A Potential Role for IL-4 and IL-13 in an Alopecia Areata—Like Phenotype: A Clinical Perspective

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Although alopecia areata (AA) has been traditionally classified as a strictly T helper type 1—mediated process, the T helper type 2 (Th2) pathway may contribute to an AA-like phenotype in some individuals. Herein, we describe three clinical cases that support the potential role of Th2 activity through the upregulation of IL-4 and IL-13 in an AA-like phenotype.

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Alopecia areata (AA) has historically been classified as a T helper type 1 (Th1)—mediated disorder given its increased IFN-γ signaling. However, recent translational findings of cytokine transcripts and gene expression profiles have indicated a potential involvement of T helper type 2 (Th2) upregulation in the immunopathogenesis of AA (Wang and Christiano, 2017). In addition, atopic dermatitis (AD), a common comorbidity of AA, is a primarily Th2-driven process with an upregulation of IL-4 and IL-13 (Chu et al., 2011; Renert-Yuval and Guttman-Yassky, 2017). These key cytokines are essential to the type 2 inflammatory response seen in atopic disease and have more recently been associated with AA (Renert-Yuval and Guttman-Yassky, 2017). The following three clinical cases demonstrate the potential role for Th2 upregulation through IL-4 and IL-13 in the patients with AA-like phenotype.

Patient 1 is a 19-year-old female with recalcitrant AA involving >40% of the scalp since age 13 years. She denied any hair regrowth with topical squaric acid for 6 months followed by monthly intralesional steroid injections for 5 years. Upon presentation, a comprehensive history was elicited and revealed a food allergy to chicken and eggs associated with gastrointestinal upset since age 1 year. After a negative skin prick test, the patient reintroduced chicken and eggs into her diet at age 12 years, several months before developing AA. Given this history, we advised the patient to avoid chicken and eggs, but she opted to continue eating them, while receiving monthly intralesional steroid injections. After an additional year of treatment without hair regrowth, the patient eliminated chicken and eggs from her diet. Within two months, she demonstrated regrowth of terminal hairs in >95% of previous patches of alopecia. This patient, moreover, demonstrates a potential association and/or shared pathophysiology of food allergy and an AA-like phenotype, as further supported by previous case reports and a recent case—control study that found a high prevalence of food allergy in patients with AA (Ibrahim et al., 2015; Magen et al., 2018). In food-allergic individuals, IL-4, IL-5, and IL-13 play an essential role in Th2 differentiation and promotion of the allergic T-cell response, which may also contribute to an AA-like phenotype in these patients triggered by an exposure to a food allergen (Vickery et al., 2011). Alternatively, the association between food allergy and AA may not be based on a similar pathogenesis but rather explained by socio-economic, genetic, or other unknown risk factors.

Patient 2 is a 26-year-old female with a history of food and environmental allergies since early childhood. She developed acute alopecia universalis 1 month after consuming a nut-containing product, which incited an anaphylactic episode. After failing a tapered course of oral prednisone, she was started on tofacitinib 10 mg b.i.d and displayed complete hair regrowth after 6 months on treatment. On her 13th month of receiving tofacitinib, the patient experienced a sudden hair loss with significant redness, tingling, and tenderness limited to her occiput scalp. She reported diligent compliance with the medication and denied any changes to her health or medications. The patient, however, related the use of a new hairspray applied to the occiput scalp for several weeks' duration. The ingredient list of the hairspray was reviewed and found to contain both limonene and linalool. The patient was instructed to discontinue the hairspray and apply topical fluocinonide solution for symptomatic relief for 2—3 weeks. She subsequently had complete hair regrowth on her occiput scalp after 1 month and denied any further hair loss at the 10-month follow-up. This case, furthermore, highlights a potential association between AA-like phenotype and allergic contact dermatitis (ACD). Although the literature is limited, a previous case series of three pediatric patients supported a temporal relationship between ACD and contact alopecia in AD-primed children (Admani et al., 2017). In contrast to these patients, contact allergens such as diphenylcyclopropenone and squaric acid dibutyl ester can be used therapeutically to treat AA through an incompletely understood mechanism potentially involving antigenic competition (Happle, 1991; Strazzulla et al., 2018). A potential hypothesis to explain this paradox may be that patients with contact alopecia simply display a similar phenotype to those with true AA rather than an identical

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pathogenesis of disease. In addition, although ACD has historically been classified as a primarily Th1-driven process, Th2 cytokine IL-4 plays an essential role in the effector phase of contact sensitivity, and biopsy specimens of patients with ACD contained higher expression levels of IL-4 and IL-13 than IFN-γ (Neis et al., 2006). Although it is possible that patients with AA are merely more prone to contact sensitization given the high prevalence of concomitant AD, contact allergens may also lead to the localized flares of an AA-like phenotype.

Patient 3 is a 13-year-old female with extensive AD and recalcitrant alopecia totalis (AT) for over a decade (Penzi et al., 2018). Previous trials of topical squaric acid and anthralin, topical steroids, pulsed oral prednisone, and oral methotrexate did not yield any hair regrowth. After 9 months of dupilumab treatment (initiated for the patient with AD), she began to grow terminal hairs on >60% of the scalp. Because of a subsequent lapse in the insurance coverage, the patient stopped taking dupilumab for an 8-week period and experienced significant shedding. Upon the reintroduction of the medication, she again showed substantial hair regrowth. This case ultimately provides the strongest evidence for IL-4 and IL-13 activities in AA because dupilumab represents a monoclonal antibody against IL-4 and downregulates Th2 activity through the blockage of IL-4 and IL-13. Further clinical controlled trials are necessary to investigate the utility of dupilumab for AA as an alternative case report described AA following dupilumab use (Mitchell and Levitt, 2018). It is possible that different immunopathology and/or broad imbalances in Th1/Th2 pathways ultimately lead to AA, appreciating that some cases may more prominently involve Th2 (as in patient 3) and others Th1 (Marks et al., 2019).

As demonstrated by these three clinical cases, IL-4 and IL-13 likely contribute, at least in part, to the immunopathogenesis of an AA-like phenotype in some patients. Although the Th1-mediated pathway may dominate in the majority of patients with AA, the interactions and influences of Th1- and Th2-mediated pathways in AA are likely more complex than historically appreciated and may further differ between the individual patients with the same patterned phenotypes of nonscarring hair loss. As we continue to understand the intricacies of the immune system in the AA phenotype, it is critical that clinicians routinely assess for a history of contact allergy, food allergy, and AD and employ a tailored approach to treatment in patients with nonscarring, patchy hair loss.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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