Section A-Research paper

An Overview about Alopecia Areata; Etiology, Pathogenesis and Diagnosis

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Abstract

Background: Alopecia areata is a type of non-scarring hair loss that impacts hair follicles, nails, and rarely, the retinal pigment epithelium. It typically presents with round patches. Alopecia areata is a disorder of hair follicle-cycling, where inflammatory cells attack the hair follicle matrix epithelium that is undergoing early cortical differentiation ; anagen hair follicles, which are then prematurely induced into the catagen phase. Immune privilege protects organs from potential harm of immune recognition by creating an anergic state that could sometimes tolerate a foreign graft within the tissue . The well-known IP sites are central nervous system, testes, placenta and eyes . Hair follicles are also thought to be immune privileged sites, exactly; the bulge throughout the hair cycle and the bulb in the anagen phase. The most common clinical presentation of AA is patchy AA with the appearance of single or multiple circumscribed patches of scalp hair loss which can either be discrete, isolated or can coalesce with other lesions to form a larger area devoid of hair. The skin within the lesions is smooth, healthy-looking, and intact while sometimes a slight oedema is palpable, but without any erythema or other signs of inflammation.

Keywords: Alopecia Areata

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Introduction

Alopecia areata is a type of non-scarring hair loss that impacts hair follicles, nails, and rarely, the retinal pigment epithelium. It typically presents with round patches **(1).**

Epidemiology:

The estimated lifetime risk of AA has been reported to be 1.7–2.1% . Approximately 20% of cases are children, with 60% of AA patients recognizing their first hair loss patch before 30 years of age . A higher prevalence of AA has been reported in patients aged 10–25 years (60%). In Africa and the Middle East, regional studies have reported a disease prevalence ranging between 0.2% and 13.8% on the basis of the individual treatment landscape of the countries . **(2).**

Some studies indicate a slight female-to-male gender bias, but this may be due to higher female concern regarding hair loss and subsequent treatment. The disorder can occur at any age. The median age at diagnosis is 33. Male patients may be more likely to be diagnosed in childhood, while females are more likely to present in adolescence and have greater concomitant nail involvement or concomitant autoimmune diseases **(3).**

Concurrent Diseases:

Diseases often associated with AA are lupus erythematosus, vitiligo, autoimmune haemolytic anaemia, allergic rhinitis, asthma, atopic dermatitis and thyroid diseases . A meta-analysis at 2019 of 17 articles, with a total of 2850 AA cases and 4667 controls, investigated the prevalence of thyroid disease in AA. Overall, the prevalence of thyroid disease in AA was significantly increased compared with that in the controls (odds ratio 3.66) **(4).**

Aside from these immune-mediated conditions, few observational studies and case reports have linked AA to type 2 diabetes, a polygenic metabolic disease and studied the risk of developing diabetes in patients with AA. This association, if confirmed, can greatly change the current perception of the pathophysiological events in AA and seriously impact therapeutic strategies . **(5).**

Paediatric AA patients have higher rates of autoimmune disorders, including atopic dermatitis, vitiligo, psoriasis, coeliac disease, ulcerative colitis, systemic lupus erythematosus, juvenile idiopathic arthritis, juvenile rheumatoid arthritis, and metabolic disorders, including obesity, hyperlipidemia, diabetes mellitus and metabolic syndrome **(5).**

Etiopathology:

Alopecia areata is a disorder of hair follicle-cycling, where inflammatory cells attack the hair follicle matrix epithelium that is undergoing early cortical differentiation ; anagen hair follicles, which are then prematurely induced into the catagen phase **(1).**

The immune system, consisting of an innate and an acquired system, is a defense system to protect the body against foreign pathogens and maintain tolerance to autoantigens. A defect of the immune privilege (IP) system and central/peripheral tolerance may play a key role in the development of autoimmune diseases. Dendritic cells are part of the innate and acquired immune system and are important known targets in other autoimmune diseases such as multiple sclerosis and cancer. **(4).**

Immune privilege protects organs from potential harm of immune recognition by creating an anergic state that could sometimes tolerate a foreign graft within the tissue . The well-known IP sites are central nervous system, testes, placenta and eyes . Hair follicles are also thought to be immune privileged sites, exactly; the bulge throughout the hair cycle and the bulb in the anagen phase **(6).**

It has been widely accepted that the collapse of the hair follicle-IP is a major precondition for the development of AA. Increasing secretion of interferon-gamma (IFN-γ) in hair follicle, upregulation of Natural killer(NK) group 2 member D(NKG2D) ligands e.g., Major histocompatibility complex (MHC) class I–related chain A (MICA) and ULBP3/6, MHC I and MHC II molecules, and chemokines e.g., interlukin (IL)-15, IL-2, and CXCLs, as well as decreasing local "IP guardians" could increase exposure of anagen hair follicle-associated autoantigens and loss of hair follicle -IP **(7).**

Upregulation of IL-15 in hair follicles initiates the recruitment and activation of NKG2D , which produce IFN-γ, and subsequent loss of hair follicle-IP. Cell signaling via IFN-γ and IL-15 occurs through the Janus kinase (JAK)-signal transducer and activator of transcription signaling (STAT) pathway . **(8).**

CD8+NKG2D+ T cells are key regulators of AA pathogenesis. As NKG2D is an activating receptor expressed in both NK cells and CD8+ T cells, CD8+NKG2D+ T cells recognize the NKG2D ligands (MICA, ULBP3, and ULBP6), which upregulate MHC expression and contribute to Hair follicle- IP collapse **(8).**

Effector CD8+T cells can be segregated into two populations on the basis of the cytokines they secrete similar to CD4+ T cells. The cytotoxic T lymphocytes cells (Tc1) characteristically produce type-1 cytokines (IL-2, TNF-α, and IFN-γ), whereas Tc2 cells secrete type-2 cytokines (IL-4, IL-5, IL-6, IL-10, and IL-13).

Tc1 cells as well as Th1 cells are involved in the protection against intracellular parasites and delayed-type hypersensitivity, but also, they play an important role in autoimmunity **(9).**

Although IFN-γ–producing Th1 CD8+ cells are a key factor in AA pathogenesis, recent investigations of differentially regulated cytokine pathways revealed upregulations of the Th2 cytokines, IL-23 and IL-9.98, 99, 100, 101. The increased Th2 response might explain the association between atopic dermatitis and AA **(10).**

The JAK/STAT pathway is a primary regulator of the immune response, inflammation, and hematopoiesis. The pathway is critical to immune system surveillance and elimination of infections and protection against cancer. Gain of function and loss of function mutations in this pathway cause autoimmune disease, immunodeficiency, and cancer **(11).**

Studies demonstrated that JAK-STAT signaling, specifically JAK 1/2 and JAK 1/3, led to T-cell mediated inflammatory responses which promoted IFN-γ and IL-15 production in hair follicles and even further amplified inflammatory responses surrounding these hair follicles **(12).**

Patients with AA had human leukocyte antigen(HLA)-A1, HLA-B62, HLA-DQ1 and HLADQ3 and HLA class two molecules have three subclasses i.e., DR, DQ, DP which are found on the specific immune cells . The interactivity among HLA-DR and HLA-DQ plays a role on T cells in AA and autoimmunity **(6).**

To sum up, The collapse of IP, MHC presentation, IFN triggering of IP collapse, and disruption of the JAK/STAT pathway are all essential and evidence-based pathogenic mechanisms of AA **(13).**

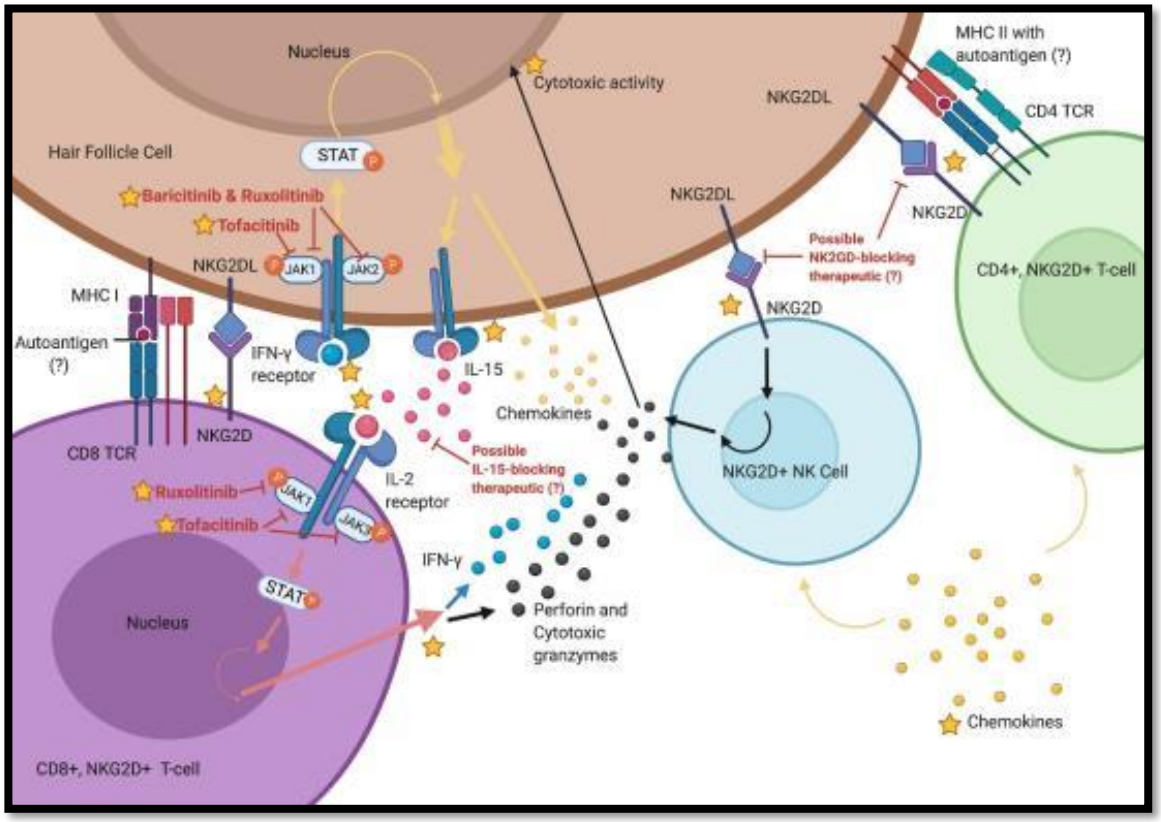


Figure (1): Immunopathogenesis of AA **(14).**

Histopathology:

Histologic examination demonstrates a characteristic “bee-swarm pattern” of dense lymphocytic infiltrates surrounding the bulbar region of anagen hair follicles. The lymphocytic infiltrate consists of CD8+ T cells in the follicular epithelium and CD4+ T cells around the hair follicles **(1).**

Genetics:

Alopecia areata is more likely to occur in patients with a family history of disease. Prevalence of disease in adult patients with a family history is estimated to range from 0% to 8.6%, and in children between 10% and 51.6%. In addition, the occurrence of the disease in identical twins, siblings and several generations of the same family, provides further evidence to support a genetic link **(15).**

Immunology:

The hair follicle is a unique mini-organ which undergoes a continuous, lifelong regenerative cyclic process. The lower part of the healthy anagen hair follicle enjoys relative IP, which protects the hair follicle from inflammatory processes and promotes immune tolerance . These distinct hair follicle compartments are characterized by factors that act as IP guardians to preserve the hair follicle- IP. The key cytokine in the induction of AA is currently considered to be IFN- γ, so AA is regarded as a type 1 inflammatory disease **(16)**

Interlukin-15 is significantly elevated in AA patients when compared to the control subjects. It is also positively correlated with the number and the extent of the disease, making it a possible marker of AA severity **(16).**

The plasmacytoid dendritic cells represent a connection between innate and adaptive immunity They were identified infiltrating around hair follicles of AA. Activated Plasmacytoid dendritic cells secrete large amounts of (IFN-α/β),which triggers CD4+ cells, CD8+ cells, and NK cells responses towards the hair follicles. **(13).**

The numbers of T- regulatory cells were significantly lower in AA skin compared to controls and other skin diseases They preserve peripheral tolerance by suppressing auto-reactive T cells. Immune tolerance collapse and T cell-mediated autoimmunity may be induced by T-regulatory cell deficiency **(13).**

Oxidative stress:

Oxidative stress has been implicated as a contributory factor in the multifactorial etiopathogenesis of AA. With the existing data, it is unclear whether oxidative stress is a cause or effect of the disease state in AA. **(17).**

The skin is continuously exposed to endogenous and environmental pro-oxidant agents, leading to the overproduction of reactive oxygen species. Reactive oxygen species (ROS) are thought to activate proliferative and cell signaling pathways, which can in turn alter apoptotic pathways that may play a role in the pathogenesis of many dermatological diseases **(18).**

Oxidative stress is characterized by an imbalance between oxidation and anti-oxidation mechanisms (enzymic and non-enzymic antioxidants), leading to an increase in oxidation intermediates such as ROS . The generation of abnormal ROS (lipid, protein, DNA free radicals etc.) has been associated with a variety of skin diseases, including AA **(19).**

The use of Oxidative stress biomarkers could become a useful diagnostic tool, potential biomarkers of Oxidative stress to be considered in the AA could be: malondialdehyde, advanced glycation end-products and ischemic-modified albumin which are always found to be increased, by speculative analysis of currently existing studies. Other potential biomarkers evaluated were: superoxide dismutase, catalase, glutathione , and paraoxonase . **(19).**

Microbiota:

The hair follicle microbiota is located near the bulge (stem cell niche) and the bulb (cellular division site to build a new hair) considered IP sites. Shifts in the hair follicle microbiome can be related to loss of homeostasis, modulation of immune reactions and the intense peribulbar inflammation in AA **(20).**

Symbiosis of Corynebateriaceae, Propionibacteriaceae, Staphylococcaceae, and Malassezia is related to a healthy scalp, while dysbiosis can cause pathological conditions. Pinto et al. found microbial shifts in individuals with AA exhibiting over–colonization with *C. acnes* along with a reduced *S. epidermidis* abundance, however, it has not been determined if these differences are cause or consequence of the disease **(21).**

Along with skin, gut dysbiosis has been linked with AA . Genes that are related to AA can affect gut colonization with microorganisms that induce a Th1 response with increased IFNγ production. There are two cases of AA with long–term hair regrowth after fecal microbiota transplants .This may support a role of the intestinal microbiome in the pathophysiology of AA **(21).**

Alopecia areata is associated with other autoimmune disorders. Gut dysbiosis can act as a common pathway in patients with both inflammatory bowel disease and AA. A variety of factors involved in hair growth and/or maintaining immunological homeostasis are affected in gut dysbiosis: bacterial production of biotin, short–chain fatty acids produced by gut microbiota and vitamin D deficiency **(22).**

Restoration of gut microbiota balance might contribute to hair regrowth in patients with AA by enhancing the absorption and synthesis of nutrients and host–related factors such as immunomodulation **(23).**

An innovative treatment option for AA is the therapeutic manipulation of the microbiome. This manipulation may be achieved by fecal microbiota transplant , or the use of microbial metabolites such as postbiotics **(23).**

Role of Stress:

Psychological variables may also play a role in the development of AA, in addition to autoimmunity. Acute psychotrauma, stressful experiences, and unfavorable familial situations have been linked by researchers to the start of AA. Not unexpectedly AA sufferers have additional symptoms. They are more likely to develop specific mental problems such as severe depression, generalized anxiety disorder, social phobia, or paranoid disease **(24).**

Psychological stress activates the hypothalamic-pituitary-adrenal axis, resulting in the secretion of corticotropin-releasing hormone. In human hair follicless, corticotropin-releasing hormone promotes the degranulation of mast cells, which releases histamine, TNF-α, IL-6, and IL-1 into the microenvironment, promoting perifollicular neurogenic inflammation followed by the collapse of IP in the hair follicles **(8).**

Role of Environment:

Although immunogenetics are the principal factors affecting patient susceptibility to AA, environmental factors including viral infections, trace elements or micronutrients, immunization, and allergies are also thought to influence the disease. After viral infection, Th1 immune responses result in supraphysiologic IFN production **(8).**

The possibility that cytomegalovirus may be involved in the pathogenesis of AA was originally proposed by **Skinner et al (25).** after detection of cytomegalovirus DNA sequences using polymerase chain reaction in scalp biopsies of AA patients; however, this hypothesis was not confirmed by subsequent authors **(26).**

Epstein–Barr virus , hepatitis B and C viruses, and swine flu virus infection have been reported to elicit AA autoimmunity In line with this, AA in a patient with coronavirus 2 infection was described. Vaccination has also been speculated to be an inducible factor. The mechanism underlying these phenomena remains elusive, but the activation of IFN-α-producing plasmacytoid dendritic cells via viral infection has been considered to be crucial. Thus, viral infections have been regarded as triggers of other autoimmune diseases **(26).**

An increased frequency of AA among those who received the hepatitis B surface protein antigen was identified, and an independent analysis revealed an increased frequency of AA in those receiving IFN-β treatment **(27).**

Boron is commonly utilized in industrial products primarily as the salt borax. Systemic exposure (e.g ingestion) or dermal exposure to boron has been correlated with, among other signs, reversible toxic alopecia **(24).**

Alopecia areata and atopic dermatitis:

Atopic dermatitis is a type 2 inflammatory disease and cases of AA with atopic dermatitis show a more refractory disease course than AA without atopic dermatitis. It has been reported that AA represents a cell-mediated autoimmune disease, and hair follicle autoantigens, such as tyrosinase, TRP1/2 and trichohyalin, are strong candidate targets of NKG2D+CD8+ T cells, which mainly produce IFN-γ. On the other hand, atopic dermatitis is the most frequent comorbidity of AA; it appears in more than 30% of patients with AA **(16)**

The immunological condition of AA may be different between atopic and non-atopic patients and between extrinsic and intrinsic atopic dermatitis patients **(28).**

Filaggrin gene mutation, a major risk factor for atopic dermatitis, is significantly associated with the presence of atopic dermatitis among patients with AA .Thirty-eight percent of patients with AA are atopic **(10).**

The dual efficacy of dupilumab on AA in patients with both AA and atopic dermatitis may indicate a new subtype of AA identifiable by the cytokine profile, carrying implications for adaptations to treatment strategies**. (16)**

Diagnosis:

Clinical features and subtypes:

The most common clinical presentation of AA is patchy AA with the appearance of single or multiple circumscribed patches of scalp hair loss which can either be discrete, isolated or can coalesce with other lesions to form a larger area devoid of hair. The skin within the lesions is smooth, healthy-looking, and intact, while sometimes a slight oedema is palpable, but without any erythema or other signs of inflammation **(29).**

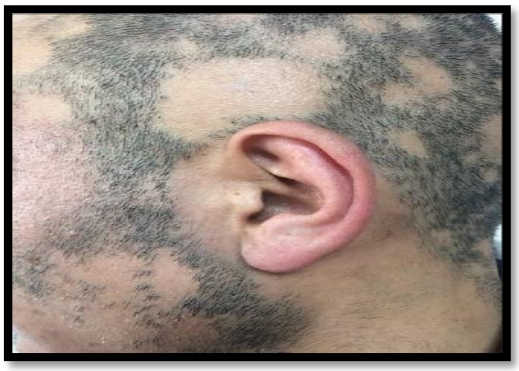


Figure (2): patchy lesions of alopecia areata **(30)**.

Typically, AA presents single or multiple nonscarring alopecic patches on the scalp, but it sometimes progresses to band-like hair loss along the hairline on the temporal and/or occipital region ;alopecia ophiasis, total scalp hair loss ;alopecia totalis, or whole-body hair loss; alopecia universalis, which are recognized as refractory AA subsets **(30)**.

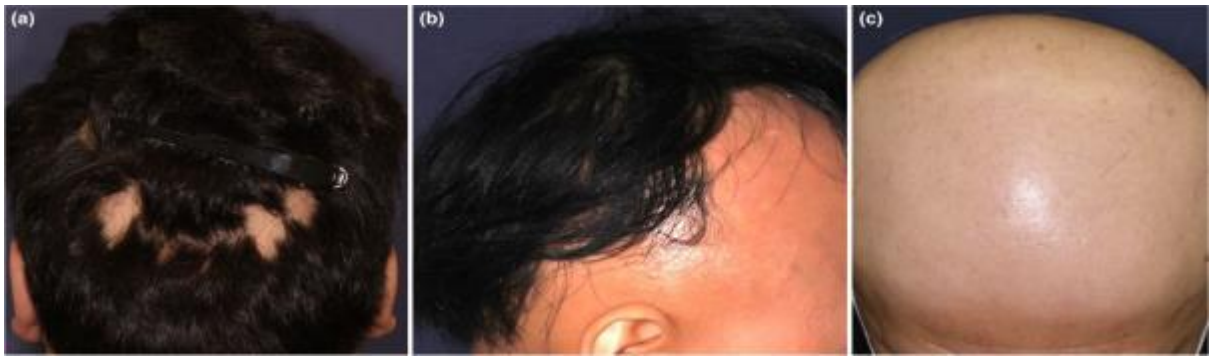


Figure (3): Clinical phenotypes of alopecia areata. (a) The most common form of alopecia areata presenting multiple hair loss patches, (b) alopecia ophiasis, and (c) alopecia totalis/universalis **(31).**

Alopecia areata affecting the beard area is well known and is referred to as AA of the beard or AA barbae when involvement is limited exclusively to the beard. It is characterized by well-demarcated, smooth-surfaced patches of hair loss on the beard of male patients. Alopecia areata patients with persisting alopecic patches beyond 1 year can be defined as the chronic subset. Another subtype of severe AA is known as rapidly progressive AA , which manifests acute and diffuse hair loss affecting almost the entire scalp with or without extra-scalp hair loss **(32).**

Nail changes:

The most common nail changes associated with AA in adults were pitting (11.4–0.6%) and trachyonychia (8–14%) **.** Other reported changes included longitudinal ridging, Beau's lines, onycholysis, punctate leukonychia, and red spotted lunulae. In children, pitting (13.2-18.8%), trachyonychia, and onychomadesis were seen. Pitting was more common in children than in adults. In AA, nail pits are classically shallow, with a grid-like distribution. This is in contrast to psoriasis, where pits are deep and randomly distributed **(33)**

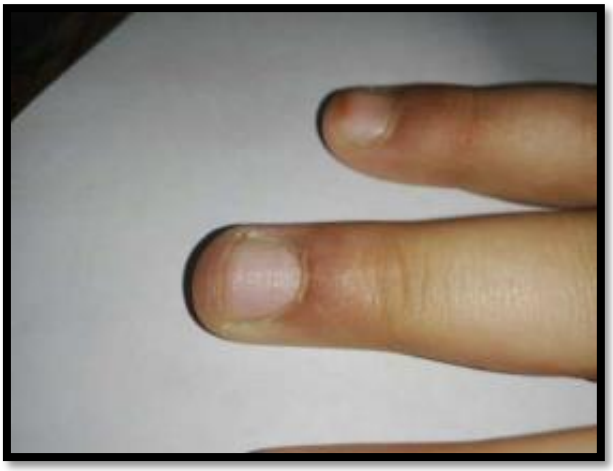
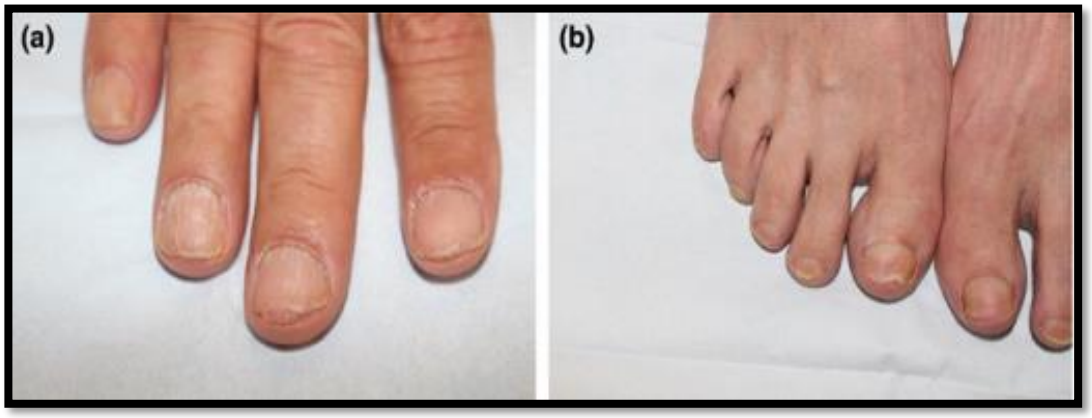


Figure (4): Pitting of nails in alopecia areata patient **(34).**



Figure(5): AA-associated trachyonychia of the fingernails (a) and toenails (b) **(33)**

White Hair In AA:

There are different clinical forms of hypopigmented hair phenomena in the setting of AA; they include transient or permanent hypopigmented hair regrowth and localized or diffuse sparing of hypopigmented hairs. The physiopathologic mechanisms of AA are complex and still unclear. However, the different clinical manifestations observed and research results suggest that the melanogenesis process is involved in the etiology of the disease **(35).**

Pull test:

A bundle of 50–60 hairs is grasped firmly close to the scalp and pulled with moderate force in the direction of growth, performed at the border of patchy lesions and at the contralateral clinically non-affected side . Hairs should not have been washed for at least one day. A positive hair pull test with epilation of ≥ 10 % of grasped hairs indicates active disease, whereas a negative test indicates a stable or resolving AA. A positive pull test on the clinically non-affected area may indicate progressive disease with diffuse progression **(29).**

Trichoscopy:

Hair and scalp dermoscopy – is a non-invasive method useful in the diagnosis of scalp and hair diseases. Numerous studies about trichoscopic findings of scalp AA and frontal fibrosing alopecia, as well as their relation to disease activity and severity have been published **(36).**

Dermoscopic features of AA include:

Yellow dots: Round or polycyclic yellow to yellow-pink dots that represent distended follicular infundibula filled with sebum and keratin remnants

Black dots: Remnant of broken hair shafts inside follicular ostia. Exclamation mark hairs: Broken hairs that tapered toward follicles (**26).**

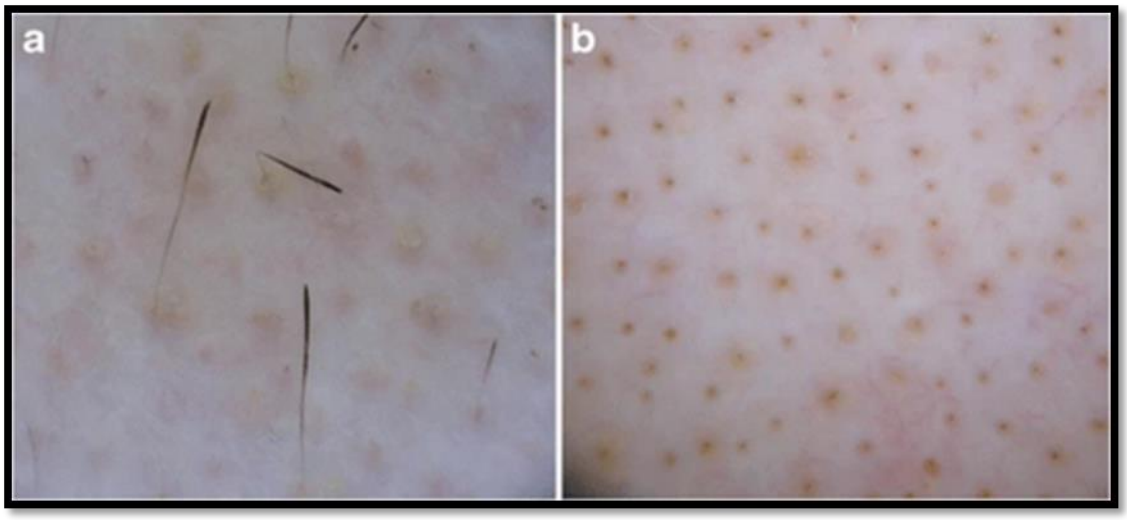


Figure (6): Dermoscopic findings in alopecia areata. (a) Exclamation mark hairs.(b) Yellow dots **(26).**

Short vellus hairs: Thin, nonpigmented hairs with length ≤10 mm may demonstrate early disease remission. Broken hairs: Due to fracture of dystrophic hair shafts or rapid regrowth of hairs that formerly manifested as black dots **(37).**

Trichoscopy enables the distinction of otherwise indistinguishable hairloss conditions. "Color-transition sign" refers to color graduation from black to white between the distal end and the proximal root of the hair shaft, presumably resulting from moderate and intermittent inflammation around the hair bulb, which can be used to distinguish AA and telogen effluvium. "Follicular microhemorrhage", which is thought to reflect the damage of capillaries within AA-affected hair follicles due to forced hair plucking, has been shown to be useful for the diagnosis of trichotillomania resembling or coexisting with AA **(26).**

Severity of Alopecia Tool score:

The classification of severity of AA was first published by Olsen in 1992 and 1997 and formalized by the National Alopecia Areata Foundation Guidelines. National AA Foundation working committee devised the "Severity of Alopecia Tool score" (SALT score). Scalp is divided into four areas, namely vertex, 40% (0.4) of scalp surface area; right profile of scalp, 18% (0.18) of scalp surface area; left profile of scalp, 18% (0.18) of scalp surface area; and posterior aspect of scalp, 24% (0.24) of scalp surface area. Percentage of hair loss in each area is determined independently and multiplied by the percentage of scalp covered in that area of the scalp **(38).**

Prognosis:

Alopecia areata is a benign, self-limiting condition with most cases resulting in spontaneous regrowth over a period of several months to years, with approximately 66% of patients showing complete regrowth of hair within 5 years. However, relapse is common and studies have reported that in patients observed over a period of 10–20 years the incidence rate of relapses ranges from 85–100%, with 100% relapse being observed in patients over a 20-year period. **(12).**

Compared with adults, early onset of AA in childhood often results in both a greater degree of hair loss and progression of disease . If the disease occurs before puberty, the risk of developing alopecia totalis is 50%, after puberty 25% . Alopecia totalis develops within 6 months from onset of hair loss in one third of adults and in one sixth of children. Children show a slower progression to alopecia totalis, but higher frequency with time **(26).**

Differential Diagnosis:

Alopecia areata is clinically defined by areas of non-scarring hair loss with 'exclamation point hairs. Additional reasons for nonscarring alopecias must be considered such as androgenic alopecia, telogen effluvium trichotillomania, and traction alopecia (**24).**

Table (1): Differential diagnosis of AA **(24).**

Diseases	Clinically
Alopecia areata	-Usually patchy but can be generalized -Exclamation-point hairs -Abrupt onset; often waxes and wanes with relapses -Prominent shedding -Onset at any age; most have their first patch before age 20 -Hair pull test: Positive; dystrophic anagen and telogen hairs
Androgenetic alopecia	-Focal balding pattern. -Generalized -Gradual onset with progression -Thinning with or without bare patches. - Minimal Shedding -Onset at puberty or older -Hair pull tests are usually negative
Telogen effluvium	- Generalized Excessive shedding of the normal telogen club hair - Onset is abrupt, often with trigger factors most commonly occur 3-6 months following pregnancy, parturition, surgery, dieting, drugs -Thinning with no bare patches -Onset at any age, but usually not childhood -Hair pull test: Positive; telogen hairs
Trichotillomania	-Obsessive-compulsive disorder of plucking hair from the scalp, eyelashes, or brows -Irregular patches of alopecia containing the hair of varying length
Syphilitic alopecia	May have a typical moth-eaten appearance on occipital scalp -May occur as generalized thinning of hair -May resemble alopecia areata

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