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POST-INFLAMMATORY HYPERPIGMENTATION: PATHOGENESIS, DIAGNOSIS, AND TREATMENT

Post-inflammatory hyperpigmentation (PIH) is a common, acquired pigmentary condition. Although it can occur in all skin phototypes, it more commonly affects individuals with darker skin phenotypes. PIH can result from endogenous inflammation such as acne vulgaris or exogenous injury or trauma to the skin, such as that associated with an energy-based procedure. PIH does not affect the patient symptomatically; however the appearance and prolonged duration can be a source of distress. This holds true especially in patients with darker skin tones as PIH is most noticeable in skin types 3 to 6. It is not a surprise therefore that PIH is one of the most common reasons for patients with darker skin tones to seek treatment from a dermatologist.

With respect to pathogenesis, PIH is caused by either endogenous or exogenous inflammation.[1] There are two mechanisms by which inflammation can cause PIH. First, inflammatory cytokines can stimulate melanocyte activity, hyperplasia, and hypertrophy.[2] Second, inflammation in the dermoepidermal junction (DEJ) can cause melanin to dropout from the epidermis into the dermis (melanin incontinence), which is then phagocytized by macrophages (melanophages).[3] The location of the melanophages determines the type of PIH; if the melanophages are more predominant in the epidermis, the resulting colour of the PIH will be tan-to-brown. In contrast, melanophages located in the deeper dermis layer will produce a blue-grey colour.[4] This colour difference is attributed to the Tyndall effect.[5] Other relevant factors that play a role in the clinical presentation of PIH would include: the patient's inherent pre-existing skin tone, the degree and depth of inflammation, and the degree of injury to the DEJ where melanocytes and pigmented keratinocytes are located.[6] The clinical presentation and understanding of the pathogenesis of PIH can be helpful in predicting the potential duration of disease and setting realistic clinical expectations for the patient.

The differential diagnosis of PIH involves the evaluation of other hyperpigmentation disorders such as melasma, hyperpigmented mycosis fungoides (rare variant most commonly affecting skin of colour), and drug-induced hyperpigmentation.[6] Drug-induced hyperpigmentation may be caused by antibiotics (minocycline), anti-neoplastic agents, antimalarials, amiodarone, and metals. There are also hyperpigmentation disorders that result in PIH and for which the differential diagnoses would include lichen planus pigmentosus (uncommon variant of lichen planus), ashy dermatosis (otherwise known as erythema dyschromicum perstans), and Riehl melanosis. The distinguishing features of these diseases include the fact that lichen planus pigmentosus presents on the sun-exposed areas such as the face, neck, and upper extremities and ashy

dermatosis typically presents on the trunk, proximal extremities and neck. Riehl melanosis, otherwise known as pigmented contact dermatitis, is classically described and commonly manifests in young middle-aged women on the forehead, temporal, and zygoma areas of the face. Other differential diagnoses of hyperpigmentation conditions which can result in PIH include phytophotodermatitis, frictional melanosis, and periorbital hyperpigmentation.[7]

The diagnosis of PIH begins with a thorough physical examination. As part of the examination, it may be beneficial for the clinician to make a visual comparison of the affected area against the patient's baseline normal skin colour either from inspecting the unaffected skin or a photograph. A useful and simple addition to the physical examination would be a Woods lamp.[8] Enhancement of the pigment would indicate epidermal PIH whereas no enhancement would indicate dermal PIH. Finally, a skin biopsy is considered helpful in delineating the diagnosis and, at the very least, useful in excluding certain differentials such as hyperpigmented mycosis fungoides.[9] Ideally, two biopsies should be done for the pathologist to compare specimens from normal and hyperpigmented skin. Histopathologic features of PIH include an increased number of superficial dermal melanophages as well as increased epidermal melanin.

There are multiple therapeutic agents available for the treatment of PIH. Prior to initiating pharmacological intervention, it is important to set realistic expectations and take sufficient time to counsel patients that PIH can be very difficult to treat, especially if predominantly dermal in nature. If the patient is unbothered by their PIH, non-active intervention and monitoring may be a very reasonable management approach. However, since this is rare and many patients seek treatment for their PIH, this paper will focus on the topical agents that most dermatologists typically prescribe to treat PIH.

One of the most common treatment options for PIH is hydroquinone 2-4 % (HQ). The mechanism of action involves the inhibition of the enzyme tyrosinase, the result of which blocks conversion of DOPA to melanin. HQ also works by degrading melanosomes and melanocytes.[10] A popular combination treatment is Kligman's formula, which is the triple combination of HQ, retinoids, and corticosteroids.[11] This treatment regimen has the most evidence and is widely considered an effective treatment for PIH. Kligman's formula is generally well-tolerated and can be used safely in all skin phototypes. The potential side effects of prolonged use may include irritation, contact dermatitis, ochronosis, and theoretical risk of carcinogenicity (demonstrated only in animal studies).[6]

The mechanism of action of retinoids is three-fold; it increases turnover of keratinocytes, inhibits tyrosinase transcription which reduces production of melanin, and reduces the transfer of melanosomes from melanocytes to keratinocytes.[12] Researchers have demonstrated that tretinoin 0.1% applied nightly yielded over 20% and just shy of 50% reductions in epidermal and dermal melanin levels respectively, compared to 3% and 7% respectively in the placebo-vehicle group[13]. In a double-blinded, placebo-vehicle-controlled study of 74 patients from darker racial ethnic groups who had acne, results showed that tazarotene 0.1% applied once-daily resulted in a 500% greater improvement in overall PIH severity and a 120% greater reduction in pigment level within 18 weeks[14]. Another randomized, investigator-blinded study in patients with moderate-to-severe acne compared tazarotene 0.1% cream to adapalene 0.3% gel and found that tazarotene was significantly more effective at treating PIH, (25% achieving resolution in the tazarotene group versus 12% in the adapalene group).[15]

Another class of medications which are commonly used to treat PIH are hydroxy acids. These agents remove the superficial layers of the skin by increasing cellular turnover of keratinocytes and decreasing melanin content within the epidermis. A randomized, evaluator-blinded, split-face study of ten subjects with Fitzpatrick skin phototypes IV to VI evaluated 20-30% salicylic acid to one-half of the face and no treatment to the contralateral half. Statistical analysis of evaluators' rating of the photographs did not yield a significant difference between the treated and untreated side, but patients reported a 40% improvement on the treated side compared to 8% on the untreated side ($p=0.004$).[16] Two randomized studies compared the use of 20% salicylic-10% mandelic acid peel to 35% glycolic acid peels for PIH following acne and found significant improvements of 66-72% and 43-47% respectively compared to baseline.[17,18] A randomized, double-blinded, split-faced study involving 36 subjects compared 30% salicylic acid peel to Jessner's solution (14g resorcinol, 14g salicylic acid, 14g lactic acid in 100mL ethanol) for the treatment of PIH following acne and found that both treatments were equally effective after 8 weeks.[19]

Corticosteroids may also be used for PIH as they have anti-inflammatory properties and work by reducing mononuclear and phagocytic cells, as well as by decreasing epidermal melanin levels by interfering with melanin synthesis in melanocytes.[20] A randomized, double-blinded, placebo-controlled study evaluated desonide, a low potency corticosteroid, for

axillary PIH and showed a 30% improvement in PIH, compared to a 6% improvement in the placebo group. However, another randomized, double-blinded study evaluated betamethasone valerate 0.12% foam for PIH in stasis dermatitis and found that although there was no overall difference between the foam and vehicle-treated leg at days 14 and 28, the steroid-treated leg, but not the vehicle-treated leg, showed statistical improvement over baseline.[21] PIH which results from stasis dermatitis is likely primarily due to hemosiderin and hemosiderophages within the dermis, which would account for the lack of efficacy[22].

Niacinamide reduces melanosome transfer from melanocytes to keratinocytes.[23] A randomized, double-blinded, placebo-controlled study evaluated 4% niacinamide for axillary PIH in a small cohort of women aged 19-27 years, and showed a 24% improvement compared to 6% improvement in the placebo group.[20]

Thiamidol, a derivative of resorcinol and an ultrapotent inhibitor of tyrosinase, was evaluated in a randomized, double-blinded, split-face study for PIH. A statistically significant improvement from baseline was found when it was applied twice daily and 4 times daily for 12 weeks.[24] Unlike hydroquinone derivatives, thiamidol is not a substrate of tyrosinase and will not be converted to a toxic quinone that can potentially induce leukoderma[25]. More studies on this promising agent are needed.

Alpha-bisabolol, a monocyclic sesquiterpene alcohol, inhibits α-melanocyte-stimulating hormone-induced melanogenesis through suppression of tyrosinase production.[26] A randomized, double-blinded, vehicle-controlled trial involving 28 females evaluated once daily application of 0.5% alpha-bisabolol and found a 73% greater improvement in UV-induced PIH after 8 weeks compared to vehicle for the majority of the subjects who tested the alpha-bisabolol-containing cream.[27]

Glehoma hederacea, a plant commonly used in oriental medicine with anti-inflammatory effects via the inhibition of nitric oxide synthase and TNF-α, has been used to treat UV-induced PIH. A randomized, double-blinded, placebo-controlled study involving 23 female subjects found that Glehoma hederacea resulted in faster and more significant improvement in UV-induced PIH compared to placebo-treated and untreated areas.[28]

The approach to the treatment of PIH should always consider individual patient characteristics such as their skin phenotype, and, additionally, the etiology of PIH. The author recommends a step-wise approach beginning with therapeutic agents that are safe, effective, and well-tolerated to ensure adherence. Beyond behavioural modifications such as strict photoprotection and the setting of realistic expectations, clinicians may consider a trial of hydroquinone or combination, topical retinoids, and hydroxy acids before pursuing additional or alternative options.

PIH is a common skin condition that predominantly affects individuals with skin of darker phenotypes. Its pathogenesis involves either endogenous or exogenous inflammation and the diagnosis of PIH requires clinicians to be aware of other hyperpigmentation disorders that may present as PIH. Common treatments for PIH include HQ, retinoids, hydroxy acids and corticosteroids. As always, the choice of treatment should consider the patient's age, underlying comorbidities and quality of life goals while balancing appropriate risks and benefits for the optimal management of PIH.

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