A Review of Postinflammatory Hyperpigmentation

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Postinflammatory hyperpigmentation (PIH) is an acquired form of hypermelanosis that occurs in response to inflammation or injury to the skin. It is the final, common pathway for a variety of inflammatory dermatoses (eg, atopic dermatitis, acne vulgaris, lichen planus, psoriasis), infectious processes, trauma, or therapeutic interventions. Although PIH can occur in any skin tone, it is more common and particularly problematic in darker individuals with Fitzpatrick skin types IV to VI. While many therapeutic interventions exist, the optimal treatment for PIH remains elusive.

Persons with skin of color represent a diverse range of ethnic groups including Africans, African Americans, Asians, Hispanics, and Native Americans. Within each group there is a broad spectrum of cutaneous pigmentation. The US Census Bureau predicts that minorities will represent more than one-half of the US population by the year 2050.[1] This transformation of the demographic landscape highlights the necessity for a more comprehensive understanding of skin disorders that are more prevalent, or unique, in persons with skin of color.

Pigmentary disorders are a common concern in persons with skin of color. A study conducted in 1983 involving 2000 African American patients from a private practice in Washington, DC, found that disorders of pigmentation were the third most frequent reason for presenting to a dermatologist.[2] A more recent study from a hospital-based faculty practice in New York, New York, illustrated similar findings; dyschromias were the second most common reason for African American patients to present to dermatologists.[3] Postinflammatory hyperpigmentation (PIH) is an acquired form of hypermelanosis that occurs in response to inflammation or injury to the skin. It is the final, common pathway for a variety of inflammatory dermatoses (eg, atopic dermatitis, acne vulgaris, lichen planus, psoriasis), infectious processes, trauma, or therapeutic interventions. Although PIH can occur in any skin tone, it is more common and particularly problematic in darker skinned individuals with Fitzpatrick skin types IV to VI.[4,5] The distribution of the hyperpigmention is determined by the causative disorder. Typically, the lesions are ill-defined and their color can vary from light brown to dark brown and blue-gray, depending on whether the pigmentary aberration resides within the epidermis or dermis. Epidermal pigment may take 6 to 12 months to resolve, and dermal hyperpigmentation can last for years before desired pigmentation is restored.

PATHOPHYSIOLOGY

Despite its widespread occurrence, the pathophysiology of this common phenomenon is poorly understood. There are 2 major processes believed to be involved in the development of PIH. The first is pigment incontinence, which occurs as a consequence of inflammation with subsequent disruption of the basal cell layer. Consequently, macrophages engulf melanin-laden keratinocytes and melanocytes.[5] Secondly, melanin production is increased. Arachidonic acid-derived inflammatory mediators have been shown in vitro to directly stimulate melanocyte production of melanin. Both prostaglandin E1 and prostaglandin D2 have been demonstrated to

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stimulate mammalian pigment cells in vitro and in vivo mouse models.[6] Human melanocytes cultured for 2 days in leukotrienes C4 and D4 and thromboxanes were larger, more dendritic, and displayed increased tyrosinase activity when compared to controls.[7] Endothelins, vasoconstrictive proteins produced by various cell types, are able to stimulate melanogenesis in the setting of inflammation.[8] Reactive oxygen species, super oxide, and nitric oxide, generated by damaged skin or released as by-products from inflammatory cells have also been shown to stimulate melanocytes. Kitawaki et al[9] demonstrated that postinflammatory pigmentation secondary to acne is enhanced by mediators IL-1 and prostaglandin E2, which are produced in keratinoctyes after oleic acid stimulation.

TREATMENT OF PIH

Postinflammatory hyperpigmentation is difficult to treat, especially in darker skinned individuals where aggressive therapy runs the risk for intensifying the hyperpigmentation. Unfortunately, there is limited information regarding the efficacy of available therapies in PIH. First and foremost, the foundation of therapy should focus on the prevention and treatment of the underlying disorder. Although the role of UV light in PIH has not been formerly investigated, patients are encouraged to wear sunscreen and practice sun avoidance. A variety of topical preparations have been used for the treatment of PIH with varying degrees of success. Hydroquinone remains the most prescribed bleaching agent and is the gold standard for the treatment of hyperpigmentation.[10] It exerts its effects by preventing melanin synthesis via the inhibition of the enzyme tyrosinase, and is also thought to reduce DNA and RNA synthesis and enhance melanosome degradation and melanocyte destruction.[10] Hydroquinone can be used as monotherapy or in combination with topical corticosteroids, topical retinoids, and sunscreen.

Retinoids reduce pigmentation primarily through inhibition of tyrosinase transcription and increasing epidermal turnover with resultant melanin clearance.[11] Two randomized, controlled trials with small sample sizes have evaluated the efficacy of tretinoin and tazarotene for the treatment of PIH. A randomized, double-blind, vehicle-controlled, 40-week trial demonstrated that significantly more patients had lighter lesions on the arm treated with tretinoin ($P<.001$).[12] A once-daily application of tazarotene 0.1% cream was superior to vehicle with greater reductions in the intensity and area of hyperpigmentation within 18 weeks.[13] Tyrosinase inhibitors, azelaic acid, and kojic acid have also shown variable efficacy in the treatment of PIH.

Chemical peels, specifically glycolic acid and salicylic acid peels, have exhibited some efficacy in the treatment of PIH. Joshi et al[14] used a randomized, split-face model to assess the efficacy and safety of topical salicylic acid peels for the treatment of PIH. Although the improvement of PIH was not statistically significant, the authors corroborated earlier findings regarding the safety of salicylic acid peels in patients with Fitzpatrick skin types IV to VI.[14]

Lastly, various lasers, including the Q-switched ruby laser and the pulsed dye laser, have been used for the treatment of PIH, which is often recalcitrant to laser therapy. However, recently Cho et al[15] reported 3 cases of PIH that were successfully treated using the 1064-nm Q-switched Nd:YAG laser with low fluence. In general, the results of laser therapy for the treatment of PIH are often disappointing and carry a high probability of adverse effects.

COMMENT

In conclusion, PIH is an established clinical problem that is common, poorly described, and represents an unmet medical need. Characterizing and defining the molecular mechanisms that underlie the development of PIH will not only aid in the establishment of more effective therapeutic interventions and improved patient outcome; these findings will also serve to provide vital information that will further our understanding of melanocyte biology.

REFERENCES

1. US Census Bureau. US interim projections by age, sex, race, and Hispanic origin: 2000-2050. http://www.census.gov/population/www/projections/usinterimproj. Accessed August 10, 2009.
2. Halder RM, Grimes PE, McLaurin CI, et al. Incidence of common dermatoses in a predominantly black dermatologic practice. *Cutis.* 1983;32:388, 390.
3. Alexis AF, Sergay AB, Taylor SC. Common dermatologic disorders in skin of color: a comparative practice survey. *Cutis.* 2007;80:387-394.
4. Lacz NL, Vafaie J, Kihiczak NI, et al. Postinflammatory hyperpigmentation: a common but troubling condition. *Int J Dermatol.* 2004;43:362-365.
5. Masu S, Seiji M. Pigmenty incontinence in fixed drug eruptions. histologic and electron microscopic findings. *J Am Acad Dermatol.* 1983;8:525-532.
6. Norlund JJ, Abdel-Malek ZA. Mechanisms for post-inflammatory hyperpigmentation and hypopigmentation. *Prog Clin Biol Res.* 1988;256:219-236.
7. Tomita Y, Maeda K, Tagami H. Leukotrienes and thromboxane B2 stimulate normal human melanocytes in vitro: possible inducers of postinflammatory pigmentation. *Tohoku J Exp Med.* 1988;156:303-304.
8. Yohn JJ, Smith C, Stevens T, et al. Autoregulation of endothelin-1 secretion by cultured human keratinocytes via the endothelin B receptor. *Biochim Biophys Acta.* 1994;1224:454-458.
9. Kitawaki A, Tanaka Y, Takada K. New findings on the mechanism of post-inflammatory pigmentation. *Pigment Cell Research.* Oxford, England: Blackwell Publishing; 2003.

10. Picardo M, Carrera M. New and experimental treatments of cloasma and other hypermelanoses. *Dermatol Clin.* 2007;25:353-362.
11. Lipworth A. Therapeutic approaches to pigmentary disorders. *The Dermatology Report*. 2009;3:29-36.
12. Bulengo-Ransby SM, Griffiths CE, Kimbrough-Green CK, et al. Topical tretinoin (retinoic acid) therapy for hyperpigmented lesions caused by inflammation of the skin in black patients. *N Engl J Med.* 1993;328:1438-1443.
13. Grimes P, Callender V. Tazarotene cream for postinflammatory hyperpigmentation and acne vulgaris in darker skin: a double-blind, randomized, vehicle-controlled study. *Cutis.* 2006;77:45-50.
14. Joshi SS, Boone SL, Alam M, et al. Effectiveness, safety, and effect on quality of life of topical salicylic acid peels for the treatment of postinflammatory hyperpigmentation in dark skin. *Dermatol Surg.* 2009;35:638-644.
15. Cho SB, Park SJ, Kim JS, et al. Treatment of post-inflammatory hyperpigmentation using 1064-nm Q-switched Nd:YAG laser with low fluence: report of three cases. *J Eur Acad Dermatol Venereol*. In press.