with follicular scars[14,21] and a minimal residual inflammatory cell infiltrate.

Neutrophilic scarring alopecias

FOLLICULITIS DECALVANS

Folliculitis decalvans is a primary neutrophilic cicatricial alopecia affecting middle-aged adults.[49] *Staphylococcus aureus* and the host immune response have been linked to its pathogenesis.

Clinically, the alopecia is localized to the vertex (Figure 8A) and occipital area, with follicular pustules, perifollicular erythema and tufting.

Histopathologically, early lesions show features characteristic of an acute dense dermal perifollicular

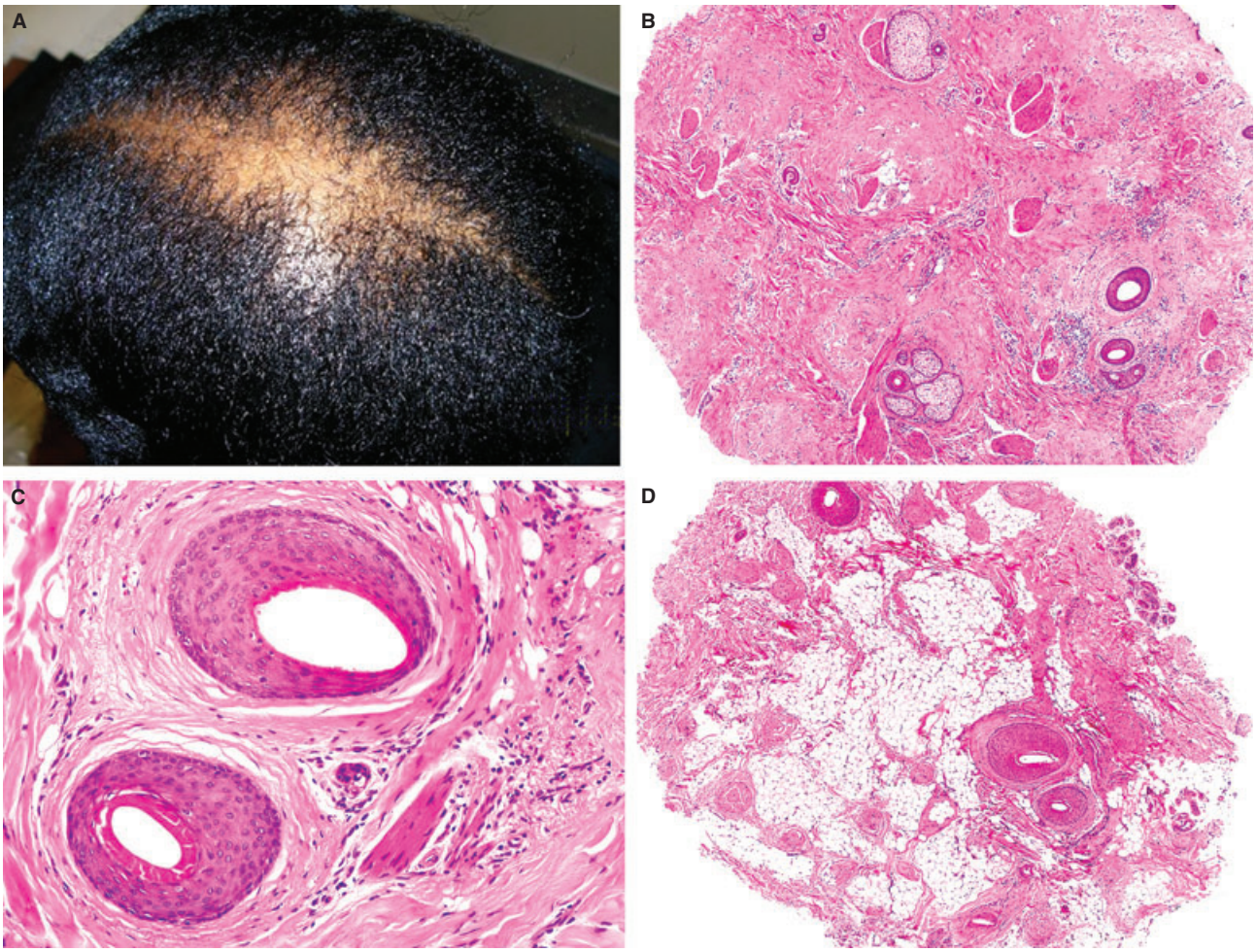


Figure 7. Central centrifugal cicatricial alopecia. **A**, Patch of scarring alopecia involving the vertex and the crown. **B**, Isthmus: near-total loss of follicular units and sebaceous glands, with replacement by follicular scars. **C**, Sub-isthmic region: high power of two residual hair follicles both showing perifollicular fibrosis and eccentric thinning of the follicular epithelium. Premature desquamation of the inner root sheath is present in the follicle at 12 o'clock. **D**, Subcutaneous tissue: numerous end-stage fibrous tracts (left); the same two hair follicles of **C** are here present, showing the previously described features (right).

neutrophilic infiltrate, and later on, as the follicle ruptures, an intrafollicular (Figure 8B) and perifollicular infiltrate of neutrophils, lymphocytes, histiocytes and plasma cells is seen. Gram stain will commonly show Gram-positive cocci of *S. aureus* (Figure 8C). Perifollicular fibrosis with fibrous tracts replacing the hair follicles, follicular tufting and interstitial dermal fibrosis are all features observed in late stages (Figure 8D).[21] PAS stain should also rule out a fungal infection.[22] This entity has been linked to CCCA,[15] as overlapping features are seen. In contrast to dissecting cellulitis, no sinus tracts are present.[22,29] A wedge-shaped loss of elastic fibres in the upper dermis, similar to that observed in LPP, has been described in vertical sections.[22]

DISSECTING CELLULITIS/FOLLICULITIS (PERIFOLLICULITIS CAPITIS ABSCEDENS ET SUFFODIENS)

This entity commonly occurs in young men of African descent. It is characterized clinically by large fluctuant nodules that begin on the occiput or vertex, but may extend throughout the entire scalp, and is often associated with sinus tracts and purulent discharge. Its pathogenesis is poorly understood, but it has been associated with disorders of the follicular occlusion triad (hidradentitis suppurativa and acne conglobata).[22] As the depth of dissection may spare a few hair follicles overlying it, the scarring alopecia ordinarily involves only half of the hair follicles.[29]

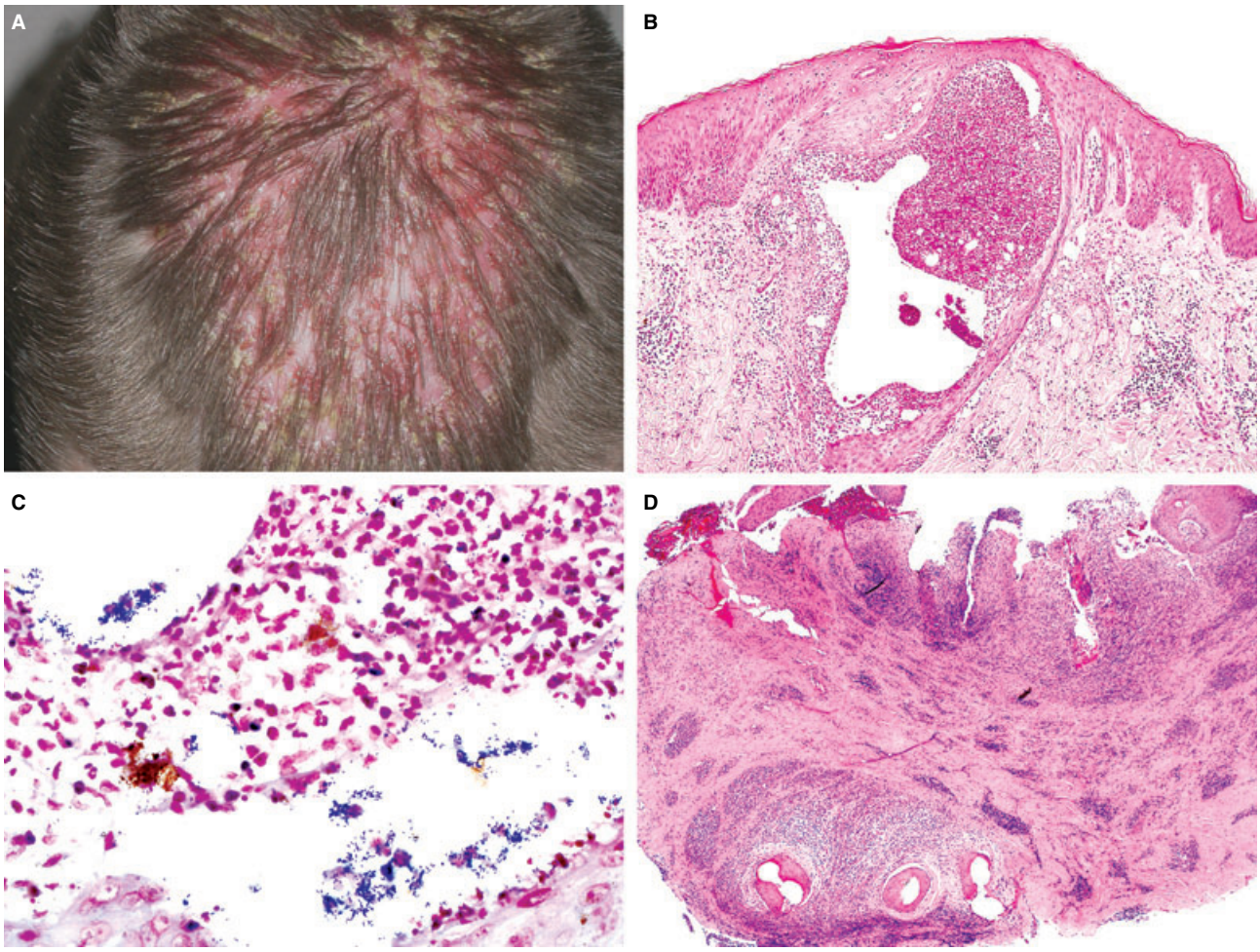


Figure 8. Folliculitis decalvans. **A**, Numerous follicular papules and pustules with erythema and scarring at the vertex. **B**, Neutrophilic microabscess within a partially destroyed follicular infundibulum. **C**, Gram stain highlights numerous Gram-positive bacterial colonies of *Staphylococcus aureus*. **D**, Late stage: dense dermal fibrosis and mixed inflammatory cell infiltrate with follicular tufting.

Histopathologically, there is a dense deep dermal and subcutaneous, predominately neutrophilic, infiltrate with follicular rupture and abscess formation. Characteristic is the formation of sinus tracts lined by squamous epithelium[16,21,22,29] with surrounding dense fibrosis.

Comment

As a footnote to the foregoing description of the scarring alopecias, it has been reported that the ratio of lymphocytic to neutrophilic alopecias is 4:1, with the former favouring middle-aged women, and the latter middle-aged men.[19]

Mixed scarring alopecias

FOLLICULITIS (ACNE) KELOIDALIS

This entity is also known as acne keloidalis nuchae, as it usually occurs on the occipital scalp in young men of African descent.[29] Clinically, it is characterized by follicular papules and pustules that progress to fibrosis, with keloid formation.[29]

Histopathologically, early in the disease there is follicular dilatation with neutrophils, and follicular rupture with perifollicular abscesses. Late lesions show perifollicular granulomas around naked hair shafts mixed with a lymphoplasmacellular cell infiltrate, and hypertrophic scar with broad eosinophilic hyalinized keloidal collagen bundles.[29,50,51] Sebaceous glands are absent in all stages of the folliculitis.[50]

Non-scarring alopecias

ANDROGENIC ALOPECIA

Androgenic alopecia is the most common type of hair loss. It is a disorder of dominant inheritance with variable penetrance,[52,53] affecting approximately half

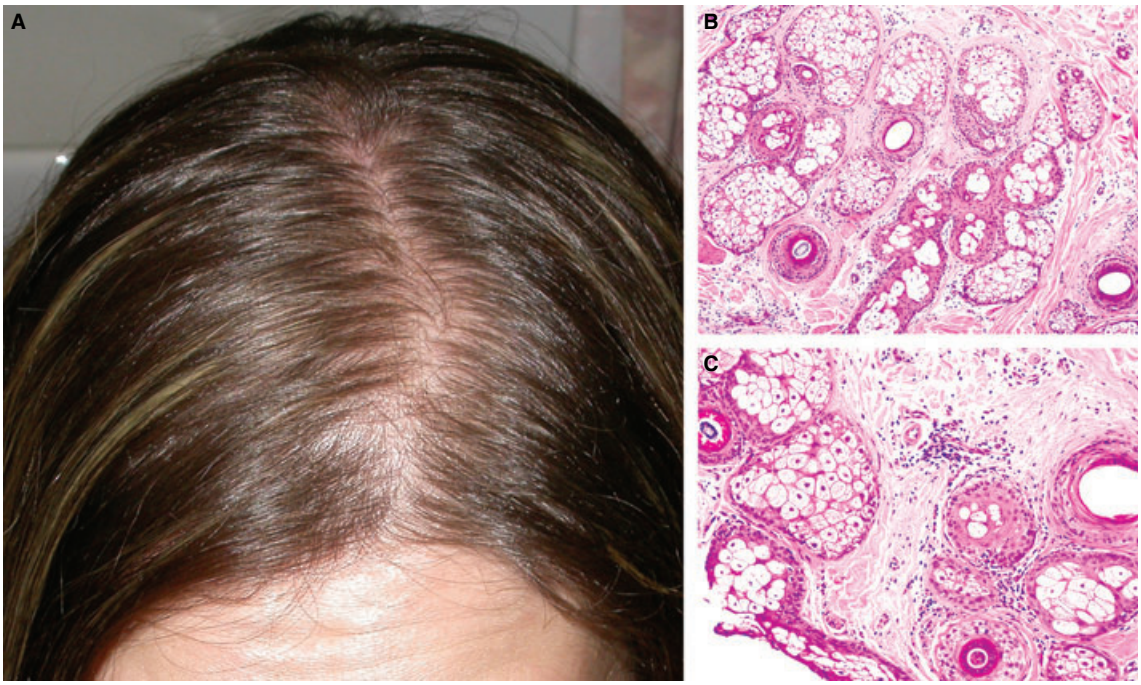


Figure 9. Female pattern hair loss. **A**, Hair 'thinning' at the vertex. **B**, Isthmus: hair follicle miniaturization with variation in hair follicle size. **C**, Mild perifollicular lymphoid cell infiltrate.

of the population by the age of 50 years, of both sexes.[53–56] The disease represents an end-organ androgen sensitivity of hair follicles[53,57] in which terminal hair follicles are genetically programmed, under the influence of androgens, to undergo miniaturization. Clinically, it is a patterned alopecia, in that it is characterized by bitemporal recession and vertex balding in men,[58] and in women (female pattern hair loss) by diffuse hair thinning of the crown with an intact frontal hairline[59] (Figure 9A).

Histopathologically, the use of transverse sections is the most valuable method to reach a diagnosis,[4] as all the hair follicles can be visualized. While the total number of hair follicles is unchanged, there is progressive miniaturization, with a variation in size of the hair follicles and increased vellus hairs (Figure 9B). The terminal (T) to vellus (V) ratio is T:V = <4:1[4,53] (normal scalp T:V = 7:1). A ratio of T:V = 3:1 or less is considered to be diagnostic.[4] This ratio does not take into account, however, the intermediate hairs that have a hair shaft diameter in between the terminal and vellus hair follicles, and are currently classified as terminal in follicular counts.[53] Other findings include an increased number of telogen hairs, decreased numbers of terminal hair follicles in the subcutaneous fat, variation of shaft diameter, and increased numbers of fibrous tracts. A mild peri-infundibular lymphocytic cell infiltrate (Figure 9C),[53,60–62] and perifollicular collagen deposition are present in 40% of cases.[53,4] A relationship between increased mast cells and perifollicular collagen deposition has been reported.[63]

TELOGEN EFFLUVIUM

Telogen effluvium is a diffuse form of alopecia, in which the hair shedding may be acute or chronic. Clinically, acute telogen effluvium can occur in both sexes and be triggered by numerous precipitating factors (major surgery, injury, severe illness, childbirth, crash diet and numerous medications);[57] there is no obvious trigger factor in chronic telogen effluvium.[57] This latter entity is characterized by diffuse scalp hair thinning in middle-aged women,[64] and has a prolonged and fluctuating course.[65,66] It may be confused with female pattern hair loss, but is distinguished from it by the lack of hair follicle miniaturization.[64,65] However, overlap cases have been reported.[67]

Histopathology of acute telogen effluvium shows a normal number of hair follicles with no miniaturization, and resembles normal scalp.[61] In chronic telogen effluvium there is also a normal number of hair follicles, but with an increased number (20–30%) of telogen hairs (normal scalp 5–10% telogen hairs), and

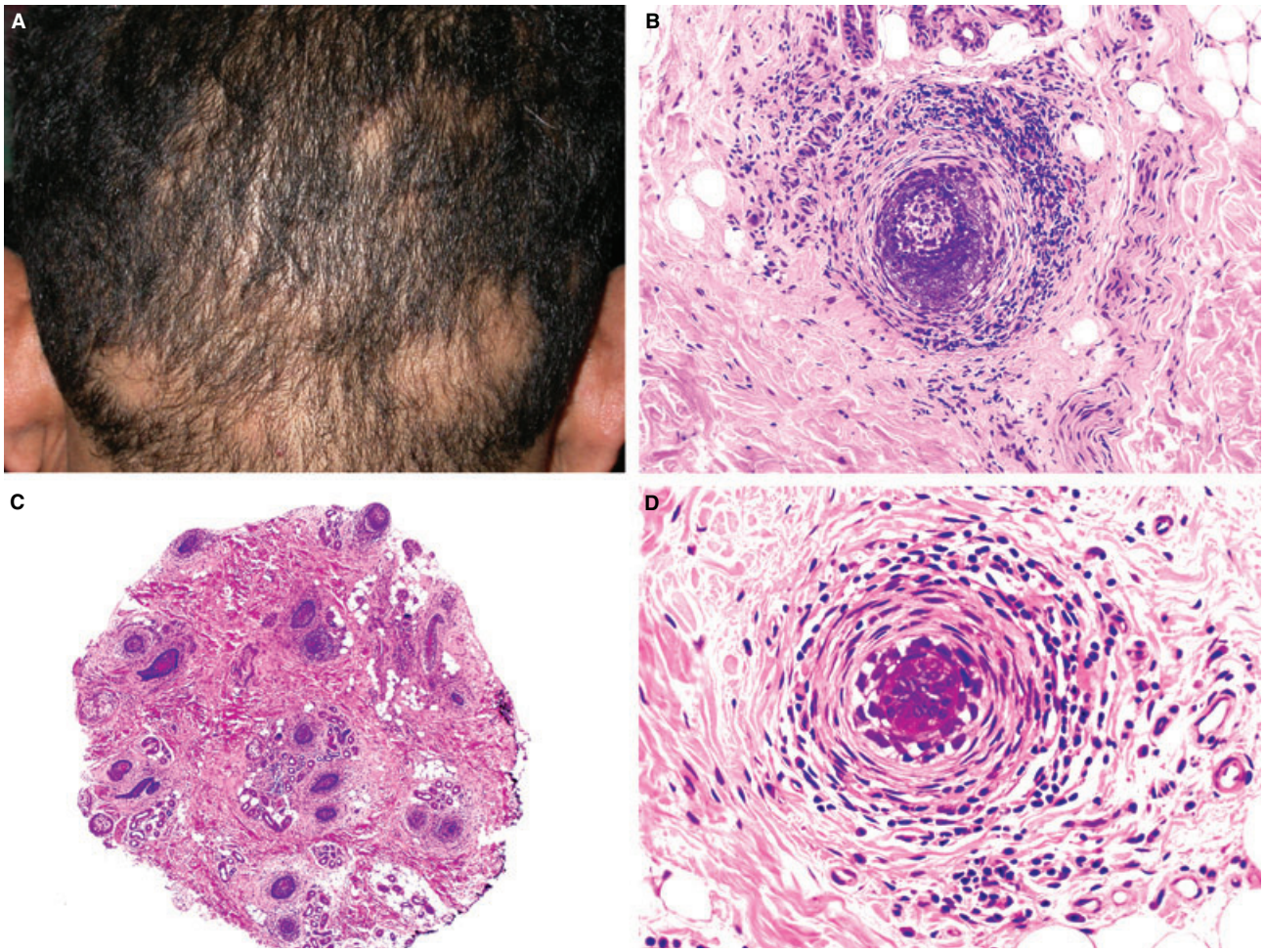


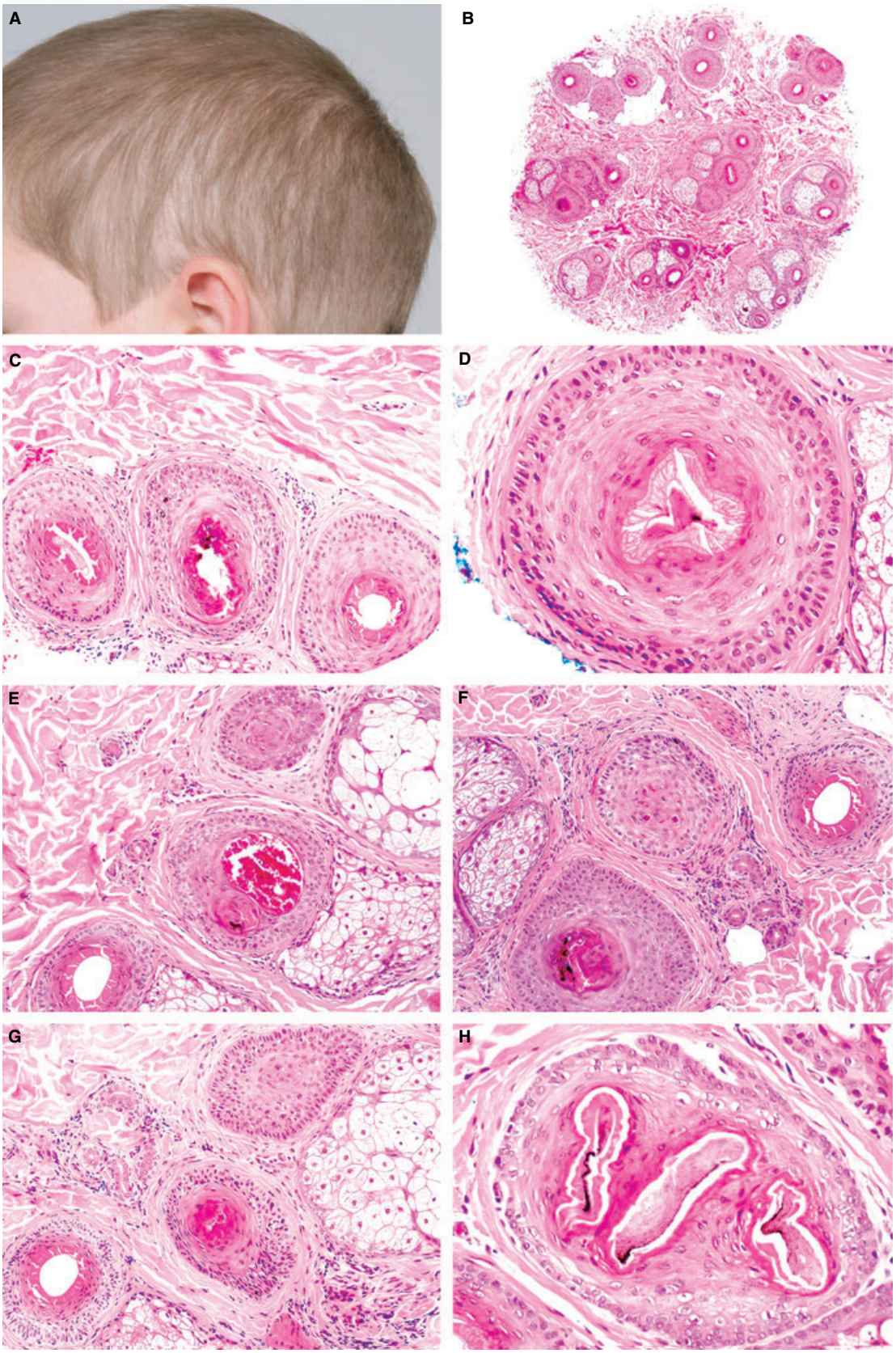
Figure 10. Alopecia areata. **A**, Multiple patches of hair loss with 'exclamation-point' hairs. **B**, Sub-isthmic region: a hair bulb with peribulbar lymphoid cell infiltrate ('swarm of bees'). **C**, 'Shift out of anagen': all the hair follicles are in telogen phase. **D**, Anagen-like nanogen hair follicle with no central hair shaft, and perifollicular lymphocytes.

some evidence of miniaturization if it is superimposed on an evolving androgenic alopecia.[61] The standard cut-off points for the differential diagnosis between chronic telogen effluvium and female pattern hair loss are T:V = >8:1 for chronic telogen effluvium, and T:V = <4:1 for female pattern hair loss,[53,68] but this difference does not include the presence of intermediate hair follicles, which would suggest early evolving female pattern hair loss. Moreover, concentric layers of perifollicular collagen have also been observed in 10% of cases of androgenic alopecia.[4,53]

ALOPECIA AREATA

Alopecia areata (AA) is thought to be an organ-specific autoimmune disorder.[69–71] It commonly occurs in association with other autoimmune diseases such as vitiligo and thyroiditis,[69] and the lifetime risk of acquiring AA is approximately 1.7%.[69,71] It equally affects males and females at all ages, and 60% of patients before the age of 20 years.[71] Clinically, it is characterized by sudden onset of patches of non-scarring hair loss, with 'exclamation-point' hairs

Figure 11. Trichotillomania. **A**, Subtle diffuse alopecia of the scalp. **B**, Isthmus: absence of inflammation and hair follicles with signs of follicular damage (trichomalacia). **C**, **D**, Irregularly shaped hair follicles. **E**, Intrafollicular haemorrhage. **F**, A melanin pigment cast within a hair shaft. **G**, A hair follicle with loss of the hair shaft. **H**, A severely distorted hair shaft.



(Figure 10A). It may undergo spontaneous remissions or exacerbations and become extensive to involve the entire scalp (alopecia totalis) and body hair (alopecia universalis). Nail changes (pitting, thickening and ridging) may be seen in 10–66% of cases.[71]

Histopathologically, the morphological features are dependent upon the duration of the episode, and may be divided into early active (acute and subacute) and longstanding (chronic) stages.[61,72,73] The early active stage is characterized by a peribulbar lymphoid cell infiltrate ('swarm of bees')[61,74] affecting the terminal hair follicles[57] (Figure 10B). This infiltrate can be quite prominent and may invade the follicular epithelium and the matrix, as well as extend above the hair bulb and into fibrous tracts.[74] Initially, the terminal hairs are attacked, but subsequently also the vellus hairs become involved. Eosinophils[75] and plasma cells may be present.[72,74] There is a 70–90% 'shift out of anagen' of the hair follicles into catagen or telogen phase[61] (Figure 10C), but the number of hair follicles is unchanged. An increased number of vellus hair follicles is also present. Additional features secondary to hair matrix damage include trichomalacia (dysmorphic hair shafts),[60, 73] and melanin pigment casts in fibrous tracts.[74,57]

In longstanding (chronic) stages, with repeated episodes, the peribulbar lymphoid cell infiltrate also involves miniaturized hairs.[57,72] The majority of the hair follicles will be in catagen/telogen phase, with the presence of nanogen hair follicles (Figure 10D).[61,72,73] These are miniaturized, rapidly cycling hair follicles with mixed features of anagen, catagen and telogen, which may contain remnants of the inner root sheath, but lack hair shafts.[72,73] Many empty infundibula may be seen,[74] corresponding to the total scalp hair loss. In a small percentage of cases (10%) with a long history of repeated attacks there is perifollicular fibrosis with follicular dropout.[57,74]

The main differential diagnosis is with the non-scarring variant of SLE, where peribulbar lymphoid cells are seen as in AA.[73] Distinguishing features are the presence in the former of vacuolar-interface changes of the infundibular epithelium, a perieccrine and perivascular lymphoplasmacellular cell infiltrate, and increased interstitial mucin,[73] particularly if in the deep dermis.[76]

TRICHOTILLOMANIA

Trichotillomania is characterized by the compulsive intentional pulling or twisting of the hair.[60,61,73,77–79] This hair loss disorder may reflect a background of emotional instability, and often occurs in children. A biopsy is an important tool to provide the clinician objective support for the diagnosis,[77] as often both the child and parents deny hair-pulling as a cause of the hair loss.[73] Clinically, the patients present with diffuse (Figure 11A) or bizarre-shaped patches of hair loss. The hair shafts have various lengths,[73,79] due to different points of fracture of the hair shafts or to the hair being pulled at different times.[79]

Histopathologically, this is a non-inflammatory non-scarring alopecia in which the morphological changes are those of follicular damage (trichomalacia) (Figure 11B) secondary to the external insult, with distortion of the hair follicle anatomy (Figure 11C,D) and with perifollicular and intrafollicular haemorrhage[60,61,73,77–79] (Figure 11E). Additional findings include melanin pigment casts (Figure 11F), loss of hair shafts (Figure 11G), and trichomalacia, where the hair shaft is dysmorphic, with incomplete cornification and irregular pigmentation (Figure 11H). The number of hair follicles is normal, with an increased number of catagen/telogen hair follicles, and without significant inflammation.

TRACTION ALOPECIA

Traction alopecia, like trichotillomania, is a non-inflammatory, non-scarring alopecia secondary to mechanical damage, which in this case is hairstyle related, and is seen in women of African descent.[73,80] Clinically, the hair loss is often seen at the margins of the scalp, involving the frontal, temporal and parietal regions.[73] In early traction alopecia the hair loss is temporary, provided that the damaging noxa is suspended, whereas in late 'burnt out' alopecia, where the excessive traction persists, the hair loss is permanent.[25,73]

Histopathologically, the features observed in early traction alopecia are similar to those seen in trichotillomania,[60,73] whereas in late traction alopecia there is marked loss of the terminal follicles with preservation of the vellus hairs and sebaceous glands.[73] The follicular units at the isthmus are replaced by fibrous tissue, consistent with a scarring process, and thus permanent alopecia.[25,73]

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