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Chapter 7

Alopecia Areata

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Additional information is available at the end of the chapter

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Abstract

Alopecia areata is an organ-specific autoimmune disease targeting hair follicles. It causes nonscarring hair loss. The prevalence rate of the disease is approximately 1 in 1000 people worldwide. The condition is most commonly seen as circular areas of hair loss, but it may sometimes be as extensive as to involve the whole scalp or whole body. The complex pathophysiology of alopecia areata involves an autoimmune basis. Association of alopecia areata with other autoimmune diseases, such as thyroiditis and vitiligo, and the good response of patients to immunosuppressive treatment support an autoimmune etiology. Although some poor prognostic signs are defined, the course of the disease is unpredictable and the response to treatment can be variable. To date, there are neither preventive nor curative measures to deal with the condition. First-line therapy for patchy disease is topical and intralesional steroids, whereas extensive disease is conventionally managed with immunotherapy. New treatment agents, such as excimer laser, low-dose recombinant interleukin 2, Janus kinase inhibitors, and simvastatin/ezetimibe, are promising.

Keywords: alopecia areata, pathogenesis, autoimmunity, squaric acid dibutylester (SADBE), diphenylcyclopropenone (DPCP)

1. Introduction

Alopecia areata is an organ-specific autoimmune disease targeting hair follicles. It causes nonscarring hair loss. The condition is most commonly seen as circular areas of hair loss, but may sometimes be as extensive as to involve the whole scalp or whole body [1]. Although some poor prognostic signs are defined, the course of the disease is unpredictable and the response to treatment can be variable [2]. To date, there are neither preventive nor curative measures to deal with the condition [3].

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2. Epidemiology

Alopecia areata is the most prevalent autoimmune disorder and the second most frequent disease causing hair loss after androgenetic alopecia [3]. The prevalence rate of the disease is approximately 1 in 1000 people worldwide; in the United States, the lifetime risk is estimated to be 1.7% [2, 4]. Alopecia areata is mainly a disease of young adults; as many as 60% of patients are under the age of 20 at first presentation. Pediatric cases constitute approximately 20% of alopecia areata patients [2]. However, patients of any age can be affected. There is no gender predilection [4]. Reported cases in elderly were of milder severity and had a better treatment response [5].

3. Pathogenesis

Alopecia areata is an organ-specific T cell mediated autoimmune disease targeting hair follicles. Peribulbar lymphocytic infiltration impairing the normal hair cycle is considered to be the main pathophysiologic mechanism responsible for the disease process. Normal hair cycle is disrupted in alopecia areata; dystrophic changes of anagen follicles along with rapid progression of hair follicles from anagen to catagen and telogen phases are observed. In alopecia areata, perifollicular inflammatory infiltrate spares the bulge region of the follicle where follicular epithelial stem cells reside. Thus, in contrast to cicatricial alopecias, the inflammation does not interfere with the hair follicle integrity [6].

The complex pathophysiology of alopecia areata involves an autoimmune basis. Association of alopecia areata with other autoimmune diseases such as thyroiditis and vitiligo is reported. Presence of lymphocytes around hair follicles and the good response of patients to immunosuppressive treatment also support autoimmune etiology [2].

Etiopathogenetic theories are based upon the loss of immune-privileged status of hair follicles leading to an immune response against follicular antigens. In fact, normal proximal epithelium of anagen hair follicles have a very low expression of MHC class I antigens and no MHC class II antigen expression, along with a potent expression of immunosuppressive cytokines, such as TGF-β1 and α-melanocyte–stimulating hormone (α-MSH) [6]. According to the recent evidence, mechanism leading to hair loss involves the following steps: firstly, hair follicles must enter an anagen phase without the immune privilege described above, making those vulnerable to immune reactions. Subsequently, perifollicular CD8+ T cell infiltration of the anagen hair bulb epithelium ensues, along with a significant increase in interferon-gamma (IFN-γ) and various other cytokines. This milieu further damages the immune-privileged status of hair follicles, autoreactive CD8+ T lymphocytes, and IFN-γ and causes hair follicle dystrophy and premature catagen induction, leading to clinical hair loss [7]. Patients with alopecia areata have also been found to have an increased frequency of hair follicle-specific autoantibodies [2].

Genetic basis is implicated in disease pathogenesis. Many patients report a family history of alopecia areata with a frequency ranging from 10% to 42% of cases [8]. Studies show a higher

concordance rate among monozygotic twins compared to dizygotic twins also supporting the role of genetics [9]. HLA-DRB1*1104 and DQB1*03 loci that have a role in regulating immunity is associated with susceptibility to alopecia areata [2].

Genome-wide association studies can recognize specific individual genes, which may represent an increased susceptibility to alopecia areata. Petukhova et al. surveyed the entire genome and identified 139 single nucleotide polymorphisms associated with alopecia areata. The study showed that genomic regions containing the CTLA4, IL2/IL21, IL-2RA and Eos genes regulating proliferation of inflammatory cells to be susceptibility loci for alopecia areata. Ligands for the NKG2D receptor were also found to be implicated in disease pathogenesis [10]. Mouse models for alopecia areata gave valuable information regarding the role of CD8+ NKG2D+ T lymphocytes in pathogenesis. Transfer of these cytotoxic cells from mice with alopecia areata induced alopecia areata in healthy mice; on the other hand, NKG2D+ T cell-depleted lymph node cells transferred from the diseased mice to the healthy mice did not cause any disease. Interferon produced by NKG2D+ T cell is thought to contribute to the loss of immune-privileged status of hair follicles [11].

4. Clinical features

Alopecia areata patches are mostly asymptomatic and are discovered incidentally. Rarely, patients may complain of burning or itching sensation preceding hair loss. Typically, hair loss presents as one or more well-demarcated round to oval skin-colored patches [1]. The affected skin has a normal appearance with visible follicular orifices. Rarely, a soft edematous infiltration can be felt upon palpation and a peachy or reddened coloration can be observed [12]. Any hair-bearing site may be affected [1]. The scalp is the most common site of involvement, with or without the involvement of other body sites, such as the eyebrows, eyelashes, and beard [3].

According to the extent of involvement, alopecia areata can be classified into alopecia circumscripta presenting with limited hair loss, alopecia totalis involving the entire scalp, and alopecia universalis involving whole body (**Figures 1** and **2**).

A clinical classification regarding the pattern of hair loss is also frequently used. Patchy alopecia is the most common type seen in up to 75% of patients. Reticular type has a net-like pattern with multiple active and regressing patches (**Figure 3**). A band-like pattern involving occipital scalp is called ophiasis type of alopecia areata. The very rare ophiasis inversus, also called sisaipho type, presents with hair loss in the central scalp, resembling androgenetic alopecia [12]. Another unusual variant, perinevoid alopecia, is reported as presenting with alopecia patches around the nevi [13]. Diffuse alopecia areata presents with widespread thinning of the scalp hair. A recently defined variant, acute diffuse and total alopecia is characterized with rapid progression, female preponderance, and a favorable prognosis [14].

Initially, white hairs may be spared in patients with graying hair. As disease progresses, the white hair will also be lost. Initial hair regrowth, spontaneous or therapy-induced may be depigmented or hypopigmented, but the color usually returns with time [2].

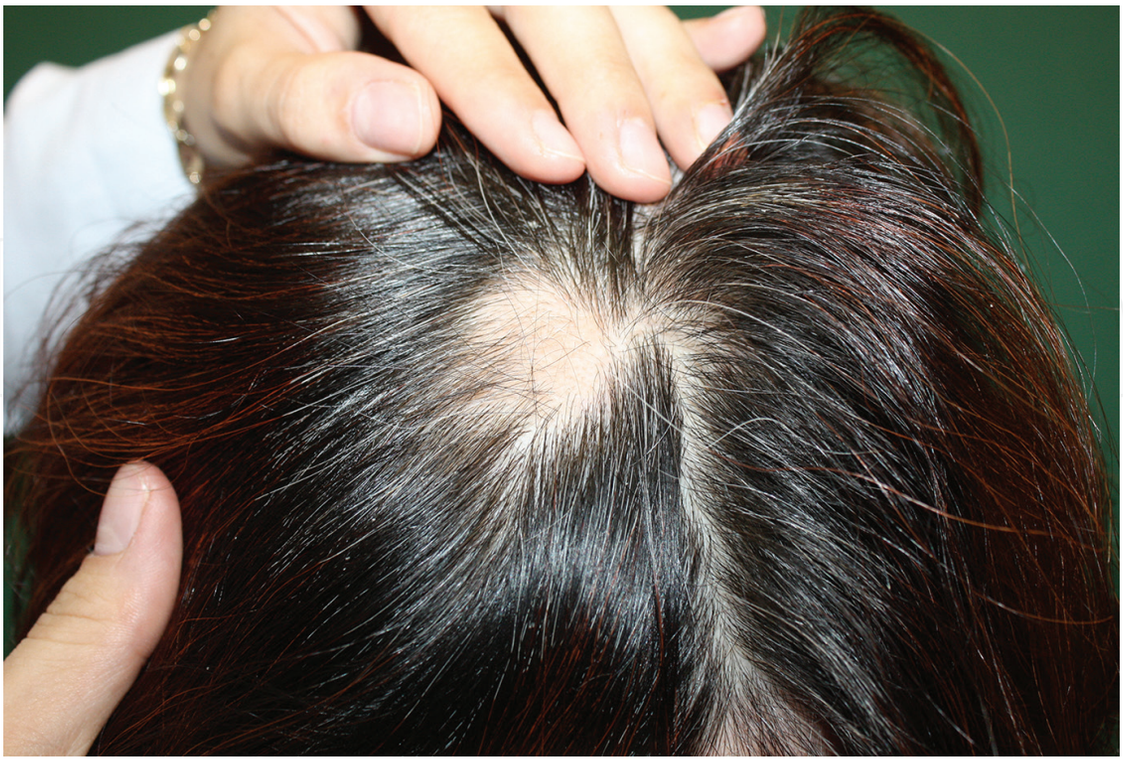


Figure 1. Circular area of nonscarring alopecia incidentally found in an adult patient.

Nail changes are observed in up to 7–66% of patients [15]. The nail matrix may be affected, resulting in pitting of the nail plate, which is the most common nail involvement in alopecia areata [6]. Other nail features found in alopecia areata are trachyonychia, Beau's line, onychorrhexis, onychomadesis, koilonychias, punctuate or transverse leukonychia, and red-spotted lunula [16]. Nail disease may precede, follow, or coexist with active hair loss [2].

5. Associated diseases

Alopecia areata is associated with many diseases, including other autoimmune diseases, atopy, ophthalmologic findings and psychiatric comorbidities.

Among autoimmune disorders, the two main associations are with thyroid disease and vitiligo [17]. Incidence of thyroid disease varies from 8% to 28% in patients with alopecia areata, compared with only 2% of the normal population. Among thyroid disorders, hypothyroidism is the most frequent association. [18] Prevalence of antithyroid antibodies is shown to be increased, but thyroid antibodies do not have any clinical correlation with disease severity [19]. Alopecia areata has also been shown to have a significant association with vitiligo; patients have a fourfold greater incidence of vitiligo compared with normal population. There are also reported associations of alopecia areata with pernicious anemia, lupus erythematosus, myasthenia gravis, rheumatoid arthritis, polymyalgia rheumatica, ulcerative colitis, and lichen planus [8]. A very strong disease association with the autosomal recessive disease autoimmune polyglandular syndrome type 1 (APS-1, chronic hypoparathyroidism-mucocutane-

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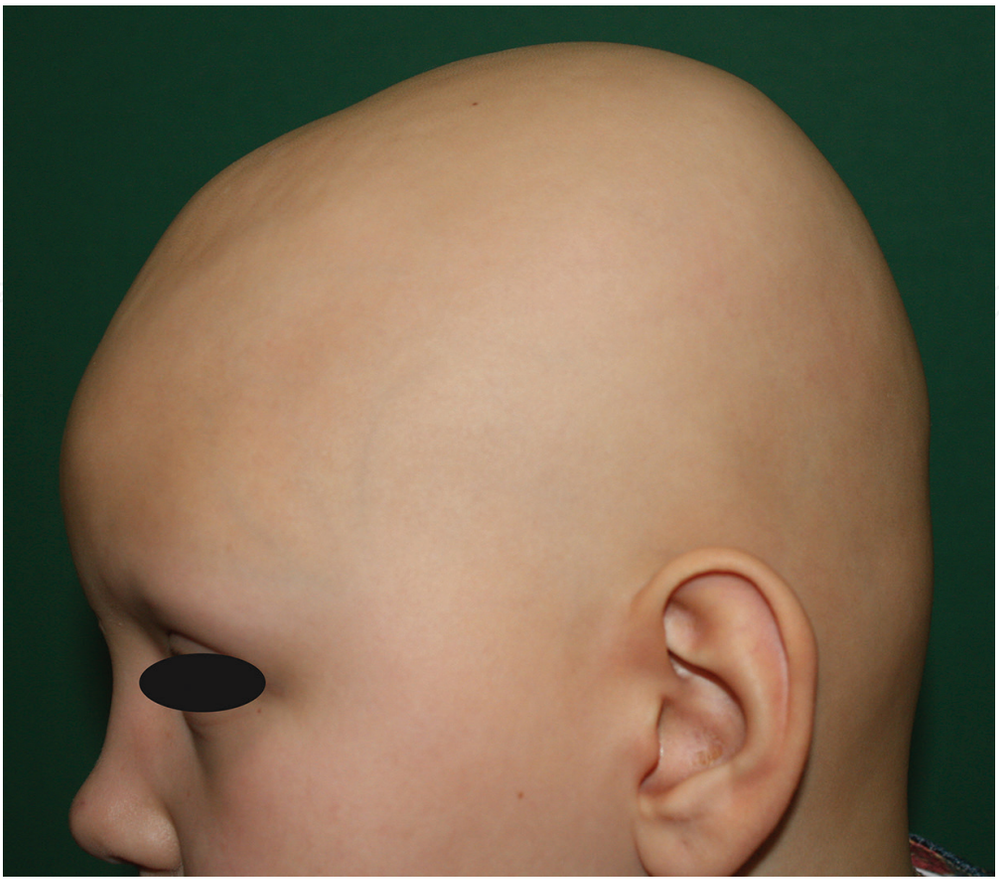


Figure 2. A patient with alopecia universalis having total loss of scalp hair and eyebrows.

ous candidiasis-autoimmune adrenal insufficiency) was recently reported [20]. Patients with Down's syndrome or Turner's syndrome also have increased risk of alopecia areata [17].

Atopic disorders, namely allergic rhinitis, asthma, and atopic dermatitis have been linked to alopecia areata. They have been found to occur in more than 40% of patients with alopecia areata, whereas their prevalence in the general population is estimated to be around 20% [17].

Interestingly, there is a decreased incidence of type 1 diabetes in alopecia areata patients and an increased incidence in their relatives. It was proposed that alopecia areata may have a protective effect against type 1 diabetes in predisposed individuals [21].

Ocular alterations, such as asymptomatic punctate lens opacities, and fundus changes can occur in up to 50% of patients with alopecia areata [22].

There may be a high psychiatric morbidity in alopecia areata patients. Depression, increased level of anxiety, generalized anxiety disorder, social phobia, posttraumatic stress disorder, and suicidal thoughts are among the reported psychiatric disturbances [23].

Incidence of nuchal nevus flammeus was reported to be increased in alopecia areata patients, especially in those showing a more severe course of the disease [24].



Figure 3. Reticular type alopecia areata with a net-like pattern.

6. Prognosis

The disease has an unpredictable course; spontaneous regrowth of hair is common as observed in about 80% of patients within one year [25]. However, patients usually present with several episodes of hair loss and hair regrowth during their lifetime [8]. Progression to alopecia totalis and universalis may occur in 5–10% of patients [3].

Extent of involvement (alopecia totalis/universalis)
Younger age of onset
Family history
Atopy
Ophiasis
Nail changes
Associated autoimmune disease

Table 1. Poor prognostic factors.

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Some clinical factors that indicate a poor prognosis is defined (**Table 1**). The most important factor is the extent of the disease [1]. The chance of full recovery is less than 10% in alopecia totalis and universalis [12]. Acute diffuse and total alopecia variant constitutes an exception. As discussed earlier in this chapter, these patients have a favorable treatment response despite the substantial hair loss [15]. Other factors reported are young age at disease onset, a positive family history, atopy, ophiasis pattern of loss, nail changes, and associated autoimmune diseases [8, 15]. Positive family history is associated with the early age of onset. In fact, positive family history among first-degree relatives has been reported to be as high as 47% for patients with early onset, in contrast to 1.6% for all patients [6].

7. Diagnosis

Diagnosis of alopecia areata is made on clinical grounds. No routine laboratory investigations are needed. Routine thyroid screening is not indicated but screening may be performed in long-standing cases, females, patients with persistent patches, and patients with alopecia totalis and universalis [8].

Upon examination, exclamation mark hairs may be observed within or at the periphery of the lesions that are short hairs tapered towards their base [1]. Exclamation mark hairs occur only in acute forms of alopecia areata and are not seen in patients with long-standing areas of hair loss [15]. Pull test can be performed to assess disease activity; six hairs or more shed from the periphery of the lesion positively correlates with the disease activity [16].

Severity of the disease can be measured by SALT score, developed by the National Alopecia Areata Foundation working committee. The scalp is divided into 4 parts, the top constituting 40% of total surface, the posterior 24%, right side and left side of scalp 18% each. Percentage of hair loss in each area is determined and is multiplied by the percentage of scalp covered in that area of the scalp, and summing the products of each area will give the SALT score [26].

Several studies have shown that dermoscopy may be a useful tool to help in the diagnosis of alopecia areata. Dermatoscopic findings reported in the literature include: yellow dots, black dots, short vellus hairs, black dots, tapering hairs, and broken hairs [27].

In ambiguous cases, a scalp biopsy is required. Histopathological examination of 4 mm punch biopsy containing subcutaneous fat is necessary to establish correct diagnosis. Biopsy should be taken from the periphery of the lesion as this is the site where the disease activity is found [28]. Horizontal sections will give a better representation of the histopathology especially in bulb infiltration than vertical sections [29].

8. Histopathology

Histopathology depends on the stage of the disease [30]. In the acute stage, there is a dense inflammatory infiltrate surrounding the terminal anagen hair bulb situated in the deep subcu-

taneous tissue. Inflammatory infiltrate consists primarily of T lymphocytes and Langerhans cells, with occasional eosinophils, mast cells, and plasma cells [31, 32]. An early and typical feature is the presence of eosinophils in stellae and within hair bulbs [29]. Anagen hairs cycle through catagen then into telogen. A dense lymphocytic inflammation can cause breaking of the hair shaft with a trichorrhexis nodosa-like fracture. This is the exclamation point hair, which is in telogen phase and therefore shed [31, 32]. The horizontal section demonstrates a significant decrease in the anagen:telogen ratio. There is also a decrease in the number of terminal hairs with a slight increase in the number of vellus hairs [31].

In the subacute stage, the number of catagen hairs is markedly increased [30]. The number of telogen hairs also increases after a few weeks. The amount of terminal hairs decreases and the vellus hair increases [31, 32].

In the chronic stage, either no or a mild chronic peribulbar lymphocytic inflammation around the miniaturized hairs situated in the papillary dermis is observed [30, 31]. The terminal:vellus hair ratio decreases to 1.3:1 rather than 7:1, which is found in the normal population. Fibrosis is an uncommon finding. However, in approximately 10% of the patients with a long history of alopecia areata, fibrosis of the upper follicle can be detected [31].

Of note, diagnosis of alopecia areata does not depend on the presence of an inflammatory infiltrate. Histopathological examination reveals increased numbers of telogen hairs in the acute and chronic stages, increased miniaturized hairs in chronic stage, and markedly increased catagen hairs in the subacute stage, helping in the diagnosis of alopecia areata [30].

9. Differential diagnosis

Many other diseases may cause hair loss in a patchy or diffuse pattern [33, 34] (**Table 2**).

In children, tinea capitis, which is the most common dermatophyte infection seen in childhood and trichotillomania should be considered in differential diagnosis of alopecia areata. Clinically, patches of tinea capitis show scaling and signs of inflammation sometimes accompanied by cervical lymphadenopathy. Direct microscopic examination with potassium hydroxide, fungal culture, and trichoscopy can also help in the diagnosis [35]. In trichotillomania, diagnosis is straightforward when the patient or relatives accept the compulsive act of pulling. In dermatological examination, there are irregularly shaped patches and broken hairs of variable lengths. Residual hairs in patches of trichotillomania are anagen hairs firmly attached to the scalp; they are of normal texture and color, whereas residual hairs in alopecia areata are usually the exclamation mark hairs with their specific morphology, which are easily detached from the scalp. [33, 36] Rarely, alopecia areata and trichotillomania can coexist [37]. Histopathologically, there is an increase in catagen hairs, follicular hemorrhage, pigment casts, and trichomalacia, without the typical inflammatory infiltrate and miniaturization of hair follicles observed in alopecia areata [31, 36].

In adults, the differential diagnosis is usually between androgenetic alopecia and telogen effluvium. Patients with androgenetic alopecia usually demonstrate gradual loss of hair with

Tinea capitis
Trichotillomania
Androgenetic alopecia
Telogen effluvium
Cicatricial alopecia
Secondary syphilis
Loose anagen syndrome
Congenital triangular alopecia
Lupus erythematosus
Pressure alopecia
Traction alopecia

Table 2. Differential diagnosis of alopecia areata.

the typical distribution pattern. The pull test is usually negative in androgenetic alopecia [8]. In some cases, a scalp biopsy may be required to establish correct diagnosis. Many miniaturized hairs are found in both androgenetic alopecia and alopecia areata, but higher telogen hair counts and a decreased anagen to telogen ratio favors diagnosis of alopecia areata. Although a perifollicular lymphohistiocytic infiltrate may be observed in androgenetic alopecia, it is usually confined to the upper follicle [31]. Telogen effluvium may be difficult to differentiate from diffuse alopecia areata. In alopecia areata, hair pull test show either telogen or dystrophic anagen hairs, while they are purely telogen in telogen effluvium [2]. Upon histopathologic examination of horizontal sections of scalp biopsies, chronic telogen effluvium shows follicular counts that are similar to that of normal controls [31].

Cicatricial alopecia is characterized by patchy hair loss with loss of follicular orifices. Erythema, scaling, and pustulation may be observed in contrast to smooth, normal skin of alopecia areata patches [15]. Other forms of alopecia, such as syphilis, loose anagen syndrome, congenital triangular alopecia, and early lupus erythematosus, should also be considered [31]. Congenital triangular alopecia is a developmental abnormality of hair follicles that usually presents after 2 years of age as a triangular or round patch of hair loss near the frontotemporal hair line. Histopathological examination reveals vellus hairs [34]. Side pins used to keep the hair in place, may cause pressure alopecia, which presents with a patch of hair loss mimicking patches of alopecia areata [38]. Traction alopecia must be differentiated from alopecia areata, especially of ophiasis pattern [39].

10. Management

Currently, there is no curative or preventive treatment for alopecia areata. The main goal of therapy is to suppress the disease activity [16].

10.1. Intralesional corticosteroids

Intralesional corticosteroids have been used in treatment of alopecia areata, since 1958 [38]. Intralesional corticosteroids are considered as the first-line agents in limited alopecia areata. Injections are made every 4–6 weeks into the deep dermis using a 0.5-inch long 30-gauge needle. For lesions of the scalp, 0.1 mL of triamcinolone acetonide at concentration of 5 mg/mL is injected at 1-cm intervals. Intralesional corticosteroid application is also effective for beard and eyebrow alopecia areata at a concentration of 2.5 mg/mL. Maximum dose of triamcinolone acetonide should be limited to 3 mL for scalp, 0.5 mL for each eyebrow and 1 mL for beard [40]. Hair regrowth is usually observed within 4 weeks and intralesional corticosteroids should be discontinued, if there is no improvement in 6 months [28]. In some patients, resistance to steroid therapy can be explained by a decreased expression of thioredoxin reductase 1, an enzyme that activates the glucocorticoid receptor in the outer root sheath [41]. The most common side effect observed is atrophy, which may be prevented by avoiding superficial injections, and reducing the concentration and volume of injections [42]. Other side effects include hypopigmentation, depigmentation, and telangiectasias [40].

10.2. Topical corticosteroids

Midpotent and potent topical corticosteroids in forms of lotions, creams, and ointments are widely used in spite of the fact that evidence of their effectiveness is limited [42, 43]. In a double-blind placebo-controlled study, rate of complete hair growth was not statistically significant with 12 weeks use of 0.25% desoximetasone cream, twice daily, when compared with placebo [44]. A half-head comparison trial performed with 0.05% clobetasol propionate foam and vehicle found at least 50% regrowth of hair after 12 weeks of clobetasol treatment. Blood levels of cortisol and ACTH were not affected during the trial [45]. A recent study showed that twice daily treatment with clobetasol propionate 0.05% cream used in 2 cycles of 6 weeks on, 6 weeks off regimen for a total of 24 weeks was more effective than hydrocortisone 1% cream used in the same regime. Compared with only 33.3% of the children in the hydrocortisone group, 85% of the children in the clobetasol group had at least 50% reduction in the surface area with hair loss at 24 weeks [46]. Folliculitis is a common side effect; skin atrophy and telangiectasia can rarely be observed [47].

10.3. Topical immunotherapy

Topical immunotherapy is the most effective treatment option for patients with chronic severe alopecia areata, with greater than 50% scalp involvement [48].

Topical immunotherapy consists of applying a contact allergen to induce a low-grade chronic dermatitis. The mechanism of action is still unclear. Antigenic competition, induction of lymphocyte apoptosis, and diversion of the T cell response from the hair follicle to the epidermis are among the various suggested theories [49–60].

Dinitrochlorobenzene was the first topical sensitizer to be used in the treatment of extensive alopecia areata; however, it was abandoned because of its mutagenic effects [42, 51]. Squaric acid dibutylester (SADBE) and diphenylcyclopropenone (DPCP) are the two compounds still in use today. Although SADBE is an ideal immunogen that is not found in the natural environment and

is not known to cross-react with other chemicals, DPCP is preferred because it is cheaper and is more stable in acetone for storage [42, 51]. DPCP is a very light sensitive compound and should be stored in amber bottles to protect it from exposure to ultraviolet and fluorescent lights [51].

Topical immunotherapy begins at first visit by the sensitization of the patient with 2% DPCP applied to a 5-cm circular area on the scalp. Two weeks later, a 0.001% DPCP solution is applied to the same half of the scalp. The concentration of DPCP is increased gradually each week to produce mild inflammation that manifests as pruritus and erythema lasting for 36–48 h. After establishing the appropriate concentration for the patient, subsequent therapy is continued once weekly with the same concentration [52]. DPCP should be left on the scalp for 48 h and the treated area must be protected from the sun during this time. Treatment of both sides is recommended only after achieving hair regrowth on the treated side. If there is no improvement in 6 months, DPCP is less likely to be successful; however, improvement in these "non-responder" patients with longer courses of DPCP therapy has been reported [42, 53]. If the patient does not develop an allergic reaction to 2% DPCP, SADBE can be tried [42]. The procedure with SADBE treatment is similar to DPCP.

The response rates of DPCP treatment in alopecia areata ranges from 5% to 85%. Patients with earlier onset of the disease or more extensive involvement were shown to be less likely to respond to diphenylcyclopropenone therapy [53].

Topical immunotherapy is generally well tolerated by most of the patients. The most commonly seen side effects are eczema, autoeczematization, blistering, and swelling of regional lymph nodes [54]. When a vesicular or bullous reaction develops, the patient should wash off the contact sensitizer and a topical corticosteroid should be applied to the affected area. Facial and scalp edema, contact urticaria, flu-like symptoms, erythema multiforme-like reactions, and pigmentary disturbances manifesting as hyperpigmentation, hypopigmentation, dyschromia in confetti, and vitiligo can also occur [42, 55, 56]. Patients may complain of burning sensation, after application of SADBE. Persistent allergic contact dermatitis of the primary site of sensitization, severe generalized dermatitis and systemic reactions characterized by fever, and arthalgias are among the rarely observed side effects [54].

10.4. Minoxidil

Topical minoxidil solution, approved by Food and Drug Administration and Health Canada for the treatment of androgenetic alopecia, can be used in alopecia areata. Evidence for the effectiveness of using 3% minoxidil, twice daily, was shown in a double-blind placebo controlled study [57]. A dose response effect exists, with the 5% solution being more effective than the 2% solution. However, few patients achieve cosmetically significant regrowth [58]. Minoxidil 5% solution, twice daily, is used in combination with topical or intralesional corticosteroids. Contact dermatitis and hypertrichosis are the most common side effects. Minoxidil foam, which does not contain propylene glycol, has less irritating effects than the solution [59].

10.5. Anthralin

Anthralin, 0.5–1%, short contact therapy is used as alternative treatment although evidence for its efficacy depends on case series without controls [47].

Anthralin 1% cream is applied daily for 15 or 20 min initially and then washed. The contact time is increased by 5 min weekly up to 1 h or to the time required to cause a low-grade dermatitis. Once the contact time sufficient to produce the mild dermatitis is found, subsequent therapy is continued daily for the established period of time. Anthralin should be applied at least 3 months before evaluating the response to treatment. Side effects include severe irritation, folliculitis, regional lymphadenopathy, and staining of skin, clothes and fair hair. Patients should avoid eye contact with this chemical, and the treated area should be protected from the sun [59].

10.6. Photochemotherapy

No controlled studies of oral or topical psoralen plus ultraviolet A (PUVA) therapy in alopecia areata have been reported [59]. The reports about the efficacy of PUVA therapy are conflicting. Several studies have shown low response rates of PUVA therapy [60, 61], while others have shown good response rates [62, 63]. PUVA therapy is thought to eradicate the mononuclear cell infiltrate, surrounding the hair follicle responsible for the disease [16]. Uncertainty about efficacy and concerns about PUVA-induced skin carcinogenesis make this therapy option a rarely chosen one [59].

10.7. Systemic glucocorticosteroids

Systemic corticosteroids have been used since 1952 in the treatment of alopecia areata; however, relapse rates are high upon dose reductions [64].

Long-term daily treatment with oral corticosteroids will produce favorable results in a part of the patients [33]. It was reported that 12–28% of patients with 1–99% scalp alopecia areata regrew 50% or more of their hair after a 6-week tapering course of prednisone therapy, starting at 40 mg daily. 2% minoxidil therapy may be useful for prolonging the response to the treatment after prednisone cessation [65]. However, oral corticosteroids are no longer used for chronic therapy of alopecia areata because of their side effects [33]. Side effects of oral steroids include avascular necrosis, weight gain, hypertension, diabetes, sleep alteration, mood changes, weakness, acneiform eruptions, irregular menses, and striae [52].

High-dose intravenous corticosteroid pulse therapy can be considered in patients with multifocal or ophiasis-type alopecia areata if treatment with topical sensitizers or highly potent topical corticosteroids during 6 months have failed. In more extensive involvement, such as alopecia totalis and universalis, treatment efficacy was shown to be diminished [64].

10.8. Immunosuppressive treatment

Immunosuppressive agents namely sulfasalazine, methotrexate, and cyclosporine can be used in the treatment of alopecia areata.

Sulfasalazine therapy can be an alternative treatment option in persistent alopecia areata cases. Studies have shown favorable treatment response, but a high relapse rate. The most common side effects include nausea, vomiting, headache, fever, and rash; less commonly hematologic abnormalities and hepatotoxicity can develop [66, 67].

Severe forms of alopecia areata resistant to conventional topical and/or systemic treatments may respond to methotrexate. In a retrospective study, weekly 15–25 mg methotrexate with or without 10–20 mg prednisolone daily was reported to be effective in 64% of cases [68].

Cyclosporine has been used alone or in conjunction with corticosteroids variable response rates [47]. Use of cyclosporine is limited because of side effects and high relapse rate. Side effects include nephrotoxicity, immune suppression, hypertension, and hypertrichosis of body hair [59].

10.9. Other therapies

10.9.1. Excimer laser

Mechanism of action of excimer laser in alopecia areata is thought to depend on induction of T cell apoptosis as proven in in vitro studies [69]. In a treatment of 18 patients with 42 alopecia areata patches with the 308 nm excimer laser, hair regrowth was observed in 41.5% of treated areas. Lesions on the extremities, patients with alopecia totalis, or alopecia universalis were resistant to the treatment [70].

10.9.2. Low-dose recombinant interleukin 2

Low-dose interleukin 2 (IL-2) is essential to proliferate Treg cells, which play a key role in alopecia areata [71]. A prospective study in 5 patients with extensive, treatment-resistant alopecia areata, 1.5 million IU/d subcutaneous interleukin 2 was administered during 5 days, followed by three 5-day courses of 3 million IU/d at weeks 3, 6, and 9. It was reported that 4 of the 5 patients attained considerable hair regrowth. Treatment adverse events were mild to moderate and included asthenia, arthralgia, urticaria, and injection site reactions [72].

10.9.3. Janus kinase inhibitors

Tofacitinib citrate is a small-molecule selective Janus kinase 1/3 (JAK 1/3) inhibitor that was approved by FDA, in late 2012, for the treatment of moderate-to-severe rheumatoid arthritis. A patient with longstanding alopecia universalis, treated with tofacitinib for psoriasis had hair regrowth, being the first documented case of alopecia areata responding to tofacitinib. After eight months of tofacitinib treatment (5 mg twice daily for 2 months followed by 10 mg in the morning and 5 mg at night thereafter), the patient had full regrowth of hair at all body sites [73]. There have been other case reports showing efficacy of tofacitinib treatment [74, 75]. Adverse effects of tofacitinib use include increased risk of severe infections including tuberculosis, anemia, neutropenia, headache, and mild nausea [74].

Another JAK inhibitor, ruxolitinib applied topically twice daily for 12 weeks in a patient with refractory alopecia universalis induced almost full eyebrow regrowth and approximately 10% regrowth of scalp hair [76].

10.9.4. Simvastatin/ezetimibe

Simvastatin 40 mg and ezetimibe 10 mg daily treatment for alopecia totalis and alopecia universalis was documented to have favorable responses in case reports [77]. In a prospective

uncontrolled study, simvastatin/ezetimibe 40 mg/10 mg daily for 24 weeks was shown to be an effective treatment option for alopecia areata [78].

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