

Melasma and Common Pigmentary Dermatoses in Asian Individuals and an Overview of their Treatment

Keywords: Acquired bilateral nevus of Ota-like macules; Asian individuals; Melasma; Mongolian spot; Nevus of Ota; Pigmentary dermatosis

Abstract

Asian patients with Fitzpatrick skin types III-V have been highlighted in publications describing pigmentary dermatoses. Melasma is particularly common in Asia, while nevus of Ota, acquired bilateral nevus of Ota-like macules (ABNOM), and Mongolian spots are also frequently seen. In Asian individuals, postinflammatory hyperpigmentation (PIH) frequently occurs after the treatment, especially laser and light therapies. Thus, prevention and management of PIH are extremely important concerns. This review discusses the pigmentary dermatoses commonly encountered in Asia, including melasma, ABNOM, nevi of Ota and Ito, and Mongolian spots, and the various treatment options that are either currently available or under investigation *in vitro*.

Introduction

Pigmentary skin disorders are of great concerns among Asian patients. This could be attributed to an increased interest on their skin conditions observed in Asian women. The exponential growth in the market of cosmetic procedures in Asia has exacerbated this trend. As a rapid increase in the populations is expected in Asian countries, pigmentary skin disorders in Asian individuals and their treatment will receive more attention over the next several decades.

Although Asian individuals have higher levels of melanin in their skins which provides better photoprotection than Caucasian individuals, cutaneous pigmentary disorders are more common. Melasma is particularly common in Asia, while nevus of Ota, acquired bilateral nevus of Ota-like macules (ABNOM), and Mongolian spots are also frequently seen. Notably, nevi of Ota and Ito occur almost exclusively among Asian individuals.

The accurate diagnosis of pigmentary dermatoses is the first step towards the safe and effective treatment. During the treatment, postinflammatory hyperpigmentation (PIH) that frequently occurs after the cutaneous damage with laser and light therapies is a major adverse effect among Asian individuals. Since laser and light therapies have rapidly become widely available in Asian countries, prevention and management of PIH are important concerns.

This review discusses the common pigmentary dermatoses in Asian countries, including melasma, ABNOM, nevi of Ota and Ito, and Mongolian spots, and the various treatment options currently available or under investigation *in vitro*.



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Melasma

Melasma is an acquired hypermelanosis characterized by symmetrical, irregular light-to-dark-brown macules and patches on sun-exposed area, especially on the face. It is common among Asian and Hispanic women during their third and fourth decades of life [1]. A genetic predisposition, chronic exposure to ultraviolet (UV) radiation, and female sex hormones are typically considered to play main roles in its pathogenesis [2-5]. Histopathological findings include epidermal hyperpigmentation accompanied by an increased number of melanocytes, overexpression of melanogenic enzymes, and overlying dermal changes [6].

Three types of melasma exist, as classified according to their distribution on the face. These include the centrofacial, malar, and mandibular patterns, but melasma often presents as a mixture of these patterns. Melasma can be further classified into epidermal, dermal, and mixed types, based on the location of pigment determined by Wood's lamp examinations.

Treatment of melasma is challenging because it is often recalcitrant to therapy, especially in the dermal type, and it frequently recurs even after successfully cleared [7]. Various treatments have been trialed, including topical hypopigmentation agents, laser or light therapies, systemic tranexamic acid (TXA), and chemical peels. Figure 1 describes a female patient with melasma who was successfully treated with oral TXA and low-fluence (1.0-1.5J/cm²), 1,064-nm Q-switched neodymium-doped yttrium aluminum garnet laser (QSNYL) for one year in our clinic.

Topical treatment agents

Hydroquinone (dihydroxybenzene) and triple combination cream: Hydroquinone (HQ) is the most extensively investigated anti-melanogenic agent. It inhibits the conversion of L-3,4-dihydroxyphenylalanine to melanin by the competitive inhibition of tyrosinase, the key enzyme involved in the rate-limiting step of melanogenesis [8]. HQ's oxidative products also cause oxidative damage to membrane lipids and proteins, including tyrosinase [9]. In a randomized, double-blind, placebo-controlled trial, Ennes *et al.* (2000) demonstrated that 38% of patients treated with 4% HQ

achieved clinical clearance of melasma in 12 weeks compared with only 8% of patients in the control group [10]. In this study, clinical improvements in melasma were observed within three weeks of treatment initiation.

The safety issue in HQ is still controversial. The European Committee (24th Dir 2000/6/EC) prohibited the use of HQ in cosmetics because of possible long-term complications, such as exogenous ochronosis and permanent depigmentation [11]. The accumulation of homogentisic acid in the dermis causes degeneration of collagen and elastic fibers, followed by the deposition of ochre-colored fibers in patients with exogenous ochronosis. This condition is extremely difficult to reverse to any degree once it appears. *Westerhof et al.* (2005) further warned the potential carcinogenic risk of HQ due to its metabolite, *p*-benzoquinone, formed in the liver [12]. On the other hand, *Nordlund et al.* (2006) reviewed the evidence for the safety of HQ and concluded that so far it is reasonable to use HQ in the treatment of hyperpigmentation [13].

Triple combination cream (TCC) containing 4% HQ, 0.05% tretinoin, and 0.01% fluocinolone acetonide, is the most effective melasma treatment, and is currently the only HQ-containing drug approved by the United States Food and Drug Administration (FDA) for the treatment of melasma [8,14,15]. Topical tretinoin also exhibits a hypopigmentation effect as well as the well-known anti-wrinkle effect [16]. Steroids suppress cytokines, including endothelin-1 (ET-1) and granulocyte macrophage colony-stimulating factor (GM-CSF), which mediate UV-induced melanogenesis by inactivating

nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [17,18].

Cestari et al. (2007) demonstrated that TCC was more effective than 4% HQ in an eight-week trial [19]. In this study, clearance of melasma lesions was observed in 35% of the patients in the TCC group compared with 5% of the patients in the HQ group, while the incidence of adverse events, including erythema, burning sensations, and desquamation, was similar in both groups. In a multicenter comparison study involving Asian patients, TCC exhibited superior efficacy in the treatment of melasma than 4% HQ cream, with 64.2% of the patients treated with TCC showing “none” or “mild” melasma at eight weeks compared with 39.4% of patients in the HQ group. Despite more adverse events occurring in the TCC group than in the HQ group in this study (48.8% versus 13.7%), most of them were mild and none were severe [20]. However, the use of TCC should be limited to twice daily for six months because of the possibility of steroid-induced atrophy, which disqualifies it from use as a maintenance therapy for melasma [21].

Other tyrosinase inhibitors: Arbutin, a naturally occurring hydroquinone β-D-glucopyranoside derived from the bearberry plant, exhibits anti-melanogenic properties at non-toxic concentrations [22]. It has been demonstrated to inhibit tyrosinase activity, without affecting its mRNA expression, and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymerase activity [23]. *Ertam et al.* (2008) demonstrated a significant decrease in the melanin index measured by a Mexameter[®] in 10 patients treated with 1% arbutin for six months [24] ($p < 0.05$).

Kojic acid (5-hydroxy-2-[hydroxymethyl]-4H-pyran-4-one), an antibiotic produced by species of *Aspergillus* and *Penicillium* bacteria, chelates the copper in tyrosinase and inhibits NF-κB in keratinocytes, thereby showing bleaching activity [25,26].

Azelaic acid, a naturally derived dicarboxylic acid synthesized by *Malassezia furfur*, weakly inhibits tyrosinase, which leads to the hypopigmented macules commonly observed in tinea versicolor [27]. In a 24-week trial, 20% azelaic acid produced “good” or “excellent” results in 65% of patients, while 72% of patients treated with 4% HQ reported the same result [28]. No statistically significant difference was noted between the two groups.

A novel anti-melanogenic compound, 4-n-butylresorcinol, has recently been shown to inhibit the activities of tyrosinase and tyrosinase-related protein-1 (TRP-1) *in vitro* [29]. In a randomized, double-blind, vehicle-controlled, split-face study that investigated liposome-encapsulated 4-n-butylresorcinol, the melanin index, determined using a Mexameter[®], showed a significant reduction on the treated side of the face compared with the control side after eight weeks of treatment (-7.5% versus -3.3%, $p < 0.05$), without any occurrence of adverse events [30].

Ascorbic acid (vitamin C) and antioxidants: Compounds with antioxidant properties interact with copper at the active sites of tyrosinase and or with o-quinones, inhibiting tyrosinase activity and preventing oxidative polymerization in melanin intermediates [31]. Ascorbic acid, a well-known antioxidant agent, interferes at different stages of melanogenesis by chelating the copper ions in



Figure 1: A female patient with melasma who was successfully treated with a combination therapy of oral tranexamic acid and laser-toning in our clinic. (a) baseline (b) one year after the initiation of the treatment.

tyrosinase, reducing dopaquinone, and blocking DHICA oxidation *in vitro* [32,33]. In our clinic, ascorbic acid in the form of vitamin C iontophoresis is used to treat melasma. In a randomized, double-blind, placebo-controlled, split-face study, colorimeter measurements demonstrated a significant decrease in the change of lightness, ΔL , determined as $L_{\text{control}} - L_{\text{lesion}}$ on the treated side, from 4.60 to 2.78, compared with the contralateral side, which decreased from 4.45 to 3.87 [34]. ($p < 0.05$)

Other oxidant compounds including α -tocopherol, hydrocoumarins (6-hydroxy-3,4-dihydrocoumarins), and thioctic acid (α -lipoic acid), also display anti-melanogenic properties *in vitro* by inhibiting lipid peroxidation, accelerating glutathione synthesis, and down-regulating NF- κ B activation, respectively [35-37]. In an animal model, methimazole, an antithyroid agent, displayed regulatory activity towards peroxidase, thereby reducing the polymerization rate of eumelanin [38,39].

We performed a clinical trial to evaluate the efficacy of a whitening agent containing 0.05% resveratrol, a natural extract derived from the roots of the Japanese Knotweed, in the treatment of melasma. Its antioxidant activity has been proved by a fourteen-fold increase in the action of superoxide dismutase 2 (SOD2) in cells treated with resveratrol [40]. A total of thirty patients applied the agent twice daily, and demonstrated a significant improvement in melanin index measured by a Mexameter[®] and clinical photographic assessment after eight weeks ($p < 0.05$) (Figure 2).

Niacinamide (vitamin B3) and melanosome transfer inhibitors: A reduction in melanosome transfer from melanocytes to keratinocytes results in hypopigmentation by blocking the dispersion of pigment to the keratinocytes. A serine protease inhibitor has been reported to modulate the activation of the protease-activated receptor 2, resulting in the accumulation of melanosomes within melanocytes *in vitro* [41,42]. Lectins and neoglycoproteins have also been shown to reduce melanosome transfer *in vitro* [43]. Hakozaiki *et al.* (2002) demonstrated that niacinamide suppresses melanosome transfer *in*

vitro, and in a split-face trial, showed that 5% niacinamide cream significantly reduced hyperpigmentation and lightened basal skin color in eight weeks [44] ($p < 0.05$).

Other compounds: Topical application of linolenic acid, linoleic acid, oleic acid, and phospholipase D2 resulted in hypopigmentation of the skin of guinea pigs after UV irradiation via the stimulation of tyrosinase ubiquitination and proteasomal degradation [45-48].

Several compounds that modify tyrosinase structures at glycosylation sites have been found to induce hypopigmentation *in vitro*, including glucosamine, tunicamycin, and calcium D-pantetheine-S-sulfonate [49,50].

Laser and light therapies

Intense-pulsed light therapy: Intense-pulsed light (IPL) therapy emits a broad spectrum of wavelengths with a cutoff shorter than the filter, and provides selective photothermolysis [51]. Li *et al.* (2008) evaluated the efficacy and safety of IPL treatment in 89 Chinese patients with melasma. After four treatment sessions with three-week intervals, significant reductions in the mean Melasma Area and Severity Index (MASI) score, from 15.2 to 5.2 ($p < 0.05$), and in the melanin index, from 140.8 to 119 ($p < 0.05$) were found [52]. In this study, transient erythema and edema were the most common adverse events, and three patients experienced PIH.

Although IPL is a good therapeutic option for melasma with promising results reported, melasma-like pigmentation following IPL treatment usually occurs, which is even more intensely pigmented than the melasma it treats. Laser energy induces hyperactive melanocytes through inflammation, increases prostaglandin and cytokine production in keratinocytes and fibroblasts, and disrupts the basement membrane. As a result, a mixture of PIH and aggravated melasma lesions forms [53,54]. Since subtle melasma is clinically invisible to the naked eye but is detected by UV photography in 28.3% of Asian patients, IPL treatment must be performed with caution [55].

Fractional 1,550-nm non-ablative laser therapy: Fractional photothermolysis creates numerous microthermal zones (MTZ) of thermal injury in the skin, while leaving the areas between them unaffected. Transepidermal elimination of the MTZ could effectively remove dermal melanophages [56]. The unaffected areas may cause a more rapid recovery and theoretically, lower the risk of subsequent inflammation and PIH.

In a small clinical trial involving four-to-six sessions of fractional non-ablative laser treatment with one-to-two-week intervals, six out of 10 patients with Fitzpatrick skin types III-V achieved 75-100% clearance of the lesion, with PIH occurring in one patient [57]. In contrast, a split-face study comparing fractional non-ablative laser treatment with TCC, found a significant worsening of pigmentation measured by a Mexameter[®] ($p < 0.05$) and a higher incidence of PIH (31%) in the laser-treated group [58]. However, in a similar eight-week trial performed by the same investigators, the study groups treated with either fractional non-ablative laser or TCC showed significant improvements in the investigator's global assessment scores, and there was no statistical difference existed between the two groups [59].

Although fractional non-ablative laser is the only laser device approved by the FDA for melasma, the results vary and the high risk

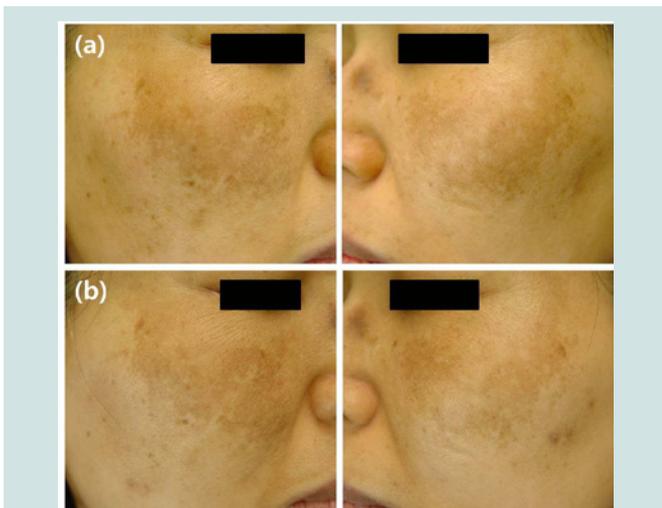


Figure 2: A female patient who demonstrated a significant improvement in melasma in a 8-week trial to evaluate the efficacy of a whitening agent containing 0.05% resveratrol and 0.06% 3,4,5-trimethylcinnamic acid thymol ester. (a) baseline (b) at week 8.

of PIH should be considered, especially in Asian patients. To lower the risk of the occurrence of PIH, treatment with lower fluences, variable pulses, and pretreatment with HQ for up to six weeks are recommended, particularly in patients who have a history of PIH [60].

Q-switched neodymium-doped yttrium aluminum garnet laser treatment: Exposure of skin to nanosecond-domain laser pulses affects the melanosomes through selective photothermolysis. However, laser treatment for melasma has been unsatisfactory because of the resulting inflammation and PIH. Since high-fluence laser irradiation increased the risk of adverse events, the concept of using collimated, low-fluence, 1,064-nm QSNYL treatment for melasma has been suggested. This “laser-toning” technique is popular in East Asian countries, and has become one of the first-line therapies for melasma. While its mechanism of action is unclear, several studies have found that ‘laser toning’ removes the melanosomes, but not the melanocytes. Furthermore, it damages the dendrites of the melanocytes without killing the cells, thereby functionally down-regulating the melanocytes in a process called “subcellular selective photothermolysis” [61,62]. Recently, reductions in the expression of proteins associated with melanogenesis, including TRP-1, tyrosinase-related protein-2, nerve growth factor, α -melanocyte-stimulating hormone, and tyrosinase, were also demonstrated after ‘laser toning’ [63].

In an eight-week trial, 58.8% of the patients who received ‘laser toning’ weekly, administered at 1.6–2.5 J/cm², demonstrated an improvement of 50–75% in investigator’s global assessment scores [64]. In this study, transient pain, erythema, and edema were commonly reported, while partially hypopigmented macules and diffuse hyperpigmentation rarely occurred. *Wattanakrai et al.* (2010) undertook a split-face trial to compare ‘laser toning’ with 2% HQ treatment [65]. They found that the side that received ‘laser toning’ weekly, administered at 3.0–3.8 J/cm² for five sessions, achieved marked improvements in the lightness index (L*) score (92.5%) assessed by a colorimeter, and in the modified MASI score (75.9%), compared with 19.7% and 24%, respectively, for the side administered 2% HQ. The investigators also reported that mottled hypopigmentation developed in three patients and melasma lesions recurred in all patients during follow-up.

Pulsed-dye laser treatment: Pulsed-dye laser (PDL) treatment is the gold standard therapy for vascular lesions. Evidence is accumulating that shows increased vascularization in melasma lesions, which may play a role in the recurrence of the disease [66–68]. An increase in the expression of vascular endothelial growth factor (VEGF) in keratinocytes has led to the suggestion that they may act in vessels, because functioning VEGF receptors were demonstrated in melanocytes *in vitro* [66,69]. Elevations in the levels of expression of c-kit, stem cell factor (SCF), and inducible nitric oxide synthase have also been observed, which could affect vascularization [70, 71].

In a split-face trial, *Passeron et al.* (2011) compared TCC plus PDL with TCC alone in patients with Fitzpatrick skin types II–IV [72]. At the end of treatment, the MASI scores were significantly lowered in both groups ($p < 0.05$). However, while the improvement was sustained at the two-month follow-up assessment in the group that received combination treatment, it was not sustained in the group that received TCC alone.

Copper bromide laser treatment: Copper bromide lasers emit two wavelengths of light either separately or simultaneously: the 511-nm green beam for the treatment of pigmented lesions, and the 578-nm yellow beam for the treatment of vascular lesions. In a recent pilot study, 10 Korean patients were treated with copper bromide laser at two-week intervals for eight weeks to evaluate its efficacy and safety [73]. At the one-month post-treatment follow-up, the mean MASI score decreased modestly from 12.3 to 9.5. L* and the erythema index (a*), measured using a Chromameter[®], showed significant improvements ($p < 0.05$). Histopathologically, reductions in the expression of melan-A, CD34, ET-1, and VEGF were observed.

Systemic tranexamic acid

Though the exact pathogenesis remains poorly understood, melasma involves alterations in different dermal components as well as increases in epidermal pigmentation. It includes disruptions and thinning of the basement membrane, prominent solar elastosis, increases in vascularization, elevations in the expression of VEGF, c-kit, and SCF, and increases in the number of mast cells [54,66,70,74]. TXA inhibits plasmin, a key molecule in angiogenesis that converts extracellular matrix-bound VEGF into its free forms [75]. TXA has also been reported to suppress neovascularization induced by basic fibroblast growth factor [76]. Therefore, TXA could reverse melasma-related dermal changes.

In a recent clinical trial that evaluated the efficacy of systemic TXA in the treatment of melasma, we demonstrated a decrease in the lesional melanin index and a* (erythema index) after 250 mg TXA was administered orally to 25 female study participants three-times daily for eight weeks (Figure 3) [77]. Histological analysis showed significant reductions in epidermal pigmentation, vessel numbers, and mast cell counts. In another trial conducted by *Wu et al.* (2012), 64.8% of the patients who were administered 250 mg TXA orally twice daily for six months showed “excellent” or “good” outcomes six months after the treatment had ceased [78]. In this study, gastrointestinal discomfort (5.4%) and hypomenorrhea (8.1%) were commonly reported, but no severe adverse events occurred.

Chemical peels

Chemicals peels are often recommended in the treatment of melasma in patients with pale skins [56]. A few decades ago, we also used chemical peels, especially glycolic acid peels, in the treatment of melasma. However, the result was unsatisfactory with the high risk of adverse effects, especially PIH. Nowadays, chemical peels are not preferred in Asian patients, especially in Korean patients, and are carefully applied to a few selected recalcitrant cases.

Acquired Bilateral Nevus of Ota-Like Macules

ABNOM, or Hori nevus, first described by *Hori et al.* (1984), is characterized by multiple bilateral speckled blue-brown or slate gray macules on the malar area or, less commonly, on the forehead, upper eyelids, and nose, with no ocular or mucosal involvement (Figure 4) [79]. It is usually found in middle-aged Asian women, with a reported incidence of 0.8% in a population-based study [80]. Histological findings include irregularly shaped, dendritic melanocytes dispersed in the papillary and mid-dermis, and particularly in the subpapillary dermis. The pathogenesis of ABNOM remains poorly understood, but it is known that ectopic dermal melanocytes resulting from

incorrect migration during embryological development are activated in response to UV exposure, excessive levels of sex hormones, chronic inflammation, or other undiscovered factors [79, 81-84].

Q-switched (QS) laser treatments, including QSNYL, QS ruby laser (QSRL), and QS alexandrite laser (QSAL), are the mainstays of ABNOM therapy [85]. While all QS laser treatments have been reported to be fairly effective in ABNOM treatment, clinical responses to each form of treatment and the complication rates vary considerably.

Kunachak and Leelaudomlipi (2000) reported that all 68 patients who received 1,064-nm QSNYL, administered at 8–10 J/cm², a 2- or 4-mm spot size, and at two- or three-week intervals, achieved 100% clearance after receiving two-to-five treatment sessions, which was sustained for 42 months [86]. In this study, transient hyperpigmentation was reported in 50% of the patients.

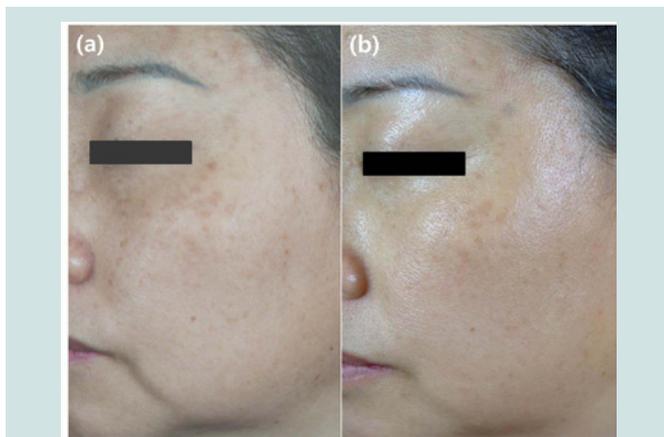


Figure 3: A female patient with melasma who was administered 250mg TXA orally three-times per day. Eight weeks after the initiation of the treatment, a decrease in the lesional melanin index was demonstrated. (a) baseline (b) at week 8.



Figure 4: A representative case of acquired bilateral nevus of Ota-like macules (ABNOM). It characteristically manifests as multiple bilateral speckled blue-brown or slate gray macules on the malar area or, less commonly, on the forehead, upper eyelids, and nose, with no ocular or mucosal involvement.

On the other hand, studies conducted by *Polnikorn et al.* (2000) and *Suh et al.* (2001) reported comparatively lower efficacies of QSNYL in the treatment of ABNOM in which 30.3% and 50% of the patients achieved good-to-excellent outcomes, respectively [87,88]. Transient hyperpigmentation occurred in 73% and nearly all of the patients, respectively.

Nevi of Ota and Ito

Nevi of Ota and Ito, and Mongolian spots are three variants of dermal melanocytosis, which can be distinguished by their clinical manifestations [89]. Nevus of Ota, first described by Ota in 1939, presents as a blue-black, brown, or gray patch on the face within the unilateral trigeminal nerve distribution at birth or during adolescence. Histologic findings are similar to those for ABNOM, except that the melanocytes in nevus of Ota are distributed diffusely throughout the papillary and reticular dermis [85].

Nevus of Ito is also a dermal melanocytic condition that usually manifests as a unilateral blue, gray, or brown patch [90]. It shares the same features as nevus of Ota, except for its distribution in the posterior supraclavicular and lateral cutaneous brachial nerves, thereby involving the shoulder, the side of the neck, and the supraclavicular area [91].

QS lasers with their short pulses, induce selective photothermal damage to dermal melanocytes and melanophages, and are the treatments of choice for nevi of Ota and Ito. In a trial in which 15 patients with nevi of Ota were treated with QSRL (6–10 J/cm²) for one to seven sessions, nevi had lightened by least at 50% in all patients, with complete clearance in four patients and transient hyperpigmentation in one patient [92]. QSAL administered at 6-8 J/cm² for one to 15 sessions, was effective in lightening of the nevi by at least 50% in 10 out of 12 patients, and mild transient hypopigmentation occurring in one patient [93]. In a trial comparing QSNYL with QSAL, QSNYL appeared to be more effective than QSAL at lightening nevi of Ota after three or four treatment sessions [94].

Recently, “laser toning” using 1,064-nm QSNYL treatment with low fluence (2.0-2.5 J/cm²), has been attempted in the treatment of nevi of Ota, and all of the 19 patients, except one, attained almost total clearance of the nevi after an average of 17.1 treatment sessions [95]. PIH was observed in one patient.

Mongolian Spots

Mongolian spots present as congenital blue-grayish macules, which are usually located in the sacral area of infants. Sometimes, they appear on the extremities or trunk and are called ectopic Mongolian spots. They can be seen in most Mongolian individuals during the neonatal period, then spontaneously regress. However, some Mongolian spots persist into adulthood, which is estimated to occur in 2.8-4.1% of Japanese patients aged 18–26 years [96,97]. Ectopic Mongolian spots are more likely to persist than typical Mongolian spots [98], and it is unlikely to spontaneously regress when a patient is older than 11 years [96,98]. Several studies have demonstrated good responses of persistent Mongolian spots to QS laser devices [99-102].

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