

## Alopecia Areata

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### Synonyms

Non-scarring hair loss; Patchy alopecia; Patchy hair loss

Alopecia areata (AA) is a disease which causes hair loss commonly on the scalp and much less frequently over other hair-bearing areas of the body (e.g., eyebrows, beard). AA has a prevalence of 0.1–0.2 % with a lifetime risk of 1.7 % in the general population (Safavi 1992). It affects individuals of all ages, gender, and ethnicity.

It is a cutaneous disease which may have nail changes. However, other organ systems are not affected. Even in the most severe sequelae of entire scalp and body hair loss, this disease does not portend a serious medical problem; however, the psychological and social impact can be immense.

There is increased incidence of AA among patients with genetically related persons having this disease (10–20 %) (Freyschmidt-Paul et al. 2010).

This condition has been associated with a personal history of atopy and has been found to occur with other autoimmune diseases such as lupus erythematosus, vitiligo, type I diabetes mellitus (Wang et al. 1994), and autoimmune thyroid disorders (Kurtev and Iliev 2005).

### Pathogenesis

The exact etiopathogenesis of AA is not fully known. There is overwhelming evidence

supporting the major role of the immune system in the pathogenesis of this disease. At present, AA is considered an autoimmune disease based on substantial research data though some crucial findings to establish true autoimmunity (e.g., identification of primary target self-hair-follicle-derived antigen/s; reactivity to self-follicular antigens leading to AA in humans) are still lacking (Freyschmidt-Paul et al. 2010).

In AA, inflammatory infiltrates are found mainly over the peribulbar region of the terminal anagen hair follicle (Whiting 2003; Dy 2011; Alkalifah et al. 2010).

The inflammatory attack does not occur over the region of the epithelial follicular stem cells (bulge area); thus, permanent damage is not seen in this disease and hair regrowth is possible.

Research findings indicate that cellular-mediated immune system plays a significant role in the pathogenesis of AA. The inflammatory infiltrate in AA consists of T cells mainly CD4 and CD8. CD4+ T lymphocytes are mainly found surrounding hair follicles, while CD8+ cells are located intrafollicularly (Freyschmidt-Paul et al. 2010; Carroll et al. 2002; McElwee et al. 2002). The activated CD8+ infiltrating inside hair follicles causes cytotoxic reaction, resulting in follicular damage. Molecules produced by cytotoxic T cells include tumor necrosis factor (TNF), granzymes, and Fas ligand (FasL) (Carroll et al. 2002; McElwee et al. 2002). Fas are highly expressed in dystrophic AA hair follicles (Bodemer et al. 2000; McElwee and Hoffman 2002). Interferon gamma (IFN gamma) produced by follicular antigen-presenting cells and mediated by CD4 T helper cells has been shown to be elevated in AA patients especially in alopecia areata totalis or universalis. This cytokine has been found to precipitate hair loss in AA (Freyschmidt-Paul et al. 2006; Arca et al. 2004).

The pathogenic role of T lymphocytes (mainly CD8 and CD4) is further supported by the induction of AA in animal models through the transfer of particular cells and grafting from AA mice to normal mice, leading to the development of patchy hair loss (McElwee et al. 2005; Freyschmidt-Paul et al. 2008). In murine

models, transferred CD8+ induced localized disease, whereas CD4+/CD25-injection resulted in minimal local hair loss but induced a systemic reaction resulting in multiple extensive patches (McElwee et al. 2005). Immunoregulatory CD4+/CD25+ cells (immunosuppressive to CD4+/CD25- and CD8+ function) were found to decrease in active AA and prior to AA onset (Zoller et al. 2002).

AA has findings which extend beyond the affected sites. There is elevation of autoantibodies in serum, in addition to those found on lesional skin of patients with AA (Tobin 2003); however, the transfer of serum or autoantibodies has failed to induce alopecic patches (Gilhar et al. 1992); thus, these antibodies do not seem to have a primary role in the pathogenesis of AA.

The normal hair follicle is considered a relatively immune-privileged site through the downregulation of major histocompatibility complex (MHC) molecules (needed for autoantigen presentation to CD8+ T cells) and expression of immunosuppressive cytokines. In AA, an aberration in immune privilege in susceptible individuals may contribute to its pathogenesis. In the follicular epithelium of AA patients, there is an increase in MHC I and II expression and lower levels of immunosuppressive cytokines in contrast to non-AA hair follicles (Gilhar 2010; Gilhar et al. 2012). The immune-inhibitory molecules produced by anagen hair follicles which were found to be decreased in AA were alpha-melanocyte-stimulating hormone (alpha-MSH), transforming growth factor beta (TGF beta), indoleamine 2,3 dioxygenase (IDO), and Red/IK (Gilhar 2010). The decreased Red/IK cytokine in the outer root sheath of the hair follicle and hair matrix functions to suppress MHC II antigen (expression of which is triggered by IFN gamma) associated with autoimmune disease (Kang et al. 2012). There are elevated numbers of NKG2D+NK cells around lesional hair follicles in AA, and an agonist of NKG2D, MHC I polypeptide sequence A (MICA), is expressed in AA (Ito et al. 2008).

Many patients have positive history of the disease in genetically related family members.

Support for AA genetic susceptibility is being provided by study findings of genes relating to the immune system and regulation of the hair follicle.

A genome-wide association study (n = 1,054 AA cases; n = 3,278 controls) done in North America looking into the genetic component of alopecia areata **has identified genes involved in autoimmunity and cell-mediated immunity specifically susceptibility loci on chromosomes 2q33.2(CTLA4), 4q27(IL2/IL21), 6p21.32(HLA), 6q25.1 (ULBP6/ULBP3), 9q31.1 (STX17), 10p15.1(IL2RA), 11q13 (PRDX5), and 12q13 (Eos/ERBB3) (Petukhova et al. 2010).**

Of the aforementioned genes, the cytotoxic T-lymphocyte-associated antigen (CTLA4), interleukin (IL)2/IL21, and IL2 receptor A (IL2RA) have T cell proliferation function. Human leukocyte antigen (HLA) is involved with antigen presentation. Cytomegalovirus UL16-binding protein consisting of ULBP6/ULBP3 genes encoding activating ligands of the natural killer cell receptor NKG2D is being expressed in the hair follicle particularly in the dermal sheath of patients with AA. Lymphocytes around hair follicles composed of CD8+ can be activated by NKG2D-activating ligand. Two hair follicle genes were identified: syntaxin (STX17) and peroxiredoxin (PRDX5) (Petukhova et al. 2010).

A follow-up genome-wide association study in Europe (n = 1,702 cases; n = 1,723 controls) confirmed the significant association with the susceptibility loci for ULBP6/ULBP3, STX17, IL2/IL21, PRDX5, and ERBB3. In addition, two other susceptibility loci were identified: IL-13 produced by T helper cells with inflammatory cell recruitment role and KIA0359/CLEC16A expressed by immune cells but whose function is not yet known (Jagielska et al. 2012).

Some of the identified susceptibility alleles have also been found in other autoimmune diseases such as rheumatoid arthritis, type 1 diabetes mellitus, celiac disease, Crohn's disease, systemic lupus erythematosus, multiple sclerosis, and psoriasis signifying common autoimmune pathways (Petukhova et al. 2010).

## Clinical Manifestations

Clinically, AA presents as non-scarring, well-defined alopecic patches mainly found over the scalp in majority of cases. Other sites which may be affected include the eyebrows, eyelashes, beard, and body hair. The lesions typically start as discrete, solitary, or multiple patches (Fig. 1) which may remain limited in size or may expand to involve larger areas. The cutaneous surface of the affected patches are normal and smooth in appearance, with skin colored or pinkish hue. Upon closer examination, there is note of intact follicular ostia. Typically this condition occurs rapidly and there is variability in terms of disease severity. In severe progression of the disease, there may be hair loss of the entire scalp (AA totalis/AT) (Fig. 2) or body hair (AA universalis/AU) (Freyschmidt-Paul et al. 2008, 2010; Shapiro 2002).

**Clinical variants based on pattern distribution include patchy, ophiasis, and diffuse type of AA. Patchy AA is the most common type affecting majority of cases. The ophiasis type is a band-like pattern which commonly starts at the occipital hairline area and extends towards the lateral temporoparietal hair margins. In diffuse AA, there are no well-circumscribed alopecic lesions but rather diffuse thinning areas over the scalp. This type is difficult to diagnose clinically and may need a biopsy for confirmation (Shapiro 2002).**

**AA may preferentially attack pigmented hairs leaving white hairs intact, resulting in the appearance of scalp hair suddenly turning white.**



**Alopecia Areata, Fig. 1** Patchy alopecia areata (Courtesy of the University of British Columbia Hair Clinic)



**Alopecia Areata, Fig. 2** Alopecia areata totalis (Courtesy of the University of British Columbia Hair Clinic)

Positive pull test over the peripheral hair margins indicates active disease. Some lesions may have exclamation point hairs which appear as short broken hair fibers tapered proximally compared to its distal end.

Nails may also be affected with development of changes such as pitting, red lunulae, and longitudinal ridging. In some cases, nail signs may precede the appearance of the alopecic patches (Freyschmidt-Paul et al. 2010; Shapiro 2002).

### Pathobiology and Histopathology

In the early stage of AA, there is a dense inflammatory infiltrate over the peribulbar region of the terminal anagen hair follicle (swarm of bees). Some infiltration may occur intrafollicularly as well (Whiting 2003; Dy and Whiting 2011).

Predominant T cells mainly CD4 and CD8 cause destruction (apoptosis and necrosis) to the

follicular epithelium. This active inflammation leads to a dystrophic anagen condition wherein the affected hair follicle's caliber/quality becomes compromised. Upon progression of the disease with increased inflammatory cell infiltrates attacking the hair follicle, these affected follicles undergo a miniaturization process with shortened rapid cycling of the anagen and telogen phases (nanogen hair follicles) (Wang and McElwee 2011).

Inflammation causes disruption of the hair follicle, leading to disease activity. The inflammatory infiltrates are found mainly over the lower part of the hair follicle (hair matrix and dermal papilla), not the bulge area. Damage to the hair shaft results in trichorrhexis nodosa-like fractures seen clinically as exclamation point hairs. There may be injury to melanocytes, leading to pigment incontinence. Repeated inflammation leads to development of miniaturized hair follicles. Terminal hairs become less and catagen/telogen hair follicles rise in number, leading to the subsequent decrease of the anagen to telogen ratio (Whiting 2003; Dy 2011).

Chronic AA has hair follicles in prolonged telogen without reentry into the anagen phase. At this stage any inflammation present would be found surrounding miniaturized hairs. There is significant increase of miniaturized hairs and decrease to absence of terminal hairs. The telogen to vellus ratio may drop to 1:3 compared to the usual normal of 7:1 (Dy and Whiting 2011).

### Treatment

To date, there is no standard curative and preventive treatment for AA. There is a high rate of spontaneous hair regrowth for localized patchy scalp disease; thus, not instituting any medical intervention is one management option.

Evaluating medications according to the evidence-based medicine criteria shows that few medications show effectivity in the treatment of AA. Among the immunosuppressive agents, potent topical and intralesional corticosteroids are reasonable first-line therapies for patients with limited patchy disease. Based on study results, the most effective topical corticosteroid

seems to be the superpotent clobetasol propionate foam for patchy AA and the 0.05 % ointment under occlusion for more extensive disease (Tosti et al. 2003, 2006).

Various clinical studies have shown efficacy of intralesional glucocorticoid ranging from 63 to 97 % (Alkhalifa 2011).

The dosage used for injections such as triamcinolone acetonide ranges from 2.5 to 10 mg/cc every 4–6 weeks.

Uncontrolled clinical trials on the pulsed administration of systemic corticosteroids have shown some efficacy; however, hair regrowth was mostly temporary with hair loss ensuing after discontinuation of treatment (Freyschmidt-Paul et al. 2010).

Many institutions consider topical immunotherapy as first-line treatment for more extensive lesions of AT and AU. The agents utilized for this treatment are Diphenylcyclopropenone (DPCP) and squaric acid dibutylester (SADBE). Various clinical trials including well-designed controlled studies on the effectivity of DPCP and SADBE showed response to treatment ranging from 29 to 78 % with a median of 49 % (Freyschmidt-Paul et al. 2010; Shapiro 2002).

The use of biologics (i.e., TNF alpha inhibitor (etanercept); LFA 3 inhibitor (alefacept)) so far has proven ineffective, and in some studies, TNF alpha inhibitors have even worsened the condition (Freyschmidt-Paul et al. 2010; Strober et al. 2009).

Other therapies such as topical minoxidil, anthralin, and phototherapy have not been proven effective in various clinical trials (Freyschmidt-Paul et al. 2010; Strober et al. 2009). Minoxidil, if used, is more of an adjunctive medication in addition to other treatments such as topical and intralesional corticosteroids.

## Course and Prognosis

The lesions of AA are non-scarring with hair regrowth being possible. The course is characterized as unpredictable with disease recurrence occurring at any given time.

Within a year, there may be spontaneous hair regrowth seen in about half of the patients with localized patchy type of AA. There is however

a high rate of recurrence within 5 years (Freyschmidt-Paul et al. 2010; Shapiro 2002).

Severe cases usually follow a chronic course. Factors associated with poor prognosis include severe type of AA (AT and AU), early age of onset, long-standing disease, presence of nail changes, and positive family history of AA and personal medical history of atopy and other autoimmune diseases (Shapiro 2002).

## Cross-References

- ▶ Cytotoxic T Lymphocytes
- ▶ Immunology of Alopecia in Autoimmune Skin Disease
- ▶ Psoriasis
- ▶ Rheumatoid Arthritis, Genetics
- ▶ Therapeutic Considerations in Kidney Diseases Due to Glomerulonephritis

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## Alopecia in Systemic Autoimmune Disease

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### Synonyms

Autoimmune disease and hair loss

### Definition

Hair loss that is directly associated with autoimmune disease involves immune mechanisms in its pathogenesis targeting the hair follicles. They may be localized or generalized, as well as scarring and non-scarring in type. Secondary factors may also play a role in hair growth, including the medications used to treat the primary disease.

### Lupus

Hair loss is one of the most common cutaneous signs of systemic lupus erythematosus (SLE)

and is present in more than half the patients at some time during the course of their illness (Moghadam-Kia and Franks 2013). Alopecia can be the presenting manifestation of SLE and may affect the scalp, eyebrows, eyelashes, beard hair, or body hair (McCauliffe and Sontheimer 1996). Alopecia may be associated with active disease and can also occur due to immunosuppressive medications used to treat lupus. Lupus alopecia can be scarring associated with discoid lupus or non-scarring. The Systemic Lupus International Collaborating Clinics (SLICC) has recently revised the American College of Rheumatology (ACR) SLE classification criteria (Petri et al. 2012). Discoid lupus has been always included in the most widely used classification criteria for SLE, including the new SLICC classification criteria. Non-scarring alopecia is also included in the new criteria as an individual criterion for SLE, as it was in the original ARA criteria.

### Non-scarring Alopecia

Non-scarring alopecia in lupus often develops during flares of systemic disease and can occur under two scenarios. One is “telogen effluvium” that is a reactive process characterized by a diffuse thinning of the scalp and hair shedding caused by a metabolic or hormonal stress, like pregnancy, or the use of glucocorticoids. Generally, the normal hair usually grows back within 6 months when the antecedent etiology resolves. In diffuse patterned hair loss in general, up to 20 % of the hair can be lost before it is cosmetically visible. Therefore, complaints of hair loss should not be discredited in individuals who still have a full head of hair. Other scenario is “lupus hair,” which is characterized by dry, course hair prominently over the frontal hairline that is very brittle and easily damaged. This condition is almost always observed during exacerbations of SLE and resolves when the disease activity abates (Aларcon-Segovia and Cetina 1974). Considerable overlap occurs between lupus hair and telogen effluvium. As in alopecia areata, non-scarring alopecia in lupus can occur as a wavy band-like area of hair loss extending across the peripheral temporal and occipital scalp

(ophiasis pattern). Ophiasis gets its name from the Greek word “ophis,” meaning snake.

### Differential Diagnosis

Non-scarring alopecia in lupus must be distinguished from many other non-scarring alopecias. The differential diagnosis includes alopecia areata, telogen effluvium, traumatic alopecia, traction alopecia, female pattern hair loss, and male pattern alopecia (Table 2).

*Alopecia Areata:* Alopecia areata is a chronic inflammatory disease that causes recurrent non-scarring alopecia. It is thought to be an autoimmune condition caused by T cell-mediated immune dysfunction. There is an increased incidence of alopecia areata in patients with other autoimmune conditions such as lupus and DLE (Werth et al. 1992). It usually affects the scalp and presents with discrete circular well-delineated smooth patches of complete hair loss with no or little inflammation. The scalp lesions may be associated with burning sensation and slight erythema. Dermoscopy or 7x loupe magnification can aid in diagnosis and can reveal yellow dots and exclamation-point hairs with a tapering base and a ragged proximal portion that are diagnostic of the disease. Hairs that grow back are temporarily or permanently hypopigmented. This is another characteristic feature of alopecia areata. Scalp biopsy is useful in equivocal cases (Alkhalifah et al. 2010a, b).

*Telogen Effluvium:* Telogen effluvium is a non-scarring alopecia in which a physiologic stressor causes an increased number of hairs to go into resting phase (telogen phase). The hair loss in telogen effluvium occurs in a diffuse pattern. A hair-pull test can result in many hairs (more than 2 hairs on a group of 50 hairs) coming out easily from their roots with an elongated hair bulb. The scalp appears non-erythematous and unremarkable. Metabolic testing, including complete blood count, iron studies, thyroid function tests, serum chemistries, and liver enzymes, should be considered in the search for systemic causes of telogen effluvium. A drug history should be obtained as well. Scalp biopsy is usually not necessary (Tosti and Pazzaglia 2007).

**Alopecia in Systemic Autoimmune Disease, Table 1** Comparative features of alopecia in lupus, dermatomyositis, and scleroderma

	Lupus	Dermatomyositis	Scleroderma
Frequency of scalp lesions	Frequently seen	Frequently seen	Occasionally seen
Frequency of alopecia	Frequently seen	Occasionally seen	Occasionally seen
Color of scalp lesions	Red, pink	Violaceous	Shiny, hypo- or hyperpigmented
Distinctive features of skin involvement	Involvement of the malar eminence, oral mucosa, dorsal fingers; hyperkeratosis	Involvement of the eyelids, periorbital areas, knuckles; pruritus	Systemic sclerosis (SSc): involvement of the fingers, hands, and face; edema and pruritus in the early stages; variable skin thickening; paucity of facial wrinkles; sclerodactyly; digital ulcers, calcinosis cutis; pitting at the finger tips; Raynaud's phenomenon Localized scleroderma: no Raynaud's phenomenon, no systemic involvement, no sclerodactyly; plaques tend to progress for 3–5 years and then arrest
Lab findings	Anti-DS DNA, Anti Smith	Autoantibodies directed against cytoplasmic RNA synthetases (Anti-Jo-1, Anti-PL-7, Anti-PL-12, Anti-OJ, Anti-EJ)	Limited cutaneous SSc: anticentromere antibody; diffuse cutaneous SSc: anti-Scl-70 (anti-topoisomerase I) Morphea: anti-histone antibodies
Pathology	Scalp DLE: intense mononuclear cell infiltrate, fibrosis, follicular hyperkeratosis, epidermal atrophy, thickened basement membrane, and basal vacuolar degeneration	Sparse perivascular lymphoid infiltrate, epidermal atrophy, basement membrane degeneration, and vacuolar changes in the basal keratinocyte layer	Intense inflammatory infiltrate at the margin at early stages and waning inflammatory infiltrate at later stages with infiltration of lymphocytes and plasma cells at the border and central fibrosis in the lower two-thirds of the dermis and upper subcutaneous tissue and eventually disappearance of pilosebaceous units and eccrine sweat glands and effacement of the rete ridges
Immunopathology	Dermal-epidermal junction granular deposits of immunoglobulin (IgG [less commonly IgM]) and complement (C3)	Dermal microvessel complement (C5 to C9) deposits (in DM, immunoglobulin deposition as opposed to complement is less common than in lupus)	Diffuse vascular deposits of immunoglobulins (predominantly IgM) and/or complement (predominantly C1q)
Associated comorbidities	SLE affects multiple organ systems	Up to 40 % of cases may be associated with occult malignancy	Epileptic seizures have been reported with en coup de sabre

**Alopecia in Systemic Autoimmune Disease, Table 2** Differential diagnosis of non-scarring alopecia in lupus

Alopecia areata	Look for discrete circular well-delineated smooth patches of complete hair loss. Hairs that grow back are temporarily or permanently hypopigmented. Exclamation-point hairs with a tapering base and a ragged proximal portion that can be seen under dermoscopy are diagnostic of the disease
Telogen effluvium	Look for the history of a stressor or new medication, diffuse pattern of hair loss, and unremarkable examination of the scalp. A positive hair test with elongated hair bulbs is suggestive
Traction alopecia	Look for the history of long-term friction. The location of the hair loss at the temporal and frontal margins of the scalp, with broken fine vellus hairs at different stages, is suggestive
Traumatic alopecia (other than traction alopecia)	Trichotillomania: look for patches of alopecia with angulated and irregular borders and hairs that are broken off at varying lengths
Female pattern hair loss (FPHL)	Look for progressive thinning of hair in the central portion of the scalp with hairs of various lengths and diameter and retention of the frontal hair line. The loss is gradual. A family history is suggestive
Male pattern alopecia (MPA)	Look for progressive thinning of hair in an M-shaped pattern in the frontal hairline with bitemporal recession. The hair loss is gradual. A family history is suggestive

*Traction Alopecia:* Traction alopecia is a form of traumatic alopecia that occurs as a result of chronic and excessive tension on the hair follicles. Severe cases of traction alopecia due to chronic long-term friction can be associated

with follicular atrophy and permanent non-scarring alopecia. Obtaining thorough history including the exact styling techniques and products used is necessary. The location of the hair loss at the temporal and frontal margins of the scalp, with broken fine vellus hairs at different stages, is a distinctive clinical feature of traction alopecia. The scalp appears normal without evidence of scarring. Scalp biopsy can be helpful in some cases that are hard to differentiate clinically (Borovicka et al. 2009).

*Traumatic Alopecia (Other Than Traction Alopecia):* These types of hair loss include trichotillomania and alopecia secondary to physical abuse. Trichotillomania usually occurs in adolescents during times of psychosocial stress. It usually presents with patches of alopecia with angulated and irregular borders and with broken hairs of different lengths, usually located on the frontotemporal or frontoparietal scalp opposite the dominant hand. Affected areas are not completely bald. Localized perifollicular erythema or hemorrhage may occur. Scalp biopsy can be helpful in complicated cases. Alopecia due to physical abuse can be difficult to differentiate from other types of alopecia. If there is concern for abuse, look for historical inconsistencies, signs of trauma such as scalp hematoma or tenderness, and psychosocial risk factors. Signs of inflammation are absent in all types of traumatic alopecia.

*Female Pattern Hair Loss (FPHL):* FPHL, also referred to as female androgenetic alopecia, is the most common type of hair loss in adult women. FPHL usually presents with diffuse thinning of the central portion of the scalp with retention of the frontal hair line. The affected area is usually widened and more obvious. Bitemporal recession is rare. The hair loss in FPHL is gradual with conversion of pigmented thick terminal hairs to shorter indeterminate hairs and finally nonpigmented miniaturized vellus hairs. These hairs of various lengths and diameter are classic signs of androgenetic alopecia. A family history of similar hair loss is suggestive of FPHL. A hair-pull test may be helpful (3 or fewer hairs on a

group of 20 hairs indicating normal shedding). Follicles are intact. Scalp biopsy may help rule out autoimmune or inflammatory disorders (Olsen et al. 2005).

**Male Pattern Alopecia (MPA):** MPA, or androgenetic alopecia, is the most common type of alopecia in adult men. It often affects men prior to the age of 40. MPA usually presents with progressive thinning of hair in an M-shaped pattern in the frontal hairline with bitemporal recession that moves posteriorly as the alopecia progresses. Similar to FPHL, the hair loss in MPA is gradual with hairs undergoing a transition from terminal hairs to indeterminate hairs to vellus hairs. Follicles are intact without evidence of scarring. Taking a family history can be helpful (Olsen et al. 2005; Sinclair 1998).

## Scarring Alopecia

### Introduction

Scarring alopecia or cicatricial alopecia associated with discoid lupus is categorized as an LE-specific skin disease on the Gilliam's classification (Gilliam and Sontheimer 1981, 1982).

### Epidemiology and Pathogenesis

Scarring alopecia is a frequent complication of discoid lupus erythematosus (DLE, a form of chronic cutaneous lupus erythematosus according to the Gilliam's classification (Ross et al. 2005)) and has been reported in more than half (34–56 %) of the patients with DLE. Scalp DLE is present in 4–14 % of patients with SLE (Yell et al. 1996). Scalp DLE can be the presenting manifestation of lupus in more than half of affected individuals and can remain the only manifestation of disease in 11–20 %. It has been shown to correlate with disease chronicity. Scalp DLE affects females more often than male (Whiting 2001; Tan et al. 2004). Onset of disease is usually between 20 and 30 years of age (Tan et al. 2004 p. 30). Onset of disease has been reported to occur less frequently in children and particularly those under age 10 (Moises-Alfaro et al. 2003).

The action of genetic, environmental, immunoregulatory, hormonal, and epigenetic factors involved in the pathogenesis of lupus results in

the generation of inflammatory T cells, inflammatory cytokines, autoantibodies, and immune complexes that may cause damage to various target organs. Progressive replacement of the follicular epithelium by connective tissue and varying degree of permanent injury to the pluripotent hair follicle stem cell region in the bulge of hair follicles (where the arrector pili muscle connects to the outer root sheath) is similar to other forms of scarring alopecia. Like other variants of cicatricial alopecia, permanent destruction of hair follicles in DLE is frequently associated with a loss of sebaceous gland (Sellheyer and Bergfeld 2006). In scalp DLE, the localization of inflammation around the upper, permanent portion of the hair follicle appears to result from antigenic stimulation of the Langerhans cells that are positioned in the follicular epithelium below the entry of sebaceous glands into the follicle. These Langerhans cells may then trigger a first-line T cell- or immune complex-mediated inflammatory response (Dutz and Sontheimer 2002). This pattern of follicular inflammation is similar to scarring folliculitides of lichen planopilaris, allogeneic graft-versus-host reaction, and atopy. In scalp DLE, the antigenic stimulus affecting the Langerhans cells appears to be ultraviolet light (Ross et al. 2005); however, its role on hair-bearing scalp, a relatively sun-protected site, needs further study. A study showed that patients with coexisting androgenetic alopecia do not preferentially develop DLE in bald areas. The Koebner phenomenon is associated with DLE. Constant rubbing and scratching can lead to new lesions in affected patients. The proinflammatory cytokines interleukin-17 (IL-17), interleukin-23 (IL-23), and IL-17-producing cells have been shown to be important in the pathogenesis of lupus and lupus nephritis (Crispín et al. 2008; Zhang et al. 2009). A recent study of 89 patients with systemic and cutaneous lupus showed that IL17 isoforms (IL-17A and IL-17 F) are implicated not only in SLE but also in DLE immunopathogenesis (Tanasescu et al. 2010). Another recent study on 15 subjects with lupus suggested that T helper 17 lymphocytes and IL-17 are involved in the immunopathogenesis of both SLE and DLE.

As previously mentioned, DLE scarring alopecia is considered a primary scarring alopecia as the target of inflammation seems to be the hair follicle. For primary cicatricial alopecia, several classification systems exist in the literature; however, it is still controversial. In 2001, the North American Hair Research Society (NAHRS) developed a provisional classification for primary cicatricial alopecia. This classification scheme is a mechanistic classification system based on pathologic interpretation of dominant inflammatory cell type existing in and around affected hair follicles in scalp biopsy taken from clinically active lesions. This scheme divides the entities into lymphocytic, neutrophilic, mixed, or unspecific. Alopecia due to DLE is considered to be the most common primary acquired lymphocytic scarring alopecia (Tan et al. 2004).

#### Clinical Manifestations

Early classic lesion presents as a quite well-circumscribed, erythematous, infiltrative patch with adherent follicular hyperkeratosis. Later, the lesion progresses centrifugally to form a coin-shaped (“discoid”) white-ivory, atrophic, depressed, smooth plaque with follicular plugging and adherent scale. Telangiectasia might also be present (Whiting 2001; Shapiro 2002; Fabbri et al. 2004; Donnelly et al. 1995). They may have features of classic discoid lesions elsewhere. In darker-skinned individuals central hypopigmentation and peripheral hyperpigmentation may occur (Sontheimer and McCauliffe 2002). The scalp lesions may resemble alopecia areata, lichen planopilaris, or linear morphea. Discoid lesions of lupus in the scalp can commonly be pruritic or tender; however, the condition may be asymptomatic. The patients might report that UV exposure worsens their symptoms.

#### Diagnosis

The initial approach to the patient with scalp DLE should include examination of the entire scalp, assessing the location and pattern of hair loss and also the presence of extracranial cutaneous and systemic features. Scalp biopsy with adjunctive use of direct immunofluorescence is

helpful in establishing the diagnosis and evaluating the degree of inflammation and differentiation of scalp DLE from other primary lymphocytic cicatricial alopecias, respectively. Scalp biopsy specimens should be from early clinically active disease, at least 4 mm in diameter, and extend into the fat. Ideally, two biopsy specimens, one for standard horizontal sections and one for longitudinal section, should be obtained for transverse and vertical suctioning (Shapiro 2002). The major histopathologic features include fibrosis, follicular hyperkeratosis, epidermal atrophy, lymphocytic infiltrate, thickened basement membrane, and basal vacuolar degeneration. Granular deposits of C3 and IgG (less commonly IgM) at the dermal-epidermal junction and/or the junction of the follicular epithelium and dermis are typical. These histopathologic aspects can resemble those found in lichen planopilaris, an inflammatory scarring alopecia (Fabbri et al. 2004).

#### Differential Diagnosis

DLE scarring alopecia must be distinguished from other conditions that cause alopecia. The differential diagnosis of scalp DLE includes lichen planopilaris, radiation-induced alopecia, central centrifugal cicatricial alopecia, sarcoidosis, psoriasis, burn scar, and squamous cell carcinoma. In addition, a variety of other scalp conditions such as tinea capitis can be very inflammatory and must also be considered. Less commonly, non-scarring alopecia can be confused for scalp DLE (Table 3).

*Lichen Planopilaris (LPP):* LPP, also known as follicular lichen plan, can cause scarring alopecia over time. As in lichen planus, LPP is an autoimmune condition that is most likely caused by cell-mediated immune dysfunction. Similar to the pattern of follicular inflammation in scalp DLE, T lymphocytes targeted at follicular antigens are involved. LPP occurs more frequently in women than men. Patient with lighter skin are more commonly affected than dark-skinned individuals. There are three variants of LPP: classic LPP, frontal fibrosing alopecia, and Graham-Little syndrome. Classic LPP is characterized by perifollicular erythema and patches of alopecia

**Alopecia in Systemic Autoimmune Disease,****Table 3** Differential diagnosis of scarring alopecia associated with discoid lupus

Lichen planopilaris (LPP)	Look for erythema that is confined to perifollicular areas (in contrast to scalp DLE) and keratotic plugs surrounding the patches of alopecia. Loss of follicular orifices can be viewed under dermoscopy. Dyspigmentation, in comparison with scalp DLE, is less common
Central centrifugal cicatricial alopecia (CCCA)	Look for shiny scarring alopecia usually seen from the vertex forward. The presence of burning sensation or pruritus in the area of hair loss can help. Premature desquamation of the inner root sheath in scalp biopsy is suggestive
Radiation-induced alopecia	Look for the history of radiation exposure and regular and sharp borders. Decreased number of follicular units with fibrosis of adjacent collagen in scalp biopsy is suggestive
Squamous cell carcinoma	Look for long-standing hyperkeratotic or ulcerated lesions and scars. Biopsy is needed to confirm the diagnosis
Tinea capitis	Look for signs of inflammation in the scalp including erythema and scaling. Positive fungal culture and examination of plucked hairs with KOH are diagnostic

with surrounding keratotic plugs. Frontal fibrosing alopecia presents with band-like scarring alopecia of the frontal hairline that commonly affects women. Graham-Little syndrome is characterized by scarring alopecia of the scalp, non-scarring alopecia of the pubic and axillary areas, and a lichenoid follicular eruption. In contrast to scalp DLE, erythema is confined to perifollicular areas in LPP. Also, dyspigmentation is less commonly seen. Dermoscopy or 7x loupe magnification can aid in revealing the perifollicular erythema and loss of follicular

orifices. A hair-pull test may reveal an increased number of anagen hairs. Scalp biopsy performed at the margin of alopecia from the most active area of disease is the most useful test for the diagnosis. Histologic features of LPP include a lichenoid interface inflammation around the infundibulum and isthmus, sparing the hair bulb. Hyperkeratosis, acanthosis, and hypergranulosis can also be seen. In advanced disease, significant perifollicular lamellar fibrosis can be seen. Direct immunofluorescence is nonspecific and may show colloid body staining with IgM. These histopathologic features can resemble those found in scalp DLE.

*Central Centrifugal Cicatricial Alopecia:* Formerly known as follicular degeneration syndrome, central centrifugal cicatricial alopecia (CCCA) is a slowly progressive scarring alopecia that usually occurs in black women. CCCA usually presents with increased follicular spacing and circle-shaped, shiny flesh-colored, smooth scarring alopecia. In contrast to scalp DLE, CCCA usually involves the crown or vertex and expands centrifugally. The presence of burning sensation or pruritus in the area of hair loss can also help to distinguish CCCA from other types of scarring alopecia. A characteristic histologic feature of CCCA on scalp biopsy is premature desquamation of the inner root sheath (Borovicka et al. 2009).

*Radiation-Induced Alopecia:* Radiation-induced alopecia commonly occurs after therapeutic radiation for head and neck cancers or inadvertent overdose. Low radiation dose will lead to reversible alopecia. Higher doses can result in severe erythema weeks after the radiation exposure followed by poikilodermatous changes and irreversible scarring alopecia. In contrast to scalp DLE, radiation-induced alopecia often has regular and sharp borders. Radiation-induced alopecia is localized to the treatment zone and the shape and pattern of the alopecia is relevant to the radiation delivery window. Histopathologic features of radiation-induced alopecia include decreased number of follicular units with fibrosis or hyalinization of adjacent collagen.

*Squamous Cell Carcinoma:* DLE lesions and particularly long-standing hyperkeratotic lesions and scars of chronic DLE are thought to be a predisposing factor for squamous cell carcinoma, with a high rate of local recurrence and metastasis. Close observation of every alopecic area is mandatory to determine ulcerated or hyperkeratotic lesions, all of which should be biopsied (Ross et al. 2005).

*Tinea Capitis:* Tinea capitis, a *Trichophyton tonsurans* infection of the scalp, is usually associated with signs of inflammation including erythema and scaling. Cervical adenopathy can be present. Positive fungal culture and examination of plucked hairs with KOH are diagnostic for tinea capitis.

#### Therapy and Prognosis

DLE scarring alopecia is usually irreversible and the inflammation affects the upper portion of the hair follicle including critical elements within the mid-follicle required for follicular reconstruction, as opposed to non-scarring alopecias such as alopecia areata that affect the lower portion of the hair follicle and wherein the follicle has the potential to regrow hair (Tan et al. 2004). DLE scarring alopecia can lead to considerable societal costs and reduced quality of life. A recent study by Ferraz et al. showed that lupus patients with alopecia had lower quality of life (Ferraz et al. 2006). In contrast, diffuse non-scarring alopecia in lupus is usually responsive to treatment of the lupus; however, it can be occasionally persistent, particularly in individuals with persistent active systemic disease (Moghadam-Kia and Franks 2013).

### Dermatomyositis

Dermatomyositis (DM) is a systemic autoimmune connective tissue disease that is classified as an idiopathic inflammatory myopathy (Dalakas & Hohlfield 2003). DM most frequently occurs between the age of 40 and 50, but it can affect any age group. There is a female

predominance (female: male, 2:1) (Tymms and Webb 1985). DM is associated with hallmark skin findings including distinctive rashes (Gottron's sign and heliotrope rash) and poikiloderma (hypo- and hyperpigmentation, telangiectasis, and epidermal atrophy). Involvement of scalp, manifested as diffuse, confluent, atrophic, violaceous, scaly plaques, can be commonly seen in DM and can be the presenting manifestation of DM; however, alopecia is only occasionally seen. In a case series of 17 patients with DM, scalp involvement was noted in 14, with alopecia present in 6 of the 14 patients (Kasteler and Callen 1994). Adult-onset classic DM and clinically amyopathic DM can be associated with scaly scalp and non-scarring diffuse alopecia that often follows a flare of the systemic disease (Euwer and Sontheimer 1996; Callen and Wortmann 2006; Callen 2000; Santmyire-Rosenberger and Dugan 2003). This diffuse violaceous scaly alopecia is one of the characteristic cutaneous features of DM, despite not being pathognomonic (Euwer and Sontheimer 1996; Callen and Wortmann 2006). Non-scarring alopecia has also been reported in juvenile-onset DM. Also, DM may rarely cause cicatricial alopecia. DM may overlap with features of other connective tissue disease, particularly scleroderma and lupus (Dawkins et al. 1998). The clinical features that can help to distinguish DM from lupus include the violaceous color of the poikiloderma (in contrast to the red poikiloderma in lupus, similar to the violaceous hue in lichen planus) and localization of lesions around the eyes and on the extensor surfaces and severe pruritus in DM. Also, the scale in DM skin lesions is usually less prominent than in lupus. The histopathologic features include epidermal atrophy, basement membrane degeneration, vacuolar changes in the basal keratinocyte layer, and a sparse perivascular lymphoid infiltrate; the changes may be difficult to distinguish from those seen in lupus on light microscopy. Like in lupus, the dermis is often pale due to the accumulation of mucin and edema. Immunofluorescence microscopy reveals an interface dermatitis (deposition of complements and immunoglobulin

at the dermal-epidermal junction) (in DM, immunoglobulin deposition as opposed to complement is less common than in lupus) (Dourmishev and Wollina 2006). Muscle biopsy can be also performed. A combination of type 2 muscle fiber atrophy and lymphocytic infiltrate in both a perifascicular and a perivascular distribution is classic.

### Scleroderma

Scleroderma is a systemic autoimmune connective tissue disease. It is more common in women and the peak age of onset is between 30 and 50 years. The disease involves the autoantibodies to characteristic cellular antigens and characteristic sclerotic changes of skin. Scleroderma is different from other autoimmune diseases involving skin (lupus, dermatomyositis) because epithelial injury does not occur (Gilliam 2008). The sclerotic changes can affect the connective tissue on any organ. When the disease is associated with internal organ involvement, it is named systemic sclerosis (SSc). There are two major subsets of SSc based on the degree of cutaneous involvement: limited cutaneous SSc and diffuse cutaneous SSc. SSc is characterized by typical cutaneous changes, including variable extent and severity of skin thickening, shiny and wrinkleless skin, diffuse hyperpigmentation, and depigmentation with sparing of perifollicular skin, leading to a salt-and-pepper appearance and flat telangiectasis. SSc usually affects the fingers, hands, and face. Autoantibodies including antinuclear antibodies (ANA) with a discrete speckled or nucleolar pattern, anti-Scl-70, and anti-RNP antibodies assist in the diagnosis (Gilliam 2008; Chung et al. 2006). Cyclophosphamide, the prototypic alkylating and immunosuppressant agent that has been used to treat systemic scleroderma, is associated with alopecia (3 %).

Localized form of scleroderma, also known as morphea, is a self-limited inflammatory disorder. Morphea is a relatively uncommon disorder that may occur at any age, but most frequently affects young adults and children. There is a female to male predominance of about 3:1, and the

condition is uncommon in blacks. Like SSc, morphea is also characterized by spontaneous sclerosis of the skin but lacks internal organ involvement, Raynaud's phenomenon, and sclerodactyly. It involves transition from an early inflammatory stage to sclerosis and subsequent atrophy after 2–3 years. It usually presents with shiny, oval, 10 cm or greater in diameter, firm, indurated plaques with surrounding erythema. The surrounding red or violaceous rim may fade and transition into hypo- or hyperpigmentation with time. Hair follicles and sweat glands are absent in well-developed lesions. The lesions usually affect the trunk and extremities. The most common forms of morphea are plaque, generalized, and linear variants. A form of linear morphea that affects the face or scalp, usually the midline or paramedian forehead, is known as en coup de sabre because the lesion is reminiscent of a cut of a sword. It usually presents as a unilateral, shiny, hypo- or hyperpigmented, atrophic, linear plaque. It can present with more than one lesion, typically following Blaschko's lines, extend onto the scalp, and cause permanent cicatricial alopecia secondary to loss of hair follicles. The diagnosis is usually made clinically but can be confirmed with a skin biopsy. Biopsies at early stages reveal an intense inflammatory infiltrate at the margin, and biopsies at later stages reveal waning inflammatory infiltrate with infiltration of lymphocytes and plasma cells at the border and central fibrosis in the lower two-thirds of the dermis and upper subcutaneous tissue and eventually disappearance of pilosebaceous units and eccrine sweat glands and effacement of the rete ridges, similar to the changes seen in SSc. Ultrasound can be used to assess skin thickness which correlates with disease severity. Table 1 summarizes the comparative features of alopecia in lupus, dermatomyositis, and scleroderma.

### Fibromyalgia

Fibromyalgia is thought to be a functional somatic syndrome caused by alterations in central nervous system's pain processing. It is characterized by chronic generalized musculoskeletal pain, fatigue, and multiple tender points at

**Alopecia in Systemic Autoimmune Disease, Table 4** Alopecia due to medications used to treat systemic autoimmune disease and fibromyalgia<sup>a</sup>

Associated medications
Citalopram
Cyclophosphamide
Danazol
Fluoxetine
Fluvoxamine
Gold
IFN alpha
IVIG
Leflunomide
Methotrexate
Mycophenolate mofetil
Phenytoin
Tacrolimus
Venlafaxine

<sup>a</sup>Many drugs that are currently used to treat systemic autoimmune disease have been reported to cause alopecia. The medication-induced hair loss is usually diffuse and non-scarring. The hair loss is usually limited to the scalp. Women are more commonly affected than men

specific soft tissue locations. There is typically no evidence of joint or muscle inflammation on physical examination or laboratory testing. Fibromyalgia is currently considered to be the most common cause of widespread musculoskeletal pain in women between 20 and 55 years of age. The prevalence is approximately 2 % and increases with age. Fibromyalgia may coexist with other inflammatory rheumatic diseases, such as SLE which can cause non-scarring or scarring alopecia. The medications that are used in the treatment of fibromyalgia can also cause alopecia. Tricyclic antidepressants including amitriptyline and desipramine can be associated with alopecia. Serotonin reuptake inhibitors, particularly fluoxetine and citalopram, can rarely (<1 %) cause alopecia (Table 4).

### Cross-References

- ▶ [Alopecia Areata](#)
- ▶ [Hair Loss in Lupus Erythematosus](#)

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## Animal Models in Rheumatoid Arthritis

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### Synonyms

Inflammatory arthritis animal model

### Definition

Rheumatoid arthritis is the most common form of inflammatory joint disease and is characterized by synovial hyperplasia, immune cell infiltration, pannus formation, cartilage destruction, and bone erosion. A variety of animal models of arthritis have been established, including those that involve the injection of TNF-alpha, proteoglycan, adjuvant, antibody, or collagen. These animal models demonstrate synovitis, pannus formation, bone and cartilage destruction, as well as other features observed in human rheumatoid arthritis. They provide a useful platform to investigate the pathogenesis and determine the effects of novel therapies for rheumatoid arthritis.

### Rheumatoid Arthritis

Rheumatoid arthritis is the most common form of inflammatory arthritis and is characterized by synovial hyperplasia, immune cell infiltration, pannus formation, cartilage destruction, and bone erosion (Feldmann and Maini 2003). In the inflamed synovial membrane, highly prevalent cells include T cells and macrophages, while fibroblasts, plasma cells, endothelium cells, and

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ISBN 978-0-387-84827-3                      ISBN 978-0-387-84828-0 (eBook)  
ISBN 978-0-387-84829-7 (Print and electronic bundle)  
DOI 10.1007/978-0-387-84828-0  
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2014944130

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