Alopecia areata

Disease characteristics, clinical evaluation, and new perspectives on pathogenesis

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Learning objectives
After completing this learning activity, participants should be able to describe the novel trichoscopic clinical features of alopecia areata as well as the more recent findings in global epidemiology and risk factors; define the new histopathologic features of the disease and how these characteristics relate to the underlying disease mechanisms; explain the new discoveries of the immunobiology of the hair follicle that is affected with alopecia areata; and identify new exciting evidence implicating the specific aspects of the immune system involved in the pathogenesis of alopecia areata.

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Alopecia areata (AA) is a common, inflammatory, nonscarring type of hair loss. Significant variations in the clinical presentation of AA have been observed, ranging from small, well-circumscribed patches of hair loss to a complete absence of body and scalp hair. Patients affected by AA encompass all age groups, sexes, and ethnicities, and may experience frustration with the unpredictable nature of their disease for which there is currently no definitive treatment. The cause of AA remains incompletely understood, though it is believed to result—at least in part—from a loss of immune privilege in the hair follicle, autoimmune-mediated hair follicle destruction, and the upregulation of inflammatory pathways. Patients with AA frequently experience marked impairment in psychological well-being, self-esteem, and may be more likely to suffer from psychiatric comorbidities. Part one of this two-part continuing medical education series describes the epidemiology, clinical evaluation, prognosis, and recent advancements in the understanding of the pathogenesis of AA. (J Am Acad Dermatol 2018;78:1-12.)

Key words: alopecia areata; alopecia totalis; alopecia universalis; pathogenesis; prognosis; subtype.

EPIDEMIOLOGY

Key point

- **Alopecia areata affects both sexes equally, affects patients of all ages, and is found in approximately 0.1% to 0.2% of the general population**

Among the US population, the cumulative lifetime incidence of alopecia areata (AA) is estimated at 2%,

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Abbreviations used:

AA:	alopecia areata
AT:	alopecia totalis
AU:	alopecia universalis
CTL:	cytotoxic T lymphocyte
CTLA-4:	cytotoxic T lymphocyte-associated protein 4
GWAS:	genome-wide association study
HF:	hair follicle
HLA:	human leukocyte antigen
IFN:	interferon
IL:	interleukin
JAK:	Janus kinase
MCH:	melanin-concentrating hormone
MCHR2:	melanin-concentrating hormone factor 2
MCHR2-AS1:	MCHR2 antisense RNA 1
MHC:	major histocompatibility complex
NKG2D:	natural killer group 2D
PRDX5:	peroxiredoxin-5
SALT:	Severity of Alopecia Tool
STX17:	syntaxin-17
Treg:	T regulatory cell
ULBP:	UL16-binding protein

while the prevalence is approximately 0.1% to 0.2%.[1,2] While AA affects both sexes equally, data from the Rochester Epidemiology Project revealed that men tended to be diagnosed earlier compared with women (mean age at diagnosis, 31.5 vs 36.2 years).[2] While some have suggested that the prevalence of AA may be greatest among pediatric populations and declines with each subsequent decade,[3,4] others found the peak incidence to be in the second and third decades of life.[5,6]

CLINICAL EVALUATION

Key points

- **Alopecia areata presents most commonly as well-demarcated patches of nonscarring, inflammatory hair loss that can progress to include all scalp or body hairs**
- **Exclamation point hairs, dystrophic hairs, and yellow dots are features of alopecia areata that can be identified with trichoscopy**
- **Nail abnormalities, such as regular pitting, brittleness, or striations, are seen in 10% to 20% of patients**

AA most commonly presents as a sudden onset of focal well-circumscribed patches of hair loss on the scalp without signs of significant inflammation or scarring (Fig 1).[7] In patients with active disease, a pull test may be positive, especially at the periphery of the lesion.[8] Generally, patients are asymptomatic, though tingling, itching, and dysesthesia are occasionally reported prior to hair loss. In severely affected individuals, AA may progress to include all scalp hairs (alopecia totalis [AT]), or all scalp and body hairs (alopecia universalis [AU]).[9] Men may be more likely to initially present with beard involvement as opposed to scalp alopecia (50.5% vs 39.3%; Fig 2).[6]

Evaluation of the patient should include trichoscopy to allow for closer evaluation of the follicle, hair shaft, and surrounding skin, and to help determine the best area from which to obtain a biopsy specimen.[10] Clinicians should look for exclamation point hairs, which are considered a common, pathognomonic indicator of AA and describe a broken hair that is thicker at the distal end relative to the base. Dystrophic, broken hairs are also frequently present, and although not specific to AA, occur when mitotic activity in anagen follicles is interrupted. Yellow dots may be observed on trichoscopy but do not correlate well with clinical disease type or severity, and can be seen in other types of hair loss, such as androgenetic alopecia.[11] A Severity of Alopecia Tool (SALT) score can be determined by visually assessing the amount of terminal hair loss in 4 views of the scalp, and can be used to track treatment response.[12] A more recent scoring system, the SALT II, is now also available and divides the scalp into smaller increments for estimating hair density.[13] Nail changes are found in approximately 10% to 20% of patients and may occur more commonly in those with severe disease. Regular pitting, longitudinal ridging, trachyonchia, and red lunula are among the changes that may be seen (Fig 3).[14,15]

DIFFERENTIAL DIAGNOSIS

Key point

- **Trichotillomania, temporal triangular alopecia, and telogen effluvium are the most important alternative diagnoses to consider**

Trichotillomania can be challenging to differentiate from AA, and in some cases the two conditions may coexist. However, in trichotillomania, incomplete hair loss and a significant number of broken hairs will be observed on trichoscopy.[16] Temporal triangular alopecia causes a circumscribed triangular-like area of nonscarring hair loss in the frontotemporal area. Patches are usually single, persistent, unilateral, do not enlarge in size like in AA, and tend to be unresponsive to treatment.[17] A biopsy specimen can also be used to distinguish this condition from AA, because temporal triangular alopecia tends to be noninflammatory, though chronic AA lesions may also lack significant inflammation.[18,19] Diffuse AA may be difficult to differentiate from telogen effluvium, and this distinction frequently requires obtaining a biopsy specimen or identifying a triggering

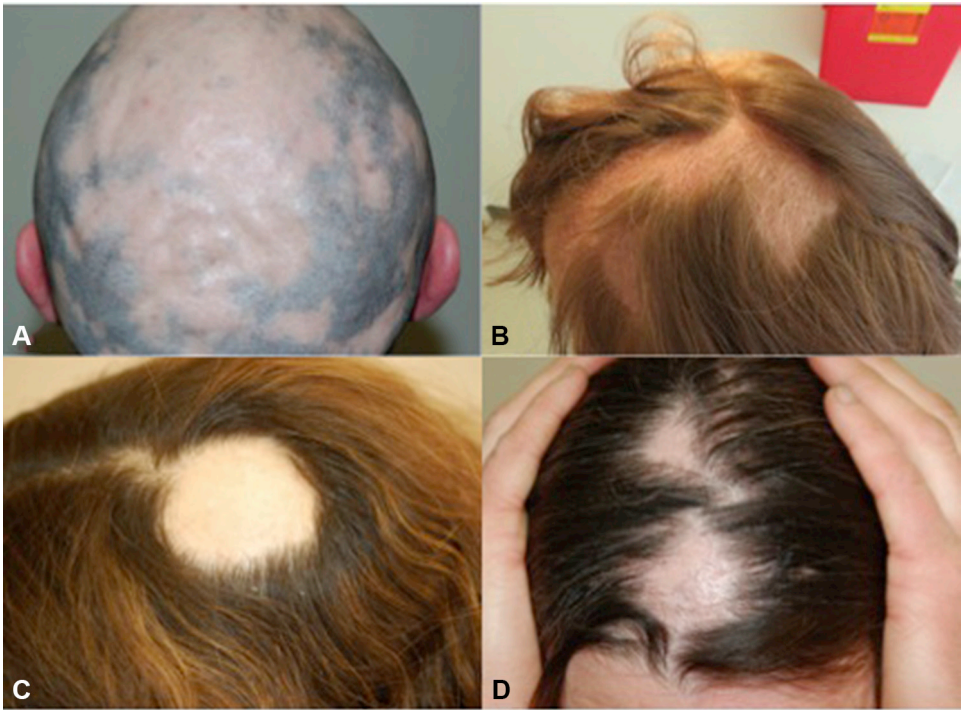

Fig 1. A-D, Well-demarcated patchy alopecia areata. No epidermal changes were observed in the affected areas.

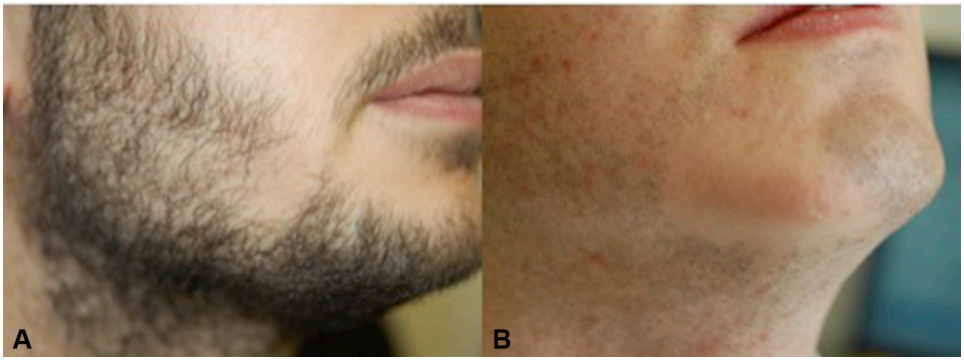

Fig 2. A and **B**, Patchy alopecia areata of the beard.

factor in the patient's history. Other disorders to consider include an early scarring alopecia, secondary syphilis (which may look histologically identical to AA), and systemic lupus erythematous.

CLINICAL SUBTYPES

Key point

- **Several subtypes of alopecia areata have distinct presentations, including ophiasis, sisaipho, sudden graying type, and diffuse forms**

Patients with the ophiasis subtype of AA (Fig 4) have band-like alopecia usually at the occipital hairline extending toward the temples, or rarely at the frontal hairline, that can be confused with frontal fibrosing alopecia.[9] The sisaipho subtype occurs in the opposite distribution, causing hair loss centrally but sparing hairs at the margin of the scalp, and appearing similar to androgenetic alopecia.[20] In addition, a "sudden graying" or "white overnight" variant of AA results in loss of pigmented hairs.[21] Perinevoid AA refers to hair loss occurring around pigmented nevi, and of note removal of the nevi does not change the hair loss.[22]

Acute diffuse and total alopecia is a more recently described variant that presents as diffuse and sudden hair loss most commonly in women, and lasting approximately 3 months followed by rapid regrowth, though recurrence may occur.[23] AA incognita is also characterized by acute diffuse shedding of telogen hairs in the areas commonly affected by androgenetic alopecia and can be confused with

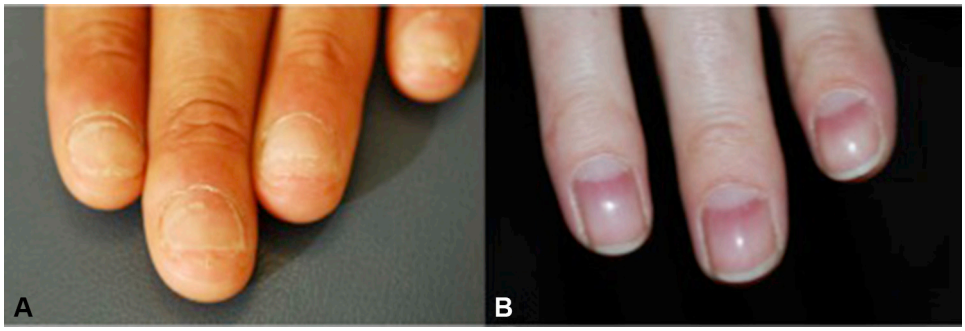

Fig 3. Characteristic nail findings in patients with alopecia areata. **A**, Brittle nails with splitting. **B**, Red lunula, the convex margin of the distal matrix.

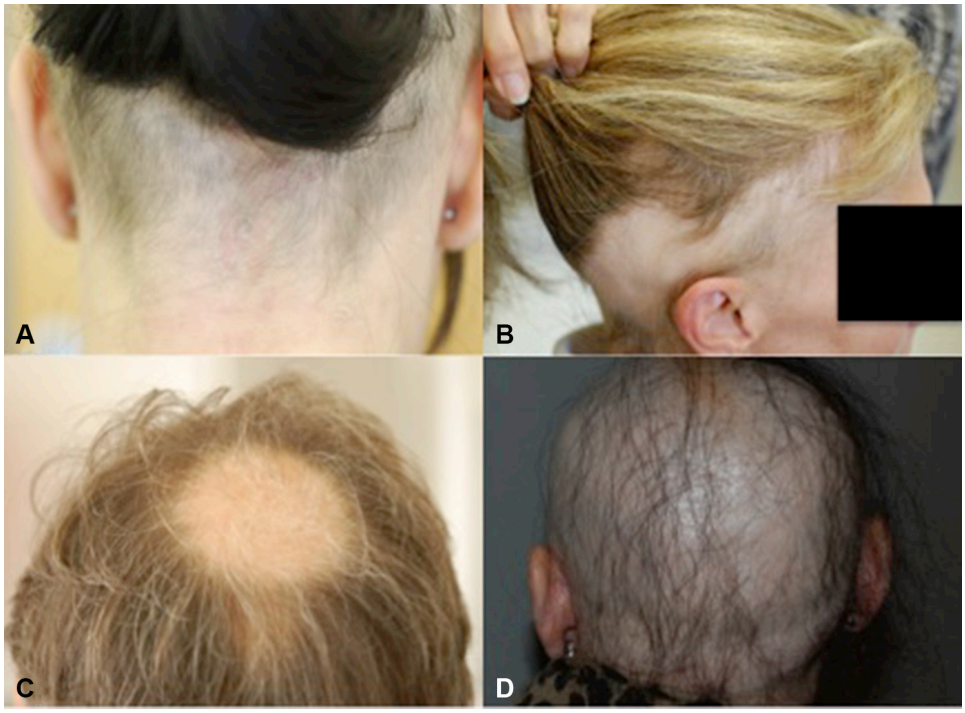

Fig 4. Different clinical presentations of alopecia areata, including (**A** and **B**) the ophiasis subtype with hair loss at the occipital scalp, (**C**) hair loss in an androgenetic distribution, and (**D**) diffuse type.

telogen effluvium; obtaining a biopsy specimen is often required for a definitive diagnosis.[24] Women are also more frequently affected by this subtype.[10]

PROGNOSIS

Key points

- **Younger age at initial presentation and severity at onset are the most important prognostic indicators**
- **Risk of progression from limited alopecia areata to alopecia totalis or alopecia universalis is approximately 5%**
- **The ophiasis subtype has a poorer prognosis and the acute diffuse and total alopecia subtype has a more favorable prognosis**

Factors that may contribute to prognosis include AA subtype, extent of hair loss, duration of hair loss, age at onset, and family history.[14] Approximately 5% of cases of patchy AA will progress to AT or AU (Fig 5).[25] Extensive involvement portends a more severe prognosis.[4] For example, Tosti et al[26] showed that among adult patients with mild disease (<25% of hair loss), 67% showed complete regrowth while those with more severe AT or AU forms of the disease tended to either remain stable or worsen overtime (mean follow-up time, 17.74 years). The patients from this study were treated with various therapies, including topical immunotherapy, which conferred a better overall prognosis to responders. Some patients in the study did not receive any treatment,

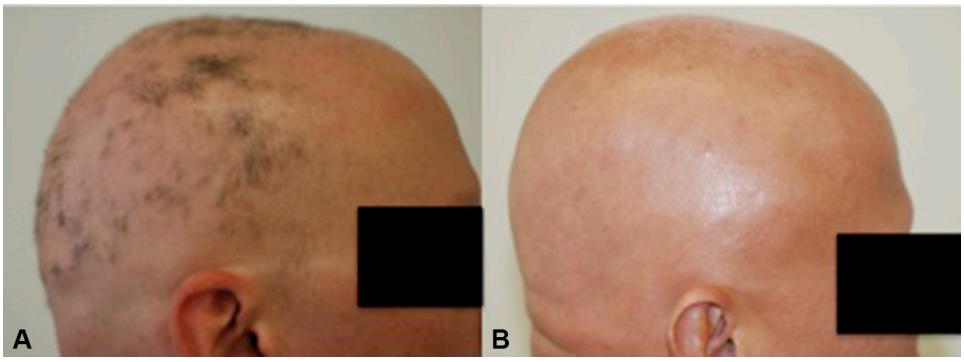

Fig 5. Progression of (**A**) patchy alopecia areata to (**B**) alopecia totalis.

and among those with 51% to 75% hair loss who were untreated 34.6% recovered or developed milder disease.[26] Younger age at onset is also regarded as a less favorable prognostic indicator.[27,28] The ophiasis subtype can have a poorer prognosis and may be less responsive to treatment, while the acute diffuse and total alopecia subtype generally has a favorable prognosis.[23,29]

PATHOGENESIS

Key points

- **The anagen hair follicle is normally an immune privileged site, but this is disrupted in alopecia areata**
- **Inflammatory immune cells lead to dystrophic hair follicle cycling with premature entry into the telogen phase**

The proximal portion of the anagen hair follicle (HF) constitutes an immune privileged site similar to the anterior chamber of the eyes, the pregnant uterus, and the testes.[30,31] This immune privilege appears to be disrupted in AA where an increase in major histocompatibility complex (MHC) I and II molecules, along with adhesion molecules, correlate with increased leukocyte trafficking into the dermis.[32] These changes enhance the presentation of antigens by HF cells and migration of T cells to close proximity of HFs in AA lesions.

Normally, the HF cycles between 3 distinct stages; active growth (anagen), followed by apoptosis of epithelial cells (catagen), and finally a resting phase (telogen).[33] In AA, this cycling becomes disrupted, leading to a dystrophic anagen phase. Also, during the catagen phase there is an infiltration of immune cells, leading to the hypothesis that the controlled apoptosis that occurs during catagen might expose the immune cells to more antigens from HF cells.[34,35] Eventually, with increased inflammation, the anagen phase follicles prematurely enter the telogen phase; this is likely in response to an immune-mediated stimulus.[36]

Autoimmune hypothesis

Key points

- **Autoreactive T cells infiltrate the hair follicle, sparing the stem cell compartment**
- **$CD8^+$ T cell density and disease severity correlate**
- **Hair follicle–derived autoantigens may be involved**

The first evidence of autoimmunity in AA against hair follicles involved the observation of a "swarm of bees" clustering of inflammatory cells (mostly T cells) toward the bulb region of hair follicles.[37] $CD8^+$ (cytotoxic T lymphocytes [CTLs]) and $CD4^+$ T cells comprise a significant portion of the infiltrate, along with an increased presence of antigen-presenting cells, such as Langerhans cells.[38,39] Of note, the lymphocyte attack in AA spares the stem cell compartment, preventing permanent organ destruction and allowing future regrowth to remain possible in most cases.[40] The clinical importance of lymphocytes in AA is highlighted by the observation that $CD8^+$ T cell density and disease severity appear to correlate.[41] Recently, the presence of mast cells in AA lesions in close association with CTLs has been identified in both AA-affected C3H/HeJ mice and humans, suggesting potential cross-communication between mast cells and CTLs during AA pathogenesis.[42,43]

The involvement of autoreactive T cells gave rise to the hypothesis of HF-derived autoantigens. The identity of the exact antigen is still being debated, but melanogenesis-associated antigens are likely involved, and this may account for the clinical observation that pigmented hairs tend to be preferentially affected by AA, and after resolution of an episode of AA, the nonpigmented hairs are typically the first to demonstrate regrowth.[9] HF

keratinocyte-derived antigens, such as trichohyalin, have also been identified as possible autoantigens for T cells[44] and autoantibodies.[37,45]

Animal models

Key points

- **The C3H/HeJ mouse model is widely used for alopecia areata research**
- **Studies in animal models support the role of autoreactive T cells in alopecia areata and the upregulation of inflammatory pathways**

While animal models cannot represent human disease completely, the C3H/HeJ mouse model is one of the most well defined and widely used for AA research, along with DEBR rats and humanized severe combined immunodeficiency mice.[46-49] The high mechanistic similarities between C3H/HeJ mice and human AA have made it an attractive model for preclinical drug testing. Evidence from these models strongly supports the hypothesis that T cells drive the pathogenesis of AA, consistent with changes in the interferon-gamma and inflammatory gene expression signatures in AA. For example, transfer of T cells (but not B cells) can cause AA in C3H/HeJ mice,[50] while depletion of $CD4^+$ and $CD8^+$ T cell subsets using monoclonal antibodies in AA-affected mice causes hair regrowth.[51,52] Upregulation of interleukin-6 (IL-6), tumor necrosis factor—alpha, IL-12, and interferon-gamma is observed among mice that develop localized or multiple patches of AA. Similar changes in interferon and inflammatory signatures were also observed in humans with AA.[41,50] These observations led to rational development of experimental therapies either via targeting specific cytokines or cell populations.[53,54]

Histologic findings

Key points

- **In active phase alopecia areata there is peribulbar lymphocytic inflammation comprised of $CD8^+$ and $CD4^+$ T cells, a shift to catagen and telogen follicles, and miniaturization**
- **In the chronic phase, the majority of follicles are miniaturized, and in catagen or telogen there is minimal to sometimes no peribulbar inflammation**

The histologic features of AA vary according to the disease stage. In acute, active disease there is peribulbar infiltration of $CD8^+$ and $CD4^+$ T lymphocytes surrounding anagen follicles, with extension into the hair matrix keratinocytes (Fig 6).[55] These lymphocytes cause disorganization and apoptosis of hair matrix cells. Degeneration results in melanin incontinence and pigment deposition within the follicular epithelium, the dermal papilla, and the follicular stela (fibrovascular tracts).[56] The inflammatory infiltrate causes anagen arrest and abrupt cessation of hair shaft formation, causing a tapered and weakened hair shaft, manifesting clinically as the so-called "pencil/exclamation point hair." As the disease progresses, anagen follicles shift to catagen and telogen and also miniaturize, although the total number follicles remains the same (Fig 7).[55] Peribulbar inflammation subsides as the number of anagen follicles is reduced. Residual inflammatory cells, including lymphocytes and eosinophils, may be present in follicular stelae (Fig 8). In chronic disease, the majority of follicles are in telogen phase and there is marked miniaturization (Figs 9 and 10). The recovery stage is characterized by a reduction in the inflammation, an increase in the proportion of anagen hairs, and a decrease in telogen hairs.[57]

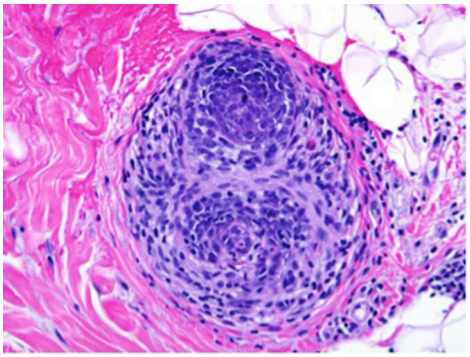

Fig 6. Hair matrical epithelial cells show disorganization and lymphocytic inflammation. (Original magnification: ×400.)

While a vertical section may be sufficient to diagnose AA in the active phase, in chronic disease, when inflammation may be less prominent, horizontal sectioning technique aids in accurate diagnosis by allowing the pathologist to visualize every follicle in the specimen, at different levels, from the subcutaneous fat to the epidermis, thereby assessing hair follicle density, diameters, and the distribution of follicles in different phases of the hair cycle.[57]

Genetic studies

Key point

- **Human leukocyte antigen I and II loci, genes involved in innate and adaptive immune pathways, and oxidative stress are implicated in AA**

Initial candidate gene studies revealed the involvement of human leukocyte antigen (HLA)

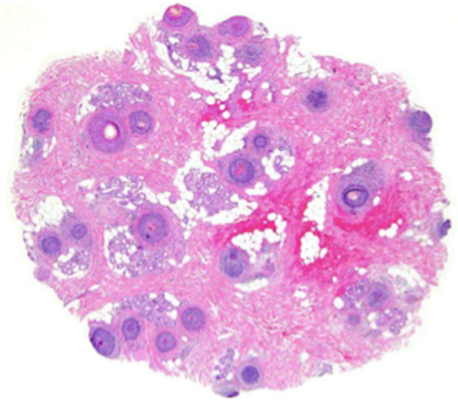

Fig 7. Peribulbar lymphocytic inflammation involving terminal and miniaturized follicles with marked shift to catagen and telogen. (Original magnification: ×40.)

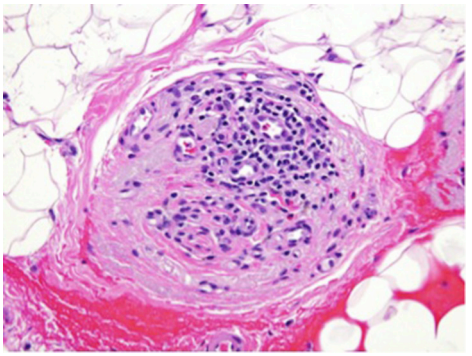

Fig 8. Lymphocytes, a few eosinophils, and melanin in a follicular stela. (Original magnification: ×400.)

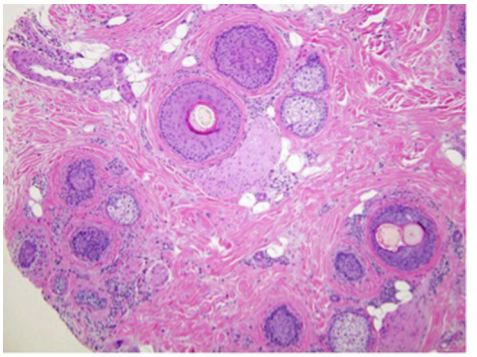

Fig 9. Horizontal sections showing a marked increase in the number of catagen and telogen follicles. (Original magnification: ×100.)

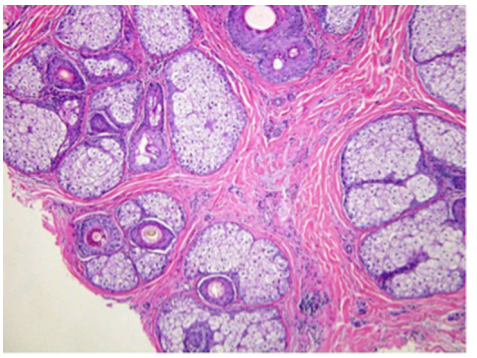

Fig 10. Miniaturized follicles in chronic disease. (Original magnification: ×100.)

genes, which are important for antigen presentation in the pathogenesis of AA, as reviewed by Gilhar et al.[40] With the establishment of the National Alopecia Areata Foundation Registry, an extensive patient cohort became available for large-scale family-based genomewide linkage studies which further confirmed the involvement of HLA genes in 20 families with AA.[58]

Genome-wide association studies (GWASs) have greatly facilitated our understanding of the immune pathways involved in AA. The first GWAS for AA compared allele frequencies from 1054 unrelated patients with AA from the National Alopecia Areata Foundation Registry to 3278 control subjects.[59] The results from this study implicated both innate and adaptive arms of the immune system, including genes encoding the natural killer cell receptor (NKG2D, [natural-killer group 2, member D]) ligands UL16-binding proteins (ULBP) 3/6, cytotoxic T lymphocyte—associated protein 4 (CTLA-4), IL-2/IL-21 locus, IL-2 receptor A, and Eos in addition to previously identified HLA class II loci. The latest metaanalysis of GWASs for AA (now with 3253 cases and 7543 controls) further strengthened the initial GWAS findings and increased the number of risk loci from 8 to 16.[60] This study revealed the association of *ACOXL/BCL2L11*, *GARP*, and *SH2B3(LNK)/ATXN2*. These genes are related to autophagy/apoptosis, regulatory T cells (Tregs), and Janus kinase (JAK) signaling.[60]

An association was also demonstrated in the GWAS for the *ULBP* gene cluster on chromosome 6q25.1 that encodes activating ligands of NKG2D and notably ULBP3/6, which are novel risk genes that have not been identified in other autoimmune diseases.[59] These NKG2D ligands are stress-induced molecules that function as danger signals to alert immune cells via interaction with the NKG2D receptor. The majority of $NKG2D^+$ cells are $CD8^+$ T cells, which supports a role for $CD8^+NKG2D^+$ cytotoxic T cells in AA.[59] Additional insight from C3H/HeJ mice suggests that $CD8^+NKG2D^+$ T cells are in fact the dominant cell type in AA.[61]

Several of the genes identified in the GWASs are involved in directing Tregs, which exert immunoregulatory capacity on a broad range of effector cell types including T-helper 1, T-helper 2, and antigen-presenting cells to prevent immune

response against self-antigens.[62] Treg differentiation is dependent on IL-2 receptor A (CD25), IL-2, and a lineage determining factor Foxp3 that is regulated by Eos, a zinc finger transcription factor,[63] while CTLA-4 is a major determinant of Treg-suppressible capability.[64] Finally, IL-21 is a proinflammatory mediator that promotes the differentiation of T_H17 effector cells while limiting Treg differentiation.[65]

Genome-wide analysis of copy number variants of candidate genes have also identified duplications in melanin-concentrating hormone receptor 2 (MCHR2) and MCHR2 antisense RNA 1 (MCHR2-AS1), which are both implicated in MCH signaling and further supports the hypothesis that genes affecting pigmentation are involved in AA.[54] Variants in syntaxin-17 (STX17), a SNARE protein, which plays a role both in autophagy and possibly pigmentation have been implicated in AA as well.[59,66] This gene is expressed in the follicle itself along with another gene, which also may be involved in AA, peroxiredoxin-5 (PRDX5). Dysregulation of PRDX5 may allow aberrant cells (potentially in response to oxidative stress) to survive which could result in the presentation of damaged self-antigens to the immune system promoting autoimmunity.[67] Identification of STX17 and PRDX5 suggested abnormalities other than immune response pathways and potential involvement of oxidative stress in the pathogenesis of AA.

The Janus kinase/signal transducers and activators of transcription signaling pathway

Key point

- **The Janus kinase/signal transducers and activators of transcription pathway is upregulated in alopecia areata but not in normal hair follicles**

Human skin biopsy specimens from patients with AA show the overexpression of JAK3 and, to a lesser extent, JAK1 and JAK2 signaling.[68] Interferon-gamma (IFN-γ) signals through JAK1/2 while IL-15 signals via JAK1/3 (Fig 11). Several studies have shown that IFN-γ is prominently expressed in lesional skin from patients with AA and is believed to contribute to the collapse of immune privilege through increased follicular expression of MHC class I and II molecules.[46,50,69-72] Blocking IFN-γ with neutralizing antibodies at the time of grafting prevents AA development in mice, while reducing MHC upregulation and infiltration of $CD8^+NKG2D$ cells.[61] The IL-15 pathway is also upregulated in AA.[61] Both the IFN-γ and IL-15 pathways are targeted by JAK inhibitors, including tofacitinib, ruxolitinib, and baricitinib (see the second article in this series for more information). In addition, blockade of CXCR3 inhibits the downstream signaling of IFN-γ and was found to prevent the development of AA in C3H/HeJ mice via inhibiting the recruitment of pathogenic T cells.[73] Blockade of CXCR3 may be a potential target of future therapeutics.

Comorbidities

Key point

- **Patients with atopy (including atopic dermatitis, asthma, and allergic rhinitis) and other autoimmune conditions may be more likely to develop alopecia areata**

Increased risk of AA development in patients with atopy, including atopic dermatitis, asthma, and allergic rhinitis has been reported in various epidemiologic studies.[74,75] Multiple autoimmune diseases (including thyroid disease, psoriasis, and vitiligo) have been shown to have a high association with AA.[76] Co-occurrence of these diseases may be a result of shared genetic risk loci, immune cell populations, and cytokine profiles as identified by the GWASs.[59,60] Of note, GWASs have also revealed shared risk loci between AA and rheumatoid arthritis, celiac disease, and type I diabetes.

The development of AA could also have systemic effects on the body other than the skin. Cardiac hypertrophy has been identified in C3H/HeJ mice with AA in conjunction with higher levels of the serum heart disease marker cardiac troponin I.[77] While no differences in cardiovascular risk in human patients with AA have been found,[78] subclinical forms of heart damage may occur in patients with AA. Although not currently substantiated in AA, the circulating inflammatory cytokines certainly have the potential to adversely affect other organs, as seen in other autoimmune diseases like psoriasis, systemic lupus erythematosus, and rheumatoid arthritis.[79-81]

OTHER FACTORS CONTRIBUTING TO ALOPECIA AREATA

Key points

- **Epigenetic mechanisms may affect susceptibility to alopecia areata**
- **Stress and diet may contribute to the development of alopecia areata**

Epigenetics. While there is a strong genetic component in AA with a 10-fold increased risk in first-degree relatives, there is only a 55% concordance rate in monozygotic twins, highlighting that there is missing heritability in AA.[82] Epigenetic mechanisms may therefore contribute to the susceptibility and rate of onset for AA. Many

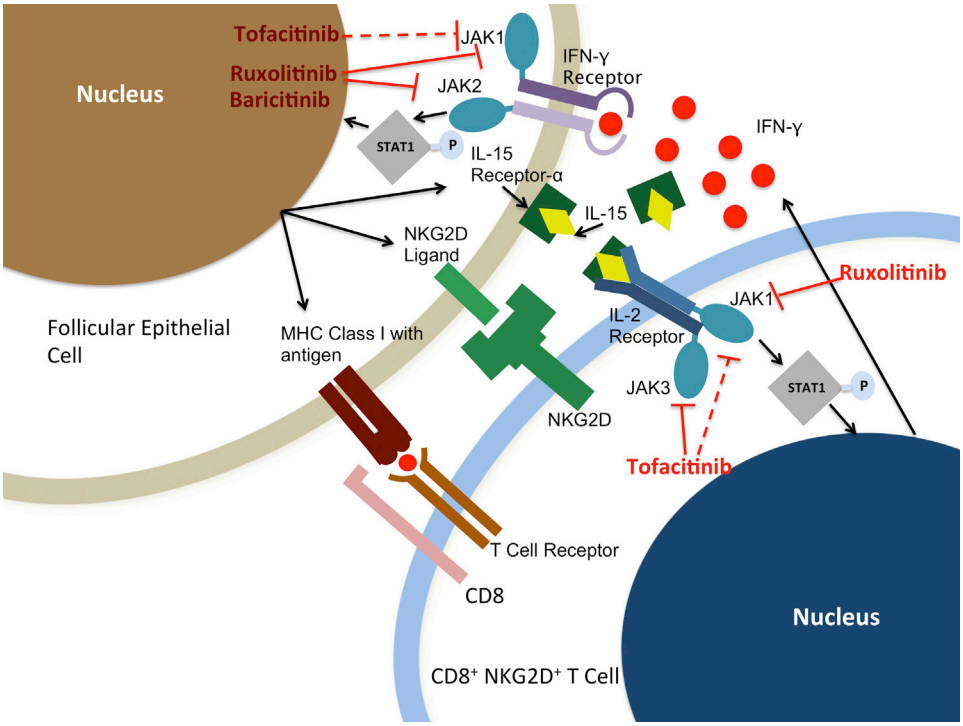

Fig 11. In alopecia areata, $CD8^+$ T cells produce interferon-gamma (IFN-γ), which signals via Janus kinases 1 (JAK1) and JAK2 to enhance production of interleukin-15 (IL-15). In combination with the IL-15 receptor-α (chaperone protein), IL-15 binds to the surface of $CD8^+$ T cells leading to signaling through JAK1 and JAK3 to produce more IFN-γ. The effect of the JAK inhibitors—tofacitinib, ruxolitinib, and baricitinib—are noted on this pathway. (Adapted with permission from Macmillan Publishers Ltd from Divito SJ, Kupper TS. Inhibiting Janus kinases to treat alopecia areata. Nat Med 2014;20:989-90. Copyright 2014.)

epigenetic mechanisms, such as histone modification, and microRNAs have recently been studied in AA, and increased methylation of genomic DNA and histone acetylation have been described in AA peripheral blood mononuclear cells.[83,84]

Stress and psychiatric problems. Stress and psychological disorders are among the most commonly cited causes of AA by patients, but the exact association is still debatable. A recent study reported a high prevalence of anxiety and depression among patients with AA.[74] However, the involvement of stress is likely at the molecular level with the secretion of stress hormones that may facilitate inflammation rather than as a direct cause.[85] In animal studies, dysregulation of hypothalamic-pituitary-adrenal activity was observed.[86] AA-affected mice displayed a delayed response to chronic psychological stress and blunted hypothalamic-pituitary-adrenal response to acute physiological stress; the expression of genes related to stress was also different in the brains of these mice.

Diet. Food with high dietary soy oil content seems to increase resistance to AA in C3H/HeJ mice.[87] Mice that received a high soy oil—containing diet showed hair regrowth after AA induction via skin graft compared to those fed with a normal diet. A high soy diet may modulate estrogen-dependent mechanisms or inflammatory activity and prevent AA. In addition, soy oil may modulate the microbiome niche in mice, which has been shown to modulate autoimmune disease susceptibility.[88,89]

In conclusion, AA affects approximately 2% of the population and has many different clinical presentations, ranging from well-circumscribed patches of hair loss to diffuse alopecia. The main factors affecting prognosis include age at onset and disease extent. Recent evidence further supports an autoimmune etiology and upregulation of inflammatory pathways in AA. GWASs have helped to characterize the pathways involved in AA, including genes involved in innate and adaptive immunity, oxidative stress, and the Janus kinase/signal transducers and activators of transcription signaling pathway.

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