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Alopecia areata-like pattern: A new unifying concept

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An accurate diagnosis of alopecia can be challenging, with disparate alopecic entities having similar features. We write this commentary to alert clinicians and dermatopathologists to a histopathological pattern, termed "Alopecia Areata (AA)-like pattern," which may occur in a number of entities beyond AA. Knowledge of this AA-like pattern allows for more accurate diagnoses.

Identification of AA-like pattern in disparate entities results from our clinical and histopathological experience complemented with knowledge of hair immunology and follicular cell growth kinetics. Taken together, we present a new, unifying concept of alopecia, based not upon a historical, established classification depending upon scarring (i.e., cicatricial or non-cicatricial) and the inflammatory cell type (i.e., lymphocytic, neutrophilic, or mixed).[1,2] While we do not intend to replace the established classification, we attempt to provide insight into the pathophysiology of disparate alopecic entities.

Acute AA is easily diagnosed because of the presence of deep, peribulbar lymphocytes in a "swarm-of-bees" arrangement. Challenges arise, however, as AA transitions to a subacute phase, wherein follicular miniaturization and a catagen/telogen shift become dominant histopathologic features, and the "swarm of bees" lymphocytic infiltrate disappears.[3,4] Profound follicular miniaturization of subacute AA may have a terminal (T) to vellus (V) hair ratio of <1:4 (normal ≥2:1) and a markedly increased catagen/telogen shift, sometimes greater than 50% (normal <15%).

Female pattern hair loss (FPHL), also known as androgenetic alopecia, and diffuse AA may have almost identical clinical and histopathological presentations, especially when FPHL presents with a superimposed chronic telogen effluvium. Scalp biopsies with concomitant FPHL or biopsies taken from patients older than 50 years (senescence) can show a T:V < 1:1. This ratio has more significance if the biopsy is taken from a non-androgen-dependent area. We showed that immunohistochemistry (IHC) may be helpful in distinguishing AA from FPHL using a CD3 IHC stain to identify deep dermal lymphocytes in empty follicular tracts in subacute AA.[5] The lymphocytes may not be apparent on H&E sections.

We, therefore, define AA-like pattern as the presence of a T:V < 1:1 combined with a catagen/telogen shift of >15% in a non-androgen-dependent area. A peribulbar lymphocytic infiltrate is either present around miniaturized bulbs, or it is absent. Cases with a peribulbar infiltrate around terminal hair bulbs do not fit into this definition because they lack follicular miniaturization. Table 1 lists entities in which an AA-like pattern may be encountered. To distinguish from AA, one uses clinical, biological, and histopathological clues.

1. Psoriatic and TNF-alpha inhibitor-induced psoriasiform alopecia

The most common AA-like pattern is from psoriasis. The clinical presentation may be patchy or diffuse alopecia, or scaly dermatitis without alopecia. Histopathology shows features typical of subacute AA. The interfollicular epidermis, however, reveals psoriasis (Figure 1). Treatment of psoriasis may result in hair regrowth if follicular miniaturization and loss is minimal.[6] TNF-alpha inhibitor associated psoriasiform alopecia may also mimic AA. Distinction between psoriatic and TNF-alpha-induced psoriasiform alopecia from AA is possible by the presence of psoriasiform hyperplasia and sebaceous gland atrophy in psoriasis. There is some evidence that the presence of plasma cells and eosinophils help distinguish TNF-alpha inhibitor from psoriatic alopecia.[7]

2. Lupus erythematosus

2a. Non-scarring alopecia of systemic lupus erythematosus (SLE) can be either patchy or diffuse, thereby producing an AA-like pattern more commonly than other types of LE.[8] Fortunately, the interfollicular epidermis usually shows an interface dermatitis with

TABLE 1 The differential diagnosis of alopecia areata-like pattern

- Subacute and chronic alopecia areata
- Psoriasis
  - Includes:
    - Psoriatic alopecia
    - TNF-alpha inhibitor-induced psoriasiform alopecia
  - Clue to distinguish from AA: psoriasiform hyperplasia in the interfollicular epidermis, parakeratosis with neutrophils, and sebaceous gland atrophy
- Lupus erythematosus
  - Includes:
    - Systemic lupus erythematosus (nonscarring alopecia)
    - Chronic cutaneous (discoid) lupus erythematosus with deep follicular involvement
  - Clue to distinguish from AA: interface change in the interfollicular epidermis
- Syphilis
  - Clue to distinguish from AA: no specific histopathologic clue. Immunohistochemistry is helpful
- Persistent (permanent) chemotherapy-induced alopecia
  - Clues to distinguish from AA: low follicular density; dystrophic telogen-like structures, different from normal telogen phase follicles; no lymphocytic infiltrate
- Systemic amyloidosis
  - Clue to distinguish from AA: amyloid surrounds dystrophic telogen-like structures
- Linear morphea (en coup de sabre)
  - Clue to distinguish from AA: usual sclerotic features of morphea

smudging of the basement membrane zone. Similar to acute AA, the peribulbar infiltrate in SLE can lead to hair shaft breakage above the scalp surface, thereby producing black dots seen on trichoscopy. Even without apparent clinical alopecia, trichoscopy may also identify hypopigmented, miniaturized hairs (so-called lupus hair) which correlate with SLE severity.[9] Identification of serum antinuclear antibodies is positive, and systemic symptoms are present.

2b. Discoid (chronic cutaneous) LE with deep perifollicular involvement may also have an AA-like pattern, because of increased catagen/telogen follicles and a peribulbar lymphocytic infiltrate.[10] In addition to vacuolar interface change, the lymphocytic infiltrate is generally more intense and diffuse than in AA (Figure 1). Identifying clusters of CD123+ plasmacytoid dendritic cells is useful in making a definitive diagnosis.[11,12] In contrast to the non-scarring alopecia of SLE, DLE shows large yellow dots on trichoscopy, correlating to dilated follicular ostia, a feature not seen in AA.

3. Syphilis

The initial presentation of syphilis may be diffuse or patchy alopecia, but showing an AA-like pattern histopathologically.[13] A diagnosis of syphilis may be challenging, because both syphilis and AA may have patchy or diffuse hair loss. Both may also show increased vellus hairs and black dots, corresponding to miniaturization and hair shaft breakage, respectively.[14] A hair pull test in secondary syphilis may also show an increased telogen count. To our knowledge, no study has correlated this telogen shift with a change in follicular size. Plasma cells are not helpful in making a distinction, as they are frequently present in scalp dermatitides and in AA. Immunohistochemical studies and serologic studies have great utility in making a definitive diagnosis.

4. Permanent chemotherapy-induced alopecia

Permanent chemotherapy-induced alopecia (pCIA) shows AA-like pattern with marked follicular miniaturization and telogen-like follicular structures. The most distinguishing factors are a low follicular density because of follicular loss and no lymphocytic infiltrate. Fortunately, a history of chemotherapy is usually provided.[15,16]

5. Systemic amyloidosis

Although quite rare, systemic amyloidosis may cause diffuse, nonscarring alopecia. Histopathologic examination shows AA-like follicular miniaturization and dystrophic telogen-like structures with surrounding amyloid deposition.[17] Trichoscopic examination reveals shows pink-orange perifollicular halos, corresponding to amyloid deposition.[18]

6. Linear morphea (en coup de sabre)

In addition to the usual sclerotic features of morphea, there are AA-like features with vellus/miniaturized follicles and telogen-like follicular structures similar to those seen in pCIA. Lymphocytes with plasma cells may be present in active disease.[19]

Trichotillomania and early, acute traction alopecia (trichotillosis), and pressure-induced (postoperative) alopecia produce a catagen/telogen shift but are not included in the AA-like pattern, because there is no follicular miniaturization. Additionally, trichotillomania and acute traction alopecia lack significant inflammation. The edge of a patch of trichotillosis shows reduced follicular density, absent terminal follicles, and a marked catagen/telogen shift. Vellus hairs are not pulled and therefore remain unaffected. Unfortunately, patients with AA often have superimposed trichotillomania. A distinction requires a close clinical and histopathological assessment. Histopathological changes of trichotillomania include epidermal acanthosis with overlying orthokeratotic hyperkeratosis reminiscent of lichen simplex chronicus, fractured hair shafts (trichomalacia), and melanin casts. However, melanin casts are seen in AA of dark-haired patients. Dissecting cellulitis of the scalp can also show increased catagen/telogen shift, particularly in the acute flares, but it lacks follicular miniaturization.

Why do such disparate entities share a common histopathologic pattern? Perhaps there are two processes at play, explaining this common pattern and allowing for a new classification of alopecia based upon the following: (a) Follicular size and differences in follicular cycle time length (anagen, catagen, telogen), and (b) immune privilege collapse.[20,21]

For follicular size and cycle length, catagen/telogen percentages increase because the anagen phase shortens as follicular miniaturization progresses. Thus, miniaturization alone can cause an increased catagen/telogen percentage. This is particularly evident in male pattern hair loss (androgenetic alopecia) which has more dramatic miniaturization than female pattern hair loss.[22] Endocrine-therapy-induced alopecia in breast cancer patients has the same pattern.[23]

Immune privilege collapse may occur in either the "permanent" epithelial stems cells of the bulge throughout the whole cycle, or the "temporary" stem cells of the lower root segment during anagen phase.[24] With immune privilege collapse, attack in the area of permanent stem cells of the bulge results in lichen planopilaris (LPP).[25]

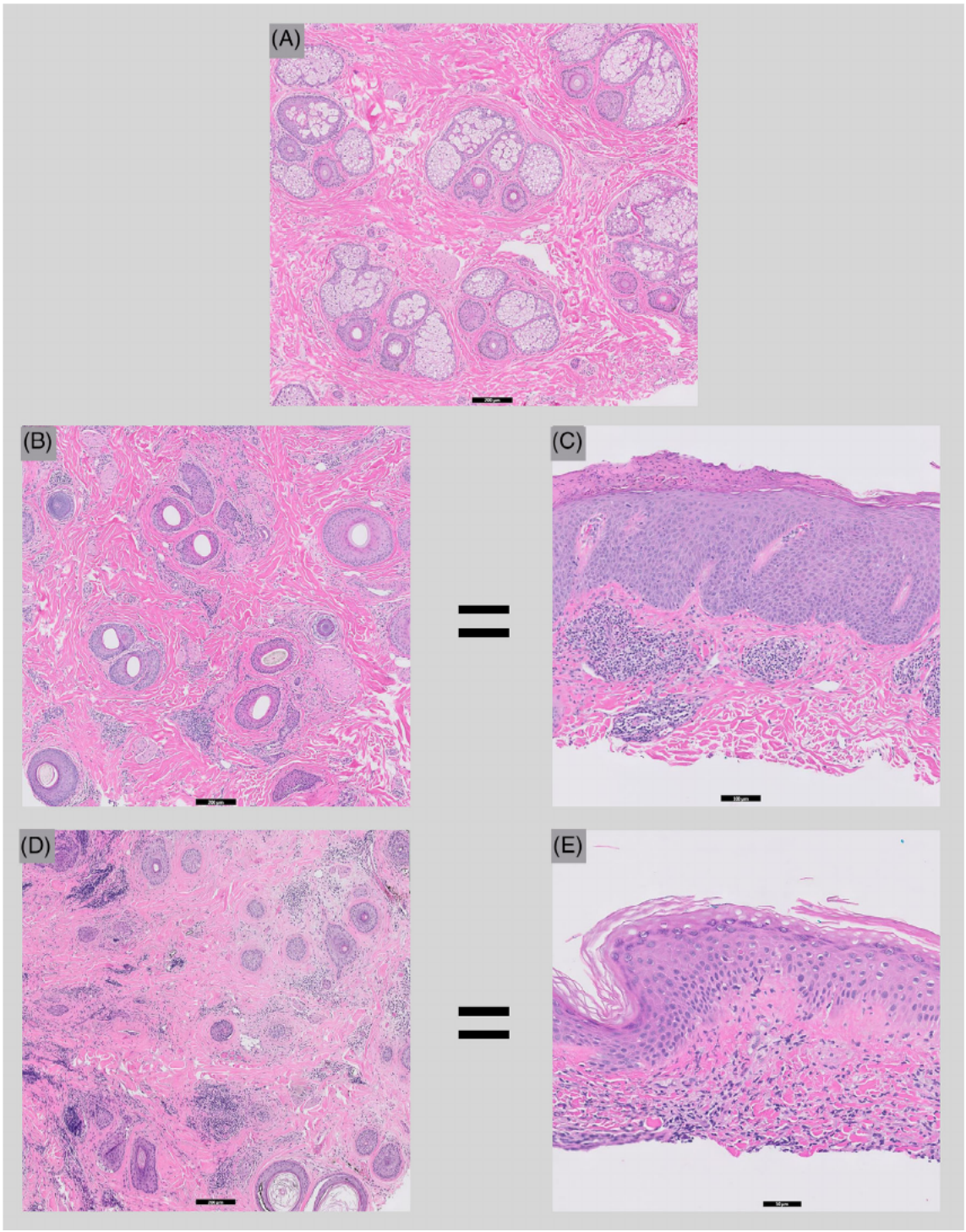

FIGURE 1 Comparison of the alopecia areata to the mimics, alopecic lupus erythematosus and psoriatic alopecia. H&E sections show that all of the entities are characterized by marked follicular miniaturization with a catagen/telogen shift and a variable-density lymphocytic infiltrate (H&E, ×20 for A, B, D and ×200 for C, E). (A) Alopecia areata in the subacute phase with a minimal lymphocytic infiltrate (H&E, ×20) (B, C) Lupus erythematosus with marked interfollicular interface change. (D, E) Psoriatic alopecia with marked epidermal acanthosis, confluent parakeratosis, and loss of the granular layer

Histopathologic features show no follicular miniaturization or catagen/telogen shift (normal or even absent catagen/telogen hairs), because loss of the permanent stem cells causes follicular dropout. This concept is supported by the observation that LPP usually has few catagen/telogen phase follicles and loss of cytokeratin 15 immunohistochemical staining.[26]

In contrast, immune privilege collapse in temporary stem cells of the lower root segment results in AA.[27,28] Unlike LPP, AA shows

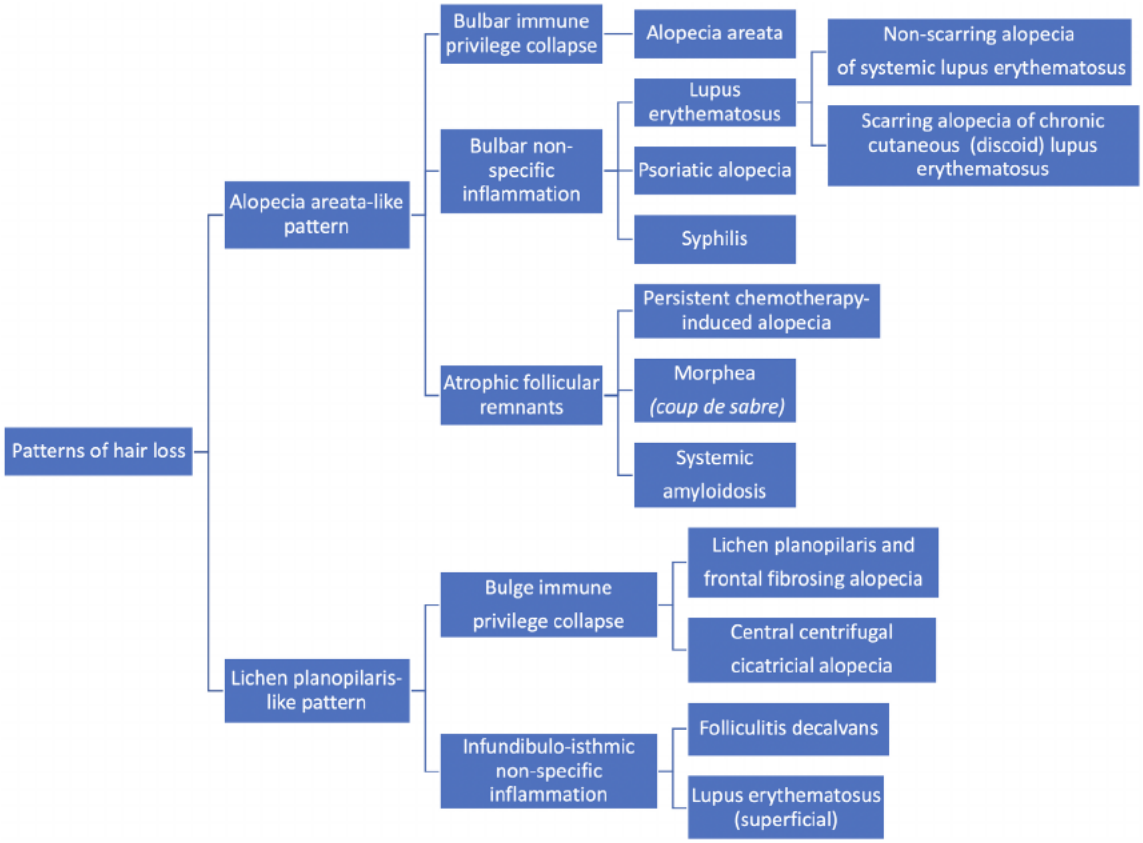

FIGURE 2 Proposed classification of hair loss based upon follicular size and cycle time length and immune privilege collapse. The classification has two patterns, "AA-like" and "LPP-like" patterns. AA-like pattern results from damage to the lower root segment, and LPP-like to the upper-segment (bulge area). Both patterns may result from either immune privilege collapse or nonspecific inflammation. Note that lupus erythematosus may be under either pattern, depending upon the location of the lymphoplasmacytic infiltrate (peribulbar for AA-like and peri-infundibulo/isthmic for the LPP-like pattern)

marked follicular miniaturization and a dramatic catagen/telogen shift as the follicular bulb is attacked. Chemotherapeutic agents are known to target the highly proliferative hair matrix cells of hair bulbs, the same target in alopecia areata.[29]

Thus, we propose a new classification of hair loss based not upon inflammatory cell types but upon (a) follicular size and cycle time length and (b) immune privilege collapse. Figure 2 shows this classification. Of note, both AA-like pattern and LPP-like pattern contain disparate entities, all of which have in common follicular injury, either in the lower- or upper-segment. As in AA, AA-like pattern may result from lower root segment damage with subsequent bulb immune privilege collapse, even though inflammation in psoriasis, syphilis and SLE is nonspecific. In contrast, permanent stem cell damage causes miniaturization and the formation dystrophic telogen hairs in pCIA, morphea, and systemic amyloidosis. In LPP and FFA, damage to the infundibulo-isthmic portion of the follicle results from bulge immune privilege collapse, similar to central centrifugal cicatricial alopecia.[30] Folliculitis decalvans and superficial forms of SLE and discoid LE (devoid of peribulbar infiltrate) result from nonspecific inflammation, usually in the infundibulo-isthmic portion of the follicle.

In conclusion, recognition of AA-like pattern and the proposed classification, while not complete, allows for a better understanding of a diverse group of alopecic entities that produce similar histopathologic features. Such an understanding may allow for more precise diagnoses and a better understanding of the pathophysiology of these entities.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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