Alopecia areata: emerging concepts

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ABSTRACT

Alopecia areata is a common, unpredictable, non-scarring form of hair loss. This disorder affects all age groups, with a higher prevalence in children and adolescents. Limited scalp involvement is the most common presentation but more severe forms of the disorder, involving the entire scalp or body, also exist. Research has linked alopecia areata with certain HLA-Class II alleles, implicating an autoimmune etiology. Various therapeutic modalities have been employed to gain clinically acceptable hair regrowth.

KEY WORDS

alopecia areata, review, etiology, treatment

Alopecia areata is a common disorder, hypothesized to be autoimmune in etiology, and estimated to affect almost 2% of the US population (1). This non-scarring alopecia affects both sexes equally and is seen in all age groups. A higher incidence is found in children and young adults, with common presentation before the age of five years (2-4). The unpredictable severity and course of the disorder exacts a high emotional cost from the affected patient and may result in psychiatric comorbidity (5).

Etiology

The etiology of alopecia areata is as of yet unclear, but is presumed to be due to an autoimmune reaction. Consistent evidence of autoantibodies directed against anagen stage hair follicle structures are found in both affected humans and in mouse models (6,7). Though autoantibodies are postulated to play an integral role in the disease process, current research implicates a cell-mediated autoimmune mechanism as the underlying pathogenic etiology (8). Supporting this theory is that activated CD4 and CD8 T lymphocytes have been found in a characteristic peri- and intrafollicular inflammatory infiltrate of anagen hair follicles of affected individuals (9-11). The transfer of alopecia areata by T lymphocytes cultivated from affected scalp and transferred to human scalp explants on a severe combined immunodeficiency mouse model has been demonstrated (12). Recent investigations on mouse models reported that transplanted alopecia areata tissue to normal mice would not induce alopecia areata if a specific monoclonal antibody, anti-CD44v10, was injected into the mice shortly after transplant surgery (8). CD44v10 is believed to be involved in the activation mechanism of CD4 and CD8 lymphocyte migration into tissue and the initiation of the subsequent defense response against antigenic stimuli (8). Similar research has demonstrated that in-

vivo depletion of CD4+ cells using CD4+ cell-depleting OX-35/OX-38 monoclonal antibody (MoAb) partially restores hair growth in rats affected with alopecia areata (11). Current investigative efforts strongly implicate CD4 and CD8 T-cell lymphocytes in the pathogenic autoimmune etiology of this disorder.

Alopecia areata, similar to many other autoimmune diseases, is linked with certain HLA-Class II alleles. The HLA antigen DQ3 (DQB1*03) has been identified as a general susceptibility marker for alopecia areata (13-15). Patients with the more severe forms of the disorder, alopecia totalis and alopecia universalis, were found to express the HLA alleles DQB1*0301, DRB1*0401 and DRB1*1104 in a significantly higher frequency (8). Milder, patchy forms of alopecia areata were also found to be associated with a significantly higher frequency of DRB1*1104, but no association was reported with the other two aforementioned alleles (8).

Clinical description

Alopecia areata usually appears abruptly as a patch of clearing on the scalp with no evidence of scarring. Scalp involvement is the most clinically distinguishing characteristic, but axillae, eyebrows and eyelashes may also be involved (16). Mild, limited involvement of the scalp is the most common presentation; multiple patches may become confluent over time. Regression may occur, with new hair growth taking place; recurrences in different locations occur unpredictably. Severe involvement may produce a loss of all scalp hair (alopecia totalis) or all hair on the body (alopecia universalis). Patients with alopecia areata that have a history of atopy may have a less favorable prognosis (17).

Clinical variants of alopecia areata exist (16). Ophiasis alopecia areata describes band-like hair loss affecting the temporal and occipital regions of the scalp. Reticular alopecia areata describes a type that clinically shows patches of hair loss in various stages of disease activity. Diffuse alopecia areata has been attributed to a short anagen phase and subsequent inability of hair to grow. Alopecia areata has also been linked with a number of autoimmune diseases (18).

Alopecia areata produces nail changes in 3-30% of affected patients (3,18-20). In one study of 201 affected children under 16 years nail changes were clinically evident in 60 (3). Of these 60 children, nail changes were more common in severely affected children (18 out of 34) than in children with localized disease (42 out of 167). In another study, 21 patients had clinical evidence of nail changes out of a total of 136 patients (103 adults, 33 children) affected with alopecia areata. Nail changes were found to be more common in children, especially in children with severe, long-standing disease (19). The nail changes associated with alopecia areata usually accompany hair loss, but may occasionally precede or follow the onset of hair loss by months or years (16). The main patterns of nail changes are: diffuse fine pitting (most common), thin and brittle fingernails and toenails, longitudinal ridging and rough surface trachyonychia (3,20-22).

Systemic associations

Atopy, vitiligo and autoimmune thyroid disease, namely Hashimoto's thyroiditis and Graves' disease, are more prevalent in patients with alopecia areata (23). Serum thyrotropin measurement has been recommended for all children with this disorder. (23) Although children are frequently screened for thyroid disease, the presence of disease in these patients is only 10% (3). A recent study on the evaluation of thyroid function in northern Indian patients with alopecia areata revealed that thyroid disease was clinically evident in only 16 (0.85%) of the 1700 affected patients evaluated over the interval of 1983-1997 (24). The incidence of thyroid structural and functional abnormalities is much higher in affected patients (78 percent) than in controls (33 percent) (21). One study of 45 affected children, 16 years of age and younger, reported thyroid function abnormalities in 24 percent of these children (25). Thyroid function abnormalities include abnormal thyroid hormone (T3,T4) and thyroid stimulating hormone (TSH) values and the presence of antithyroid and antimicrosomal antibodies (25). Celiac disease, systemic lupus erythematosus and diabetes mellitus may also possibly be increased in incidence in patients with alopecia areata (2,3,26-29).

Differential diagnosis

Mild forms of alopecia areata are seen as solitary areas of non-scarring hair loss on the scalp and should be distinguished from trichotillomania and tinea capitis. Other forms of non-scarring alopecia, including traumatic alopecia and congenital hair loss syndromes such as congenital triangular alopecia, must also be considered in the differential diagnosis (30-33). Alopecia neoplastica, a rare form of alopecia, is associated most commonly with breast cancer; it may resemble localized alopecia areata (34,35). Systemic lupus erythematosus, syphilis and post-febrile alopecia may also at times resemble alopecia areata (16).

Alopecia areata may be first evident in young patients as the sudden onset of diffuse alopecia (16,17). Telogen effluvium, believed to be associated with high

fever, severe emotional stress, sudden starvation and certain medications, must also be considered in the differential diagnosis of diffuse alopecia. Other conditions associated with diffuse alopecia include acrodermatitis enteropathica, arsenicism and thallium poisoning, though these conditions usually have systemic symptoms (16). Recent research has identified the human hairless gene, equivalent to a gene studied in mouse models (hairless IRS/3 mouse), and has confirmed its association with a disease called atrichia or atrichia with papules (8,36). This condition was previously named alopecia universalis congenita. These patients are born with hair, but the hair matrix cells progressively undergo apoptosis by the third month, culminating in permanent hair loss (8,36).

A skin biopsy specimen is diagnostic of alopecia areata, and is sometimes necessary to make a diagnosis (37,38). On histological examination a peribulbar lymphocytic infiltrate resembles a "swarm of bees." (39). Scarring is characteristically absent.

Treatment

Treatment of alopecia areata may be divided into four different categories of widely accepted therapeutic modalities (9,18,23,40-55): immune inhibitors such as steroids or psoralen and UV-A light (PUVA); topical sensitizers such as squaric acid dibutylester (SADBE) and diphenylcyclopropenone (DPCP); non-specific irritants (anthralin) and the vasodilator minoxidil. Treatment goals are hair regrowth that is cosmetically acceptable to the patient; hair loss is not prevented with these treatments (23,53,56).

Mild forms of alopecia areata are mostly treated by intralesional injection of a glucocorticoid, usually triamcinolone, every four to six weeks (16,23). Steroid injection may produce minimal transient atrophy or, less commonly, severe atrophy of the targeted skin; the most common side effect of steroid injection is pain, which is a complicating factor in treatment of children (53). Topical steroid application to areas of hair loss, usually applied twice daily, has also been found to be efficacious clinically, although combination treatment with minoxidil, anthralin or injected steroids is probably more therapeutic (23,53,57). Systemic steroids are reserved for use in rapidly progressive or extensive alopecia areata (53).

Anthralin, the only non-specific irritant widely used for hair growth in alopecia areata, is applied topically as a 0.5 or 1% cream to affected areas once per day for 20-45 minutes; overnight application can also be used in certain patients who can tolerate the side effects (23,53). Application of topical anthralin may cause pruritus, erythema, scaling and folliculitis, necessitating the short application time (53). The combination therapy of anthralin and minoxidil has also shown favorable results in a group of treatment-resistant patients (58,59).

Minoxidil (5% topical solution) is applied twice daily to areas of hair loss. Side effects are limited to mild local irritation and, less frequently, allergic contact dermatitis (60-62). Topical sensitizers induce an allergic contact dermatitis in applied areas of hair loss; weekly re-stimulation with the potent allergen is needed. Topical sensitizers have proven efficacy in patients with long-standing alopecia areata involving more than 50 percent of the scalp (23,57,63). Squaric acid dibutylester (SADBE) has shown good tolerability and mild side effects. In one study of 144 patients with varying degrees of alopecia areata, an 80% rate of regrowth was demonstrated in patients with mild alopecia areata and a 49% rate of regrowth was demonstrated in more severely affected patients (52). A study of squaric acid dibutylester in a pediatric population of twenty-eight children under the age of 13 with severe, long-standing, refractory alopecia areata reported nine patients achieving cosmetically acceptable or complete regrowth, and six patients achieving significant regrowth (64). Diphenylcyclopropenone (DPCP) is also an accepted modality for treatment of severe alopecia areata. One study demonstrated a 70% response rate in DPCP-treated patients with severe alopecia areata affecting more than 40% of the scalp (65). Of these patients, 30.9% demonstrated complete remission, while 39.7% underwent partial remission (65). Pruritus, dermatitis, urticaria, face and scalp edema and the development of vitiligo are known side effects of DPCP use (66).

Cyclosporine is a potent immunomudulatory agent whose mechanism involves inhibition of T4 lymphocyte activation (67). A known side effect of cyclosporine is hypertrichosis, which has been attributed to prolongation of the anagen phase of hair growth (68). In one study of 15 alopecia areata patients treated with systemic cyclosporine, seven patients obtained cosmetically acceptable hair regrowth (67). Teshima et al describe a 24 week regimen containing cyclosporine (2.5 mg/kg daily) and prednisolone (5mg/day) which produced a 100% response rate in six patients with persistence of hair regrowth six months after cyclosporine was discontinued (69,70). A similar study combining cyclosporine with prednisone reported two out of eight patients developing cosmetically acceptable hair regrowth (71). Gupta et al report cosmetically acceptable hair regrowth in three of six patients treated with 6 mg/kg cyclosporine daily for 12 weeks; hair loss occurred in all patients within 3 months of discontinuation of cyclosporine (72). Larger studies need to be performed to determine the efficacy of systemcic cyclosporine in the treatment of alopecia areata. The significant side-effect profile of

cyclosporine deters long-term treatment (73).

Cryotherapy has also been employed to stimulate hair growth in alopecia areata (49,50). One study, utilizing both children and adults, revealed hair regrowth in greater than 60% of affected areas in 70 of 72 patients (49).

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