Acta Dermatovenerol Croat 2010;18(2):124-129 REVIEW

Melasma: Insights and Perspectives

Yuri T. Jadotte, Robert A. Schwartz

Dermatology, New Jersey Medical School, Newark, NJ, USA

Corresponding author:
Robert A. Schwartz, MD, MPH, Professor & Head
Dermatology, New Jersey Medical School, MSB H-576
185 South Orange Ave,
Newark, NJ 07103
USA
roschwar@cal.berkeley.edu

Received: October 2, 2009
Accepted: April 11, 2010

SUMMARY Melasma is a common disorder in women of reproductive age with darker skin tones, but may also affect adolescents, older women on certain medications, and sometimes men. It usually appears as hyperpigmented macules and patches distributed symmetrically on the face, neck and rarely the upper limbs. Although its pathogenesis remains unclear, known risk factors include ultraviolet (UV) radiation, hormonal variations of pregnancy and thyroid disease, and anti-seizure medications. The increase in melanin may be due to both an increase in melanogenesis and melanocytosis. Prevention should target a reduction of exposure to risk factors, such as consistent protection against UV radiation. The principle treatment options include topical hypopigmenting agents, chemical peels, laser therapy and superficial dermabrasion. The impact of melasma on the quality of life of patients should be considered.

KEY WORDS: melasma, ultraviolet light, hormones

INTRODUCTION

Melasma comes from the Greek word "*melas*", meaning a "black spot", consistent with its clinical appearance. Also known as "chloasma" or "mask of pregnancy", it primarily occurs on the face and neck. Most cases are associated with identifiable risk factors, although it may also be idiopathic, particularly in men.

EPIDEMIOLOGY AND ETIOLOGY

Most cases of melasma occur in women, particulary those of darker skin tones (1). Melasma appears more prominently in individuals with skin types IV to VI, but people of all races and skin colors may be affected. Up to 70% of pregnant women and 10% of men may experience this disorder (2-4). Melasma has strong associations with certain risk factors, although it may be idiopathic (5). The hyperpigmented macules are due to an increased amount of melanin in the skin, which occurs via two mechanisms: increased melanocytosis, or increased melanogenesis (5). The importance of ultraviolet (UV) radiation in the pathogenesis of melasma is well supported by clinical evidence of improvement in many patients during the winter relative to the summer, as well as histological evidence of solar elastosis in the mac-

Acta Dermatovenerol Croat
2010;18(2):124-129

ules and patches of melasma (6,7). UV radiation increases the levels of the dermal stem cell factor and the alpha-melanocyte stimulating hormone in the skin, which may explain the increased melanocytosis and melanogenesis, respectively (8-14).

Hormonal changes are also important etiologies. In particular, the presence of melasma in up to 75% of pregnancies, the increased incidence of the disease in women on oral contraceptive pills (OCP), the histological finding of increased estrogen receptor expression in affected skin, the strong correlation between estradiol levels and melanogenesis, and the association of melasma with hormone replacement therapy in post-menopausal women all support this theory (15-21). Endocrine organ dysfunction such as thyroid gland abnormalities, and family history of the melasma are also important risk factors (22-25). Cosmetic products, anti-seizure or photosensitive medications may play a role as well (26).

CLINICOPATHOLOGICAL FINDINGS AND DIAGNOSIS

The macules of melasma tend to occur in three distinct facial patterns: malar, centrofacial, and mandibular (27). Although they are usually symmetrical, the macules may also have an irregular border and color pattern (28). A rare variant has been shown to appear on the arms. (18,19). Three histological patterns have been identified, based on the primary location of pigment accumulation: epidermal, dermal, and mixed (6). The epidermal pattern shows increased melanin deposits in the basal and suprabasal epidermal layers, while the dermal pattern shows many melanin-laden macrophages in the perivascular spaces (29). Mixed melasma shows a combination of the other two patterns. There is a strong correlation between the histological subtype and the gross appearance of the macules (5,11).

The diagnosis of melasma primarily depends on the clinical findings of the history and physical examination. Because of the Tyndall effect, dermal melasma appears slightly bluish on gross examination. Wood's lamp examination may help distinguish the histological subtypes, thus making a biopsy unnecessary in most cases. Epidermal melasma, which normally appears light brown, shows enhanced color contrast with this simple tool. However, a biopsy for histological analysis is indicated when the diagnosis of melasma is unclear, or to rule out other potentially significant disorders of hyperpigmentation. The differential diagnosis of melasma includes post-inflammatory hyperpigmentation, freckles, café-au-lait macules, solar lentigines, epidermal nevi, tinea versicolor, and lentigo malignant melanoma (30).

MANAGEMENT

Managing this cosmetic disorder requires an understanding of its impact on the patient's quality of life. The Melasma Quality of Life Scale (MELASQOL) has shown that this disorder may have a significant effect on patient quality of life (2,31,32). This is particularly true of facial lesions, which are the primary manifestations of melasma (32). Areas of life most affected by this disorder include social life, recreation, emotional well-being, physical health, and money matters (33,34). Given that clinical assessment of the severity by a physician may differ from the patient's perception of severity, this condition may be insufficiently diagnosed or treated (31,34,35).

There are two categories of therapies for melasma: biologic modulators and locally destructive agents. The biologic modulators are also known as topical hypopigmenting agents, and can be organized into two specific groups: biochemical and physiologic modulators. The biochemical modulators of pigmentation inhibit tyrosinase and thus significantly reduce melanin synthesis. They include hydroquinone, azelaic acid, kojic acid, and ascorbic acid. The physiologic modulators of pigmentation interfere with normal melanin distribution and commonly include tretinoin and glycolic acid. Additional treatment options include chemical peels, superficial dermabrasion and various laser therapies. These induce localized tissue destruction, and depend on the skin's ability to regenerate to accomplish the clinical result of hypopigmentation.

The most well studied and effective topical hypopigmenting agent used to treat melasma is topical hydroquinone (28). The 4% hydroquinone solutions are standard monotherapy, although 2%-4% solutions are available (36). Clinical response may not be seen for at least 4-6 weeks (35). The use of hydroquinone-based topical agents is controversial, as the numerous side effects have led to its removal from the European and Japanese markets (37,38). Exogenous ochronosis is a particularly distressing side effect; contact dermatitis and localized hypopigmentation may also occur (39,40). In the United States, triple combination therapy, involving hydroquinone, tretinoin and a corticosteroid, is usually the initial treatment

(27,40). A commonly used triple combination therapy cream consists of 4% hydroquinone, 0.01% flucinolone, and 0.05% tretinoin. This combination may have increased effectiveness for facial melasma and for various skin types (41,42). It can be safely used for continuous treatment of moderate to severe melasma for up to 6 months (43).

The controversy surrounding hydroquinone has spurred efforts to develop alternative topical hypopigmenting agents (37). For example, 20% azelaic acid may be more effective than 2% hydroquinone, and while 5% ascorbic acid may be less effective than 4% hydroquinone, it is certainly more tolerable to the patient (44,45). Two additional hypopigmenting agents deserve particular consideration. Tretinoin is known to accelerate keratinocyte proliferation and turnover, thereby decreasing melanin deposition and causing localized hypopigmentation (46,47). It may be used as an alternative monotherapy for melasma, although the timeframe for a measurable clinical effect may be prolonged. Also, 2% mequinol and 0.01% tretinoin may be a safe alternative to 3% hydroquinone (48).

Glycolic acid thins the stratum corneum, disperses melanin in the epidermis and improves the distribution of other drugs in the skin, thus making it a useful adjunct to other topical hypopigmenting agents. The combination of glycolic acid and hydroquinone is very effective in treating melasma (49). For example, 10% glycolic acid, when added to 4% hydroquinone, vitamin C, E and sunscreen, hastens clinical improvement (50). A recent advance is the emergence of oligopeptides as a new class of tyrosinase inhibitors that may also be beneficial alternatives to hydroquinone, due to their minimal cytotoxicity and improved inhibitory efficacy (51). In particular, twice daily topical application of an emulsion containing 0.01% decapeptide-12 (Lumixyl ™ cream) in 5 patients showed a 50% clinical improvement over a 16-week period with minimal side effects (52).

Other agents are used when the topical hypopigmenting agents fail or are not indicated, such as in case of recalcitrant melasma. Chemical peels are useful because they induce hypopigmentation secondary to skin exfoliation and revitalization. Low concentration alpha-hydroxy acid chemical peels, such as glycolic acid, are recommended for melasma (48). It is the most commonly used agent for this purpose, although 1% tretinoin may be effective as well (53). There are many other known chemical peel agents, including kojic acid, salicylic acid and Jessner's solution, to name a few.

Superficial dermabrasion disrupts the epidermal and dermal layers of the skin. Although there are many side effects, such as pruritus, milia, and permanent hypopigmentation, it may have good long-term effectiveness, given that no recurrence has been reported after 5 years in up to 97% of patients (54).

Q-switched alexandrite laser (QSAL) monotherapy has been shown to be effective in treating melasma, although double therapy with QSAL and CO_2 pulsed laser may be more effective (55-57). Fractional laser therapy, also known as fractional photothermolysis, may be useful for resistant cases and may also be very effective: up to 60% of patients in one study reported complete or near complete clinical resolution (58,59). Additional modalities have been applied to treat melasma, including microdermabrasion, intralesional injection of tranexamic acid and photodynamic therapy.

PROGNOSIS AND PREVENTION

The prognosis of melasma primarily depends on the treatment choice relative to the histological subtype, and on the risk factors present. Epidermal melasma shows clinical improvement with topical hypopigmenting agents. Fortunately, it may be the most common subtype, as it has been shown to be present in 48%-69% of cases (60,61). Dermal melasma tends to be resistant to topical agents, and may require lasers or superficial dermabrasion, while the mixed subtype may be responsive to a combination of different therapies (28,29). The effect of pregnancy as an etiologic agent on prognosis is relatively well studied. As a physiologic change of pregnancy, melasma often undergoes remission without treatment a few months postpartum, although it may persist in up to 30% of cases (15,60,62). For this reason, and because of drug safety concerns, melasma is generally not treated during pregnancy. Despite postpartum resolution, recurrence may occur in approximately 8% of patients with melasma of pregnancy (60). Discontinuation of oral contraceptives may offer some clinical remission, although it may be slow and only partial (29).

An effective preventive strategy for melasma entails a reduction of exposure to UV radiation and other known risk factors. Patients should consider using various methods that help achieve this goal. For example, broad-spectrum UVA and UVB sunscreens should be regularly applied to exposed skin. The American Academy of Dermatology now recommends formulations with SPF 30 instead of SPF 15 as a general preventive measure against

sun-induced disorders, including various types of skin cancers. Given that it is the main site of clinical occurrence, patients should reduce facial UV exposure by wearing hats that shade the face during daytime. Also, another preventive option is stopping the offending agent when it is known and when possible.

CONCLUSION

Melasma is primarily a cosmetic disorder that affects women in their reproductive age, during pregnancy in particular. The identification of some of the etiologic factors has provided guidance for preventive strategies. With further study, it may ultimately lead to the elucidation of the pathogenesis of this disorder, which remains unclear. An appropriate management approach requires tailoring treatment options to the histological subtypes, selecting appropriate maintenance therapy or alternative treatments based on the clinical response and tolerance, as well as addressing the psychological effects of the disorder.

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