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Review Article

Pathogenesis and Update on the Management of Melasma

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Abstract

Melasma is a disfiguring skin disorder characterised by brown or grey-brown patches on the skin, often affecting the face. It is frequently recalcitrant to treatment. Melasma treatment options vary in mode and effectiveness, including topical creams, laser therapies, and systemic medications. Despite the array of available treatments, achieving consistent and satisfactory results remains difficult, which necessitates ongoing research to develop safer and more effective therapeutic strategies for treatment of melasma. The aim of the article is to provide a comprehensive review of the current understanding of melasma's complex pathogenesis, as well as to examine and evaluate existing and emerging treatment options to guide clinical approaches for more effective and individualized management of melasma.

Keywords: melasma; chloasma; topical treatment; systemic treatment; laser; tranexamic acid

Introduction

Melasma is a condition resulting in increased pigmentation of the skin. It typically arises as bilateral darkened patches or macules on areas of the face such as the cheeks. Still, it also affects other areas such as the chin, forehead, upper lip and forearms [1]. Melasma more frequently occurs in females and usually in those aged between 20 and 40 years. Frequent occurrence noted in Fitzpatrick skin types IV-VI and the prevalence was found mainly in certain ethnicities, including Hispanic, African American and Asian women [2].

Pathogenesis

The underlying pathophysiology of melasma is complex. Primarily, it involves increased melanin production, which is either deposited in the dermis or phagocytized by keratinocytes [3]. Over the years, numerous processes have also been identified as contributing to melasma, basement membrane disruption leads to the descent of melanocytes down into the dermis, this is driven by elevated levels of MMP-2 and MMP-9 [3]. Chronic UV exposure plays a significant role and consequently facilitates vascularization which requires anti-aging and anti-angiogenic treatment, moreover, mast cells may initiate epidermal pigmentation, which is the main feature of melasma [4].

Thus, it has been identified that there is not one specific triggering factor for melasma, but rather a number of contributing factors, including genetic predisposition, pregnancy, sun exposure, and certain medications [5].

Several phenotypic alterations have been identified in the epidermis and upper dermis in melasma, primarily related to the deficit of autophagy in melanocytes, and the senescence of fibroblasts. The role of endocrine factors and oxidative stress are matters for future investigation regarding their systemic and local microenvironment actions and how radiation of different wavelengths interferes with melanogenesis in melasma [5].

Pathological Findings

Histopathological findings include increased melanin staining of the basal keratinocytes and increased melanophages in the upper dermis (Figures 1 and 2). Other nonspecific findings have also been described, including moderate to severe solar elastosis, basal cell vacuolar degeneration, increased vascularization, and an increased number of mast cells [6].

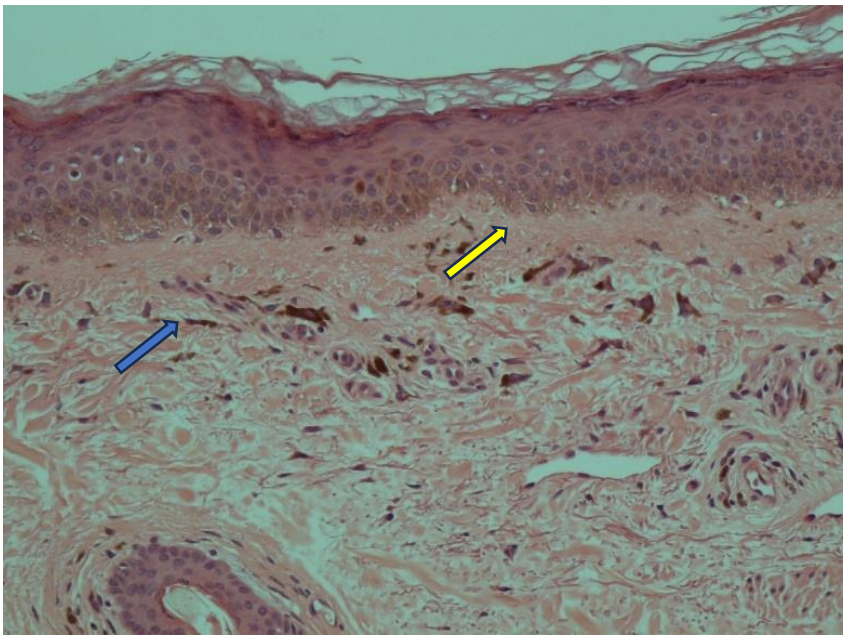

Figure 1: H&E stain x 200: Basal epidermal hyperpigmentation (yellow arrow) and melanophages in the upper dermis (blue arrow)

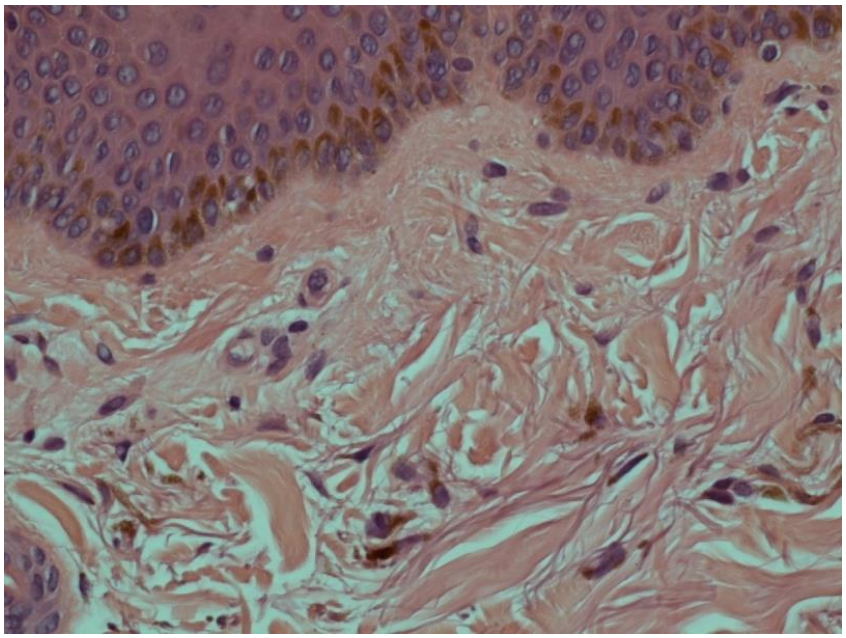

Figure 2: H&E x 400 higher magnification of figure 1 (Courtesy of Dr F Kubba)

Topical therapies

Topical therapies are the first-line therapy for melasma [8]. Typically, the target is inhibiting melanin production.

Management Melasma therapy appears challenging due to its compound, multifactorial aetiology, high recurrence rate and treatment resistance. Management ranges from topical therapies to light and laser therapies. These varying approaches, target different pathways in the pathogenesis of melasma, including melanogenesis, melanocyte production and angiogenesis. Managing melasma is particularly challenging, and often a combination approach is required. This in turn, can have quite significant psychological impacts on patients [7].Hydroquinone is one of the most well-known agents used in melasma [9]. It usually takes effect by interacting with tyrosinase to reduce the melanin produced. Hydroquinone, in varying strengths, has been used in managing melasma for a long time (most commonly 2% to 5% cream formulations).

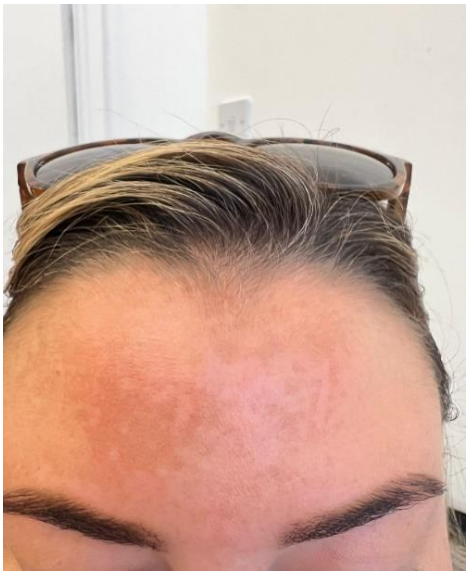

Figure 3: ill-defined hyper-pigmented patches on the forehead

However, its safety and side effects remain a concern due to its unstable form. Side effects include ochronosis and irritant dermatitis. The latter has frequently been identified as a dose dependent side effect. Given its varying efficacy and side effects, hydroquinone is often used in combination with other treatments including steroids, retinoids and peels.

A triple combination cream (TCC) also known; Kligman's formula, is a combination therapy involving 4% HQ, 0.05% tretinoin, and 0.01% fluocinolone acetonide [10]. TCC is the only HQ-containing drug approved by the United States Food and Drug Administration (FDA) for the treatment of melasma and is highly effective with improvement or clearance in a large **proportion** of patients. The components of Kligman's formula can be combined or individually [11, 12].

Topical steroids inhibit endothelin-1 production and granulocyte macrophage colony-stimulating factor, both are crucial for UV-induced melanogenesis [13,14] this contributes to treatment of melasma as an anti-inflammatory way as well as suppression of melanin production. They have been identified as more effective, when used in combination with other topical agents. It is prudent that the effects of long-term steroid use are highlighted to avoid further dermatological issues such as skin atrophy, striae and telangiectasia [15]. Common steroids that are used in managing melasma include dexamethasone, hydrocortisone, and mometasone furoate.

Retinoids are another standard mode of topical therapy. The most common in this group is tretinoin which demonstrates an anti-ageing effect and depigmenting properties16. Retinoids were identified to be useful, when used in conjunction with hydroquinone and steroid [17]. However, following its repeated use, it was found to be as effective as an individual therapy [18]. This agent has impacts at various stages of melanin production including reducing tyrosinase activity and epidermopoiesis. Side effects with retinoids use include dryness, scaling and erythema.

Acids such as kojic acid, azelaic acid and tranexamic acid are further topical treatments that have also been widely used [4]. These are recommended before chemical peels and laser therapy.

Camouflage creams, although they do not impact melasma's pathogenesis, they are found to be significant in improving patient welfare and self-esteem [19]. They are well recognised and frequently used to manage the psychological impacts of conditions like melasma.

Oral therapies

Recently, systemic treatment has emerged as a potential armamentarium in melasma, among which are antioxidants that have been described to show effects in the treatment for melasma [20]. However, no standard oral regimen has been launched so far. Vitamin E is mainly combined with vitamin C. Vitamin E stabilizes cell membranes and decreases UV-induced oxidative damage. Polypodium Leucotomos extract is a natural extract with photoprotective and antioxidant properties. It can help in preventing UV-induced skin damage. Glutathione acts as a robust antioxidant endogenous to cells that can reduce melanin production, and can be administered orally or intravenously for skin lightening [17].

Tranexamic acid is an oral agent that inhibits plasmin and significantly decreases the lesional melanin index and the erythema index. Histological examination showed marked reduction in the level of epidermal pigmentation and the number of mast cells and vessels [3].

Oral tranexamic acid was found effective in treating melasma, either as stand-alone or adjunct therapy [21].

Chemical skin peels

Chemical peels are treatment option for melasma and are typically considered a secondary approach in the management plan.

The mechanism of action involves increasing the speed of desquamation and encouraging epidermal "remodelling", which results in the removal of epidermal melanin and suspending the transfer of melanosomes [22].

Important active ingredients in peels include alpha and beta hydroxy acids, which act on reducing tyrisonase activity. These should be used with caution given the risk of exacerbation or relapse in patients with melasma.

Chemical peels like glycolic acid demonstrate promising effects when combined topical products [23].

Other agents, including SA, TCA, and lactic acid, have been explored for chemical peeling in patients with melasma [20].

Lactic acid was found to be an effective and safe peeling agent in the treatment of melasma, and it was as effective as Jessner's solution [24].

Light and laser therapy

Laser uses energy to identify and ablate chromophores such as melanin. Although it is an identified therapy for melasma, it is far from being a first-line treatment given the poor aesthetic outcome [7]. A frequent side

effect is post-inflammatory pigment alteration. Another form of light therapy is intense pulse light, otherwise known as IPL. IPL has been proven effective in several small-scale studies as an individual and combined therapy [25, 26, 27].

In regards to energy-based device monotherapy, ablative lasers like CO2 laser and Er:YAG laser are used in the treatment of melasma. The mechanism of action is not entirely understood. Still, a consequence of tissue vaporization, CO2 laser can indirectly reduce melanin deposits from both the epidermis and dermis and decrease the epidermal melanocytes and melanin content, during the healing process. The outcome is epidermal regeneration which can ameliorate hyperpigmentation [28]. The risk of postprocedural dyspigmentation is an imminent problem.

The efficacy of combined approach including lasers was more effective than monotherapy.

PDL improves mMASI scores and a significant decline in the expression of VEGF levels [29]. Moreover, both pixel Q-switched Nd:YAG (PQSNDY), and Pixel Er:YAG, showed positive results as monotherapy in melasma[24]. Picosecond and nanosecond Nd:YAG 1064nm were compared in a split face randomised trial, although efficacy was found to be the same, picosecond was less painful and carried less chance of melasma exacerbation [30].

The concept of laser toning is currently adapted in the treatment of melasma [31]. This entitles employing a 1064nm Nd: YAG laser with a low-fluence, multi-pass technique. By affecting melanocytes and late-stage melanosomes, this laser therapy improves the outcome with fewer adverse effects. However, punctate leukoderma is a developing concern [19].

In the same context, radiofrequency (RF) devices, employing alternative energy sources, showed promising outcomes especially RF with microneedling enhancing as it helps with melanin elimination [32].

Sun protection

Alongside the above medical agents used in managing melasma, several broader measures are advised to promote skin protection. These include encouraging patients to minimise heat and light exposure, use high-protection factor sun lotion all year round (this should involve protection from UVA, UVB, and visible light), and wear broad-brimmed hats while outside and exposed to the sun. Although cosmetically not appealing, it is evident that sunscreen with either iron oxide or large-size (>200 nm) titanium dioxide and zinc oxide is advised [33].

Conclusion

In this review, we have listed the available therapies for melasma, which is often refractory to treatment and has a high chance of recurrence. Thus, a combined and safe treatment algorithm aiming for epidermal depigmentation and improving dermal photoaging is crucial to prevent recurrence. Melasma management can be effectively pursued through a stepwise strategy. This approach begins with implementing sun protection and topical treatments and gradually progresses to more advanced interventions. Such a method aims to minimize potential side effects while optimizing the efficacy of the therapy.

Individuals with different skin tones require distinct treatment approaches. It is essential to consider the potential side effects and complications of the planned treatments, as well as the specific characteristics of their melasma.

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