Alopecia universalis is an uncommon form of alopecia areata (AA) involving hair loss over the entire scalp and body and is often difficult to treat. Tumour necrosis factor (TNF) inhibitors have been largely unsuccessful in treating AA and have been reported to induce or worsen AA in patients. We report herein a case of alopecia universalis successfully treated with adalimumab and discuss the possible mechanism.

CONCLUSIONS AND RELEVANCE Tumour necrosis factor has multiple important roles in the pathogenesis of AA, and its interplay with other cytokines, specifically interferons, may be responsible for the development of AA in patients treated with TNF inhibitors. Pharmacogenetics and the inherent physiologic levels of TNF may explain why TNF inhibitors cause AA in some individuals, while treating AA in others. These conclusions warrant further investigation on this subject.

Report of a Case
A woman in her 30s with a history of moderate atopic dermatitis was seen for evaluation of patches of alopecia on the parietal and temporal scalp. The patient had first experienced a patch of alopecia at age 7 years that was successfully treated with triamcinolone acetonide (5 mg/mL) injections. At age 28 years, she began to notice patches of alopecia on her temporal scalp. The appearance of alopecia coincided with emotional stressors in the patient's life. Her medical history included atopic dermatitis, kidney stones, and hypothyroidism that was well-controlled on a levothyroxine sodium regimen. Laboratory results for comprehensive metabolic panel and complete blood cell count, as well as iron, total iron-binding capacity, ferritin, vitamin D, thyrotropin, free thyroxine, and lipid panel levels were all within normal limits. Antinuclear antibody was positive, with a titer of 1:80 and a homogeneous pattern. Double-stranded DNA antibody and rheumatoid factor were negative.

The patient was diagnosed as having AA and was started on monthly injections of triamcinolone acetonide in concentrations of 3 to 5 mg/mL. She had minimal response to injections during the course of 1 year. She then began to experience dramatic hair loss on the sides of the scalp, with eventual progression to the loss of her eyebrows and eyelashes. During the next year, the patient was treated with diphenylcyclopropene in concentrations of 0.0001% to 0.1% (poorly tolerated by the patient, with some response but eventual relapse) and with squaric acid in concentrations of 0.0001% to 0.001% (with no response), as well as oral prednisone tapers, mycophenolate mofetil, halobetasol propionate cream, and 0.03% bimatoprost topical solution, with no improvement.

Two years after her initial presentation, the patient had developed AU with complete loss of scalp, eyebrow, eyelash, and body hair (Figure 1). At this time, her atopic dermatitis flared, and she was started on adalimumab (40 mg subcutaneously) every other week. Verbal informed consent was obtained from the patient at this time. Within 2 weeks of initiation of adalimumab therapy, the patient noted regrowth of her hair in all affected areas, with total regrowth at 6 months (Figure 2 and Figure 3). The hair texture, density, and color were all identical to her baseline hair before diagnosis. She was maintained on a regimen of adalimumab, with complete remission of alopecia for approximately 1 year. The patient noted that she...
would sometimes experience hair shedding in between doses that ceased with her next dose. The patient then developed Staphylococcus infections and viral meningitis, resulting in 1 year off of the adalimumab regimen. During this time, the patient had a complete relapse of her condition, with loss of scalp, eyebrow, and body hair within 1 month. The patient was restarted on the adalimumab regimen, with again full regrowth of her hair in all affected areas within 1 year.

Discussion

Alopecia areata is a common form of immune-mediated non-scarring hair loss occurring worldwide. The major types of AA include patchy AA, alopecia totalis, and the most severe form, AU. The overall incidence of AA in the United States has been estimated at 20.2 cases per 100,000, although the incidence of the severe forms of AA (totalis and universalis) is lower and ranges between 3.5% and 30% of all cases. Alopecia areata can manifest at any age, but most cases are seen before age 20 years. It occurs equally in men and women, without any preference for race/ethnicity or age. Alopecia areata has been associated with various autoimmune diseases, most commonly autoimmune thyroid diseases and vitiligo.

Alopecia areata is typically classified based on the location and extent of hair loss. The most common type is patchy AA, which classically manifests as an asymptomatic, well-demarcated, smooth, oval, or round patch of nonscarring alopecia. Frequently, “exclamation mark hairs” can be observed within or bordering the patches and are described as short hairs that are wider distally and more narrow proximally. This pattern of hair loss involves the entire scalp in alopecia totalis and the entire scalp and body in AU. Generally, only 5% of patchy AA cases will progress to these more severe forms.

Up to 50% of patients with AA spontaneously recover within 1 year, with or without treatment. However, full recovery from AA without relapse is uncommon, especially with the more severe forms of alopecia totalis and AU, for which the...
chance of complete remission is less than 10%. Treatment of AA is often difficult and frustrating because of the lack of effective treatments. First-line therapy includes topical and intralesional glucocorticoids and topical immunotherapy; various second-line treatment options include systemic glucocorticoids, minoxidil, anthralin, phototherapy, prostaglandin analogues, cyclosporine, sulfasalazine, methotrexate, and azathioprine. Many drugs that target different cytokines implicated in the pathogenesis of the disease are being evaluated.

The exact pathogenesis of AA remains unknown. Genetics, environmental factors, and stress are believed to have a role. Pathology specimens in patients with active disease characteristically show perifollicular inflammation and, in particular, a peribulbar lymphocytic infiltrate surrounding anagen hair follicles. It is believed that CD4+ and CD8+ T cells infiltrate the hair and become reactive to hair bulb autoantigens, leading to inflammation, alterations in hair cycling, and ultimately hair loss. Many other factors have been implicated in the process, including antigen presentation, cytokine release, cytotoxic T-cell activity, and cell death. The role of TNF in the pathogenesis is less clear.

Tumor necrosis factor is a proinflammatory cytokine with many functions. Its actions have been implicated in the pathogenesis of many helper T-cell type 1-mediated chronic inflammatory disorders, specifically autoimmune diseases. Tumor necrosis factor antagonists have been successfully used to treat such diseases, including rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, and Crohn's disease. Although effective in treating autoimmune disease, a paradoxical reaction has been known to occur in which patients treated with TNF antagonists have been reported to develop an autoimmune phenomenon unrelated to the disease being treated (eg, antinuclear antibodies) and less frequently develop autoimmune diseases (eg, systemic lupus erythematosus and psoriasis).

Tumor necrosis factor is not only involved in mediating inflammation and immunity but is also active in cell proliferation and differentiation. It has been shown to inhibit hair growth in vitro, and high levels of TNF have been found in patients with AA, with the highest levels in those with AU compared with healthy individuals. Although this evidence suggests that blocking TNF activity may improve AA, a clinical trial of 17 individuals found that etanercept, a TNF inhibitor, was ineffective in treating all types of AA, and some participants worsened with therapy. Some authors have speculated that TNF may have a protective role in hair loss, with more than 20 case reports describing the development or worsening of AA during treatment with various TNF inhibitors (adalimumab, infliximab, and etanercept) that sometimes improved with treatment discontinuation or after switching from one agent to another.

Several studies have proposed possible mechanisms for the paradoxical development of autoimmune diseases with TNF inhibitors, which may help to explain these case reports of worsening of AA on this therapy. The phenomenon is thought to involve plasmacytoid dendritic cells and interferon (IFN) production. Tumor necrosis factor regulates IFN production, and IFN production by plasmacytoid dendritic cells becomes unchecked with anti-TNF therapy. Interferons have been implicated in the pathogenesis of many autoimmune diseases, including AA. Patients receiving interferon alfa treatment have been reported to develop AA, suggesting a possible role of IFN in promoting inflammation in AA. It is possible that in predisposed individuals TNF inhibitors induce aberrant IFN production at the tissue level, leading to the loss of immune privilege that is essential in the development of AA.

Genetics has an important role in the pathogenesis of AA, which may account for the variability in response to TNF inhibitors. Specific HLA class II alleles and various cytokine gene polymorphisms have been associated with AA. In particular, single gene polymorphisms in the TNF gene region have been associated with AA, especially with the severe forms. Pharmacogenetic investigations have revealed that these gene polymorphisms contribute to an individual's response or nonresponse to anti-TNF therapy. These genes can be involved in various functions such as the regulation of transcription and production of TNF and TNF-mediated production of other cytokines and cell apoptosis. In theory, these gene polymorphisms can alter the cellular amounts of TNF available for anti-TNF blockade in certain individuals. Those who produce less TNF at the cellular level can experience complete blockade of TNF, leading to different responses in various disease states. This might be considered beneficial in patients with rheumatoid arthritis, for which TNF is one of the major instigators of inflammation. However, because TNF seems to have multiple roles in the pathogenesis of AA, in which both high levels and low levels seem to promote AA, it is possible that either extreme in susceptible individuals can induce AA. Individuals who inherently produce less TNF at the cellular level may experience complete blockade when exposed to anti-TNF agents and develop AA via uncheckered IFN activity. Those who inherently produce more TNF at the cellular level may be naturally predisposed to the development of AA and may achieve great therapeutic effect when treated with anti-TNF agents.

Conclusions

We describe a patient whose AU was successfully treated with adalimumab. When the patient first began treatment, she attained remarkable results within weeks, with total hair regrowth over the entire body. When treatment was discontinued because of various infections, the patient relapsed and lost all of her hair. With treatment rechallenge 1 year later, she regrew all of her hair. Tumor necrosis factor has been shown to inhibit hair growth in vitro, and anti-TNF agents have been shown to produce AA via indirect effects on other cytokine activity. It is possible that our patient had a specific TNF gene polymorphism that caused severe AU but rendered her amenable to anti-TNF therapy. More research is warranted to definitively confirm this theory.
A cutaneous disease can be classified according to its distribution (Latin. dis., apart + tribuere, assign, allot → distribuere → distribut, divided up). The distribution of skin disease may be described as follows:

**Photodistributed** (Greek. phōs, phōt, light + distributed)\(^1\)\(^2\)

**Lymphangitic** (Latin. lympha, lymph, + Greek. ἁγγείον, angeion, vessel, container, + -it forming adjectives and nouns corresponding to nouns ending in -itis (Greek. forming names of inflammatory diseases -itis)\(^3\)

**Intertriginous** (Latin. *interteriere, inter-, together + terere, to rub + -osus, having to do with, inclined to)\(^1\)\(^3\)

**Symmetric** (Greek. αὐξ, syn, together + μέτρον, métron, measure → αὐξμέτρος, sūmmetron → αὐξμέτρια, summetría, agreement in dimensions, due proportion, arrangement)\(^2\)

**Asymmetric** (Greek. α-; an-, not, without + symmetric)\(^2\)

**Dermatomal** (derma + Greek. tomos, a small section, a piece cut off)\(^1\)

**Acral** (Greek. ἀκρος, akros, topmost / ἀκροπ, akron, end, extremity, or peak)\(^1\)

**Scattered few** (Middle English. schoteren, to shatter) + (Old English. feowe, feow, from an Indo-European root shared by Latin paucus and Greek pauros, small)\(^1\)\(^2\)

**Lymphangitic** (Greek. lympha, lymph, + Greek. ἁγγείον, angeion, vessel, container, + -it forming adjectives and nouns corresponding to nouns ending in -itis (Greek. forming names of inflammatory diseases -itis)\(^3\)

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