Finasteride Associated Melasma in a Caucasian Male

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ABSTRACT

Melasma is an acquired hypermelanosis that typically affects sun-exposed areas on the face and presents as symmetric brownish macules and patches. It is most commonly reported in women and thought to be related to the effects of estrogen and progesterone on melanocytes. Since the advent of finasteride 1mg daily tablets for the treatment of androgenic alopecia, we have noticed an increase in the number of men presenting with melasma. Here we present one of those cases. We hypothesize this could be related to the effects of finasteride on estrogen and progesterone concentrations in the skin.

J Drugs Dermatol. 2014;13(4):484-486.

INTRODUCTION

Melasma is an acquired hypermelanosis that typically affects sun-exposed areas on the face and presents as symmetric brownish macules and patches coalescing in a reticular pattern.[1] An estimated 6 million women in the US and 45-50 million women worldwide are affected by melasma.[2] Men comprise 10% of the affected population.[3] Histologically, melasma typically presents with hyperpigmentation of the basal layer of the epidermis with or without a slight increase in the number of melanocytes. In the papillary dermis, there is often solar elastosis and mast cells compared to normal skin, along with variable number of melanophages and free pigment.[3] Oral contraceptive pills, estrogen replacement therapy, ovarian tumors, ovarian and thyroid dysfunction have been shown to induce melasma, suggesting a role for hormonal changes in melasma pathogenesis.[1,4]

Finasteride is currently approved for the treatment of benign prostatic hyperplasia (BPH) and androgenetic alopecia. It exerts its effects via inhibition of 5α-reductase, the enzyme, which converts testosterone to dihydrotestosterone. Decreased libido, sexual dysfunction, depression, and gyencomastia have been reported as side effects of finasteride use for BPH.[5-10] These side effects are thought to be subsequent to the hormonal changes induced by finasteride. We report here the case of one patient who developed melasma post treatment with low-dose finasteride (trade name Propecia®) for androgenetic alopecia. We hypothesize that hormonal changes elicited by finasteride use for androgenetic alopecia are responsible for the development of melasma in select patients.

CASE REPORT

A 27-year-old Caucasian man with no past medical history presented to our clinic complaining of brownish discoloration on this bilateral temples and forehead. He reported that this rash initially started on his bilateral temples two years ago, approximately 6-8 months after having started low-dose finasteride (Propecia®) for prevention of androgenetic alopecia. He denied any sunburns, rashes, chemical exposure or topical application of medical or cosmetic agents to these areas prior to noticing the discoloration. The patient reported noticing an association between his rash and low-dose finasteride, and as such discontinued the medicine approximately 6 months prior to his dermatology appointment. Nonetheless, he reported that his rash continued to progress onto his forehead. On examination, symmetric, slightly reticulated, tan-brown patches were noted on the patient's forehead and bilateral temples (Figure 1-3).

Given his presentation, the patient was diagnosed with melasma. Over the ensuing several months, the patient underwent treatment with a series of chemical peels, as well as strict sun protection, and noted moderate improvement in his melasma.

DISCUSSION

Studies have suggested that estradiol and progesterone may be responsible for the pigmentary changes observed in melasma via increasing melanocyte number or increasing tyrosinase activity. In fact, significantly increased levels of serum progesterone were reported in Japanese melasma patients.[11]

Immunohistochemical evaluation of melasma affected lesions showed increased expression of progesterone receptors as well as estrogen receptor beta (ERβ) around small vessels when compared to unaffected epidermal areas.[12] Another study illustrated a donor specific response of estrogen

FIGURE 1. Symmetric, slightly reticulated, tan-brown patches on forehead.

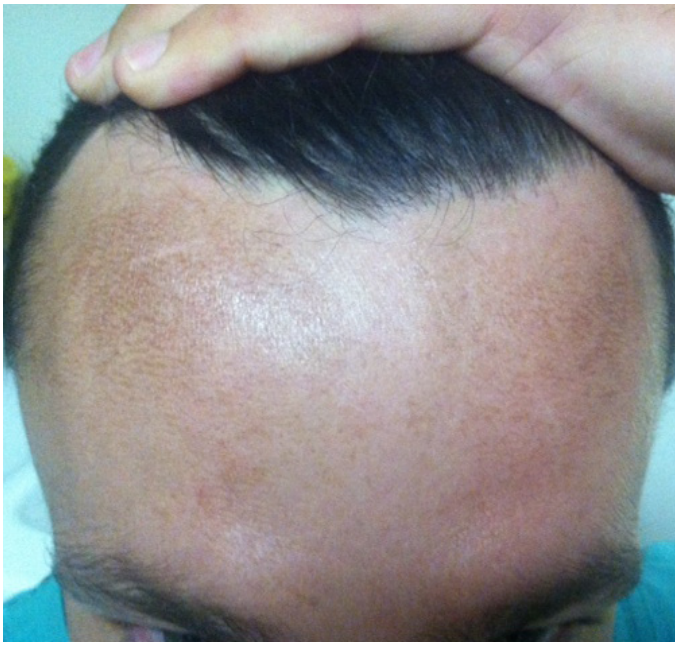
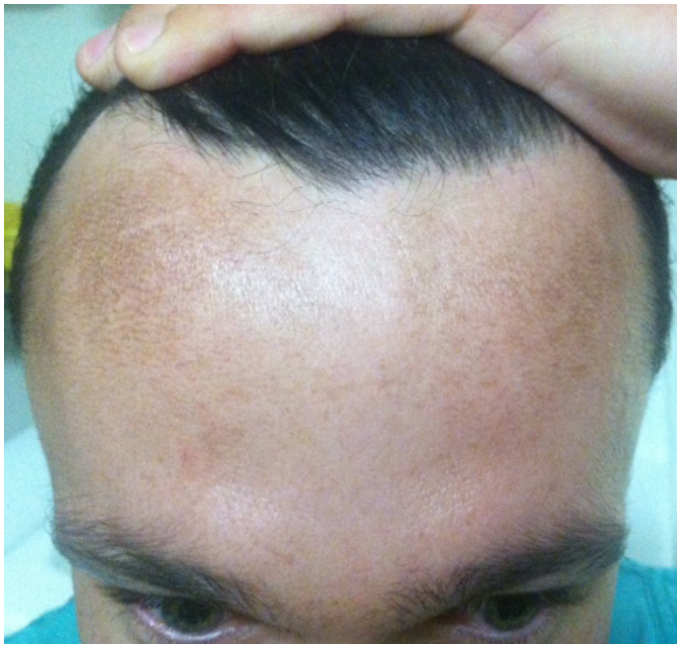
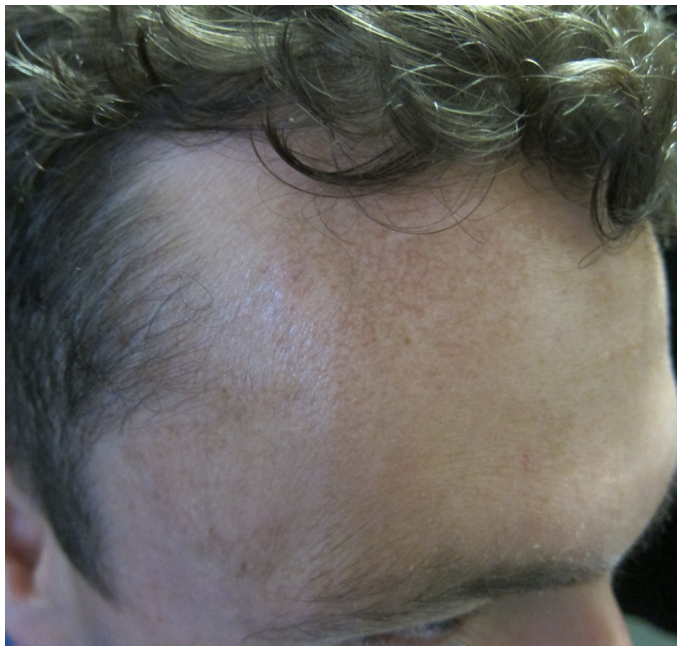


FIGURE 2. Closer view of symmetric, slightly reticulated, tan-brown patches on forehead.



and progesterone on human melanocytes.[13] When human melanocytes were exposed to estrogen at concentrations of 1nM and 100nM, 2 out of 5 samples showed enhanced basal pigmentation. Furthermore, when melanocytes from 8 donors were exposed to estrogen and progesterone for 6 days, a donor-specific response was noted: in three, the number of melanocytes and tyrosine hydroxylase activity increased; one donor showed only increased tyrosinase activity; 4 donors remained unchanged. Kippenberger et al. showed that when in vitro cultured melanocytes were treated with estradiol, tyrosinase acitivity increased 1.5-2.5 fold, and tyrosinase-related-protein (TRP-2) activity increased approximately 20-fold, again suggesting that estradiol mediates hyperpigmentation by inducing tyrosinase activity.[14] Furthermore, Maeda et al. demonstrated that a a two-day incubation of human melanocytes in estradiol, estriol, and progesterone induced melanocyte enlargement.[15]

FIGURE 3. Slightly reticulated, tan-brown patches on right forehead.



Finasteride's effects on progesterone may underlie its association with melasma. Finasteride inhibits the type II isoform of 5α-reductase, which is also partially responsible for the conversion of progesterone to dihydroprogesterone.[16] We proprose that inihibition of 5α-reductase leads to increased levels of progesterone in the skin, which induces the hyperpigmentation observed in melasma.

Finasteride treatment in androgenetic alopecia has also been shown to increase free testosterone levels and decrease dihydrotestosterone (DHT).[17,18] DHT exerts an inhibitory effect on P450 aromatase, which carries out the aromatization of testosterone to estrogen.[19] Thus, with finasteride treatment, reduced levels of DHT and increased levels of testosterone would be expected, which may result in enhanced activity of P450 aromatase, and enhanced aromatization of testosterone to estradiol. In fact, moderate increase in serum levels of estrone (E1) and estradiol (E2) has been reported in patients on finasteride therapy. [19] Increased conversion of testosterone to estradiol has also been suggested to play a role in the development of gyne-

comastia in BPH patients on finasteride therapy.[8-10] Therefore, we hypothesize that the development of melasma observed in our patients on finasteride therapy may be due to the potential increased activity of P450 aromatase and increased levels of estradiol induced by finasteride, locally in the skin. Additional research in this area will be needed to confirm this hypethesis.

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In conclusion, we propose two mechanisms underlying the association between melasma and finasteride: 1) finasteride's inhibition of 5α-reductase leads to increased levels of progesterone available to drive the pigmenatry changes observed, and 2) finasteride induces decreased DHT levels and increased testosterone levels available for aromatization to estradiol, which subsequently induces enhanced pigmentation. Furthermore, physicians and patients should be aware of this uncommon, though unwanted, potential side effect of finasteride for androgenetic alopecia.

DISCLOSURES

The authors do not have any financial interests to disclose.

REFERENCES

1. Lapeere H, Boone B, Schepper SD, Verhaeghe E, Ongenae K, Geel NV, Lambert J, Brochez L, Naeyaert J. Chapter 73. Hypomelanoses and Hypermelanoses. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, eds. *Fitzpatrick's Dermatology in General Medicine*. 7th ed. New York: McGraw-Hill; 2008. http://www.accessmedicine.com/content.aspx?aID=2973170. Accessed February 23, 2012.
2. Melasma. Available at http://www.medicinenet.com/melasma/article.htm. Accessed Feb 24, 2012.
3. Wolff K, Johnson RA, Suurmond D. Section 13. Pigmentary Disorders. In: Wolff K, Johnson RA, Suurmond D, eds. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*. 6th ed. New York: McGraw-Hill; 2009. http://www.accessmedicine.com/content.aspx?aID=5187746. Accessed February 24, 2012.
4. Newcomer V D, Lindbert MC, Stenbert T H. Melanosis of the face ('chloasma'). *Arch Dermatol* 1961: 83:284–297.
5. Irwig MS, Kolukula S. Persistent sexual side effects of finasteride for male pattern hair loss. *J Sex Med*. 2011;8(6):1747-53.
6. Traish AM, Hassani J, Guay AT, et al. Adverse side effects of 5α-reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. *J Sex Med*. 2011;8(3):872-84.
7. Römer B, Gass P. Finasteride-induced depression: new insights into possible pathomechanisms. *J Cosmet Dermatol*. 2010;9(4):331-2.
8. Ramot Y, Czarnowicki T, Zlotogorski A. Finasteride induced Gynecomastia: Case report and Review of the Literature. *Int J Trichology*. 2009;1(1):27-9.
9. Ferrando J, Grimalt R, Alsina M, et al. Unilateral gynecomastia induced by treatment with 1 mg of oral finasteride. *Arch Dermatol*. 2002;138(4):543-4.
10. Carlin BI, Seftel AD, Resnick MI, et al. Finasteride induced gynecomastia. *J Urol*. 1997;158(2):547.
11. Sato N. Endocrine environment in adult females with chloasma. *Jpn J Dermatol* 1987; 97: 937-43.
12. Jang YH, Lee JY, Kang HY, et al. Oestrogen and progesterone receptor expression in melasma: an immunohistochemical analysis. *J Eur Acad Dermatol Venereol*. 2010;24(11):1312-6.
13. Im S, Lee ES, Kim W, et al. Donor specific response of estrogen and progesterone on cultured human melanocytes. *J Korean Med Sci*. 2002;17(1):58-64.
14. Kippenberger S, Loitsch S, Solano F, et al. Quantification of tyrosinase, TRP-1, and Trp-2 transcripts in human melanocytes by reverse transcriptase-competitive multiplex PCR--regulation by steroid hormones. *J Invest Dermatol*. 1998;110(4):364-7.
15. Maeda K, Naganuma M, Fukuda M, et al. Effect of pituitary and ovarian hormones on human melanocytes in vitro. *Pigment Cell Res*. 1996 Aug;9(4):204-12.
16. Finn DA, Beadles-Bohling AS, Beckley EH, et al. A new look at the 5alpha-reductase inhibitor finasteride. *CNS Drug Rev*. 2006;12(1):53-76.
17. Duskova M, Hill M, Starka L. Changes of metabolic profile in men treated for androgenetic alopecia with 1 mg finasteride. *Endocr Regul*. 2010 Jan;44(1):3-8.
18. Camacho FM, García-Hernández MJ, Fernández-Crehuet JL. Value of hormonal levels in patients with male androgenetic alopecia treated with finasteride: better response in patients under 26 years old. *Br J Dermatol*. 2008 May;158(5):1121-4.
19. Castro-Magana M, Angulo M, Fuentes B, et al. Effect of finasteride on human testicular steroidogenesis. *J Androl*. 1996 Sep-Oct;17(5):516-21.

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