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# Combined Therapy Using Q-Switched Ruby Laser and Bleaching Treatment With Tretinoin and Hydroquinone for Acquired Dermal Melanocytosis

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**BACKGROUND AND OBJECTIVE.** Acquired dermal melanocytosis (ADM; acquired bilateral nevus of Ota-like macules) is known for its recalcitrance compared with Nevus of Ota, and we assume that one of the reasons is a higher rate and degree of postinflammatory hyperpigmentation (PIH) seen after laser treatments.

**METHODS.** Topical bleaching treatment with 0.1% tretinoin aqueous gel and 5% hydroquinone ointment containing 7% lactic acid was initially performed (4 to 6 weeks) to discharge epidermal melanin. Subsequently, Q-switched ruby (QSR) laser was irradiated to eliminate dermal pigmentation. Both steps were repeated two to three times until patient satisfaction was obtained (usually at a 2-month interval for laser sessions). This treatment was performed in 19 patients with ADM. Skin biopsy

was performed in six cases at baseline, after the bleaching pretreatment, and at the end of treatment.

**RESULTS.** All patients showed good to excellent clearing after two to three sessions of QSR laser treatments. The total treatment period ranged from 3 to 13 (mean of 8.3) months. PIH was observed in 10.5% of the cases. Histologically, epidermal hyperpigmentation was observed in all specimens and was dramatically improved by the topical bleaching pretreatment.

**CONCLUSION.** QSR laser combined with the topical bleaching pretreatment appeared to treat ADM consistently with a low occurrence rate of PIH and lessen the number of laser sessions and total treatment period and may also be applied to any other lesions with both epidermal and dermal pigmentation.

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NEVUS OF OTA, first described in 1939 by Ota and Tanino<sup>1</sup> as nevus fuscocaeruleus ophthalmomaxillaris, is usually unilaterally located in the area innervated by the ophthalmic and maxillary branch of the trigeminal nerve. A typical nevus of Ota is a flat blue-black or slate-gray macule intermingled with small, flat, and brown spots. Pigmented macules are also often present in ocular, oral, and nasal mucous membranes. On the other hand, acquired bilateral nevus of Ota-like macules (Hori's nevus) is a pigmented lesion involving bilateral grayish brown facial macules that was first reported by Hori et al.<sup>2</sup> in 1984. This condition and similar ones have been referred to

as acquired dermal melanocytosis (ADM) by some Japanese dermatologists.<sup>3,4</sup> ADM onsets later in life, usually after the age of 20 years, and represents bilateral involvements, with the malar regions almost always affected, and a lack of mucosal and optic involvement.<sup>2</sup> It is rare in whites but is relatively common in Asian females and is seen much more frequently than nevus of Ota.<sup>5</sup> There is a report that it occupied 7.5% of cosmetic skin complaints in Japan.<sup>6</sup> Clinically, it can be easily distinguished from nevus of Ota by bilateral presentation, spot distribution, and difference in color, whereas in some atypical cases, it can be misdiagnosed as melasma. ADM on bilateral cheeks usually has a round spot distribution and is more grayish in color than melasma, although we experienced several cases in which melasma-like lesions were initially seen on both cheeks, and round grayish spots were detected only after tretinoin bleaching was completed.

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The authors previously described an aggressive and optimal use of tretinoin along with hydroquinone for various kinds of skin hyperpigmentation.<sup>7-9</sup> This topical bleaching treatment was very effective for removal of epidermal pigmentation. Therefore, we tried the bleaching pretreatment before Q-switched ruby (QSR) laser for ADM in order to eliminate epidermal hyperpigmentation and decrease the risk of postinflammatory hyperpigmentation (PIH) after QSR laser treatment. This combination therapy was applied for patients with ADM, and its efficacy and usefulness were evaluated.

## Methods

### *Preparation of Ointments*

Tretinoin aqueous gels (tretinoin gel) at three different concentrations (0.1%, 0.2%, and 0.4%) were originally prepared at the Department of Pharmacy, University of Tokyo, Graduate School of Medicine. The precise regimen of tretinoin aqueous gel was described before.<sup>8</sup> These gels can be prepared relatively easily because the tretinoin powder (Sigma Chemical, St. Louis, MO) is commercially available. Aqueous gel is most suitable for ointment base of tretinoin because of its good permeability. An ointment, including 5% hydroquinone and 7% lactic acid (HQ-LA ointment), and one including 5% hydroquinone and 7% ascorbic acid (HQ-AA ointment), were also prepared. Plastibase (petrolatum polyethylene ointment base; Taisho Pharmacology, Osaka, Japan) was used as the ointment base of the HQ-LA ointment, whereas the hydrophilic ointment was used for the HQ-AA ointment. Because tretinoin gel, HQ-LA, and HQ-AA ointments (especially tretinoin gel) are pharmacologically unstable, fresh ointments were prepared at least once a month and were stored in a dark and cool (4°C) place.

### *Evaluations of Results*

Photographs were taken for every patient at baseline and after treatment with a high-resolution digital camera (Canon EOS-D30). The percentage of pigmentary clearance was evaluated via the photographs by two experienced plastic surgeons who did not perform this treatment. The mean data of the pigmentary clearance of each patient were classified into four categories: "excellent" (80% or more clearance), "good" (50% to less than 80% clearance), "fair" (0% to less than 50% clearance), and "poor" (no change or worse).

### *Patients*

Nineteen Japanese patients with ADM were treated with our treatment protocol. All patients were women.

The patient age at the start of the treatment ranged from 24 to 50 years old (mean  $\pm$  SD, 37.9  $\pm$  8.7). The age of onset of ADM was 15 to 40 years old (mean  $\pm$  SD, 24.7  $\pm$  7.5). Pigmented lesions were located bilaterally on the malar area in all 19 cases (100%), on the nose in 4 cases (21%), on the temporal area in 2 cases (11%), and on the forehead in 1 case (5%). The follow-up time after the final laser session ranged from 3 to 13 months (mean  $\pm$  SD, 8.3  $\pm$  3.7).

### *Treatment Methods*

Our treatment was composed of two steps. The first step was a topical bleaching treatment using tretinoin gel and hydroquinone ointment (6 to 8 weeks), and the second step was QSR laser irradiation. Both steps were repeated until patient satisfaction was obtained.

### *Topical Bleaching Treatment*

The purpose of this treatment is to improve epidermal pigmentation by accelerating discharge of epidermal melanin (by tretinoin) and suppressing new epidermal melanogenesis (by hydroquinone). The two-phased (bleaching and healing) treatment was performed as follows.

### *Bleaching Phase*

Both 0.1% tretinoin gel and HQ-LA ointment were initially applied to the skin lesions twice a day. Tretinoin gel was carefully applied only on pigmented spots using a small cotton-tip applicator, whereas HQ-LA ointment was widely applied with fingers (e.g., all over the face) a few minutes later, after allowing the applied tretinoin aqueous gel to dry. The method of ointment application is critical in this aggressive treatment in order to obtain maximal bleaching effects with minimal irritant dermatitis. In case severe irritant dermatitis was induced by HQ-LA ointment, HQ-AA ointment was used instead. Patients were requested to visit our hospital at 1, 2, 4, 6, and 8 weeks after starting this treatment and every 4 weeks thereafter. When the appropriate skin reaction (i.e., mild erythema and scaling) was not observed at 1 week, the concentration of tretinoin was changed to 0.4% because 0.2% tretinoin gel was usually not strong enough to get a sufficient reaction in these cases. The concentration of tretinoin and frequency of its application were appropriately modified according to the skin condition and degrees of erythema and scaling. In most cases, it took 4 to 6 weeks to finish this phase. In the second bleaching step, tretinoin gel of the final strength used in the first step was used from the beginning.

### Healing Phase

After the 4- to 6-week bleaching phase, the application of tretinoin gel and HQ-LA ointment was discontinued, and application of HQ-AA ointment was used in order to prevent PIH until the redness was sufficiently reduced. It usually took 2 to 4 weeks to complete this phase. Topical corticosteroids were not employed in either the bleaching or healing phase.

### QSR Laser Treatments

In all patients, topical anesthesia (lidocaine patch; Penles, Wyeth Lederle Japan Inc., Tokyo, Japan) was applied 60 to 120 minutes before the laser treatment. For QSR 694.5-nm laser (Model IB101; Niic Co., Tokyo, Japan) treatment, a spot size of 5 mm, a 1-Hz repeat rate, a pulse duration of 20 ns, and fluences ranging from 4.0 to 5.0 J/m<sup>2</sup> were used. After laser treatment, topical gentamicin sulfate ointment (Gentacin, Schering-Plough, NJ) was applied twice a day until a scale or thin crust disappeared (usually for 5 to 7 days). At 2 weeks after laser treatment, application of HQ-AA ointment was started.

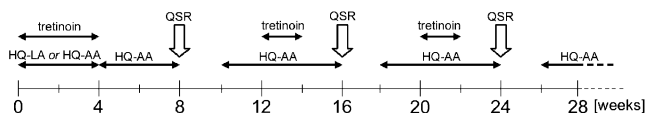
At 4 weeks after each laser treatment, the topical bleaching treatment with tretinoin gel of appropriate concentration (usually same as the final concentration in the bleaching phase) and HQ-AA ointment were started as a pretreatment of the next laser irradiation and also as a treatment of postlaser PIH in some cases. In most cases, the bleaching phase for 2 weeks was long enough, and we can usually estimate the clinical result at 8 weeks after each laser treatment. When some hyperpigmentation remained, we can go for the next session. An example of the typical time course was demonstrated in Figure 1.

Skin biopsy of pigmented regions with a diameter of 2 mm was performed in six cases at baseline, just after the first bleaching treatment, and at the end of the treatment. Sections were stained with Masson-Fontana staining for visualization of melanin granules.

## Results

### Clinical Results

In the topical bleaching treatment, erythema was usually seen in a few days, followed by continual



**Figure 1.** A representative time course of the combined treatment. Tretinoin is used for 4 weeks in the initial bleaching pretreatment and for 2 weeks in the following pretreatments. QSR laser treatment is performed three times, and the total treatment period is 30 weeks.

**Table 1.** Clinical evaluations (Clearance of pigmentation)

Excellent	15/19	78.9%
Good	4/19	21.1%
Fair	0/19	0.0%
Poor	0/19	0.0%
Total		100.0%

**Table 2.** Number of QSR laser treatments performed

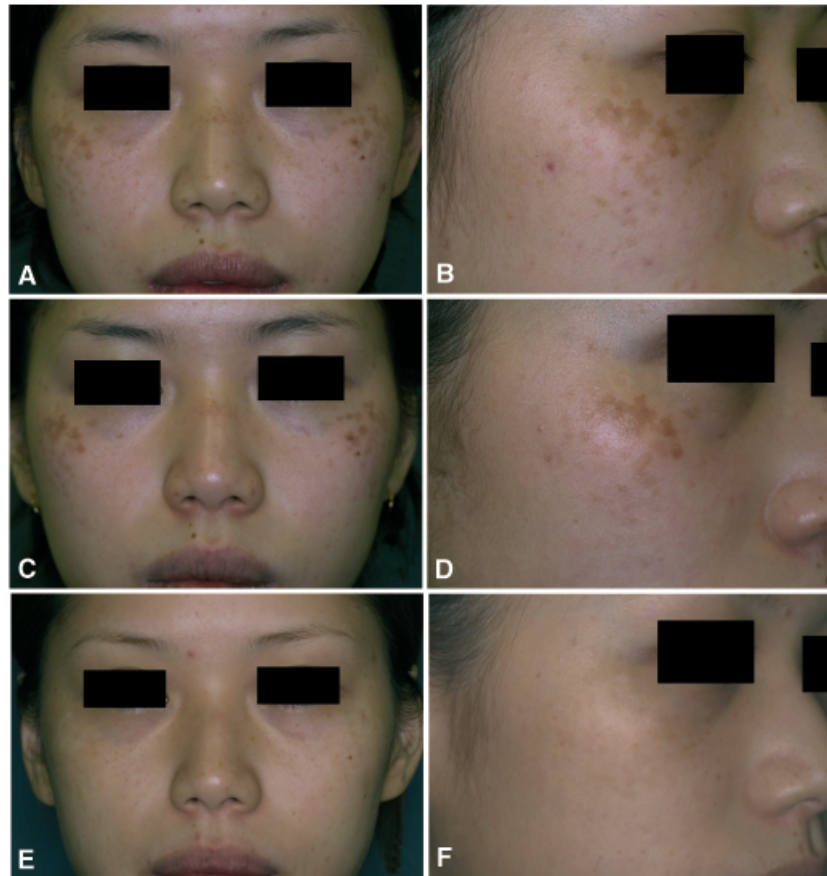
Once	0/19	0.0%
Twice	7/19	36.8%
Three times	12/19	63.2%

scaling during the first week. Erythema and scaling were usually seen continually throughout the bleaching phase. On the other hand, erythema gradually declined with time in the healing phase. The difference in color of the macules was usually observed between before and after the first topical bleaching treatment, for example, a color change from brown to gray-brown or from gray-brown to bluish black, suggesting clearance of epidermal pigmentation.

All patients showed “good” to “excellent” clearing after two or three laser treatments without any complications such as scarring and persistent depigmentation. Fifteen of 19 cases were evaluated as “excellent” and the other 4 cases as “good” (Table 1). No cases were regarded as “fine” or “poor.” QSR laser treatments were performed twice in 7 of 19 cases, and 3 times in the other 12 cases (Table 2). Although PIH apparently occurred in 2 of 19 cases (10.5%) after the first laser treatment, PIH was not clearly seen in any cases after the second and third laser treatments. We diagnosed pigmentation as PIH at 4 weeks after laser treatment when the pigmentation got worse than before or 1 to 2 weeks after laser treatment. The average treatment period was 24.8 ± 3.6 (mean ± SD) weeks, and the average number of QSR laser treatment was 2.63 ± 0.5 (mean ± SD) times. Although patients had unpleasing irritant dermatitis during the topical bleaching treatment, all achieved sufficient satisfaction with the final results, and they were followed for 8.3 ± 3.7 (mean ± SD) months (3 to 13 months) without any evidence of recurrence. The representative three cases are shown in Figures 2–4.

### Histologic Results

At baseline, not only dermal melanocytosis but also epidermal melanosis around the basal layer was seen in all six samples (Figure 5). In the upper dermis, elongated, slender, and pigment-bearing melanocytic cells dispersed between the collagen fibers were



**Figure 2.** Case 1. (A and B) Baseline photos of a 24-year-old woman with ADM. (C and D) Just after the bleaching treatment with tretinoin and hydroquinone. The color change of the macules was moderate, but the histologic change was apparent, as shown in Figure 6. (E and F) Six months after the third QSR laser treatment. Note the complete clearance of pigmentation.

observed. In addition, all six specimens showed disappearance of rete ridges. In most cases, epidermal melanin granules were significantly cleared after the initial bleaching treatment, whereas dermal pigmentation appeared not to change at all (Figure 6).

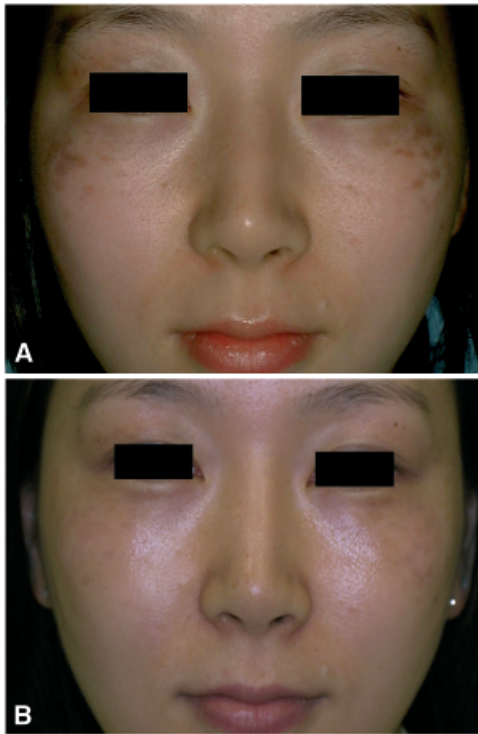
## Discussion

The first reported treatment of ADM was cryotherapy,<sup>10</sup> but it showed an unpredictable result with a high risk of permanent scarring and hypopigmentation. Kunachak et al.<sup>11</sup> treated ADM using dermabrasion with successful results. Despite its advantage as a single session procedure, this approach is invasive.<sup>12</sup> Therefore, QS lasers are considered to be main treatments of ADM today as well as nevus of Ota.

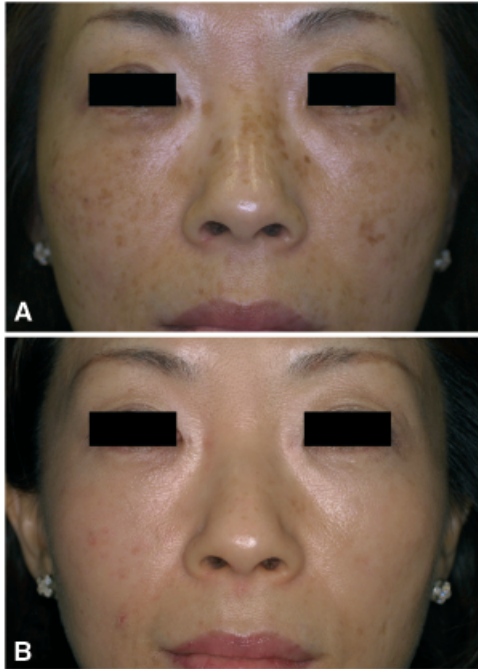
Although previous reports of QS laser treatments showed good clearance of ADM,<sup>12-16</sup> it has been pointed out that PIH and hypopigmentation are frequently observed afterward. In ADM, it is known that PIH occurs 2 to 4 weeks after laser irradiation in

higher degrees and frequency than in nevus of Ota. Kunachak et al.<sup>12</sup> employed repetitive treatment sessions at only 1- to 2-week intervals. They performed the second laser session before PIH appeared and reported successful clearance of ADM but relatively high (5.7%) risk of hypopigmentation. Polnikorn et al.<sup>13</sup> and Kunachak and Leelaudomlipi<sup>14</sup> both used QS Nd:YAG laser to treat ADM and reported that the rate of PIH was 71% and 50%, respectively. Polnikorn et al.<sup>13</sup> waited for disappearance of PIH before the next session of laser treatment, which was 3 to 6 months. Lam et al.<sup>15</sup> used QS alexandrite laser with the mean session number of seven, and most patients showed postlaser PIH. In our own experience using QSR laser for ADM without any pretreatments, PIH was almost always observed 2 to 4 weeks after the first laser treatment.

The typical color of ADM is grayish brown.<sup>2-5</sup> It is more brownish than typical nevus of Ota (blue black or slate gray). There are two significant differences in histology between nevus of Ota and ADM: (1) Melanocytes are distributed diffusely throughout the

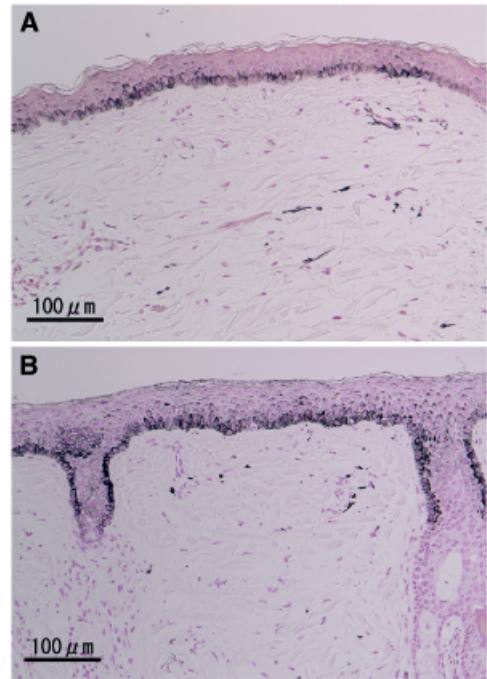


**Figure 3.** Case 2. (A) A baseline view of a 29-year-old woman with ADM. (B) Ten months after the third QSR laser treatment. The clinical result was evaluated as "excellent."



**Figure 4.** Case 3. (A) A baseline view of a 46-year-old woman with ADM. (B) Three months after the third QSR laser treatment. The result of the clearance was evaluated as "good."

entire dermis in nevus of Ota,<sup>17</sup> whereas they are located only in the upper dermis in ADM,<sup>2</sup> and (2) epidermal hyperpigmentation is not usually seen in

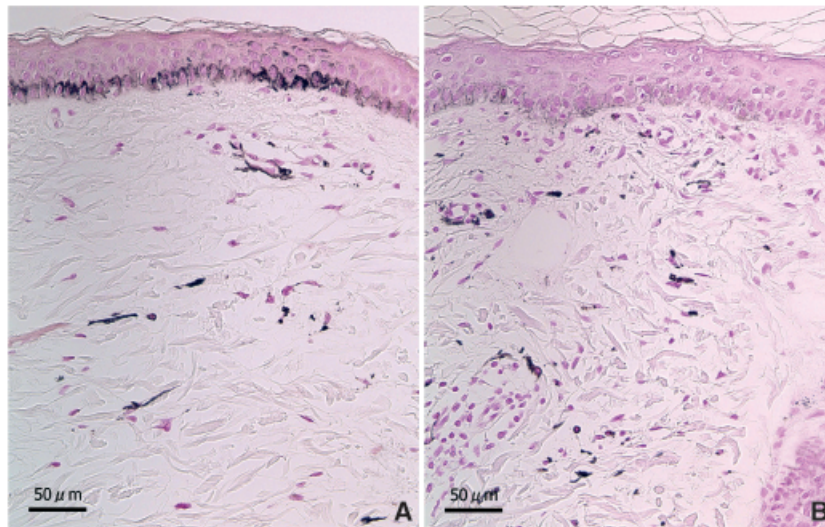


**Figure 5.** Histology of ADM before treatments. Both sections demonstrated epidermal hyperpigmentation around the basal layer, melanocytosis in the upper dermis, disappearance of rete ridges, and slight thinning of the epidermis (Masson-Fontana staining,  $\times 100$ ).

nevus of Ota, whereas it is always prominent in ADM; the latter was not well documented before, but we confirmed epidermal hyperpigmentation in all specimens examined in this study (Figure 5). The difference in color between nevus of Ota and ADM is due to these histologic differences. Although nevus of Ota responds to Q-switched lasers very well,<sup>18-22</sup> ADM is known for its recalcitrance to conventional treatments,<sup>13-16</sup> and one of the reasons seems to be a high rate of PIH seen after laser treatments.<sup>13-15</sup> The authors assumed that it was mainly due to the presence of epidermal hyperpigmentation in ADM.

In addition, all biopsy specimens showed disappearance of rete ridges, whereas surrounding intact skin had normal rete ridges in some cases. This finding may clinically mean suppression of both epidermal turnover and discharge of epidermal melanin and may be related to the epidermal hyperpigmentation seen in ADM, whereas the reason for epidermal hyperpigmentation in ADM is not clarified, and we suspect that the epidermal hyperpigmentation in ADM is mainly due to abnormal melanin production by melanocytes like melasma.

In this study, we confirmed histologically that accumulated melanin granules around the basal layer were cleared up after treatment with tretinoin and hydroquinone, but the melanin deposits (dermal melanocytes) in the dermis appeared not to change in



**Figure 6.** Histology of ADM in case 1. (A) at baseline and (B) just after the topical bleaching pretreatment. (A) At baseline, the section demonstrated epidermal hyperpigmentation as well as the scattered dermal melanocytes featuring a highly pigmented, elongated dendritic appearance. (B) Just after the topical bleaching pretreatment, epidermal pigmentation was significantly improved, whereas the dermal melanocytosis appeared not to change at all (Masson-Fontana staining,  $\times 200$ ).

ADM (Figure 6). Taken together with our previous studies,<sup>9,23–25</sup> this finding supports our previous hypothesis for mechanism of this topical bleaching therapy: Tretinoin acts as a discharger of epidermal melanin by accelerating epidermal turnover and promoting keratinocytes proliferation, whereas hydroquinone suppresses new melanin production by epidermal melanocytes.

It is considered that the present combination therapy with QSR laser and the aggressive bleaching treatment has the following advantages: (1) high efficiency of the QSR laser treatment in improving dermal pigmentation (after the pretreatment removing epidermal pigmentation [basal melanosis], the laser radiation can be expected to more efficiently get to the dermis because its energy absorption by epidermal melanins is thought to be lower), and (2) decreasing the rate of PIH (we assume that if there is a significant amount of epidermal pigmentation, considerable inflammation would be induced in the entire epidermis, resulting in occurrence of PIH usually 2 to 4 weeks after laser irradiation). In this sense, therefore, the pretreatment to discharge epidermal melanins seems to be quite important. Indeed, with the bleaching pretreatment, the frequency of PIH after initial laser treatment was as low as 10.6%, which is significantly lower than other studies. In addition, PIH was not clearly detected after the second or third laser treatment.

Nevus of Ota, which can usually be well treated by several sessions of QSR laser, has predominantly dermal pigmentation. This is because, unlike ADM, it does not have significant epidermal hyperpigmenta-

tion, which induces PIH after laser treatments and makes it more difficult to treat consistently. Therefore, we prefer the topical bleaching therapy with tretinoin and hydroquinone for epidermal pigmentation and QS lasers for dermal pigmentation, with the exceptions of hyperkeratotic lesions such as solar lentigines on extremities and trunks (these lesions have thick stratum corneum) that we treat with a QSR laser first and tretinoin bleaching for PIH induced by QSR laser treatment. It may be desirable to perform laser treatments after pretreatment of epidermal pigmentation for lesions with both epidermal and dermal pigmentation, such as ADM, friction melanosis, dermal melasma, and hyperpigmentation after atopic dermatitis. The topical bleaching therapy can treat almost any kinds of epidermal hyperpigmentation without hyperkeratosis, including PIH and melasma, which can not be treated with lasers.

For treatment of PIH after laser treatments, topical tretinoin and hydroquinone appeared to be best, as we and others<sup>15</sup> did, although the bleaching protocols are not the same. Otherwise, we can wait for spontaneous clearance of PIH; however, the clearance is not guaranteed, and intervals between laser sessions become much longer, such as 3 to 6 months.<sup>13</sup> PIH is one of the easiest pigmented lesions to treat with the topical bleaching treatment,<sup>8</sup> and in this study, a mild treatment with tretinoin for only 2 weeks was usually sufficient, whereas hydroquinone was used continually for over 1 month. Even if the pretreatment is performed, intervals between laser treatments can be shortened up to 6 to 8 weeks, therefore leading to shortening of the total treatment period compared

with methods waiting for spontaneous disappearance of PIH.

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