Alopecia is a common disorder in India. The causes of alopecia are diverse, and a specific diagnosis is made by a concert of detailed clinical history, accurate description of lesions, histopathologic evaluation of scalp biopsies taken from appropriate sites, and sometimes, special techniques such as direct immunofluorescence (DIF).[1-4] Of these, the contribution of histopathology is paramount. The presently followed NAHRS classification of scarring/cicatricial alopecia according to the nature of the dominant inflammatory cell infiltrate is based purely on morphology.[5] It is the single most important tool in understanding disease pathogenesis and yet is underutilized. It is also the most objective method to estimate/predict the response to treatment. Many pathologists are unfamiliar with the special handling required for these biopsies right from the level of grossing to interpretation. An important point to bear in mind is that classic lesions are rarely biopsied and chances of finding overlaps, confounding and atypical features on biopsies are quite frequent.

This review attempts to bridge these gaps and address issues of practical significance. It will address only the common diseases and their diagnostic challenges.

INTRODUCTION

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CLINICAL FINDINGS

The most important clinical input necessary for biopsy interpretation is whether the alopecia is scarring or non-scarring. Non-scarring alopecia shows preservation of follicular ostia, implying that hair loss is potentially reversible and regrowth of hair is possible. In scarring alopecia, the scalp appears smooth with loss of ostia.[2,4] This implies that the hair loss is not reversible. In such instances, the goal of treatment is to prevent further scarring. Sometimes, it may be difficult to distinguish scarring versus non-scarring hair loss on clinical grounds. Dermoscopy can be of great value in these instances and should also be used to select the biopsy site.[6]

It also follows that a biopsy for scarring alopecia should be taken from the edge of the lesion, where the disease process is more likely to be active. A 4-mm punch biopsy including the subcutis is the optimum sample.[2,4]

It is important to bear in mind that the so-called “non-scarring” alopecias, such as alopecia areata (AA) and androgenetic alopecia (AGA), evince follicular dropout in late stages, can also result in irreversible hair loss.

The other useful piece of clinical information is whether the hair loss is diffuse or patchy. Diffuse hair loss is the consequence of disruption of one phase in the follicular cycle, the most common example being telogen effluvium (TE).[2]
GROSSING TECHNIQUE

It is widely believed that two samples are recommended for the evaluation of alopecia, one for vertical and one for transverse sections, particularly in non-scarring alopecia. There are also techniques such as HoVert and Tyler, by which the same can be done on a single sample.[7,8] While this is ideal, transverse sections are technically difficult to obtain even by experienced technologists; what we actually end up seeing are “oblique” sections. Interpretation of transverse sections requires expertise not just in normal transverse anatomy but also in recognizing artefacts.[9] We have yet to come across an instance where we made the diagnosis on transverse sections but not on vertical. If there is only a single biopsy specimen, standard vertical sections give excellent diagnostic yield.[10] In our practice, we use a disposable microtome blade rather than scalpel blade, which makes it easier to bisect the specimen.

NORMAL ANATOMY AND HISTOLOGY

The starting point for alopecia diagnosis is a sound knowledge of the histology and cyclical changes of normal hair.[11]

Types of follicles

There are two types of follicles, namely vellus and terminal. Vellus refers to short, thin hair with its’ bulb located in the reticular dermis and present on most of the body. Terminal follicles have long, thick hair with bulb located deep in the subcutis present on scalp, eyebrows, eyelashes, beard in men, axillae, and pubic areas. These hairs have a medulla.

Both vellus and terminal hair follicles have a stationary upper segment and a dynamic lower segment. The lower segment goes through alterations of the follicular cycle: anagen (growing), catagen (involuting), and telogen (resting) phases.

Anagen hair anatomy

The upper segment comprises of infundibulum and isthmus while the stem and bulb make up the lower segment [Figure 1].

The most superficial portion of the hair follicle is the infundibulum, which extends from the skin surface to the point of entry of the sebaceous duct. Its lining cells show epidermal keratinization, with a granular layer.[3]

Below this is the isthmus, the short portion between the entry of the sebaceous duct and the attachment of the arrector pili muscle. Histologically, it is a narrow strip of the follicle which connects the stem with the infundibulum. Isthmus comes into existence at the point where the inner root sheath desquamates. One sees only the outer root sheath with pink cells here. Cell borders are barely detectable. Inner surface shows a brightly eosinophilic cornified layer with a corrugated appearance. Granular layer is characteristically absent. The cells of the outer root sheath undergo trichilemmal keratinization at this level.

Stem is the portion between the base of isthmus and Adamson’s fringe and is the longest part of a follicle. Adamson’s fringe is the boundary between the nucleated cells of the hair in bulb and the anucleate cells of the stem. Various layers begin to differentiate in this zone. Starting from the centre is the hair cortex, which is covered by the shaft cuticle. External to the shaft cuticle are the three layers forming the inner root sheath: inner sheath cuticle, Huxley’s layer, and an outer Henle’s layer. The shaft cuticle intermeshes with the inner sheath cuticle to form a single anatomical layer. The Henle’s layer is the first to cornify. It undergoes keratinization through formation of reddish trichohyaline granules. Outside the inner root sheath is the outer root sheath, which is composed of clear cells rich in glycogen, which is one cell thick at this level.[11]

The bulb is the lowermost portion of the follicle, with an inverted cup-like, expanded lower end that consists of matrical cells and supramatrical cells (immature epithelial cells with large, crowded, round, nuclei, and many mitotic figures). They appear dark blue on H and E sections. Cells just above the follicular papilla are palisaded. Matrical cells differentiate into

![Figure 1: Parts of a terminal anagen hair follicle: (a) Bulb, (b) Stem, (c) Isthmus, and (4) Infundibulum (H and E, ×40)](image1.png)

![Figure 2: Histology of the follicular bulb: (a) Papilla, (b) Dendritic melanocytes, (c) Matrical cells, note the palisading just above the papilla, (d) Inner root sheath, (e) Outer root sheath (H and E, ×400)](image2.png)
outer sheath, inner sheath, and hair. There are also dispersed dendritic melanocytes [Figure 2].

The follicular papilla has the shape of an inverted pinecone [Figure 2]. It is composed of connective tissue, fibrocytes, mucin, and a capillary. It is continuous with the perifollicular fibrous sheath. Between the hair follicle and the fibrous root sheath is the basement membrane, which stains PAS positive.\(^{[3,11]}\)

**Catagen hair anatomy**
At the beginning of the catagen phase, the hair matrix disappears and is replaced by thin strands of epithelial cells. The lower follicular epithelium undergoes degeneration by apoptosis. The basement membrane becomes thickened and wrinkled [Figure 3].

The hair papillae migrate upward into the dermis and come to rest below the bulge region. The epithelial cells form hair club as the cells begin to cornify from the center outward. The collapsed fibrous root sheaths containing blood vessels are also termed as fibrous or follicular streamers/tracts or stelae.\(^{[3,11]}\) These serve as guiding tracts into which new anagen hair grows in the next cycle [Figure 4].

**Telogen hair anatomy**
At the beginning of the telogen phase, the hair papilla forms a ball of spindle-shaped cells which lies below the nipple of epithelium called secondary germ. At the end of this phase, the telogen club is shed, and the transition back to new anagen phase begins.

In vertical sections, it is hard to differentiate between late catagen and telogen follicles as the lower segment would have completely disappeared. In transverse sections, telogen hair appears like an asterisk-shaped cluster of dark blue cells.

Throughout the hair growth cycle, the dermal/follicular papilla which constitutes the mesenchymal connective tissue trails along upward with the involution of hair follicle.\(^{[3,11]}\)

**Classification**
The NAHRS classification for primary cicatricial alopecia is based on the inflammatory cell content in active disease.\(^{[5]}\) This classification is neither complete nor precise as diseases are grouped based solely on the nature of the infiltrate. From a microscopist’s point of view, it is not merely the nature of the infiltrate, but also its location, associated with epidermal and dermal changes that contribute to diagnosis. The practical classification depicted in Table 1 is based on Ackerman’s algorithmic approach and includes the commonly encountered conditions.\(^{[12]}\)

**Examination under Scanning Magnification**
Evaluation of biopsies under scanner view of 2× or 4× is the first and vital step, which is often understated.

a. Adequacy of the sample: The presence of subcutis indicates that the biopsy is sufficient. Subcutis

| Table 1: Histologic classification of common alopecias |
|-----------------------------------------------|
| **Alopecia with inflammation**                  |
| **Peri-infundibular and perifollicular**        |
| Lymphocyte predominant                          |
| Lichen planus (planopilaris)*                   |
| Lupus erythematosus*                            |
| Morphea*                                       |
| Neutrophil predominant                          |
| Folliculitis decalvans                         |
| Dissecting cellulitis                           |
| Tinea capitis                                   |
| Plasma cell and histiocyte predominant          |
| Syphilis                                       |
| Folliculitis decalvans (late stage)             |
| **Exclusively peribulbar**                      |
| Lymphocyte predominant                          |
| Alopecia areata*                                |
| **Alopecia without inflammation**               |
| Normal-sized follicles                          |
| Trichotillomania                               |
| Miniaturized follicles                          |
| Telogen effluvium                               |
| Androgenetic alopecia                          |
| Late stages of diseases marked with asterisk (*) may have little or no inflammation |

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**Figure 3:** Catagen hair follicle: (a) Involuting lower segment (arrow) (H and E, ×200), (b) Apoptotic cells (arrows) and cornification of outer root sheath (star) (H and E, ×200), (c) Thick corrugated basement membrane (arrow) (H and E, ×200)
may be obliterated in diseases such as morphea and late stages of folliculitis decalvans (FD), due to scarring.\textsuperscript{[2,4]} The presence of terminal hair follicles can also be assessed.

b. Epidermis: Epidermal atrophy and loss of rete pegs can be well appreciated on scanning magnification. This is commonly encountered in lupus erythematosus (LE) and morphea\textsuperscript{[2]}

c. Distribution and number of terminal follicles: It is important to assess whether the follicles are distributed evenly throughout the biopsy. Scarring or follicular dropout results in uneven distribution and is a clue to irreversible hair loss\textsuperscript{[2,4]} [Figure 3]. The presence of blank spots in a biopsy, i.e., arrector pili muscles unaffiliated with pilosebaceous units, is a clue to scarring\textsuperscript{[2,4]}

d. Location of the bulb: The bulb of normal terminal hair follicles should be present deep in the subcutis.\textsuperscript{[11]} If they are situated higher up, it indicates miniaturization, as seen in AGA

e. Presence and location of inflammatory infiltrate: Location of the infiltrate, i.e., peri-infundibular, perifollicular (throughout the length of the follicle) or peribulbar can be determined. One must remember that diseases that show peri-infundibular/perifollicular inflammation often involve the bulb, whereas AA is exclusively peribulbar\textsuperscript{[2,11]}

f. Interfollicular dermis: Scanning view also tells us if the dermis between the follicles is normal, inflamed or shows fibrosis/scarring

g. Follicular spongiosis/mucin: A pale/edematous appearance of the infundibulum/follicle is a clue to presence of edema or mucin, best appreciated on scanning magnification

h. State of sebaceous lobules: Scarring alopecia is often accompanied by loss of sebaceous lobules.\textsuperscript{[2,4]} Psoriatic alopecia, increasingly being recognized, is another condition where sebaceous lobules can be atrophic/absent, in contrast to the “hyperplasia” encountered in AGA.\textsuperscript{[13]}

**Evaluation of scarring**

The next important step is to identify the presence of scarring. As mentioned earlier, uneven distribution of follicles is an important clue to scarring.\textsuperscript{[2,4,14]} The features of scarring differ with temporal evolution of the disease. Early scarring is accompanied by inflammation, which may mask the process. Collapsed fibrous root sheaths containing blood vessels, also termed as fibrous streamers or stelae, normally accompany the follicle as it migrates upwards in catagen/telogen phases. This should not be confused with scarring. Stelae comprise of loose, vascular tissue, whereas a scar is dense and avascular.\textsuperscript{[4]}

A fully evolved scar shows a column-like band of fibrosis near arrector pili, with the absence of sebaceous lobules. This results in blank spots [Figure 5]. With time, the scar fades and appears paler in comparison to the surrounding dermal collagen. Another telltale sign of scarring in late stages is the presence of naked hair shafts in the dermis. Earlier in the process, these may be surrounded by foreign body giant cells. Giant cells in scarring can also be seen when lipid from sebocytes is extruded. Stains such as Verhoeff show loss of elastic fibres within the scar, but these are not mandatory in routine practice.\textsuperscript{[2]}

**Evaluation of follicle number, size, and phase**

Whiting demonstrated that there should be around 39 hair follicles in a 4-mm punch biopsy in Caucasians and Sperling \textit{et al.} noted about 21 follicles in African-Americans.\textsuperscript{[15,16]} No such data is available for Indian population, but the number would be closer to the latter. Scalp shows a mixture of terminal and vellus hair, with a normal ratio of 2:1.\textsuperscript{[4]} Terminal hairs have their bulb in the subcutis while vellus hair bulbs are located in the mid-dermis. Vellus hair shafts are much smaller than terminal, and their diameter is less than the thickness of the inner root sheath. When a scalp biopsy appears to possess only vellus hairs, it indicates AGA. This results from progressive miniaturization with each follicular cycle.

Normal scalp should have >85% anagen hair follicles (9:1 ratio).\textsuperscript{[4]} In a 4-mm punch, one should not see more

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**Figure 4:** Fibrous tract/streamer/stela: (a) A stela (arrow) in the wake of an involuting catagen terminal follicle (H and E, ×40), (b) Longitudinal view of an empty stela composed of connective tissue and blood vessels (H and E, ×200), (c) End on view of stela (H and E, ×200)

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**Figure 5:** Scar versus “follicular drop out:” (a) A blank space (arrow) adjacent to arrector pili muscle which is unaffiliated with pilosebaceous units and composed of dense fibrous tissue denotes a follicular scar (H and E, ×200), (b) Delicate, inconspicuous stelae (arrows) in the subcutis on its journey towards “follicular drop out” (H and E, ×100)
than one non-anagen follicle, as a rough indicator. It is not necessary to distinguish catagen and telogen follicles; they can be grouped as non-anagen follicles. The bulb of a catagen follicle lies in the lower or mid-dermis, encased by a thickened, corrugated basement membrane. In well-oriented sections, these are traced by thin fibrovascular stelae.

Precise counts can be performed only on transverse sections.[16] This is mostly an academic exercise, and in practice, it is not necessary to give actual counts or ratios.

**Assessment of Inflammation**

The next step is to identify the presence, site, and type of inflammation. The infiltrate can be confined to the upper portions of the follicle (peri-infundibular), extend throughout the length (perifollicular), or target the lower part (peribulbar) exclusively. As given in the classification, the location is an important clue to diagnosis.[11] The most common cell type seen are the lymphocytes. A neutrophil-predominant infiltrate implies that an infectious cause like fungus should be excluded. Plasma cells can abound in syphilis, late stages of FD, and at times, LE. It is also important to note whether the lymphocytes show cytologic atypia, especially when they also invade the follicular epithelium. This is a red flag for folliculotropic mycosis fungoides (FMF).

**Lymphocyte-predominant Alopecias**

There are three important diseases in this group: lichen planopilaris (LPP, peri-infundibular), LE (peri-follicular), and AA (peribulbar). The first two are scarring while AA is non-scarring.

**Lichen planopilaris versus lupus erythematosus**

From a therapeutic and prognostic point of view, it is important to distinguish LPP from LE.[2,17] Classic LPP presents clinically as diffuse or patchy hair loss with itchy, hyperkeratotic follicular papules and spines surrounded by mild erythema. Chronic LE typically affects young women. Clinical presentation includes follicular plugging, erythematous scaly plaques in the early stage and telangiectasia, and loss of follicular ostia in the late lesions.[18]

The salient histopathologic features of the two are summarized in Table 2:[14,18-20] [Figures 6-8].

In active disease, it is not difficult to tell apart LPP from LE. Early lesions of LPP appear similar to lichen planus, with infundibular hyperplasia and lymphocytes “hugging” the infundibulum.[19] Late lesions show peri-infundibular scarring with mucinous fibroplasia, retraction, and, on occasion, foreign body reaction to hair shafts.[19] [Figure 6].

The problem arises when inactive/burnt out lesions are biopsied in patients with long-standing disease. Biopsies are often accompanied by a clinical diagnosis of “pseudopelade of Brocq,” which represents end-stage disease, commonly due to LPP.[14]

In such cases, there is a paucity of both follicles and inflammation, which is seen in about 30% of cases.[14] Jung and Boer used connective tissue changes in such instances to attempt diagnosis.[21] The changes affecting papillary dermis, reticular dermis, and the adventitial dermis of follicles (fibrous tracts) were studied. If the papillary dermis is normal and rete ridges are preserved, possible diagnoses are LPP and AA. If the rete ridges are flattened, the possible diagnoses are LE and FD. The reticular dermis is largely normal in LPP and AA. Abundant mucin is seen in LE. We used these features and were able to render a diagnosis in a majority of biopsies from late-stage scarring alopecia.[14] If one is unable to render a specific diagnosis even after using all known criteria, it is better to sign out such biopsies as end-stage scarring alopecia.
Role of immunofluorescence
The characteristic DIF finding in LE is linear and granular deposits of IgG and C3 along the epidermal and follicular basement membrane zone. Globular deposits of IgM, rarely IgA and C1q deposits, are also observed. However, negative results do not exclude the diagnosis. We have not found DIF to be useful in differentiating alopecia of LE from LPP.

Role of immunohistochemistry
There are recent reports suggesting that plasmacytoid dendritic cells (PDCs) abound in LE and using markers such as CD123 to highlight them aid in differential diagnosis. The are found in clusters in LE and absent or occasional in LPP. In our experience, we found clusters of PDC in 85% of LE with established scarring whereas only 6% of other alopecias demonstrated PDC, that too, as scattered cells (unpublished data). This seems to be a promising marker.

Alopecia areata
AA is characterized by round or oval, smooth patchy hair loss involving any hair-bearing area with preserved follicular markings denoted as “exclamation marks.” Spontaneous remissions and exacerbations occur and may become extensive enough to involve the entire scalp.

The histopathologic findings in AA depend on the duration of the episode and are divided into acute/active, subacute, and chronic stages. The active stage is characterized by peribulbar inflammatory infiltrate (“swarm of bees”) composed of activated T-lymphocytes, admixed with few histiocytes, plasma cells, and eosinophils. This pushes the follicle into catagen or telogen, with inversion of anagen: telogen ratio. This classic feature may be seen in only 38% of biopsies. In subacute stage, there is increase in number of catagen followed by telogen hairs, which often exceed 50% of the total follicles. As the disease is episodic, all the affected follicles appear to be in the same stage of catagen. Some remnant inflammation is seen in and around the fibrous tracts. Pigment casts are seen around the bulb and within fibrous tracts, which can overlap with LPP and LE. Their presence merely indicates that the inflammation has involved the bulbar matrical epithelium and is not a specific feature.

With repeated episodes of inflammation, follicles diminish in size and become miniaturized. These are termed nanogen follicles. These follicles lack hair shafts and contain remnants of outer root sheath. In chronic stage, the miniaturized follicle may still show the infiltrate in some cases. Empty follicular infundibula are seen. Eventually, perifollicular fibrosis and follicular dropout set in.

Cases of AA with miniaturization and lacking inflammation can be mistaken for AGA. This is particularly true for patients of AA presenting with diffuse involvement. It is very difficult to tell apart the two and the clues are very subtle. If one carefully observes the fibrous stelae trailing the follicles, a few lymphocytes can be discerned. Immunostains for T-cells, such as CD3, can be used to highlight them. Eosinophils in fibrous tracts are also

Figure 6: Lichen planopilaris: (a) Peri-infundibular lichenoid lymphocytic infiltrate. Note the retained rete pegs in the surface epidermis and the hypergranulosis at the infundibular ostia (H and E, ×100), (b) Interface folliculitis (H and E, ×400), (c) Late lesion showing perifollicular mucinous fibroplasia with retraction giving an “onion skin appearance” (H and E, ×200)

Figure 7: Scarring alopecia of lupus erythematosus. Note the atrophic epidermis, abundant melanophages, dermal scars corresponding to the “graveyards of the erstwhile majestic follicles” (arrows), perifollicular inflammation, and interfollicular dermis showing inflammatory infiltrates extending deep (H and E, ×40)
supposed to serve as a clue, but we have not encountered them.\textsuperscript{[11]} Rarely, AA can show scarring.\textsuperscript{[28]} In these instances, we have seen remnants of catagenic basement membranes (highlighted by PAS stain) within these scars and elsewhere in the sections. Coupled with miniaturized follicles, this a soft clue to AA.

Morphea is an under-recognized cause of alopecia. Clinically, the linear en coup de sabre variant can show hair loss.\textsuperscript{[12]} Biopsies from such lesions show absence of follicles, sebaceous glands, eccrine units, and dense dermal sclerosis. Perineural lymphoplasmacytic infiltrate has also been described.\textsuperscript{[31]}

Neutrophil-predominant Alopecias

If a biopsy done for alopecia shows a predominance of neutrophils, an infectious etiology should first be excluded.\textsuperscript{[2,4]} Fungal stains such as PAS and GMS are mandatory to identify Tinea capitis and its clinical variants. Once this has been excluded, possibilities of FD or dissecting cellulitis (DC) should be entertained.

Clinically, FD presents as pustules with perifollicular erythema and tufting, generally involving the vertex or occiput. DC is generally seen in Africans and presents as boggy scalp swellings with discharging sinuses.\textsuperscript{[2,4]} It is rare in Indians.
Early lesions of FD are characterized by a dense dermal perifollicular and intrafollicular neutrophilic infiltrates. Later, the follicles rupture and infiltrates of neutrophils, lymphocytes, histiocytes, and plasma cells are found.[2,4] Naked hair shafts with granulomatous response are frequent [Figure 12]. In healed lesions, follicular tufting and marked dermal fibrosis with thick tracts are seen. DC shows similar features with tracts lined by squamous epithelium, in addition.[2]

Tufting of follicles, i.e., tufts of hair emerging from a common, dilated infundibulum, also termed “six packs” or “doll’s hair” is frequently seen in later lesions of FD/DC[34] [Figure 12]. This is a reflection of distorted follicular architecture following extensive inflammation, scarring, and regeneration.

**Plasma Cell-rich Alopecia**

Plasma cells are abundant in late lesions of FD.[2] Syphilitic alopecia also shows many plasma cells. It can be patchy (moth-eaten), diffuse, or a combination of the two. There is a dense peribulbar inflammatory cell infiltrate composed of plasma cells, lymphocytes, resembling AA. However, the abundance of plasma cells in the infiltrate and positive serological tests for syphilis helps in differentiation.[1,18] One must not forget that LE can also show a dominance of plasma cells at times, in combination with other typical features.

**Alopecia without Inflammation**

**Androgenetic alopecia**

The most important disease under non-inflammatory alopecias is AGA. One should remember that androgen sensitivity of the hair follicle varies depending on the region of the scalp. Occipital hair follicles are androgen independent. Classic AGA in men is clinically distinctive and rarely biopsied. It starts as bitemporal recession, followed by frontal and parietal involvement. In women, diffuse thinning of the central scalp is seen. This can mimic diffuse AA as stated earlier.

**Trichotillomania**

Trichotillomania is a self-inflicted condition usually seen in young patients, with asymmetrically distributed, patchy hair loss with shafts of different lengths.
Early lesions may only show an increase in catagen follicles. The histopathologic changes in fully evolved lesions reflect distorted follicular anatomy. There are pigment casts, melanin pigment in the collapsed fibrous sheath, perifollicular and intrafollicular hemorrhage. This results from repeated twisting and pulling of hair.

Trichomalacia is not always present but is diagnostic when seen, typified by hair shafts that are pleated and crumpled, containing clumps of melanin and irregularly cornified. Trichomalacia may not be evident in all sections and the increase in catagen follicles can mimic AA. Trichomalacia is often present in the infundibulum and can disappear when serial sections are taken or the block is trimmed too much, in which case it may not be seen at all! The lack of inflammation and random distribution of catagen follicles admixed with anagen follicles serve as useful clues to exclude AA. It is interesting to note that nevi from the face or scalp can frequently show changes of trichotillomania, as a consequence of repeated handling. Multifactorial alopecia

Wohltmann and Sperling found multiple coexisting forms of alopecia in a single biopsy specimen in about 12% of their cases and introduced the term multifactorial alopecia to describe these. AGA frequently coexisted with other diseases, such as traction alopecia, end‐stage scarring alopecia, TE, and AA. They opine that in such cases, having a control biopsy from uninvolved scalp helps to identify AGA. Neoplasms with alopecia

Destruction of hair follicles resulting in alopecia can be seen in both benign (such as syringoma) and malignant neoplasms, such as squamous and basal cell carcinomas, angiosarcoma, and metastatic gastric carcinoma.

The most common malignancy presenting as alopecia, of utmost concern for a pathologist, is FMF, variously designated as MF with follicular mucinosis, alopecia mucinosa, or follicular MF. It presents in young adults with alopecia of scalp and eyebrows and can be accompanied by plaques/nodules elsewhere. Histologically, there are numerous lymphocytes peppering the infundibulum or the entire follicle frequently with deposits of mucin within the follicular epithelium. This can simulate spongiosis unless the pale blue hue is appreciated and special stains such as Alcian blue are performed. The lymphocytes need not show atypia, and epidermal changes of MF are absent. Eosinophils are seen frequently as are granulomas. All these simulate inflammatory conditions, and the diagnosis is often missed. Multiple biopsies may be necessary to be certain. Infiltration of eccrine units and sebaceous glands serve as an additional clue to FMF. TCR gene rearrangements to demonstrate clonality can be used and is valuable if the same clone is demonstrable in multiple samples. It is vital not to miss this diagnosis as FMF is often refractory and progresses faster in comparison to conventional MF.

Conclusion

Despite advances in noninvasive techniques for the diagnosis of alopecia, histopathology still remains the most objective and useful tool. Completeness of clinical information, proper selection of biopsy site (aided by dermoscopy), adequacy of sample, and a stepwise microscopic approach as described in the initial part of this article are the ground rules to maximizing
diagnostic yield. The checklist provided in Table 3 serves to highlight this. In our experience, transverse sections, regarded by many as crucial, are not essential and most of the diseases can be diagnosed on vertical sections alone. Combining traditional microscopy with newer techniques may offer fresh insight into pathogenetic mechanisms and help us break new ground in refractory diseases, offering hope to those afflicted.

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