DOI: 10.3315/jdcr.2010.1041

Journal of Dermatological Case Reports

Alopecia areata developing paralell to improvement of psoriasis during ustekinumab therapy

Monika Słowińska[1], *Agnieszka Kardynal*[1], *Olga Warszawik*[1], *Joanna Czuwara*[1], *Lidia Rudnicka*[1,2,3]

1. Dept. Dermatology CSK MSWiA, Warsaw, Poland
2. Faculty of Health Sciences, Warsaw Medical University, Warsaw, Poland
3. Polish Academy of Sciences, Warsaw, Poland

Corresponding author:

Monika Slowinska, MD

Dept. Dermatology CSK MSWiA

Woloska 137, 02507 Warsaw

Poland

E-mail: *monika.slowinska@yahoo.com*

Key words:

biological drugs, confocal reflectance microscopy, dermoscopy, interleukin-23, psoriasis, Renbök phenomenon, trichoscopy

Abstract

Background: Ustekinumab is a new immunosuppressive anti-psoriasis agent. The drug targets the p40 subunit of IL-12 and IL-23 and indirectly inhibits cytokine production by Th17 cells.

Main Observations: We present a case of a 36-year-old male patient with psoriasis, who received ustekinumab therapy, applied in 45mg subcutaneous injections at week 0, 4 and than every 12 weeks. After 7 months of therapy PASI decreased from 10,1 to 0,9. At this phase of therapy he developed two patches of alopecia areata on the scalp. The diagnosis was made based on clinical appearance and was confirmed by trichoscopy (hair and scalp dermoscopy) and reflectance confocal microscopy. The development of alopecia areata was preceded by emotional stress and dental infection.

Conclusion: Ustekinumab seems an unlikely cause of alopecia areata in this patient. However, lack of efficacy is preventing hair loss may indicate that interleukin-12 cytokine family is not a key player in pathogenesis of alopecia areata.

Introduction

According to sparse epidemiological data up to 21% of patients with alopecia areata have psoriasis as coexisting disease.[1] In both diseases an autoimmune process is the likely pathogenic mechanism, and both show at least partial response to classical immunosuppressive therapy.[2,3]

Attempts to treat alopecia areata with biological, immunosuppressive, anti-psoriasis drugs, which target specific molecules, such as tumor necrosis alpha (adalimumab, etanercept, infliximab), CD2 (alefacept) or CD11a (efalizumab) were unsuccessful.[4] This may lead to the in indirect conclusion that these molecules do not play a key role in alopecia areata. In contrast, IL-12 is believed to be an important player in autoimmune reactions responsible for both diseases, psoriasis and alopecia areata.[5]

We present a case of a patient, who developed alopecia areata during treatment of psoriasis with the new immunosuppressive biological drug, ustekinumab, which targets the p40 subunit of IL-12 and IL-23.

Case report

A 36-year-old, otherwise healthy, male patient with a 4 year history of moderate to severe psoriasis. Family anamnesis was negative except for an episode of alopecia areata in his mother. The patient's psoriasis was previously treated unsuccessfully with PUVA, UVB 311 nm and acitretin. Ustekinumab was applied in 45mg subcutaneous injections at week 0, 4 and every 12 weeks thereafter. After 7 months of therapy the patient achieved significant improvement. PASI (Psoriasis Activity and Severity Index) decreased from 10,1 to 0,9. Body surface area affected by psoriasis lesions decreased from 20% to 0,2%. At this time, the patient developed two patches of hair loss, 3 and 4 cm in diameter, clinically corresponding to alopecia areata (Fig. 1a).

According to anamnesis the development of these lesions was preceded by emotional stress, which occurred few weeks prior to hair loss and a dental infection, which developed few days before onset of hair loss.

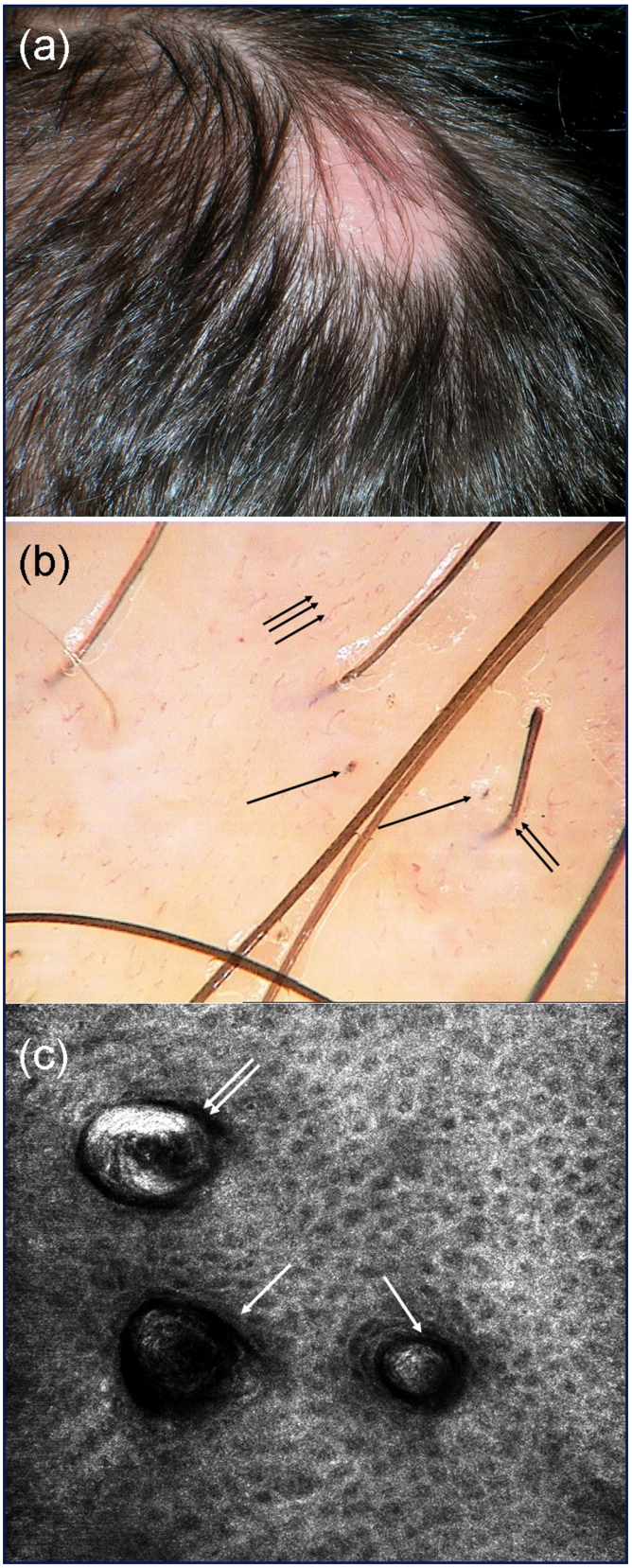

Figure 1

Hair loss in the patient treated with ustekinumab (a); Trichoscopy image of the lesion shows black dots (single arrows) and a tapered hair (double arrow) (b). Regularly aligned shoe lace-like blood vessels (triple arrow) may correspond to the remainder of psoriatic lesions, which are macroscopically not visible (70-fold magnification); Reflectance confocal microscopy image shows empty hair follicles (single arrows) and a cadaverized hair (double arrow). The epidermis is normal (c).

Trichoscopy (hair and scalp dermoscopy) of the affected areas, performed with Fotofinder II, showed regularly distributed empty hair follicle openings, "cadaverized hairs" (black dots), and tapered hairs. Average hair thickness of terminal hairs was normal (Fig. 1b).

Reflectance confocal microscopy, performed with Vivascope 1500, showed multiple empty hair follicles and cadaverized hairs in the affected area, surrounded by dermal papillae with slightly dilated microvessels. The epidermis and hair structure were normal (Fig. 1c).

Additionally fungal infection was excluded based on light microscopy and culture.

Discussion

The IL-12 family of cytokines plays a key role in the regulation of T cell responses and in autoimmunity.[5] IL-12 is a heterodimeric cytokine composed of two covalently linked chains with masses of 35 and 40 kDa. IL-12 is produced by dendritic cells, skin Langerhans cells, B lymphocytes and phagocytic cells. It promotes differentiation of naïve T-cells into Th1 cells. IL-12 also stimulates production of several cytokines, including interferon γ and tumor necrosis factor α (TNF-α) by T lymphocytes and natural killer (NK) cells. The cytokine also enhances the cytotoxic activity of NK cells and CD8+ cytotoxic T lymphocytes. Several data indicate that IL-12 is involved in the pathogenesis of alopecia areata. Serum concentration of this cytokine is significantly increased in patients with alopecia areata. Elevated expression of IL-12 has been found in skin lesions from patients with alopecia areata and C3H / HeJ AA mice.[6]

Another cytokine of the IL-12 family is IL-23. IL-23 shares with IL-12 the p40 subunit.[7] IL-23 is produced by activated macrophages and dendritic cells. It mediates inflammation and autoimmunity by stimulatin proliferation of Th17 cells, which produce proinflammatory cytokines, such as IL-6, IL-22, TNFa and cytokines of IL-17 family.[7] This cytokine was not studied in alopecia areata.

Ustekinumab (CNTO-1275) is a fully human monoclonal antibody that neutralizes IL-12 and IL-23 bioactivity by blocking interactions between the shared p40 subunit and the receptor IL-12Rβ1.[8] Ustekinumab was shown to decrease mRNA expression of IL12p40, IL23p19, and INF-γ in the skin and to inhibit IL-12- and IL-23-induced IFN-γ, IL-17A, TNF-α, IL-2, and IL-10 secretion.[8] This agent was approved for psoriasis in 2009 and is now in the approval process for psoriatic arthritis.

Our patient with psoriasis achieved significant improvement upon treatment with ustekinumab. After 7 months of therapy he developed alopecia areata of the scalp, confirmed by trichoscopy[9] and reflectance confocal microscopy.[10] The triggering factor of alopecia areata is unclear. It seems unlikely that this was an adverse event related to ustekinumab therapy. Emotional stress and dental infection might have contributed to development of alopecia areata.

What draws attention is that ustekinumab did not prevent hair loss, despite high IL-12 expression being a shared immunological abnormality in psoriasis and alopecia areata.[5]

Cases of developing alopecia areata during treatment with other immunosuppressive anti-psoriatic biological drugs were previously decribed. This included alopecia areata in patients, who received adalimumab, etanercept, infliximab, alefacept and efalizumab for psoriasis. A phase II, placebo-controlled trial of efalizumab treatment showed no statistically significant effect on hair regrowth, quality-of-life, or changes in biologic markers of disease severity in patients with alopecia areata.[2]

Development of alopecia areata during biological therapy of psoriasis shows features of a "biological drug-induced Renbök phenomenon". The Renbök phenomenon or inverse Köbner phenomenon refers to normal hair growth in psoriatic lesions observed in patients with coexisting psoriasis and alopecia areata.[1] It may be hypothesized that in severe psoriasis the immune system inhibits development of alopecia areata, in patients who would otherwise have the disease. Successful therapy of psoriasis may contribute to an immune switch, which facilitates alopecia areata in these patients. There are however no immunological data to support this hypothesis.

References

1. Criado PR, Valente NY, Michalany NS, Martins JE, Romiti R, Aoki V, Vasconcellos C. An unusual association between scalp psoriasis and ophiasic alopecia areata: the Renbök phenomenon. *Clin Exp Dermatol*. 2007; 32: 320-1.
2. Kos L, Conlon J. An update on alopecia areata. *Curr Opin Pediatr*. 2009; 21: 475-80.
3. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, Gottlieb AB, Koo JY, Lebwohl M, Lim HW, Van Voorhees AS, Beutner KR, Bhushan R. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol*. 2009; 61: 451-85.
4. Tosti A, Pazzaglia M, Starace M, Bellavista S, Vincenzi C, Tonelli G.Alopecia areata during treatment with biologic agents. *Arch Dermatol*. 2006; 142: 1653-4.
5. Gee K, Guzzo C, Che Mat NF, Ma W, Kumar A. The IL-12 family of cytokines in infection, inflammation and autoimmune disorders. *Inflamm Allergy Drug Targets*. 2009; 8: 40-52.
6. Barahmani N, Lopez A, Babu D, Hernandez M, Donely SE, Duvic M. Serum T helper 1 cytokine levels are greater in patients with alopecia areata regardless of severity or atopy. *Clin Exp Dermatol*. 2009 Oct 23. [Epub ahead of print]
7. Tan ZY, Bealgey KW, Fang Y, Gong YM, Bao S. Interleukin-23: immunological roles and clinical implications. *Int J Biochem Cell Biol*. 2009; 41: 733-5.
8. Elliott M, Benson J, Blank M, Brodmerkel C, Baker D, Sharples KR, Szapary P. Ustekinumab: lessons learned from targeting interleukin-12/23p40 in immune-mediated diseases. *Ann N Y Acad Sci*. 2009; 1182: 97-110.
9. Inui S, Nakajima T, Itami S. Coudability hairs: a revisited sign of alopecia areata assessed by trichoscopy. *Clin Exp Dermatol*. 2009 Oct 23. [Epub ahead of print]
10. Rudnicka L, Olszewska M, Rakowska A. In vivo reflectance confocal microscopy: usefulness for diagnosing hair diseases. *J Dermatol Case Rep*. 2008; 4: 55-59.