CLINICAL VIGNETTE

Tamoxifen-Induced Melasma

Lumbini Chandrasekera, Aarthi Arasu, MD and Jennifer Han, MD

Case

A 52-year-old female with breast cancer and osteopenia presented to endocrinology for evaluation of melasma. Patient was diagnosed with stage 2 estrogen receptor-positive (ER+) progesterone receptor-positive (PR+) invasive lobular carcinoma of the right breast in ten years prior. She underwent bilateral mastectomy one month after with no adjuvant chemotherapy or radiation treatment. She was started on tamoxifen postoperatively for a ten-year course. A few months after initiating tamoxifen, the patient developed melasma of the face, which acutely worsened on year seven of treatment. She was evaluated and followed by dermatology and is on a regimen of hydroquinone, glycolic peels, tretinoin, tranexamic acid and cysteamine.

The patient reports she had a copper intrauterine device placed in 8 years prior and has been experiencing irregular menstrual cycles for one year prior to our visit with her last menstrual period six months prior. She also reports recent weight gain of ten pounds over nine months despite four to five hours of weekly exercising weightlifting and cardio. On physical examination, vital signs are stable and body mass index is 24.75. Laboratory data includes estradiol level of 256 pg/mL, Follicle-Stimulating Hormone of 27.9 mIU/mL, Luteinizing Hormone of 24.1 mIU/mL, Free Thyroxine of 1.10 ng/dL, and Thyroid Stimulating Hormone of 3.6 mcIU/mL.

After initial evaluation, the patient was started on metformin as a possible endocrinologic intervention to control melasma. At four-month follow-up, she reports mild, subjective lightening in her melasma without side effects.

Discussion

Melasma is a common acquired hyperpigmentary disorder seen most often on the face[1] and affecting people of darker skin types more significantly.[2] The reported prevalence of melasma ranges between 8.8% - 40%, depending on ethnic background and geographical area.[2] It is often the main consequence of female hormone stimulation on a predisposed genetic background.[1] There is a complex interaction between epidermal melanocytes, keratinocytes, dermal fibroblasts, mast cells, and vascular endothelial cells with hormonal, genetic, and UV influence.[2] Two notable pathomechanisms of melasma are the inappropriate activation of melanocytes as well as aggregation and overproduction of melanin in the dermis and epidermis.[3]

Acquired pigmentary disorders can be cosmetically disfiguring to individuals and negatively affect their quality of life.[4] In a study of patients diagnosed with pigmentary disorders, 47.3% were self-conscious of their skin, 21.8% felt others focused on their skin, 32.7% felt unattractive because of their skin, 32.7% spent effort hiding pigmentary changes, and 23.6% felt their skin affected their daily leisure and routine activities.[4] Melasma has high incidence among pigmentary disorders causing emotional distress, with negative impact on social life.[5] Out of twelve studies comparing Melasma Area and Severity Index (MASI) with Melasma Quality of Life (MELASQoL), five studies showed that MASI and MELASQoL scores were inversely correlated.[5] A systematic review and meta-analysis of melasma influence on patients' quality of life concluded melasma was associated with psychological distress causing frustration, embarrassment, loss of confidence with negative impact on relationships.[5]

Tamoxifen rarely causes melasma. Tamoxifen is used often in adjuvant therapy to reduce risk of recurrence and death in women with ER+ breast cancers.[6] Tamoxifen is a selective estrogen-receptor modulator (SERM), having mixed estrogen receptor agonist and antagonistic activity, with antagonistic activity assisting treatment of breast cancer.[7] We found only one other report where a female developed pigmented macules on the face after a one-month administration of tamoxifen for treatment of breast cancer.[8] There may be a causal relationship of melasma by tamoxifen, but the exact mechanism is unknown. Binding studies utilizing radioactive estradiol demonstrated the presence of estrogen receptors (ERs) on the skin, with greater concentrations on the face compared to other parts of the body such as the thigh or breast.[9] Our studies concluded that SERMS such as tamoxifen and raloxifene act as estrogen agonists on the skin, opposite to their antagonistic effect on the breast.[10] Additional binding studies have shown the presence of ERs on melanocytes and the direct stimulating effect of estrogen treatment on those melanocytes.[11] Furthermore, both estradiol and raloxifene have strong stimulating effects on skin fibroblasts[12] which cause them to secrete factors that affect melanogenesis and melanocyte proliferation.[1] Proliferation and stimulation of melanocytes increases the production of melanin which may explain how tamoxifen, an estrogen agonist on skin, can cause hyperpigmentation consistent with melasma.

Promising treatments include oral tranexamic acid (oTA), microneedling, chemical peeling, topical treatments, lasers such as Q-switched Nd:YAG laser (QSNY), and light therapy such as intense pulsed light (IPL).[2] Treatment of melasma is challenging considering its complex pathogenesis is not yet completely elucidated, making it difficult to target therapy, and increases recurrence risk post treatment.[13] The mainstay of physician prescribed melasma treatment has been topical creams including hydroquinone (HQ) and triple combination cream (TCC) due to their convenience, affordability, efficacy, and low recurrence rates of melasma.[2] A meta-analysis compared the efficacy of melasma treatment between multiple interventions using a SUCRA score, a percentage representing the efficacy of an intervention compared with placebo (14). It determined QSNY to have the highest SUCRA of 85.0%, followed by IPL at 79.6%, ablative fractional laser (AFL) at 78.6%, TCC at 75.8%, topical Vitamin C at 68.5%, oTA at 63.3%, and topical tranexamic acid, tretinoin, and HQ having lower scores at 33.2%, 32.9%, and 29.4% respectively.[14]

Metformin, an oral antihyperglycemic drug is used to treat insulin resistance in patients with diabetes. It also has been shown to have positive effects on inflammatory skin diseases like psoriasis, acne, and allergic contact dermatitis. It is especially effective in acanthosis nigricans, hyperpigmentation in patients with obesity or insulin resistance.[15] A small study, involved patients with insulin-dependent juvenile acanthosis nigricans associated with obesity treated with metformin reported marked resolution of their acanthosis nigricans.[16] Another study investigated the inhibitory effects of metformin on melanogenesis in vitro and in vivo. They reported metformin reduced melanin content in melanoma cancer cells as well as normal human melanocytes.[17] Topical metformin's depigmenting effect was successfully demonstrated on reconstituted human epidermis and human skin biopsies.[17] This suggests that metformin can be used for treatment of skin hyperpigmentation such as melasma.

The direct relationship between tamoxifen and melasma has not been fully investigated and metformin treatment for melasma needs further confirmation. We report this case to remind providers to caution patients of melasma as a possible outcome of tamoxifen given as adjuvant therapy for breast cancers.

REFERENCES

1. **Passeron T, Picardo M**. Melasma, a photoaging disorder. *Pigment Cell Melanoma Res*. 2018 Jul;31(4):461-465. doi: 10.1111/pcmr.12684. Epub 2018 Jan 12. PMID: 29285880.
2. **Neagu N, Conforti C, Agozzino M, Marangi GF, Morariu SH, Pellacani G, Persichetti P, Piccolo D, Segreto F, Zalaudek I, Dianzani C**. Melasma treatment: a systematic review. *J Dermatolog Treat*. 2022 Jun;33(4): 1816-1837. doi: 10.1080/09546634.2021.1914313. Epub 2022 Mar 23. PMID: 33849384.
3. **Artzi O, Horovitz T, Bar-Ilan E, Shehadeh W, Koren A, Zusmanovitch L, Mehrabi JN, Salameh F, Isman Nelkenbaum G, Zur E, Sprecher E, Mashiah J**. The pathogenesis of melasma and implications for treatment. *J Cosmet Dermatol*. 2021 Nov;20(11):3432-3445. doi: 10.1111/jocd.14382. Epub 2021 Aug 19. PMID: 34411403.
4. **Yadav A, Garg T, Mandal AK, Chander R**. Quality of life in patients with acquired pigmentation: An observational study. *J Cosmet Dermatol*. 2018 Dec;17(6):1293-1294. doi: 10.1111/jocd.12686. Epub 2018 Jul 11. PMID: 29998547.
5. **Zhu Y, Zeng X, Ying J, Cai Y, Qiu Y, Xiang W**. Evaluating the quality of life among melasma patients using the MELASQoL scale: A systematic review and meta-analysis. *PLoS One*. 2022 Jan 27;17(1):e0262833. doi: 10.1371/journal.pone.0262833. PMID: 35085327; PMCID: PMC8794204.
6. **Shien T, Iwata H**. Adjuvant and neoadjuvant therapy for breast cancer. *Jpn J Clin Oncol*. 2020 Mar 9;50(3):225-229. doi: 10.1093/jjco/hyz213. PMID: 32147701.
7. **Osborne CK, Zhao H, Fuqua SA**. Selective estrogen receptor modulators: structure, function, and clinical use. *J Clin Oncol*. 2000 Sep;18(17):3172-86. doi: 10.1200/JCO.2000.18.17.3172. PMID: 10963646.
8. **Kim SW, Yoon HS**. Tamoxifen-induced melasma in a postmenopausal woman. *J Eur Acad Dermatol Venereol*. 2009 Oct;23(10):1199-200. doi: 10.1111/j.1468-3083.2009.03113.x. Epub 2009 Feb 2. PMID: 19192013.
9. **Hasselquist MB, Goldberg N, Schroeter A, Spelsberg TC**. Isolation and characterization of the estrogen receptor in human skin. *J Clin Endocrinol Metab*. 1980 Jan;50(1): 76-82. doi: 10.1210/jcem-50-1-76. PMID: 7350189.
10. **Hardman MJ, Emmerson E, Campbell L, Ashcroft GS**. Selective estrogen receptor modulators accelerate cutaneous wound healing in ovariectomized female mice. *Endocrinology*. 2008 Feb;149(2):551-7. doi: 10.1210/en.2007-1042. Epub 2007 Nov 1. PMID: 17974625.
11. **Ranson M, Posen S, Mason RS**. Human melanocytes as a target tissue for hormones: in vitro studies with 1 alpha-25, dihydroxyvitamin D3, alpha-melanocyte stimulating hormone, and beta-estradiol. *J Invest Dermatol*. 1988 Dec;91(6):593-8. doi: 10.1111/1523-1747.ep12477126. PMID: 2848074.
12. **Haczynski J, Tarkowski R, Jarzabek K, Wolczynski S, Magoffin DA, Czarnocki KJ, Ziegert M, Jakowicki J, Jakimiuk AJ**. Differential effects of estradiol, raloxifene and tamoxifen on estrogen receptor expression in cultured human skin fibroblasts. *Int J Mol Med*. 2004 Jun;13(6): 903-8. PMID: 15138633.
13. **Rajanala S, Maymone MBC, Vashi NA**. Melasma pathogenesis: a review of the latest research, pathological findings, and investigational therapies. *Dermatol Online J*. 2019 Oct 15;25(10):13030/qt47b7r28c. PMID: 31735001.
14. **Liu Y, Wu S, Wu H, Liang X, Guo D, Zhuo F**. Comparison of the Efficacy of Melasma Treatments: A Network Meta-Analysis of Randomized Controlled Trials. *Front Med (Lausanne)*. 2021 Sep 29;8:713554. doi: 10.3389/fmed.2021.713554. PMID: 34660626; PMCID: PMC8511390.

15. **Chang JE, Choi MS**. A Molecular Perspective on the Potential Benefits of Metformin for the Treatment of Inflammatory Skin Disorders. *Int J Mol Sci*. 2020 Nov 25;21(23):8960. doi: 10.3390/ijms21238960. PMID: 33255783; PMCID: PMC7728327.
16. **Hermanns-Lê T, Hermanns JF, Piérard GE**. Juvenile acanthosis nigricans and insulin resistance. *Pediatr Dermatol*. 2002 Jan-Feb;19(1):12-4. doi: 10.1046/j.1525-1470.2002.00013.x. PMID: 11860562.
17. **Lehraiki A, Abbe P, Cerezo M, Rouaud F, Regazzetti C, Chignon-Sicard B, Passeron T, Bertolotto C, Ballotti R, Rocchi S**. Inhibition of melanogenesis by the antidiabetic metformin. *J Invest Dermatol*. 2014 Oct;134(10):2589-2597. doi: 10.1038/jid.2014.202. Epub 2014 Apr 22. PMID: 24756109.