Renbök Phenomenon and Contact Sensitization in a Patient With Alopecia Universalis

John E. Harris, MD, PhD; John T. Seykora, MD, PhD; Robert A. Lee, MD, PhD

Background: Immune responses are largely regulated by cytokines that are secreted by activated T cells. Interactions among these cells are complex, and the interaction between 2 responses may alter the effect of either response alone. It has been established that contact sensitization–induced inflammation can reverse hair loss due to alopecia areata. In parallel, the Renbök phenomenon demonstrates how 2 distinct autoimmune diseases—psoriasis and alopecia areata—interact to result in clinically active psoriasis suppressing alopecia areata.

Observations: We describe a patient with concurrent psoriasis and alopecia universalis with terminal hairs within plaques on his extremities, representing the only normal hair growth on his body. Adjacent biopsy specimens confirmed our clinical suspicion of plaque psoriasis with normal hair follicles and alopecia universalis with a peribulbar lymphocytic infiltrate. Our patient’s psoriatic plaques cleared rapidly with narrow-band UV-B phototherapy, but hair growth at the site was maintained. His scalp alopecia responded to squaric acid dibutyl ester contact sensitization therapy.

Conclusions: This case represents a natural experiment in which 3 distinct but overlapping immune responses favored psoriasis or contact dermatitis over alopecia areata. The precise mechanism responsible for these effects remains unclear; however, based on recent reports, we speculate that cytokine cross-regulation plays a role in competition among these distinct immune responses.

Arch Dermatol. 2010;146(4):422-425

IMMUNE RESPONSES ARE COMPLEX, as they serve widely variable roles in vivo, including infectious defense, tumor protection, and transplant rejection as well as autoimmune and allergic disease. These responses vary in triggers and effector functions and are largely dependent on T cells. T-cell responses are composed of individual subsets that are each characterized by a specific panel of cytokines to provide “help” to the response, permitting the response to escalate or, in some cases, regress. These T-cell subsets are unique to the response and tend to polarize and exclude other subsets. How this occurs in vivo is not well understood, but it appears that the cytokines from a particular subset are able to suppress the development of other competing T-cell subsets, which results in a unified, single-purpose response.1

Two previous reports have summarized a total of 5 cases involving overlapping scalp alopecia areata and scalp seborrheic psoriasis that resulted in hair growth that was localized within affected plaques.2,3 This phenomenon was named the Renbök, or reverse Köbner, phenomenon owing to the ability of psoriatic inflammation to “normalize” hair growth within patches of alopecia areata.2 Furthermore, the treatment of extensive alopecia areata using contact sensitization has been well characterized, proving effective in 29% to 78% of patients, likely depending on the severity of involvement.4

We report a case that demonstrates 3 separate immune responses: 2 spontaneous autoimmune responses and 1 immune response that occurred through induced contact dermatitis. At sites where there was overlap between 2 competing processes, the result favored psoriasis or contact dermatitis at the expense of alopecia areata, to the clinical benefit of the patient. We believe that this case provides insight into cytokine cross-regulation among competing T-cell subsets within a human subject, a patient from our clinic.

Report of a Case

A 33-year-old man presented to our clinic with hair loss that began in a patchy distribution in his beard and became widespread to involve his entire scalp, his face, and the rest of his body over a course of about 6 years. He had a 12-year history of...
plaque psoriasis on the extensor aspect of his extremities. He was otherwise well and was not taking any medications. He reported a history of psoriasis in a distant cousin and alopecia areata in an aunt. Physical examination revealed widespread nonscarring hair loss involving his entire body. On the extensor aspect of his extremities, he had well-defined, scaly, red plaques with terminal hair growth (Figure 1A), representing the only areas on his body with normal hair growth. His fingernails revealed regular pitting as well as “oil spots” and onycholysis (Figure 1B). Laboratory tests demonstrated normal thyroid function. Two punch biopsy specimens were obtained from adjacent areas. One specimen, from a hairless patch, revealed a hair follicle with a peribulbar lymphocytic infiltrate (Figure 2A). The second specimen, from a scaly plaque with normal hair growth, showed regular acanthosis, confluent parakeratosis, loss of the granular layer, and a perivascular lymphocytic infiltrate (Figure 2B). Anagen hair follicles were identified within this specimen showing normal histologic features without evidence of peribulbar inflammation (Figure 2C). The patient underwent phototherapy with narrow-band UV-B 3 times a week, clearing his psoriatic plaques within 8 to 10 weeks. Hair growth was maintained within previously affected areas despite resolution of his psoriatic plaques. For his alopecia, the patient was first sensitized topically to squaric acid dibutylester and then subsequently treated topically once a week with squaric acid dibutylester, 0.2%, in acetone. Within 1 to 2 months, he noted significant regrowth of his hair despite the prior presence of alopecia universalis for 3 to 4 years (Figure 3).

**COMMENT**

We report a case of psoriasis and alopecia universalis that overlapped on the extremities, resulting in terminal hair growth that was limited to plaques of psoriasis. The Renbök phenomenon was first reported in 1991 by Happle et al., who described 4 patients with extensive alopecia areata of the scalp with hair growth within plaques of seborrheic dermatitis. While the Koechner phenomenon describes an escalation of psoriatic inflammation by trauma or other inflammatory response, the Renbök phenomenon describes the opposite, an inhibition of a particular inflammatory response by psoriasis. An additional case was reported in 2001. The term was later extended to include patients with mosaic phenomena, one with alopecia areata that spared a nevus flammeus, and another a congenital nevus. The protective mechanism in mosaic skin might occur through altered expression of immunomodulatory proteins within the protected skin and therefore may be distinct from that in overlapping inflammatory diseases. The mechanism of antagonism between separate inflammatory conditions is not well understood; however, the ability of T-cell subsets to suppress competing responses through cytokine secretion has been documented in vitro, in mice, and in human beings.

The best-characterized T-helper inflammatory subsets include Th1, Th2, Th17, and T-regulatory cells. Classically, autoimmune responses resulting in a cytotoxic T-cell response were classified as Th1, and antibody-mediated responses as Th2. Th1 cells are induced by interleukin (IL)-12 and interferon gamma (IFN-γ) and secrete IFN-γ, while Th2 cells are primarily induced by IL-4 and secrete IL-4 and IL-10. Recently, multiple autoimmune diseases initially thought to be Th1-mediated diseases have been reclassified as Th17-mediated diseases, which are induced by transforming growth factor β, IL-21, IL-23, and IL-6 and secrete IL-17, IL-21, and IL-22. In contrast, T-regulatory cells are immunosuppressive and capable of potently limiting a wide range of inflammatory responses. Each of the inflammatory subsets (Th1, Th2, and Th17) enhances its own response through positive cytokine feedback, while antagonizing alternative, competing responses and serving to polarize and recruit T cells to a singular purpose. Therefore, individual responses are mutually exclusive when overlapping within tissue. For example, Th1 cells can suppress Th2 and Th17 responses through IFN-γ, while Th2 responses suppress Th1 and Th17 responses through IL-4 secretion. While it has been specu-

---

Figure 1. Clinical findings. A, Scaly red plaques are evident on the extremities, with terminal hair growth despite surrounding alopecia. B, Fingernails reveal regular pitting as well as “oil spots” and onycholysis.
lated that TH17 cells can suppress TH1 and TH2 responses (possibly through transforming growth factor β), this theory has not been directly confirmed in vitro or in vivo.

Alopecia areata in both mice and humans has been characterized as a TH1-mediated disease, with secretion of IFN-γ, IL-1β, and IL-2,10 and recently psoriasis was reported to be mediated by TH17 inflammatory cytokines.11 Contact sensitization of patients with alopecia areata with diphenylcyclopropenone revealed a decrease in IFN-γ, with a concomitant increase in IL-2, IL-8, IL-10, and tumor necrosis factor α.12 Although it is still unknown what effect individual cytokines play in this reversal, IL-10 is a TH2 cytokine that has been shown to inhibit TH1 responses,13 while tumor necrosis factor α plays a role in TH17 responses in general11 and in psoriasis in particular.14 Interestingly, the local injection of IL-4, a TH2 cytokine, can reverse alopecia areata in a mouse model as well as psoriasis in human patients.15,16 These findings illustrate how opposing inflammatory responses can manifest clinically. First, in our patient, the TH17 psoriatic inflammation antagonized the TH1 alopecia areata inflammatory response, presumably through cytokines central to this response. Why the TH17 response was dominant is not clear, nor is whether it would dominate every time this overlap occurred. An alternative explanation has been proposed—that the Renbök phenomenon occurs because hair growth is necessary for psoriatic inflammation to occur, and so hair growth is a “fertile” medium for psoriatic involvement.2 We think that this explanation is unlikely in our case because the psoriasis was present before the alopecia, the alopecia was universal, and the overlap occurred in a pattern characteristic of psoriasis, suggesting that it was the psoriasis that drove this phenomenon. A case report in 2007 described the opposite history: the patient had long-standing alopecia areata and new-onset scalp psoriasis that induced the Renbök phenomenon.3 Another case of overlapping scalp psoriasis and alopecia areata was described in a patient with Turner syndrome in whom the alopecia may have prevented the psoriasis.17 Therefore, it is unclear whether 1 subset is inherently dominant.

Second, our patient’s alopecia areata responded to contact sensitization with squaric acid dibutylester. Multiple mechanisms have been proposed for the clinical effects of contact sensitization on alopecia areata, including T-cell
apoptosis, reduction of homing markers on inflammatory T cells, and a reduction in antigen-presenting cell number or function. These hypotheses are not mutually exclusive to the notion of cross-regulation and may all be affected through the action of cytokines.

The response of our patient’s psoriatic plaques to narrow-band UV-B phototherapy was not unexpected, but the persistence of hair growth within previously affected areas owing to the Renbök phenomenon was interesting. It is possible that the dermal portion of the psoriatic infiltrate continued to secrete antagonistic cytokines, while the more superficial epidermal changes resolved. Alternatively, the protective effects of the Renbök phenomenon may be long lasting, and only continued observation will determine whether the alopecia will return. Incidentally, we subsequently transitioned our patient to treatment with topical calcipotriene/betamethasone ointment, and he remains clear of psoriasis, with continued hair growth.

In summary, the clinical, histopathologic, and therapeutic observations in our patient with psoriasis, alopecia universalis, and contact dermatitis are consistent with cytokine cross-regulation, which has previously been characterized in vitro, in mouse models, and in a small number of human studies. Our case represents a natural experiment that provides insight into the complex inflammatory interactions that are otherwise difficult to investigate in humans.

Accepted for Publication: August 26, 2009.
Correspondence: John E. Harris, MD, PhD, Department of Dermatology, Hospital of the University of Pennsylvania, 3600 Spruce St, 2 Maloney Bldg, Philadelphia, PA 19104 (john.harris@uphs.upenn.edu).

Author Contributions: Drs Harris and Lee had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Harris, Seykora, and Lee. Acquisition of data: Harris, Seykora, and Lee. Analysis and interpretation of data: Harris, Seykora, and Lee. Drafting of the manuscript: Harris and Lee. Critical revision of the manuscript for intellectual content: Harris, Seykora, and Lee. Study supervision: Harris and Lee.
Financial Disclosure: None reported.
Previous Presentations: This study was presented in part in abstract form at the American Society of Dermatology 2008 Annual Meeting: October 16, 2008; San Francisco, California; and in abstract form as a “Case of the Month” in Skin and Allergy News, February 2009.