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Appearance of alopecia areata during treatment with tildrakizumab for severe palmoplantar psoriasis

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Abstract

We report the case of a 50-year-old woman with severe palmoplantar psoriasis who developed alopecia areata (AA) 2 months after initiating treatment with tildrakizumab (100 mg subcutaneously). The patient had no personal or familial history of autoimmune disorders, and the diagnosis of AA was confirmed by clinical and trichoscopic evaluation. Tildrakizumab was discontinued, and the patient was treated with topical corticosteroids and low-dose oral methylprednisolone, achieving complete hair regrowth within 6 months. Psoriasis subsequently recurred, and treatment was successfully switched to bimekizumab, with sustained remission and no adverse events. To the best of our knowledge, published reports of new-onset alopecia areata during tildrakizumab therapy for psoriasis are lacking. The temporal correlation, lack of confounding risk factors, and resolution upon drug withdrawal suggest a causal relationship. This case expands the spectrum of paradoxical reactions (PRs) to biologic therapies and highlights the need for vigilance regarding autoimmune manifestations during interleukin (IL)-23 inhibition.

Introduction

Alopecia areata (AA) is a common autoimmune condition characterized by rapid, non-scarring hair loss, with a lifetime prevalence of approximately 2%.[1-3] Although its exact pathophysiology remains unclear, it is thought to involve genetic susceptibility and environmental triggers, including psychological stress, infections, toxins, and dietary factors.[4] AA has been described as a paradoxical reaction (PR) during treatment with tumor necrosis factor-alpha (TNF-α) inhibitors. However, to date, no cases have been reported linking tildrakizumab, an anti-interleukin (IL)-23 monoclonal antibody, with the onset of AA.

Case Report

A 50-year-old woman with a 10-year history of palmoplantar psoriasis, treated with tildrakizumab, developed AA about 2 months after starting the therapy. The patient was initially treated with narrow-band ultraviolet B (nb-UVB; TL-01) associated with oral acitretin, with initial benefit but progressive loss of efficacy over a few months. Due to persistent hyperkeratotic plaques, especially on the plantar region, causing difficulty in walking, she started systemic treatment with cyclosporin A, leading to rapid improvement of skin lesions. Unfortunately, after tapering the dose to 3 mg/kg daily, psoriatic plaques recurred, accompanied by the onset of hypertension not controlled by specific therapy. For this reason, treatment with cyclosporin A was discontinued. After ruling out contraindications, a new treatment with the adalimumab biosimilar (GP2016) at the standard dose was initiated, with initial benefit but subsequent loss of efficacy after 6 months, associated with marked worsening of plantar

lesions. In agreement with the patient, we decided to discontinue adalimumab and initiate a new therapy with tildrakizumab, 100 mg subcutaneously at baseline, then after 4 weeks, and every 12 weeks thereafter. One month after the second dose of tildrakizumab, the patient showed progressive onset of AA, localized on the eyebrows and on the scalp, particularly in the parietal and occipital areas (Figure 1). She denied any recent infections, vaccinations, major psychosocial stressors, or initiation of new medications or supplements in the preceding 6-8 weeks.

The diagnosis was based on clinical evaluation and confirmed by trichoscopy, which revealed hallmark features of AA, such as yellow dots, black dots, exclamation mark hairs, and short vellus hairs. Baseline laboratory investigations were performed, including complete blood count, thyroid-stimulating hormone (TSH) with thyroid antibodies, ferritin/iron studies, and vitamin D and B12 levels; all results were within normal limits. The affected areas showed partial, non-scarring hair loss, consistent with the ophiasis pattern of AA. She had no personal or family history of autoimmune conditions, nor any previous episodes of AA. The absence of known risk factors and the temporal relationship between AA onset and tildrakizumab administration strengthen the hypothesis of a drug-related adverse event. We considered this clinical presentation an adverse event related to the ongoing tildrakizumab treatment, which was therefore discontinued. AA was treated with topical steroid ointment, associated with oral low-dose methylprednisolone (0.2 mg/kg/day) for 6 weeks, leading to a rapid initial benefit and full restoration of scalp and eyebrow hair within 6 months (Figure 2).

Due to the recurrence of psoriatic lesions on the plantar area, significantly affecting the patient's quality of life, a new biological treatment with bimekizumab was started, resulting in stable disease remission without adverse events.

Discussion

AA is an autoimmune disorder that affects about 2% of the general population, resulting in rapid, non-scarring hair loss.[1,2] In its acute phase, clinical presentation involves small, well-defined circular patches of alopecia and may evolve to involve larger areas or even the entire scalp. In some cases, AA may regress spontaneously within 12 months after onset.[3]

The pathophysiology remains largely unclear, but it is believed to involve genetic predisposition and environmental triggers such as psychological stress, infections, toxins, and diet.[4] The hair follicle (HF) is considered an immune-privileged site, protecting against autoimmune responses by downregulating major histocompatibility complex (MHC) class I expression in the anagen phase, thus preventing autoantigen presentation to $CD8^+$ T cells. The collapse of this immune privilege is believed to be a key factor in AA pathogenesis. Interferon-gamma (IFN-γ) plays a significant role in AA development, acting as a potent $CD8^+$ T cell activator that directly attacks hair follicles. IFN-γ

also upregulates MHC class I expression on hair follicle keratinocytes, increasing their vulnerability to immune-mediated damage. Inflammation can drive HF into dystrophic anagen and premature catagen phases. The effectiveness of Janus kinase inhibitors (JAKi), which inhibit IFN-γ signaling, supports this pathophysiological mechanism.[1] IL-23 is another critical cytokine in sustaining inflammation, acting by enhancing Th17 activity. It binds to a receptor complex composed of IL-12Rβ1 and IL-23Rα, activating intracellular JAK-signal transducer and activator of transcription (STAT) signaling, which leads to IL-17A, IL-17F, and IL-22 production. These cytokines act on epithelial cells via distinct signaling pathways. In psoriatic lesions, IL-23 stabilizes the pathogenic Th17 phenotype and boosts IL-17 production. Th17 cells also release IL-22, IL-26, and IL-29, elevated in psoriatic lesions. Consequently, biologic therapies targeting IL-23 can reduce lymphocyte-derived cytokines such as IL-17 and decrease pathogenic T cell populations in psoriatic skin.[5] This is particularly effective with IL-17 and IL-23 inhibitors.[6] However, the increasing use of these therapies has led to reports of PR, defined as the onset or worsening of immune-mediated inflammatory diseases during biologic treatment aimed at similar pathologies.

AA has been reported as a PR, especially with anti-TNF agents, such as adalimumab, typically appearing after a mean of 16.7 months of therapy and often occurring with other PRs.[7] Reports on PR with newer molecules such as IL-17 and IL-23 inhibitors are scarce.[8] Although IL-23 blockade is effective in psoriasis, it may cause an immune imbalance, potentially activating cytotoxic T cells ($CD8^+$), involved in AA pathogenesis. Reduced Th17 activity might also affect the regulation of inflammatory signals, undermining immune tolerance at the hair follicle level.[8]

Although AA has been most frequently described in association with anti-TNFα therapies, emerging reports indicate that IL-17 and IL-23 inhibitors may also induce paradoxical onset of AA (Table 1). In 2022, Macklis *et al.* described a case of AA occurring in a 50-year-old woman after approximately 18 months of guselkumab therapy, an IL-23 inhibitor used for plaque psoriasis. Notably, the onset of hair loss occurred shortly after a Tdap booster vaccination, raising the question of whether the vaccine, rather than the biologic agent, may have played a contributory or even triggering role. The patient declined systemic treatment for AA and experienced persistent hair loss.[9] Similarly, Şentürk and Çetin described a case of AA induced by guselkumab in a 24-year-old male with psoriasis. The patient developed well-demarcated alopecic patches approximately 4 months after starting guselkumab therapy. No other known factors potentially responsible for AA were identified. Following discontinuation of guselkumab and initiation of topical clobetasol treatment, complete hair regrowth was observed within 3 months.[10]

With regard to IL-17 inhibitors, several cases have been published. Zhang *et al.* reported a case of AA developing shortly after completion of the induction phase of secukinumab therapy in a 35-year-

old woman with palmoplantar pustulosis. No other potential triggers, such as autoimmune comorbidities, emotional stress, or abnormal laboratory findings, were identified, making secukinumab the most likely causative factor. The drug was discontinued, and the patient was treated with tofacitinib 5 mg twice daily, resulting in complete hair regrowth within 1 month.[11] Another report by Öğüt *et al.* described a case of a 32-year-old male patient with long-standing psoriasis vulgaris and human leukocyte antigen (HLA)-B27-positive axial psoriatic arthritis who developed paradoxical hidradenitis suppurativa during adalimumab treatment and subsequently developed AA during secukinumab therapy. The AA manifested around week 16 of secukinumab treatment, with no other identifiable triggers. The patient had a remote history of AA 6 years prior, but no recurrences until then. He was treated with monthly intralesional triamcinolone acetonide injections (5 mg/mL), leading to complete hair regrowth after two sessions. At follow-up, the patient remained on secukinumab with stable control of psoriasis, psoriatic arthritis, hidradenitis suppurativa, and no further episodes of AA.[12] In a further case, Eldirany *et al.* reported AA induced by ixekizumab in a 70-year-old white male with plaque psoriasis and psoriatic arthritis. The patient had been undergoing treatment with ixekizumab for 13 months when he developed elongated patches of hair loss, which were confirmed as AA through scalp biopsy. Ixekizumab was discontinued after 15 months of use. The patient was subsequently treated with topical clobetasol solution, 5% minoxidil, and clobetasol mousse. Near-complete hair regrowth was observed 3 months after discontinuation of the biologic.[13] These cases illustrate that AA induced by biologic therapies targeting IL-17 and IL-23 is a rare but increasingly recognized phenomenon. Clinical outcomes appear variable, ranging from spontaneous regrowth to persistent alopecia, depending on the treatment strategy and patient characteristics. Discontinuation of the offending biologic, with or without adjunctive therapy (topical corticosteroids, systemic agents such as JAK inhibitors or corticosteroids), appears beneficial in most cases. In our patient, causality was assessed using the Naranjo adverse drug reaction probability scale, yielding a score of 6 (probable).[14]

Conclusions

Compared with previous reports, our case expands the spectrum of hair disorders temporally associated with IL-23 inhibition, suggesting a possible link between tildrakizumab and AA. The absence of prior autoimmune history, combined with the full resolution of AA after discontinuation and short-term treatment, underscores the plausibility of a causal relationship. These findings support the hypothesis that IL-23 blockade may alter the delicate immunologic balance at the hair follicle level, potentially unleashing cytotoxic $CD8^+$ T cell responses in predisposed individuals. This case expands the spectrum of PRs associated with biologic therapies and underlines the importance of

careful monitoring for unexpected autoimmune phenomena in patients undergoing treatment with novel immunomodulators.

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Figure 1. Clinical appearance after 2 months of treatment with tildrakizumab for psoriasis.

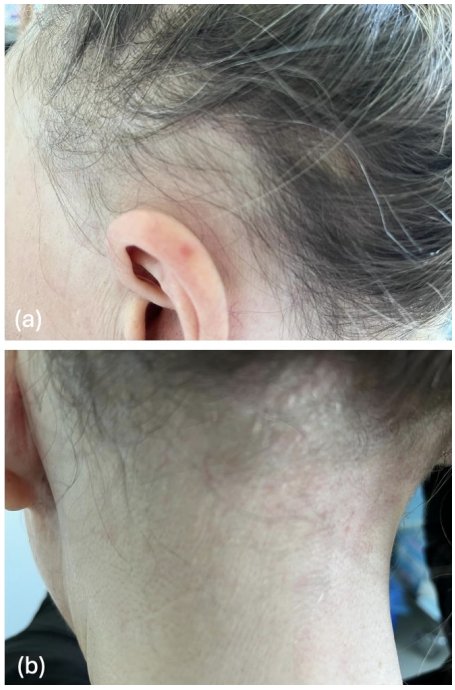

Figure 2. Complete hair regrowth 6 months after the interruption of the treatment with tildrakizumab and with topical and systemic corticosteroid therapy.

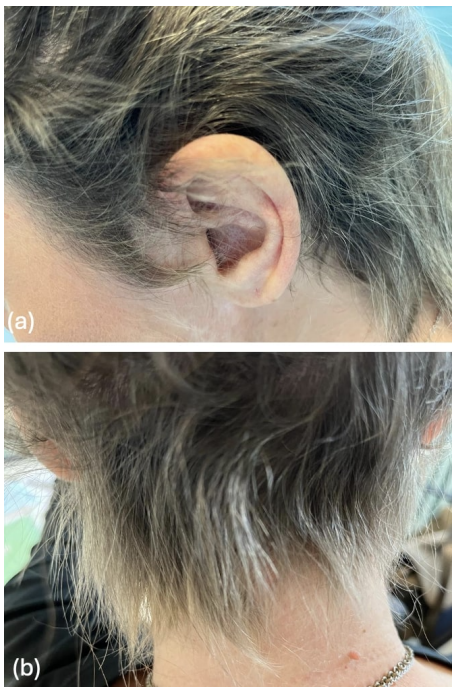

Table 1. Summary of selected published cases of alopecia areata associated with IL-17 or IL-23 inhibitors.

Authors, journal (year)	**Sex/Age**	**Drug**	**Duration of therapy until AA onset**	**AA Treatment**	**Outcome**
Our case	F/50	Tildrakizumab	8 weeks	Drug discontinuation + topical steroid ointment + oral low-dose methylprednisolone (0.2 mg/kg/day for 6 weeks)	Complete regrowth of scalp and eyebrows after 6 months
Şentürk N *et al.*, *Australas J Dermatol* (2023)	M/24	Guselkumab	16 weeks	Drug discontinuation + topical clobetasol	Complete regrowth in 3 months
Zhang C *et al.*, *Clin Cosmet Investig Dermatol* (2023)	F/35	Secukinumab	4 weeks	Secukinumab discontinuation + tofacitinib 5 mg BID for 1 month	Complete regrowth after 1 month
Öğüt ND, *J Eur Acad Dermatol Venereol* (2023)	M/32	Secukinumab	16 weeks	Intralesional triamcinolone acetonide (5 mg/mL) × 2 sessions	Complete regrowth; maintained on secukinumab without further flares
Macklis P *et al.*, *J Drugs Dermatol* (2022)	F/50	Guselkumab	18 months	Drug discontinuation; declined prednisone and methotrexate	Persistent alopecia universalis; possible cofactor role of Tdap vaccine
Eldirany SA *et al.*, *JAAD Case Rep* (2019)	M/70	Ixekizumab	13 months	Drug discontinued after 15 months + topical clobetasol solution + minoxidil 5% + clobetasol mousse	Near-complete regrowth 3 months after discontinuation

AA, alopecia areata.