FEATURE ARTICLE

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Shades of Frustration

Understanding the Histologic Variation of, and Topical Treatment Options for, Postinflammatory Hyperpigmentation in Patients With Acne Vulgaris

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ABSTRACT: Postinflammatory hyperpigmentation (PIH) is a distressing condition associated with a number of inflammatory etiologies, with acne vulgaris being one of the most common. Even when resolution of inflammatory papules is achieved through treatment, patients are often dissatisfied with their overall appearance if their PIH is not addressed and treated appropriately. Because PIH can be associated with pigment deposition that extends beyond the epidermis, a number of topical therapies available to treat epidermal PIH often fail to provide meaningful improvement when deeper tissue is involved. A review of PIH as a disease process will be explored, and the mechanisms and limitations of first-line topical therapies will be discussed.

Key words: Acne, Pigmentary Disorders, Postinflammatory Hyperpigmentation, Skin of Color

Acne vulgaris is one of the most common skin diseases encountered in dermatology. It is estimated that up to 85% of Americans between the ages of 12 and 24 years are affected by some degree of acne (Bhate & Williams, 2013). As dermatology providers, we are fortunate to have an array of treatment options for acne that are safe and effective. However, once resolution of active lesions is achieved, the frustrating aftermath of postinflammatory hyperpigmentation (PIH) often persists. PIH is an acquired pigmentary disorder that can occur in the setting of inflammatory cutaneous diseases, with acne vulgaris being a well-established cause. A study examining 324 patients with acne showed that the prevalence of PIH was 58.2%, although most of the patients (80.2%) were deemed to have only mild-to-moderate acne (Abad-Casintahan et al., 2016). Perhaps, the feature of PIH that is most frustrating to patients is that the deposited pigment can last for years. In the same study, 22.3% of the subjects had lesions of PIH that persisted for 5 years or longer (Abad-Casintahan et al., 2016). Although grade of inflammation in acne lesions is commonly correlated with degree of PIH, it is important to recognize that PIH may develop in the setting of mild comedonal acne even when inflammation may not be evident on clinical examination (Yin & McMichael, 2014). Early, aggressive treatment of PIH should therefore be a priority for all patients affected, even when inflammation is clinically absent.

Unfortunately, the psychological impact of PIH can be marked. According to a study that attempted to quantify the psychological impact of PIH in patients with acne vulgaris, significantly worse quality-of-life scores were observed in the group with concomitant acne and PIH versus those with acne alone. Specifically, 60% of the patients with PIH and acne reported Grade 3 or "very markedly" to one or more of the seven quality-of-life indicators, whereas no patients with acne without PIH reported a score of this severity (Darji et al., 2017). It is important to recognize that, even after the resolution of active acne is achieved, the residual burden of PIH may continue to negatively impact the psychological well-being of those affected.

Many expert groups view topical depigmenting agents as an appropriate first-line treatment option. However, such therapies often fail to provide meaningful improvement largely because of the multifactorial histological characteristics involved in postinflammatory skin conditions. A solid understanding of basic cutaneous anatomy is imperative when selecting, evaluating, and modifying treatment as necessary, while also managing patient expectations. This article aims to provide a detailed explanation of the

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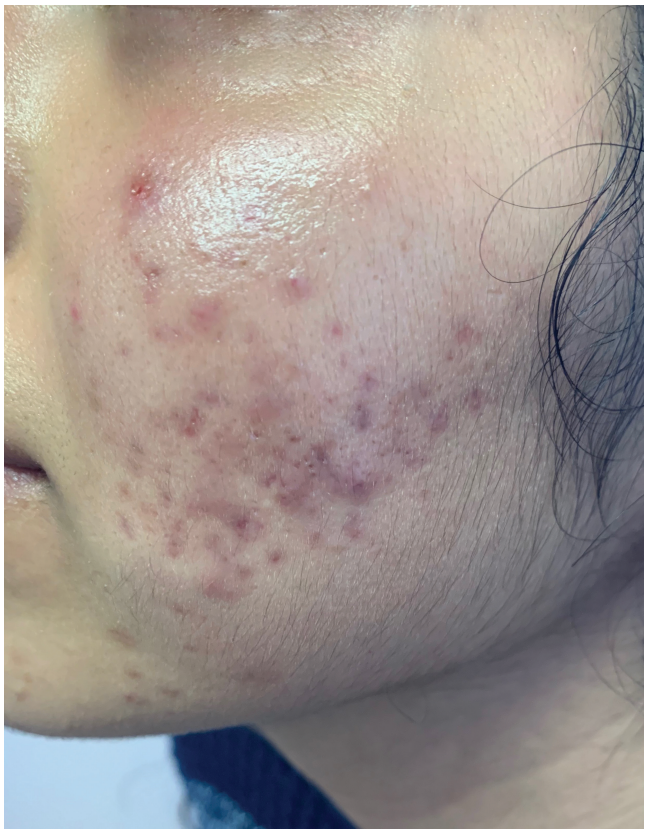

FIGURE 1. Postinflammatory hyperpigmentation and erythema on the cheek.

basic anatomical, physiological, and histological characteristics of PIH in patients with a history of acne vulgaris. The pharmacology of available topical treatments will be explored, and the limitations of such treatments will also be discussed.

PATHOPHYSIOLOGY

Melanogenesis occurs by the enzymatic oxidization of tyrosine. Once synthesized, melanin is distributed by epidermal melanocytes to neighboring keratinocytes. The type and amount of melanin in the skin are driven by genetic factors that determine skin tone. Inflammation observed in skin conditions such as acne vulgaris causes the release of prostaglandins, cytokines, leukotrienes, and other inflammatory mediators that directly stimulate melanocytes to increase melanin production and transfer to keratinocytes in the epidermis (Davis & Callender, 2010). However, it is important to note that the distribution of postinflammatory pigment is not limited to the epidermis, and dermal hyperpigmentation is often implicated in many cases.

DERMAL HYPERMELANOSIS

Epidermal inflammation can cause damage to basal layer keratinocytes, which weakens the integrity of the basement membrane and allows for melanin leakage and subsequent deposition into the dermal layer below (Park et al., 2017). This dermal melanin becomes phagocytized by melanophages, which accumulate in the upper dermis (Figure 1) (Callender et al., 2011). Depth of pigment determines the appearance of these lesions; on visual examination, dermal melanosis is described as having a bluish/gray tone versus epidermal hypermelanosis that appears as various shades of brown (Zawar et al., 2015). Wood's lamp evaluation is a noninvasive assessment tool that helps the clinician determine the location and depth of pigment. Under the Wood's lamp, epidermal pigment is readily enhanced and well defined in comparison with normal surrounding skin. Dermal pigment may appear poorly circumscribed and does not intensify (Stratigos & Katsambas, 2004).

EPIDERMAL HYPERMELANOSIS

The epidermis is unique to other skin layers in that it is continuously renewed; proliferative basal keratinocytes differentiate as they make their way up to the outermost layer of the epidermis to become the anucleate cells of keratinized stratum corneum and are ultimately desquamated (Chu, 2012). Under normal circumstances, this process takes approximately 28 days. The continuous cell turnover and epidermal renewal can explain why acquired epidermal PIH is shorter lived in comparison with dermal PIH; epidermal pigment can resolve spontaneously in months to years, whereas dermal pigment can persist for much longer. Fortunately, most cases of acne-related PIH are associated with epidermal hyperpigmentation, which is the site of action for many topical therapies (Silpa-Archa et al., 2017).

AVAILABLE TREATMENTS

Because it is pointless to clean up ashes without first putting out the fire, aggressive treatment of the palpable, inflammatory acne lesions driving the dyspigmentation must be achieved before treatment of PIH can begin. This often involves systemic treatment with agents like isotretinoin and oral tetracyclines. The topical therapies used to treat the resulting PIH can be loosely organized by their primary mechanism, yet significant overlap exists. Treatments can be categorized by those with tyrosinase-inhibiting depigmenting abilities (hydroquinone [HQ] and azelaic acid) and those that augment the physiologic keratinocyte turnover (topical retinoids).

TYROSINASE INHIBITORS

HQ is a common depigmenting agent that has long been regarded as the gold standard treatment for PIH. HQ inhibits tyrosinase, thereby preventing the conversion of dihydroxyphenylalanine to melanin. In the United States, HQ 2% is available over the counter. Higher concentrations are available with a prescription, and 4% is the typical prescription strength used for treatment of PIH. HQ is often used in combination with a topical retinoid to allow for improved penetration, yet irritation can be marked (Ortonne & Passeron, 2005). It is important to note that most topical therapies are often very irritating and have the

potential of worsening existing PIH. Exogenous ochronosis is a rare complication associated with HQ use whereby blue–black discoloration appears in collagen-containing tissue as a result of the accumulation of a homogentisic acid byproduct (Lapeere et al., 2012). This complication is permanent and is typically seen when HQ is used at higher concentrations for an extended period. However, it is important to note that cases of exogenous ochronosis have been reported with strengths as low as 2% for treatment durations as short as 3 months (Ko & Wang, 2015). In addition, application of HQ to nonaffected skin may cause inadvertent hypopigmentation of nonaffected skin. Azelaic acid is another topical therapy that is commonly used for treatment of PIH. The mechanism of action involves inhibition of tyrosinase by oxidization of unsaturated fatty acids, which suppresses melanocyte activity. Azelaic acid is also shown to impair the action of mitochondrial enzymes and promote a cytotoxic effect on abnormally hyperactive melanocytes (Callender et al., 2011). This selective activity explains why azelaic acid may have only limited lightening effect on perilesional skin not involved by PIH.

TOPICAL RETINOIDS

Topical retinoids are the mainstay therapy for most types of acne but are also helpful in reducing postinflammatory pigment. Topical retinoids increase the rate of keratinocyte turnover and foster the removal of excess pigment in the epidermis. In addition, retinoids are shown to inhibit tyrosinase and decrease the transfer of pigment to keratinocytes (Gollnick et al., 2017). Tazarotene, adapalene, and tretinoin are three forms of topical retinoids with proven efficacy against PIH when used as monotherapy (Chaowattanapanit et al., 2017).

COMBINATION THERAPIES

Combination therapies containing topical retinoids and HQ are often coformulated with a corticosteroid. The addition of corticosteroids is thought to suppress the secretory function of melanocytes (Menter, 2004). The anti-inflammatory effects of corticosteroids also help to mitigate the irritant reactions often caused by HQ and topical retinoids. The addition of a topical retinoid not only facilitates epidermal turnover but also allows for better penetration of HQ, leading to improved efficacy of either component alone (Ahmad Nasrollahi et al., 2019).

ULTRAVIOLET BLOCKADE

Because of the direct effect of ultraviolet (UV) radiation on melanocyte activity, the importance of UV protection must be emphasized as an essential adjunct to the topical therapies discussed. Although pigmenting effects are observed upon exposure to both UVB and UVA, the effects of UVA radiation may be greater, especially among those with darker skin types (Moyal, 2004). Most commercial sunscreens manufactured in the United States have adequate protection against UVB, primarily preventing solar erythema in fair-skinned individuals. The sun protection factor is a rating system used to illustrate the level of protection the product provides specifically against UVB radiation. Many sunscreens purchased outside the United states (such as those from Europe and Asia) follow product labeling regulations that also rate the degree of UVA blockade, versus the pass/fail grading system utilized in the United States. According to a study comparing 20 broad-spectrum U.S. sunscreens, only 11 of the 20 met European standards in regard to the strength of UVA blockade (Wang et al., 2017). Because PIH is most evident among individuals with Fitzpatrick Types III–VI, UVA exposure may have significant consequences on treatment outcome. A study by Buchanan Lunsford et al. (2018) showed that, because largely of a lower perceived risk of skin cancer, Black and Hispanic populations are less likely to engage in sun-protective behaviors. Given this understanding, education emphasizing the importance of broad-spectrum sunscreen use and other sun-protective behaviors among this population is crucial. Although the selection of sunscreens offering robust UVA protection is somewhat limited in the U.S. market, physical blocks containing zinc oxide and titanium or chemical blocks containing avobenzone or ecamsule lend some degree of UVA protection in comparison with other available agents (Glaser & Tomecki, 2020).

DISCUSSION

Despite successful clearance of acne lesions, many patients feel dissatisfied with treatment if PIH is not also addressed. The long, damaging battle with acne vulgaris is one many patients wish to forget, and for many, the imprint of PIH serves as a lasting reminder of their history with the disease. As discussed, first-line topical therapies for PIH primarily target epidermal dyspigmentation, and their mechanisms fail to address the possibility of targeting deeper dermal pigment. Determining the tissue depth of postinflammatory pigment is crucial in selecting treatment and managing expectations. Although commonly used topical therapies such tyrosinase inhibitors and retinoids may be helpful in reducing epidermal PIH, full resolution can be difficult if dermal pigmentation is involved. In such cases, more invasive treatment modalities such as chemical peels and laser therapies can be considered after careful patient selection. In tackling the PIH conundrum, it is important for practitioners to have a thorough understanding of the condition to identify the limitations of current therapies and select those most appropriate. ■

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