Title
Onset of frontal fibrosing alopecia during inhibition of Th1/17 Pathways with ustekinumab

Journal
Dermatology Online Journal, 25(7)

Authors
King, Andrew D.
Lam, Lauren
Goh, Carolyn

Publication Date
2019

DOI
10.5070/D3257044808

Onset of frontal fibrosing alopecia during inhibition of Th1/17 Pathways with ustekinumab

Andrew D. King[1], PhD, Lauren Lam[2] MD, Carolyn Goh[1] MD

Affiliations: [1]Division of Dermatology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA, [2]Division of Dermatology, University of Alberta, Edmonton, Canada

Corresponding Author: Carolyn Goh MD, University of California Los Angeles, 200 UCLA Medical Plaza, Suite 450, Los Angeles, CA 90095, Tel: 818-461-8148, Email: cgoh@mednet.ucla.edu

Abstract

The mechanism underlying frontal fibrosing alopecia (FFA) is unknown, but proposed mechanisms share commonality of T cell-mediated destruction of the hair follicle bulge. IL-12 and IL-23 are key cytokines involved in CD4 T cell differentiation towards Th1 and Th17 phenotypes. We present a 62-year-old woman who developed persistent FFA while on ustekinumab for treatment of preexisting psoriasis. This case presents evidence against Th1 and Th17 pathways as essential to pathogenesis in FFA. This case also suggests that IL-12 and IL-23 inhibition is ineffective for this form of scarring alopecia.

Keywords: frontal fibrosing alopecia, ustekinumab

Introduction

Frontal fibrosing alopecia (FFA) is a primary cicatricial alopecia that presents as progressive band-like hair loss involving the frontotemporal hairline, eyebrows, and body hair and is predominantly seen in postmenopausal women. Frontal fibrosing alopecia is considered a clinical variant of lichen planopilaris (LPP), as both have a similar appearance on histology. In both FFA and LPP, there is a perifollicular lymphocytic infiltrate, concentric fibrosis, and apoptosis of keratinocytes. The mechanism of pathogenesis of FFA is unknown. However, several hypotheses exist, including antigen cross-reactivity [1], loss of immune privilege [2], and defective PPAR-gamma activity [3]. All these proposed mechanisms share the same principle of pathogenesis: that activation of T lymphocyte-mediated destruction of keratinocytes in the hair follicle bulge leads to obliteration of the hair follicle over time.

Ustekinumab is a monoclonal antibody approved for use in psoriasis, psoriatic arthritis, and Crohn disease. It targets the common p40 subunit of cytokines IL-12 and IL-23. Binding this subunit inhibits differentiation of CD4+ helper T lymphocytes towards Th1 and Th17 phenotypes, which are reliant on IL-12 and IL-23 signaling, respectively. Psoriasis is a Th17-driven disease; thus, ustekinumab is an effective therapy for psoriasis. However, its effects on FFA and inflammation in the hair follicle have not been studied.

Case Synopsis

A 62-year-old woman with well-controlled psoriasis treated for 5 years with ustekinumab 90mg subcutaneously every 12 weeks presented with loss of eyebrows, fronto-temporal patchy hair loss, erythema, and pruritus (**Figure 1**). A scalp biopsy showed a perifollicular lichenoid infiltrate involving the upper segment of the hair follicle, concentric perifollicular fibrosis, and loss of sebaceous glands (**Figure 2**). Horizontal sectioning also showed a reduced number of terminal and vellus hair follicles, along with a reduced anagen-to-catagen/telogen ratio of 1:1 (reference 15.5:1) and elevated telogen fraction of 0.5 (reference 0-0.15). A diagnosis of frontal fibrosing alopecia was made.

The patient was subsequently treated with numerous therapies over the course of three years,

including multiple intralesional triamcinolone injections, minocycline 100mg twice daily orally for over one year, hydroxychloroquine 200mg twice daily orally for 6 months, twice daily topical fluocinonide 0.05% solution, once daily topical tacrolimus 0.1% solution, once daily topical clindamycin to the scalp, daily minoxidil foam, and finasteride. Despite these therapies, the patient continued to have mild recession of the frontal hairline, progressing from 11cm to 13cm measured at her midline, from the glabella. Her left temporal hairline also continued to recede, from 9 to 10cm over the course of three years. Ustekinumab therapy for psoriasis was continued during these three years.

Case Discussion

In our case, we observed the onset and progression of FFA while incidentally on ustekinumab in addition to typical FFA treatments. Currently, no systematic studies of FFA treatment have been performed, but a small case series showed limited efficacy of topical corticosteroids and minoxidil as observed in our patient [4]. One case report noted that initiation of ustekinumab with active LPP was ineffective at preventing progression [5].

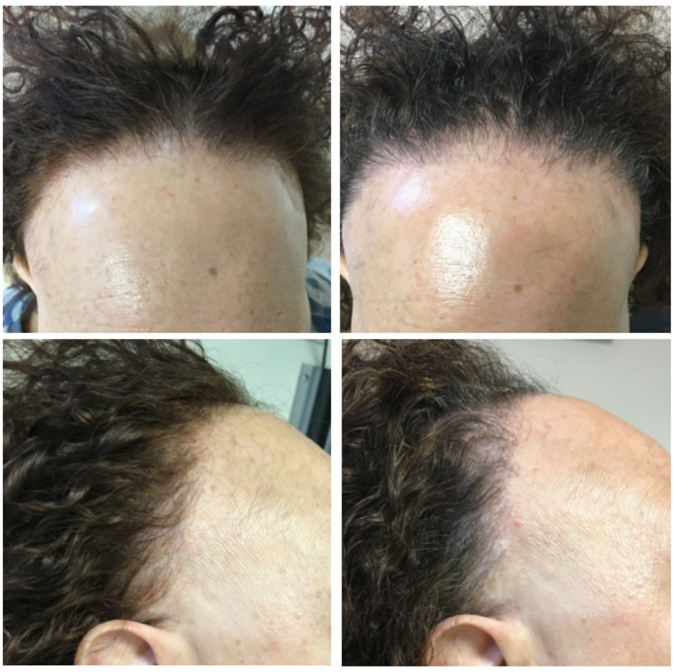

Figure 1*: Clinical image of frontal fibrosing alopecia. Progressive alopecia over frontotemporal hairline (left) and one year later (right) while continuing ustekinumab therapy.*

The initiation of FFA while on an anti-IL12/23 p40 monoclonal antibody suggests that the Th1 and Th17 pathways do not play a major role in FFA, as FFA developed despite inhibiting these pathways. Histologic characterization of LPP shows a predominance of effector CD8+ lymphocytes with CD8:CD4 ratios of 1.2:1 versus 0.4:1 in normal controls, indicating the importance of CD8+ T cells in LPP [2]. The lymphocytic predominance with an absence of neutrophils in LPP also supports the idea that the Th17 pathway is dispensable, in contrast with psoriasis in which neutrophilic infiltrate is present. These findings together suggest a Th1- and Th17-independent mechanism in FFA.

Several possible mechanisms may explain our observations. Paradoxical activation of pro-inflammatory mediators, such as IL-17, though IL-12 inhibition may serve as a potential mechanism [6]; the progression of FFA in our patient while on ustekinumab therapy may be suggestive. Another theory postulates involvement of MHC-I upregulation in keratinocytes, leading to activation of CD8+ T lymphocytes, which may bypass Th1/17 inhibition [2]. Theoretically, cross-presentation by dendritic cells could also directly activate CD8+ T cells and elicit a cytotoxic T lymphocyte response, which would rely less on Th1/17 pathway activation.

Although androgenetic alopecia and telogen effluvium, two hair loss disorders whose pathogenesis have no known inflammatory

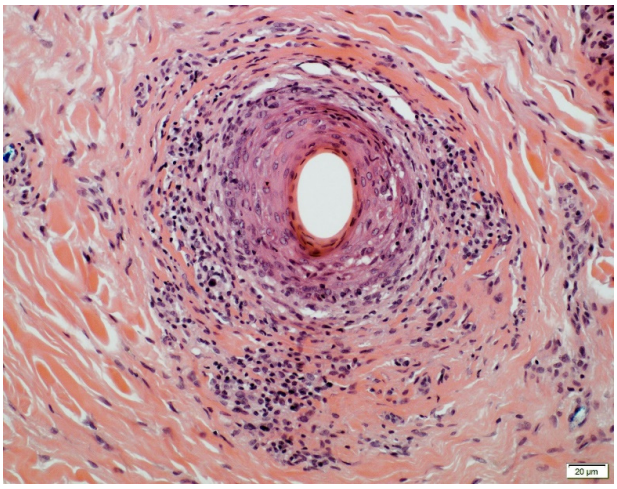

Figure 2*: Representative histology of frontal fibrosing alopecia. Lichenoid inflammation with localized infiltrate in peri-isthmus (bulge) region. H&E, 200x.*

component, have been noted to persist in patients while on ustekinumab, this is the first case, to our knowledge, noted with FFA onset and persistence during ustekinumab treatment. Other authors have postulated that the pathophysiology behind FFA is analogous to alopecia areata (AA), with inflammation localized to the bulge in FFA rather than the bulb in AA [7]. Alopecia areata has been mechanistically linked to the Th1 pathway, with case studies of successful treatment with ustekinumab. These case series together support the possibility that FFA and AA may have differences in their pathophysiology.

Our case suggests that although there is no clear link between the Th1 and Th17 pathway and its pathogenesis in FFA, it appears that inhibition of these pathways are not effective in treatment or prevention of the onset of FFA. Further observations and comparisons of LPP or FFA occurring in patients while on biologic medications of differing targets would be required to establish this association.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Shiohara T, Mizukawa Y, Takahashi R, Kano Y. Pathomechanisms of lichen planus autoimmunity elicited by cross-reactive T cells. *Curr Dir Autoimmun*. 2008;10:206–226. [PMID: 18460888].
2. Harries MJ, Meyer K, Chaudhry I, et al. Lichen planopilaris is characterized by immune privilege collapse of the hair follicle's epithelial stem cell niche. *J Pathol*. 2013;231:236–247. [PMID: 23788005].
3. Karnik P, Tekeste Z, McCormick TS, et al. Hair follicle stem cell-specific PPARγ deletion causes scarring alopecia. *J Invest Dermatol* 2009;129:1243–1257. [PMID: 19052558].
4. Rácz E, Gho C, Moorman PW, Noordhoek Hegt V, Neumann HAM. Treatment of frontal fibrosing alopecia and lichen planopilaris: a systematic review. *J Eur Acad Dermatol Venereol*. 2013;27:1461–1470. [PMID: 23531029].
5. Webster G. Failure of lichen planopilaris to respond to ustekinumab. *Dermatol Online J*. 2015;21(11). [PMID: 26632941].
6. Hoeve MA, Savage NDL, de Boer T, et al. Divergent effects of IL-12 and IL-23 on the production of IL-17 by human T cells. *Eur J Immunol*. 2006;36:661–670. [PMID: 16482511].
7. Tziotzios C, Stefanato CM, Fenton DA, Simpson MA, McGrath JA. Frontal fibrosing alopecia: reflections and hypotheses on aetiology and pathogenesis. *Exp Dermatol*. 2016;25:847–852. [PMID: 27198858].