Recovery of Hair in the Psoriatic Plaques of a Patient With Coexistent Alopecia Universalis

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PRACTICE **POINTS**

- The Renbök phenomenon, or reverse Köbner phenomenon, describes cases where secondary insults improve dermatologic disease.
- Current evidence suggests that alopecia areata (AA) is driven by a helper T cell (T_H1) response whereas psoriasis vulgaris is driven by T_H1, T_H17, and T_H22.
- Patients with concurrent AA and psoriasis can develop normal hair regrowth confined to the psoriatic plaques. Developing methods to artificially alter the cytokine milieu in affected skin may lead to new therapeutic options for each condition.

To the Editor:

Both alopecia areata (AA) and psoriasis vulgaris are chronic relapsing autoimmune diseases, with AA causing nonscarring hair loss in approximately 0.1% to 0.2%[1] of the population with a lifetime risk of 1.7%,[2] and psoriasis more broadly impacting 1.5% to 2% of the population.[3] The helper T cell (T_H1) cytokine milieu is pathogenic in both conditions.[4-6] IFN-γ knockout mice, unlike their wild-type counterparts, do not exhibit AA.[7] Psoriasis is notably improved by IL-10 injections, which dampen the T_H1 response.[8] Distinct from AA, T_H17 and T_H22 cells have been implicated as key players in psoriasis pathogenesis, along with the associated IL-17 and IL-22 cytokines.[9-12]

Few cases of patients with concurrent AA and psoriasis have been described. Interestingly, these cases document normal hair regrowth in the areas of psoriasis.[13-16] These cases may offer unique insight into the immune factors driving each disease. We describe a case of a man with both alopecia universalis (AU) and psoriasis who developed hair regrowth in some of the psoriatic plaques.

A 34-year-old man with concurrent AU and psoriasis who had not used any systemic or topical medication for either condition in the last year presented to our clinic seeking treatment. The patient had a history of alopecia totalis as a toddler that completely resolved by 4 years of age with the use of squaric acid dibutylester (SADBE). At 31 years of age, the alopecia recurred and was localized to the scalp. It was partially responsive to intralesional triamcinolone acetonide. The patient's alopecia worsened over the 2 years following recurrence, ultimately progressing to AU. Two months after the alopecia recurrence, he developed the first psoriatic plaques. As the plaque psoriasis progressed, systemic therapy was initiated, first methotrexate and then etanercept. Shortly after developing AU, he lost his health insurance and discontinued all therapy. The patient's psoriasis began to recur approximately 3 months after stopping etanercept. He was not using any other psoriasis medications. At that time, he noted terminal hair regrowth within some of the

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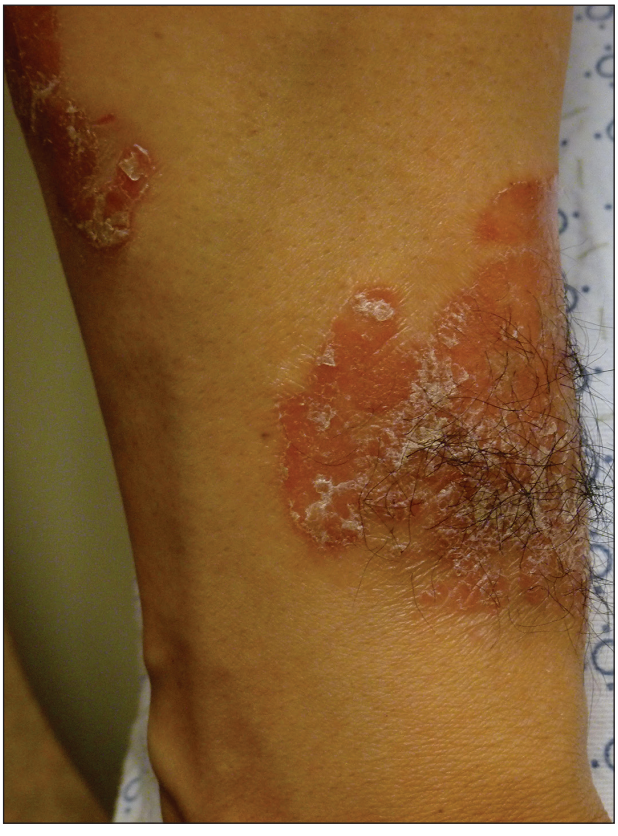
psoriatic plaques. No terminal hairs grew outside of the psoriatic plaques, and all regions with growth had previously been without hair for an extended period of time. The patient presented to our clinic approximately 1 year later. He had no other medical conditions and no relevant family history.

On initial physical examination, he had nonscarring hair loss involving nearly 100% of the body with psoriatic plaques on approximately 30% of the body surface area. Regions of terminal hair growth were confined to some but not all of the psoriatic plaques (Figure). Interestingly, the terminal hairs were primarily localized to the thickest central regions of the plaques. The patient's psoriasis was treated with a combination of topical clobetasol and calcipotriene. In addition, he was started on tacrolimus ointment to the face and eyebrows for the AA. Maintenance of terminal hair within a region of topically treated psoriasis on the forearm persisted at the 2-month follow-up despite complete clearance of the corresponding psoriatic plaque. A small psoriatic plaque on the scalp cleared early with topical therapy without noticeable hair regrowth. The patient subsequently was started on contact immunotherapy with SADBE and intralesional triamcinolone acetonide for the scalp alopecia without satisfactory response.



Hair regrowth in a psoriatic plaque on the forearm.

He decided to discontinue further attempts at treating the alopecia and requested to be restarted on etanercept therapy for recalcitrant psoriatic plaques. His psoriasis responded well to this therapy and he continues to be followed in our psoriasis clinic. One year after clearance of the treated psoriatic plaques, the corresponding terminal hairs persist.

Contact immunotherapy, most commonly with diphenylcyclopropenone or SADBE, is reported to have a 50% to 60% success rate in extensive AA, with a broad range of 9% to 87%[17]; however, randomized controlled trials testing the efficacy of contact immunotherapy are lacking. Although the mechanism of action of these topical sensitizers is not clearly delineated, it has been postulated that by inducing a new type of inflammatory response in the region, the immunologic milieu is changed, allowing the hair to grow. Some proposed mechanisms include promoting perifollicular lymphocyte apoptosis, preventing new recruitment of autoreactive lymphocytes, and allowing for the correction of aberrant major histocompatibility complex expression on the hair matrix epithelium to regain follicle immune privilege.[18-20]

Iatrogenic immunotherapy may work analogously to the natural immune system deviation demonstrated in our patient. Psoriasis and AA are believed to form competing immune cells and cytokine milieus, thus explaining how an individual with AA could regain normal hair growth in areas of psoriasis.[15,16] The Renbök phenomenon, or reverse Köbner phenomenon, coined by Happle et al[13] can be used to describe both the iatrogenic and natural cases of dermatologic disease improvement in response to secondary insults.[14]

A complex cascade of immune cells and cytokines coordinate AA pathogenesis. In the acute stage of AA, an inflammatory infiltrate of $CD4^+$ T cells, $CD8^+$ T cells, and antigen-presenting cells target anagen phase follicles, with a higher $CD4^+$:$CD8^+$ ratio in clinically active disease.[21-23] Subcutaneous injections of either $CD4^+$ or $CD8^+$ lymphocyte subsets from mice with AA into normal-haired mice induces disease. However, $CD8^+$ T cell injections rapidly produce apparent hair loss, whereas $CD4^+$ T cells cause hair loss after several weeks, suggesting that $CD8^+$ T cells directly modulate AA hair loss and $CD4^+$ T cells act as an aide.[24] The growth, differentiation, and survival of $CD8^+$ T cells are stimulated by IL-2 and IFN-γ. Alopecia areata biopsies demonstrate a prevalence of T_H1 cytokines, and patients with localized AA, alopecia totalis, and AU have notably higher serum IFN-γ levels compared to controls.[25] In murine models, IL-1α and IL-1β increase during the catagen phase of the hair cycle

and peak during the telogen phase.[26] Excessive IL-1β expression is detected in the early stages of human disease, and certain IL-1β polymorphisms are associated with severe forms of AA.[26] The role of tumor necrosis factor (TNF) α in AA is not well understood. In vitro studies show it inhibits hair growth, suggesting the cytokine may play a role in AA.[27] However, anti–TNF-α therapy is not effective in AA, and case reports propose these therapies rarely induce AA.[28-31]

The T_H1 response is likewise critical to psoriatic plaque development. IFN-γ and TNF-α are overexpressed in psoriatic plaques.[32] IFN-γ has an antiproliferative and differentiation-inducing effect on normal keratinocytes, but psoriatic epithelial cells in vitro respond differently to the cytokine with a notably diminished growth inhibition.[33,34] One explanation for the role of IFN-γ is that it stimulates dendritic cells to produce IL-1 and IL-23.[35] IL-23 activates T_H17 cells[36]; T_H1 and T_H17 conditions produce IL-22 whose serum level correlates with disease severity.[37-39] IL-22 induces keratinocyte proliferation and migration and inhibits keratinocyte differentiation, helping account for hallmarks of the disease.[40] Patients with psoriasis have increased levels of T_H1, T_H17, and T_H22 cells, as well as their associated cytokines, in the skin and blood compared to controls.[4,11,32,39,41]

Alopecia areata and psoriasis are regulated by complex and still not entirely understood immune interactions. The fact that many of the same therapies are used to treat both diseases emphasizes both their overlapping characteristics and the lack of targeted therapy. It is unclear if and how the topical or systemic therapies used in our patient to treat one disease affected the natural history of the other condition. It is important to highlight, however, that the patient had not been treated for months when he developed the psoriatic plaques with hair regrowth. Other case reports also document hair regrowth in untreated plaques,[13,16] making it unlikely to be a side effect of the medication regimen. For both psoriasis and AA, the immune cell composition and cytokine levels in the skin or serum vary throughout a patient's disease course depending on severity of disease or response to treatment.[6,39,42,43] Therefore, we hypothesize that the 2 conditions interact in a similarly distinct manner based on each disease's stage and intensity in the patient. Both our patient's course thus far and the various presentations described by other groups support this hypothesis. Our patient had a small region of psoriasis on the scalp that cleared without any terminal hair growth. He also had larger plaques on the forearms that developed hair growth most predominantly within the thicker regions of the plaques. His unique presentation highlights the fluidity of the immune factors driving psoriasis vulgaris and AA.

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