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Case presentation

Repigmentation of hair following adalimumab therapy

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Abstract

Repigmentation of canities, or age-related grey or white hair, is a rare occurrence. Generalized repigmentation of grey-white hair has been reported following inflammatory processes,[1] and heterochromia (localized patches of hair repigmentation) is even more unusual, reported in association with medication use and malignancy.

Tumor necrosis factor (TNF) inhibitors are increasingly utilized medications for inflammatory disorders, including psoriasis, rheumatoid arthritis, and inflammatory bowel disease. Hair loss, or alopecia, has been described among the side effects of these medications,[2] but changes in hair pigmentation in association with this class of drugs have not previously been reported. We describe a patient with hair repigmentation associated with adalimumab therapy.

Keywords: **biologics, TNF inhibitors, achromotrichia, aging**

Abbreviations:
IL: interleukin
RA: rheumatoid arthritis
TNF: tumor necrosis factor

Case synopsis

A 75-year-old African-American woman with a 30-year history of uniformly grey-white hair presented to clinic describing the return of her natural, brown-black hair color over the frontal, temporal, lateral parietal, and occipital regions of the scalp over the past two-and-a-half months. Her past medical history was significant for rheumatoid arthritis (RA), asthma/hyperreactive airway disease, hypertension, esophageal reflux disease, keratoconjunctivitis sicca, and anxiety. Four months prior to presentation, due to persistent activity of her RA, her rheumatologist discontinued etanercept therapy and initiated adalimumab, 40 mg subcutaneously every two weeks.

Her other medical conditions were controlled on stable doses of medications (fluticasone nasal spray, albuterol sulfate inhaler, losartan, omeprazole, cyclosporine ophthalmic emulsion, lubricant eye drops, benzonatate, and lorazepam). The patient also had received occasional courses of prednisone over the past several years at times of increased RA disease activity. She denied pruritus, tenderness, flaking, or other scalp symptoms, had not recently used new hair or facial products, cosmetics, or topical medications, and denied any recent illnesses.

On exam, the patient had fine, grey-white hair with diffuse non-scarring alopecia of her crown (Figure 1). Repigmented dark brown-black terminal hairs were observed symmetrically across her frontal scalp as well as along the lateral parietal and posterior occipital regions (Figures 2 and 3). There was no underlying erythema, pustules, crust or scale, and the hair pull test was negative. The patient declined biopsy.

Figures 1, 2, and 3

Given initial control of the patient's RA with adalimumab and the patient's lack of concern regarding the change in hair color, drug withdrawal was unnecessary. Subsequently, however, the patient had increased disease activity and switched from adalimumab to golimumab (50 mg subcutaneously once every 4 weeks). After one year with good RA control on golimumab, the patient's hair continued to grow dark brown with increased pigmentation extending more centrally (Figure 4). Per the patient's report, her medical history and medications had not otherwise changed in in the past 12 months.

Discussion

While hair loss is a common and usually reversible side effect of many medications, drug-associated changes in hair color (darkening or lightening) and texture (kinking or curling) are rarely reported. To our knowledge, this is the first report of hair repigmentation in association with use of a tumor necrosis factor (TNF) inhibitor.

Isolated cases of hair repigmentation in association with latanoprost, lenalidomide, para-aminobenzoic acid, acitretin, etretinate, corticosteroids, cyclosporine, L-thyroxine, verapamil, tamoxifen, levodopa, cisplatin, erlotinib, and imatinib have been reported,

with an average latency period of 3 to 12 months [3-5]. Of these, etretinate, erlotinib, and lenalidomide have been the most commonly reported (three, two and two cases, respectively)[4,6-8]. In only two of the reported cases has the diagnosis of drug-induced repigmentation been supported by the return of the patients' original hair color upon discontinuation of the drug (etretinate in both cases).[6]

The pathogenesis of drug-induced hair repigmentation is unclear. Active follicular melanogenesis occurs only during the anagen phase, unlike epidermal melanogenesis, which is continuous,[8] and is dependent upon numerous cytokines, neurotransmitters, and hormonal signals to initiate the synthesis of melanin in hair bulb melanocytes and its subsequent transfer to hair bulb keratinocytes.[9,10]

TNF is one of many known inhibitors of melanogenesis;[10] others include agouti protein, melatonin, interleukin (IL)-1, IL-6, transforming growth factor-β, interferon-gamma, glucocorticoids, triiodothyronine, and dopaminergic and cholinergic agonists. Interestingly, lenalidomide, a medication associated with hair repigmentation, is also known to inhibit TNF.[4]

Adalimumab is a fully human monoclonal IgG1 antibody that binds both soluble and transmembrane TNF. Of all the currently available TNF inhibitors, it is most structurally similar to golimumab, which is also a fully human monoclonal IgG1 antibody. The pharmacokinetics of the two drugs are very similar. It is plausible that the presence of TNF in the hair follicle microenvironment mediates a reduction in melanosome transfer from melanocyte stem cells to keratinocytes. For instance, in a recent study of psoriasis, a T-helper 1 (Th1) and Th17-mediated disease with elevated levels of TNF in patient serum and lesions, lesions displayed an increase in melanocyte number and a simultaneous decrease in pigmentation signaling.[11]

Up to the age of 45 years, there are approximately 7 to 15 melanocyte replacement cycles, a number that is largely genetically determined.[10] Pigment loss in greying hair follicles results from reductions in melanogenically-active melanocytes in the hair bulb, although the precise events by which active melanocytes are lost are unclear.[9] There appears to be a specific defect of melanosome transfer from melanocyte to keratinocyte in greying hair follicles,[12] suggesting that alteration of follicular microenvironment cytokines, such as TNF, may stimulate melanocyte migration, differentiation, and activation.[9]

Inducers of melanogenesis act both sequentially and in parallel and include alpha-melanocyte stimulating hormone, adrenocorticotrophic hormone, β-endorphin, prostaglandins, endothelins 1 and 3, estrogens, androgens, histamine, vitamin D3, and bone morphogenic proteins.[10] The nutritional factors L-tyrosine and L-dopa may also act as stimulators of melanogenesis, in addition to their primary function as substrates of melanin.[10]

Cases of repigmentation of scalp hair in areas surrounding melanomas and lentigo malignas[13,14] highlight the importance of close surveillance of patients who present with hair repigmentation of unknown etiology, and suggest paracrine secretion of mediators of these malignancies may activate hair follicle melanocytes via alteration of the cellular milieu affecting tyrosine kinase receptor activity.[13]

To the authors' knowledge, this is the first reported case of hair repigmentation associated with TNF inhibitor therapy. While causation in this case is not definitive, the temporal onset of hair repigmentation, absence of new exposures, lack of new hair practices, and stable doses of her other medications strongly support the association of her hair repigmentation with adalimumab and golimumab. Although there is limited research on the subject, this association has theoretical merit that TNF inhibition can lead to hair repigmentation.

References

1. Seckin D, Yildiz A. Repigmentation and curling of hair after acitretin therapy. The Australasian journal of dermatology. Aug 2009;50(3):214-216. [PMID: 9659987].
2. Lutf A, Hammoudeh M. Weight Gain and Hair Loss during Anti-TNF Therapy. International journal of rheumatology. 2012;2012:593039. [PMID: 22927859].
3. Etienne G, Cony-Makhoul P, Mahon FX. Imatinib mesylate and gray hair. The New England journal of medicine. Aug 8 2002;347(6):446. [PMID: 12167692].
4. Dasanu CA, Mitsis D, Alexandrescu DT. Hair repigmentation associated with the use of lenalidomide: graying may not be an irreversible process! Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners. Jun 2013;19(2):165-169. [PMID: 22440400].
5. Cheng YP, Chen HJ, Chiu HC. Erlotinib-induced hair repigmentation. International journal of dermatology. Jan 2014;53(1):e55-57. [PMID: 23432346].
6. Nanda A, Alsaleh QA. Hair discoloration caused by etretinate. Dermatology. 1994;188(2):172. [PMID: 8136552].

7. Vesper JL, Fenske NA. Hair darkening and new growth associated with etretinate therapy. Journal of the American Academy of Dermatology. May 1996;34(5 Pt 1):860. [PMID: 8632091].
8. Paus R, Cotsarelis G. The biology of hair follicles. The New England journal of medicine. Aug 12 1999;341(7):491-497. [PMID: 10441606].
9. Tobin DJ. Human hair pigmentation--biological aspects. International journal of cosmetic science. Aug 2008;30(4):233-257. [PMID: 18713071].
10. Slominski A, Wortsman J, Plonka PM, Schallreuter KU, Paus R, Tobin DJ. Hair follicle pigmentation. The Journal of investigative dermatology. Jan 2005;124(1):13-21. [PMID: 15654948].
11. Wang CQ, Akalu YT, Suarez-Farinas M, et al. IL-17 and TNF synergistically modulate cytokine expression while suppressing melanogenesis: potential relevance to psoriasis. The Journal of investigative dermatology. Dec 2013;133(12):2741-2752. [PMID: 23732752].
12. Tobin DJ, Paus R. Graying: gerontobiology of the hair follicle pigmentary unit. Experimental gerontology. Jan 2001;36(1):29-54. [PMID: 11162910].
13. Inzinger M, Massone C, Arzberger E, Hofmann-Wellenhof R. Hair repigmentation in melanoma. Lancet. Oct 5 2013;382(9899):1224. [PMID: 24095196].
14. Dummer R. Clinical picture: hair repigmentation in lentigo maligna. Lancet. Feb 24 2001;357(9256):598. [PMID: 11558486].