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# Alopecia areata in patients with inflammatory bowel disease: an overview

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**Abstract:** Alopecia areata (AA) is one of the most common causes of non-scarring hair loss, which is associated with the premature induction of hair follicle regression. The pathogenesis of AA is unknown, although it is believed that a complicated autoimmune mechanism with Th1 lymphocytes and proinflammatory cytokines, such as IFN-γ, TNF-α, IL-1 and IL-2, may be involved.
AA may occur as a single disease entity or coexist with other autoimmunological disorders. In some cases the relationship with inflammatory bowel disease (IBD) was observed and the link between molecular pathways and main proinflammatory cytokines in IBD and AA has been suggested. AA is also described in literature as a side effect of biological therapy with the anti-TNF-α agents.
To address the association between AA and IBD, in this review we discuss the most relevant clinical studies and case reports found in MEDLINE, Pubmed and EMBASE.

**Key words:** alopecia areata, inflammatory bowel diseases, Crohn's disease, ulcerative colitis, biological therapy.

## Introduction

Skin lesions observed in patients with inflammatory bowel diseases (IBD) can be classified as extraintestinal manifestations of the disease (specific and non-specific), or drug induced lesions [1]. *Alopecia areata* (AA) is a non-scarring temporary or permanent alopecia that may refer to any hairy skin area of the body, usually the scalp. AA is one of the most common causes of hair loss and it affects from 0.15%

to 3.8% of patients attending dermatology clinics. Male and females are affected with equal frequency.

The main manifestation of AA is commonly a circumscribed totally bald, smooth patch, which may occur in patients at any age. Patches may be very discreet and noticed only by chance by a partner, hairdresser, friend, or by careful examination [2, 3]. Patches of alopecia have different sizes (mostly with a diameter of 5–10 cm) and shapes (usually round or oval) (FIGURE 1). In 1–2% of cases, the alopecia foci can spread to the entire scalp (*alopecia totalis*) or to the all hairy areas of the body (*alopecia universalis*) [4]. AA most often affects the scalp and beard, but may also occur on any hair-bearing areas of the body.

Exclamation point hairs, narrower along the length of the strand closer to the base, may be seen at the margin of the patches. These hairs are more frangible and the residues of the broken hairs form characteristic shaft located at the level of the skin.

The remission of the lesions is observed in the majority of patients, and a complete regression within one year is observed in 50% of cases [5]. Regrowth starts at the centre of the bald patch with hair initially devoid of pigment; with time comes repigmentation. In 44% of AA patients pitting of nail plates or trachyonychia may develop [6].

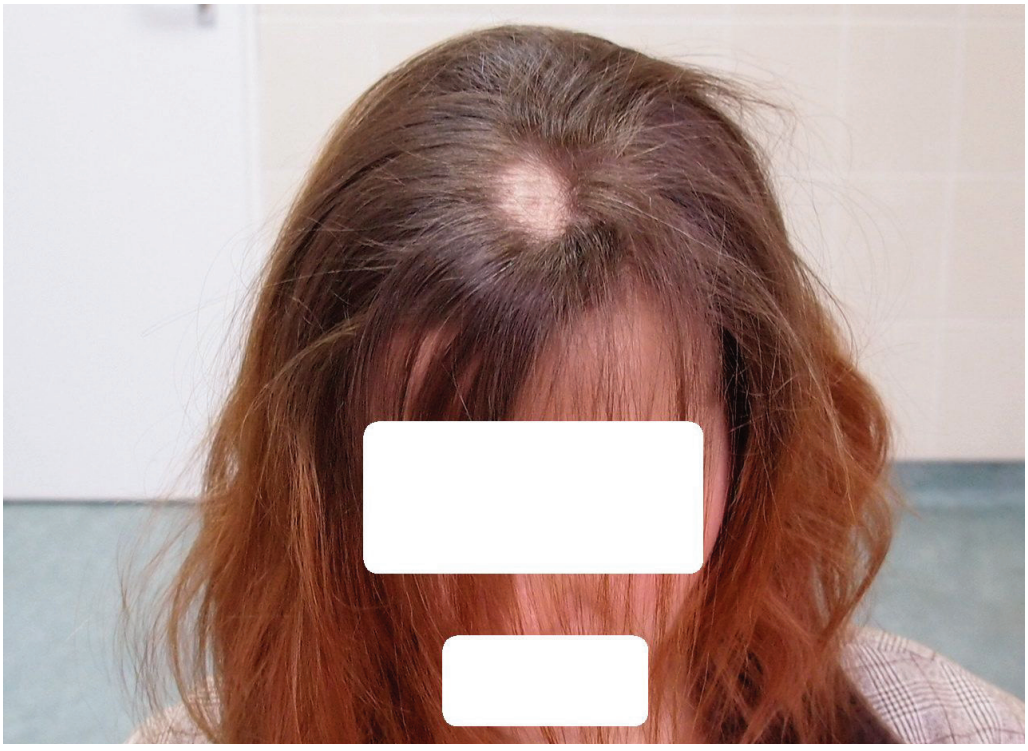

**Fig. 1.** Alopecia areata patch on the scalp of a patient with Crohn's disease during anti-TNF-α therapy.

AA is a disease with a very characteristic course, what facilitates the correct diagnosis based on clinical features. In AA patients, trichoscopy shows an increased percentage of hair in catagen and telogen phase, and the presence of characteristic, but not specific for AA, regularly distributed "yellow dots". A "yellow dot" is characterized by a large, yellow amorphous area and pinpoint white dot with a whitish halo. "Yellow dots" are caused by the presence of keratin deposits and sebaceous debris contained within the dilated ostium of anagen and miniaturized hair-containing follicles [2]. A skin biopsy of lesions is rarely needed in AA patients. The histopathological examination shows a characteristic peribulbar lymphocytic infiltrate, so-called "swarm of bees". Other findings helpful for diagnosis include the pigment incontinence in the hair bulb and follicular streamers, as well as the shift in the anagen-to-telogen ratio towards telogen [5].

## Alopecia areata as an autoimmune disease

AA is an autoimmune disease with no obvious signs of superficial skin inflammation. The pathogenesis of the hair loss in AA patients is not entirely identified and understood, although it is believed that both, T lymphocytes and proinflammatory cytokines are involved. An excessive activation of the immune system comes as a result of the interaction of various environmental and infectious factors, and genetic predisposition. Inflammatory infiltration with predominance of Th1 lymphocytes is observed around hair follicles, with simultaneous reduction of their serum levels [7]. Inflammatory cells are mainly allocated around the hair bulb. Of note, there is no inflammation around the stem cells of the hair, what allows the hair regrowth. High expression of IFN-γ, IL-1, IL-2, IL-12, IL-18 and TNF-α is observed in higher serum and tissue levels in AA patients than in healthy controls. IFN-γ, a representative Th1 cytokine, is prominently expressed in AA lesions, and as a main proinflammatory cytokine it may induce the collapse of hair follicle immune privilege by upregulation of the MHC I, MHC II and adhesion molecules (ICAM-1). Consequently, hair follicle autoantigens and ICAM-1 may be recognized and attacked by CD4+ and CD8+ autoreactive cytotoxic T cells. However, the precise autoantigen of the hair follicle, initiating an inflammatory process, is still unknown [3, 8].

Several studies indicate the role of melanocytes in the development of AA. It has been suggested that peptides associated with melanogenesis, expressed by melanin-producing hair follicles in anagen phase are the main autoantigens targeted by autoreactive cytotoxic CD4+ and CD8+ T lymphocytes. Confirmation of this theory may be sparing of white or gray hair in AA patients [9].

The incidence of a family history in AA ranges from 4% to 27%. The mode of AA inheritance has been suggested to be autosomal with a variable penetrance. DQB1*03 and DRB1*1104 have been reported as specific marker alleles of susceptibility to AA. Several human leukocyte antigens (HLA) studies have shown that the onset and progression of AA is associated with specific HLA class II alleles [10, 11].

AA may be associated with other autoimmune diseases, particularly with the Hashimoto's thyroiditis, Basedow's disease, vitiligo, scleroderma and IBD. Association between AA and IBD may be caused by the coexistence of a common molecular pathway, key cytokines, and/or genetic factors [12].

## Association of alopecia areata with inflammatory bowel diseases

Crohn's disease (CD) and ulcerative colitis (UC) belong to a group of IBD, and are characterized by a chronic, intestinal inflammation with periods of exacerbation and remission. The IBD symptomatology is non-specific and very diverse. General symptoms, such as fever, weakness, and weight loss are accompanied by symptoms associated with chronic inflammation of the intestinal mucosa, such as abdominal pain and chronic diarrhea. Extraintestinal manifestations (EIMs) are common in both UC and CD. EIMs may involve nearly any organ system, including the musculoskeletal, dermatologic, hepatopancreatobiliary, ocular, renal, and pulmonary systems, and significantly change the management of IBD patients [1, 13].

In the literature, an increased attention to the co-morbidity of IBD and AA was paid. The hair loss characteristic for AA is a relatively common manifestation observed in clinical practice in IBD patients. It has been suggested that AA observed in IBD patients may belong to EIMs, or may be caused by biologic therapy with anti-TNF-α agents [14–17].

In UC patients, the prevalence of AA is significantly higher than in general population. It has also been observed that the prevalence of UC was considerably greater in AA patients than the prevalence in the general population (1:47 vs. 1:125–1:2439) [18]. The association of AA with UC has been reported in several studies and a link between genetic predisposition, familial aggregation and HLA has been suggested. Based on a case study, Treem *et al.* reported the occurrence of AA and UC in a mother and son, suggesting an inherited predisposition to autoimmune phenomena [19]. This assumption was strengthened by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) positivity in both individuals.

The Th1 and Th2 pathways are considered responsible for co-occurrence of UC and AA. Activation of Th2 cells and secretion of IL-4, IL-5, IL-6, IL-10, IL-13, and TGF-β were found to play a significant role in the UC-associated intestinal inflammation, however the Th2 cytokine profile in AA may indicate a good course prognosis of skin lesions. Furthermore, increased TNF-α serum levels, which is a proinflammatory mediator that plays an integral role in the pathogenesis of AA, have been demonstrated in UC patients.

On the other hand, a growing body of evidence suggests that UC patients have an increased colonic expression of Th-1-related cytokines, including high serum levels of IFN-γ, responsible for development of the AA patches. Moreover, in analogy with the clinical severity in UC, a significant association between severity of AA and polymorphism in the IL-1 receptor antagonist gene has been reported [20]. Finally, the T lymphocyte

resistance against apoptosis, contributing to inappropriate T cells accumulation and perpetuation of the chronic inflammatory process in UC patients, may also affect easier formation of peribulbar lymphocytic infiltrate in the AA skin lesions [21]. Based on this observation it has been suggested that the association between AA and UC may be a result of abnormal regulation of apoptosis, mainly involving T lymphocytes, and common immunological pathways [20–23].

Similarly to AA and UC, the association of AA with CD was presented as co-existence of autoimmune diseases. Assessment of the prevalence of immune-related CD manifestations identified a three times higher occurrence of AA in CD patients than in the background population [24]. In a genetic analysis of predisposition for co-occurrence of CD and AA, Martinez-Mir *et al.* found in the *NOD2* gene of the AA genome the alleles predisposing to CD. Similarly, two susceptibility loci common to AA and CD (PRDX5 and IL2RA) were identified [25]. This study also discovered a region on the chromosome 16 in a genome scan in patients with AA that overlaps with region near a CD susceptibility locus.

Association of AA and CD has been confirmed by the observations of similar cytokine profile, in which a common molecular pathway and key cytokines were observed. It is suggested that imbalance between proinflammatory and anti-inflammatory cytokines leads to a disproportionate activation of Th1 cells and overproduction of IL-1β, IL-2, IL-10, IL-12, IL-18, TGF-β and TNF-α. The clinical manifestations of CD are induced by elevated levels of several of these cytokines, mainly TNF-α. TNF-α affects the TNF-R1 and TNF-R2 receptors allocated in the intestinal wall membrane, leading to activation and secretion of proinflammatory factors. In CD patients TNF-α influences the development of lymphocytic infiltrate in the intestinal wall, whereas in AA patients TNF-α influences the formation of peribulbar lymphocytic infiltrate. However, there were no specific causal factors targeting the immune response in AA to a particular pathway [26].

Interestingly, Ganzetti *et al.* postulated that AA may be an EIM of CD. This hypothesis is supported by the common lymphocytic profile, co-occurrence of AA with exacerbations of CD intestinal lesions, and three times higher prevalence of AA in patients with CD [27]. AA skin involvement in CD patients may be presented as a spectrum, from a single sub-centimeter patch to alopecia universalis. Therefore, in most studies evaluating EIMs of CD the less severe clinical AA lesions may be under-reported and under-diagnosed, masking their true prevalence [28].

## Anti-TNF-α monoclonal antibodies and alopecia areata

Anti-TNF-α monoclonal antibodies, infliximab, adalimumab and certolizumab, are effective agents in the therapy of IBD, with good clinical response in both, CD and UC patients. Anti-TNF-α monoclonal antibodies act by suppressing the immune pathway, which is dependent on TNF-α. Biological drugs interfere with the immune system and

can cause a variety of side effects, such as hypersensitivity to the drug, opportunistic infections including reactivation of tuberculosis, autoimmunity with the formation of antibodies, demyelinating disease, an increased risk of lymphoma, and cancer development. A broad, diverse group of anti-TNF-α side effects are skin lesions [29–31]. There is an increasing number of reports on anti-TNF-α agents, including infliximab and adalimumab, causing AA. The pathomechanism for this effect remains unclear, but it probably involves anti-TNF-α agents, plasmacytoid dendritic cells (PDCs) and INF-α. Due to the lack of the inhibitory effect of TNF-α, PDCs produce an increased amount of IFN-α, IL-1, IL-12, and IL-15. The signal transmitted by IFN-α and IL-15 may promote the maturation of myeloid dendritic cells, prolonging their survival, which may increase the expression of Th1 cells. Additionally, anti-TNF-α agents may influence the distribution of Th1 lymphocytes, leading to their systemic activation and sequestration, what may lead to the formation of AA. The activated PDC in skin themselves may be responsible for the development of peribulbar lymphocytic infiltrate and hair loss in AA patients [32–34].

## Pharmacological treatment of alopecia areata in inflammatory bowel diseases

Management of AA in IBD patients represents a major challenge to the treating physician. Lack of good knowledge on the co-existence of these diseases impedes correct and effective treatment. In addition, careful patient evaluation for underlying pathophysiologic mechanism and exclusion of other causes of hair loss in IBD patients is required for maintaining appropriate therapy course. For example, a differential diagnosis of AA should be regarded in IBD patients, considering alopecia caused by psoriatic-like lesions, which are observed under anti-TNF-α therapy. It is also important to differentiate AA from a drug-induced alopecia (sulfasalazine, azathioprine) and nutritional deficiencies hair loss [12].

Treatment of AA in IBD patients consists of topical or systemic therapies: corticosteroids, immunotherapy, anthralin and minoxidil are the primary local drugs for AA patients. In case of severe disease, psolaren with UV-A, systemic steroids, cyclosporine are available [35]. If AA is a side effect of anti-TNF-α agents, there is no reason to discontinue primary therapy. Initially topical drugs, and for more advanced cases systemic treatment should be used. Only if there is no response to topical or systemic treatment, a change to another anti-TNF-α agent or discontinuation of therapy should be considered [36].

## Conclusion

In conclusion, the pathogenesis of AA occurring in IBD patients remains unclear. The hair loss, characteristic for AA, is observed in clinical practice in IBD patients, but often remains unnoticed. Therefore, IBD patients require the careful observation of the skin and cooperation with a dermatologist.

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