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A therapeutic strategy based on histological assessment of hyperpigmented skin lesions in Asians☆

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Summary Hyperpigmentation is the most common cosmetic skin complaint in Asians, but there is no standard treatment strategy. The aim of this study was to establish a simple therapeutic strategy based on the histological features of hyperpigmented skin lesions in Asians. Fifty-nine biopsies were analysed from 49 Japanese patients with 17 types of hyperpigmented skin lesions. In 10 patients, skin samples were also taken during a topical bleaching treatment that used tretinoin and hydroquinone. These samples were evaluated after staining with haematoxylin–eosin and Fontana–Masson stains. Our experience of treating a variety of pigmented lesions with aggressive topical bleaching and lasers was reviewed.

Hyperpigmented lesions were classified into seven categories based on pathological features, especially on the degree of hyperkeratosis and epidermal melanin deposits, and on the existence of melanin incontinence and the location of dermal melanocytes. Tretinoin and hydroquinone therapy was histologically effective for treating epidermal melanin deposits, but not dermal melanosis or dermal melanocytes. Based on pathological features and our extensive clinical experience with hyperpigmented skin, we propose a therapeutic strategy for treating hyperpigmented skin lesions, which may be particularly useful in Asian populations.

In Caucasians, the most common complaints about photoaged skin are fine wrinkles and telangiectasia, but these complaints are less common in populations with darker skin. In Asians, hyperpigmentation is the most common cosmetic complaint, but a standard strategy for treating hyperpigmented skin lesions has not been established. We have found that aggressive use of topical tretinoin (0.1–0.4%) along with hydroquinone can successfully treat various skin hyperpigmentation conditions in Asians.[1–8]

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Although the bleaching protocol we routinely use requires two steps (a bleaching step and a healing step), and severe but transient adverse skin reactions are possible, this protocol is quite effective in removing epidermal pigmentation and especially useful for treating pigmented lesions that are not effectively treated by lasers, such as melasma, post-inflammatory hyperpigmentation (PIH) and pigmented nipples/areolas. Unfortunately, this bleaching protocol has less or no effect on dermal pigmentation and hyperkeratotic pigmented lesions.

In order to establish a simple therapeutic strategy that addresses a wide range of hyperpigmented conditions, we used a topical bleaching treatment, Q-switched (QS) ruby laser, CO_2 lasers or combination treatment in our clinic, and analysed histological specimens from patients. This analysis and our clinical experience led us to propose a therapeutic strategy for treating pigmented skin conditions based on histological features.

Methods

Fifty-nine biopsies were taken from 49 Japanese female patients (four males and 45 females; age range 16–60 years, mean 36.16) with hyperpigmented skin lesions after informed consent using an IRB-approved protocol. The lesions were clinically diagnosed as follows: acquired dermal melanocytosis (ADM) ($n = 12$); solar (senile) lentigines ($n = 8$); lichen pilaris ($n = 4$); ripple/reticulate hyperpigmentation in atopic dermatitis (RHAD) ($n = 7$); nevus spilus (café-au-lait macules) ($n = 4$); pigmented contact dermatitis ($n = 4$); pigmented nipple areolar complex (PNAC) ($n = 3$); pigmentatio petaloides actinica (PPA) ($n = 4$); ephelides ($n = 2$); friction melanosis ($n = 2$); periorbital hyperpigmentation ($n = 2$); nevus of Ota ($n = 2$); post-inflammatory hyperpigmentation resulting from a single inflammatory event (PIH-S) ($n = 1$); seborrheic keratosis ($n = 1$); melasma ($n = 1$); pigmented external genitalia ($n = 1$); and erythromelanosis follicularis faciei et colli (EFFC) ($n = 1$). In addition, 10 samples were taken from 10 patients at baseline and during our topical bleaching therapy with tretinoin (all-trans retinoic acid; RA) and hydroquinone (HQ) (RA-HQ therapy; see below for details). These were diagnosed as ADM ($n = 1$), solar lentigines ($n = 1$), lichen pilaris ($n = 2$), RHAD ($n = 1$), nevus spilus ($n = 1$), pigmented contact dermatitis ($n = 2$), PNAC ($n = 1$) and PPA ($n = 1$).

Biopsied tissue was fixed in 4% buffered neutral formaldehyde solution and embedded in paraffin for sectioning. The sections were stained with haematoxylin–eosin and Fontana–Masson stains. The pathological examination focused on the existence of hyperkeratosis and the location (layers) of melanin deposits or melanocytes, since these two factors determined our therapeutic strategy. Comparing samples obtained before and during treatment, morphological alterations due to the RA-HQ treatment were observed.

RA-HQ therapy

The purpose of this treatment is to improve epidermal pigmentation by accelerating discharge of epidermal melanin (with aggressive use of tretinoin) and suppressing new epidermal melanogenesis (with hydroquinone). Details of the RA-HQ protocol were described previously[4–6] and a brief outline is presented here.

Preparation of ointment

Tretinoin aqueous gels (tretinoin gel) at three different concentrations (0.1%, 0.2% and 0.4%), 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 originally prepared at the Department of

Table 1 Summary of histological characteristics of samples stained with Fontana–Masson

Clinical diagnosis	Epidermis		Dermis	
	Hyperkeratosis	Melanin deposits	Melanophages (pigmentary incontinence)	Dermal melanocytes
PIH-S	−	+	−	−
PNAC	−/+	+/++	−	−
Ephelides	−	+/++	−	−
Nevus spilus	−/+	+/++	−	−
Lichen pilaris	+	+/++	−/+	−
Seborraic keratosis	+++	++	−	−
Solar lentigines	−/+/++	+/++	−/+/++	−
Melasma	−	+/++	−/+/++	−
Pigmented external genitalia	−/+	++	+	−
Pigmented contact dermatitis	−	++	++/+++	−
Friction melanosis	−/+	+/++	++/+++	−
RHAD	−/+	+/++	++/+++	−
PPA	+	++/+++	++	−
EFFC	++	++	++	−
ADM	−	+/++	−	+ (upper dermis)
Periorbital hyperpigmentation	−	+/++	−	+ (upper dermis)
Nevus of Ota	−	−	−	++ (throughout the dermis)

−: negative, +: slightly positive, ++: positive, +++: highly positive; e.g.: '−/+' means 'negative or slightly positive'.

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Table 2 Proposed seven-category classification for hyperpigmented lesions

Category	Pathological features	Morbidities	Comments
I	Melanosis with hyperkeratosis	Soborrheic keratosis Lichen pilaris*	Hyperkeratosis is marked and the lesion is clinically protruded
II	Reactive epidermal melanosis	PIH Sunburn	Epidermal melanocytes are activated, mainly by external factors
III	Epidermal melanosis	Solar lentigines* PNAC Ephelides Nevus spilus Lichen pilaris* Lentigino simplex Melasma*	Genetic alterations in epidermal melanocytes lead to enhanced melanin production. Histological findings similar to those of Category II lesions
IV	Reactive epidermal melanosis & dermal melanosis	Pigmented external genitalia Friction melanosis RHAD Pigmented contact dermatitis	Exposure to external factors, such as UV irradiation and inflammation, activates epidermal melanocytes and leads to enhanced melanin production. Melanin deposits are observed in the epidermis and upper dermis (pigmentary incontinence)
V	Epidermal melanosis & dermal melanosis	Solar lentigines* Melasma* (dermal melasma) EFFC PPA	Genetic alterations in epidermal melanocytes lead to enhanced melanin production, and melanin deposits are observed in the epidermis and upper dermis (pigmentary incontinence). Histological findings similar to those of Category IV lesions
VI	Epidermal melanosis & dermal melanocytosis	ADM Periorbital hyperpigmentation	Enhanced melanin production by epidermal melanocytes. Dermal melanocytosis can be observed in the upper dermis
VII	Dermal melanocytosis	Nevus of Ota Nevus of Ito Mongolian spots	Dermal melanocytes are scattered throughout the dermis

* Morbidities classified into two categories.

Pharmacy, University of Tokyo Hospital. The precise regimens of those ointments were previously described.[2] These gels can be easily prepared, as the tretinoin powder (Sigma Chemical Co., St. Louis, MO, USA) is commercially available. Aqueous gel is most suitable for the ointment base of tretinoin because of its good permeability. Tretinoin gel is pharmacologically unstable, so fresh batches were prepared at least once a month and stored in a dark, cool (4 °C) place.

Bleaching treatment protocol with tretinoin gel and hydroquinone ointment (RA-HQ)

The two-stage (bleaching and healing) treatment was performed as follows.

(a) Bleaching phase: 0.1% tretinoin gel and HQ-LA ointment were initially applied to the skin lesions twice a day. A small amount of tretinoin gel was carefully applied only on pigmented spots using a small cotton-tip applicator (excess gel was wiped off), while the HQ-LA ointment was widely applied with fingers (e.g. all over the face) a few minutes later, after allowing the 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 cases in which severe irritant dermatitis was induced by the HQ-LA ointment, HQ-AA ointment was used instead. Patients were requested to visit our

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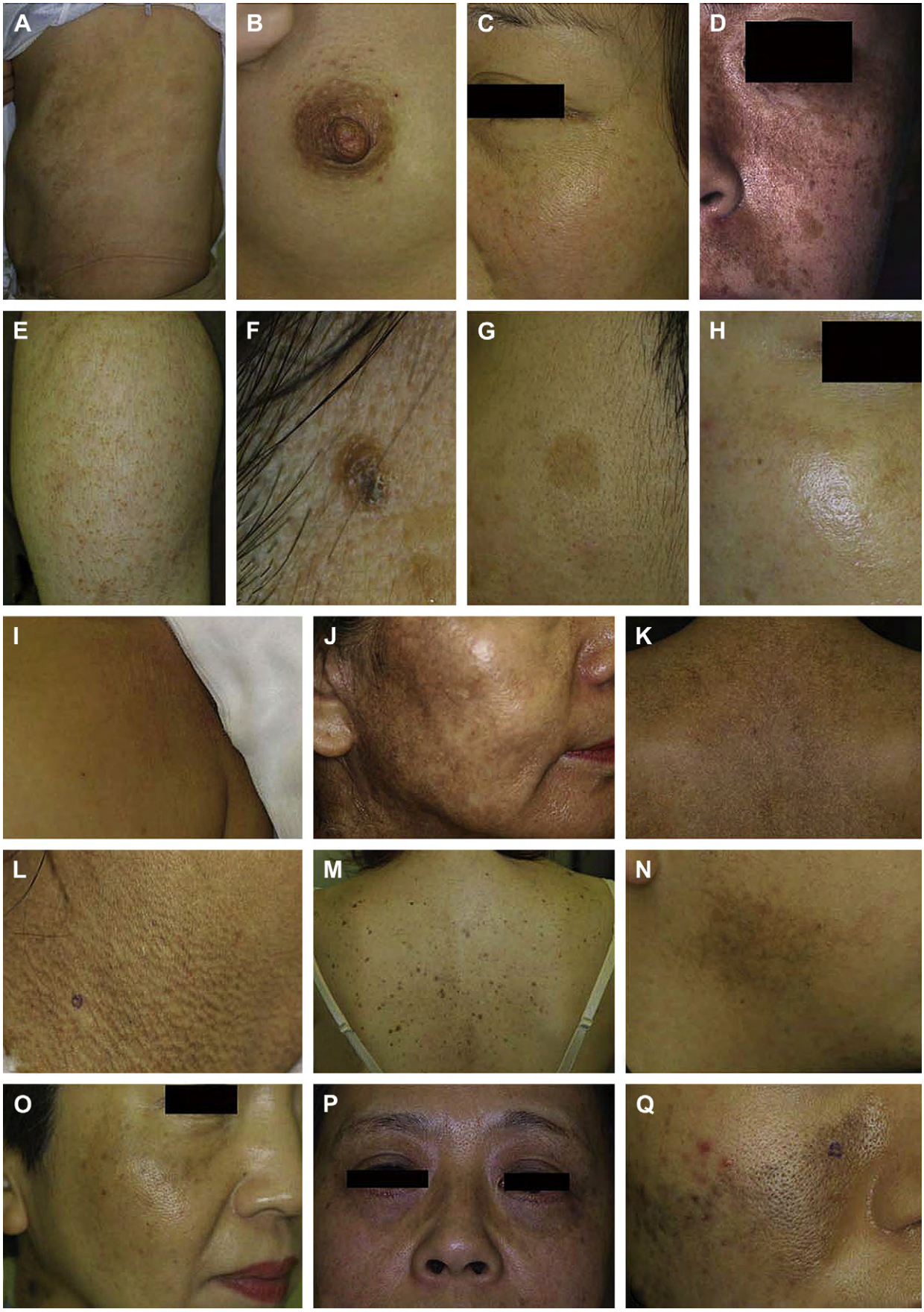

Figure 1 Hyperpigmented lesions in Asians: clinical manifestations. (A) PIH-S. (B) PNAC. (C) Ephelides. (D) Nevus spilus. (E) Lichen pilaris. (F) Seborrheic keratoses. (G) Solar lentigines. (H) Melasma. (I) Pigmented external genitalia. (J) Pigmented contact dermatitis. (K) Friction melanosis. (L) RHAD. (M) PPA. (N) EFFC. (O) ADM. (P) Periorbital hyperpigmentation. (Q) Nevus of Ota.

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hospital at 1, 2, 4, 6 and 8 weeks after starting treatment, and every 4 weeks thereafter. If the appropriate skin reaction (mild erythema and scaling) was not observed at 1 week, the concentration of tretinoin was increased to 0.4%, as 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 degree of erythema and scaling. It took 2–8 weeks to complete this phase.

(b) Healing phase: After the bleaching phase, the application of tretinoin gel and HQ-LA ointment was discontinued, and application of HQ-AA ointment was initiated in order to prevent PIH until redness was sufficiently reduced. It usually took 4 weeks to complete this phase. Topical corticosteroids, which reduce melanin discharge accelerated by tretinoin, were not employed in either the bleaching or healing phase.

Results

Biopsies of pigmented lesions

The histological characteristics and diagnoses of the biopsied samples are summarized in Table 1 and pigmented morbidities tentatively categorized in Table 2. Clinical appearance and histology of representative cases for each morbidity are shown in Figs. 1 and 2, respectively.

Horny layers

In general, dermatoses located on the trunk and extremities rather than on the face have a physiological tendency toward hyperkeratosis. Solar lentigines and relatively flat seborrheic keratoses resembled each other histologically and were characterized by distinctive hyperkeratosis. Note that in solar lentigines mild hyperkeratosis was observed even in lesions that appeared flat. Lichen pilaris and EFFC also showed mild hyperkeratosis, but this feature was more distinctive in lichen pilaris. No other dermatoses investigated in this study showed hyperkeratosis.

Epidermal pigmentation

Epidermal pigmentation was enhanced in all the morbidities in this study except for the nevus of Ota case. The degree of epidermal melanin pigmentation varied among the morbidities, and substantial differences were found between cases.

Dermal pigmentation

Dermal melanosis (melanin incontinence) was observed in some of the morbidities. Lesions resulting from chronic or repeated inflammation, such as pigmented contact dermatitis, friction melanosis, RHAD and PPA, showed breakdown of the dermo-epidermal junction and severe dermal melanosis (deposits of melanophages) in the upper dermis. Some melanophage deposits in the upper dermis were also seen in cases of melasma and solar lentigines, although degenerative changes of the dermo-epidermal junction were not detected. ADM and periorbital hyperpigmentation (a subtype of ADM) had dermal melanocytes with a highly pigmented, elongated dendritic appearance in the upper dermis, while dermal melanocytes were scattered throughout the dermis in nevus of Ota. In several morbidities such as PIH-S, ephelides and nevus spilus, dermal pigmentation, either melanosis or melanocytosis, was not detected irrespective of the degree of epidermal pigmentation.

Samples taken during RA-HQ treatment

The histological and clinical manifestations of representative cases of hyperpigmentation are shown in Figs. 3 and 4. In sections obtained during RA-HQ therapy, substantial epidermal hyperplasia, dramatic reduction of melanin deposits around the basal layer and temporal enhancement of parakeratosis were consistently observed (Fig. 3B and D). These changes were most likely a result of enhanced basal keratinocyte mitosis and accelerated turnover of the epidermis. Epidermal pigmentation was significantly reduced, while dermal melanophages or melanocytes, if any, appeared unchanged (Fig. 4B and D). The clinical observations agreed with the histological findings. In lesions without dermal pigmentation involvement, the pigmented colour was clinically improved (Fig. 3E), while in lesions with dermal pigmentation, the colour change was usually moderate (Fig. 4C) until laser therapy was also used (Fig. 4E).

Discussion

The total amount of epidermal melanin, the main determinant of skin colour, is the result of the balance between production and discharge of melanin. Production of epidermal melanin can be enhanced by external factors such as UV irradiation[9] and inflammation, and suppressed by agents such as hydroquinone that are toxic to melanocytes or inhibit melanogenesis. The discharge of epidermal melanin is determined mainly by epidermal turnover, which can be increased by topical retinoids. External factors such as topical corticosteroids and aging can also attenuate melanin discharge. The regulatory mechanism of epidermal pigmentation (skin colour) is a key concept for establishing our bleaching strategy to epidermal hyperpigmentation; that is, a combined use of tretinoin (a discharge enhancer) and hydroquinone (a production suppressor).

Based on the categorization of pigmented skin lesions (Table 2) and our extensive clinical experience, we propose a simple therapeutic strategy that involves CO_2 laser therapy, QS ruby laser irradiation and topical bleaching treatment (RA-HQ therapy). This is schematically summarized in Fig. 5. For QS ruby laser (694.5 nm, Model IB101, Niic Co. Ltd, Tokyo, Japan) treatment, a spot size of 5 mm, pulse duration of 20 ns, 1-Hz repeat rate, and fluences ranging from 3.5 to 5.0 J/m^2 were routinely used. Fluence was adjusted on each occasion to the minimal value that induced immediate whitening of the irradiated area. After laser treatment, topical antibiotic ointment was applied twice a day until a scale or crust disappeared (usually for 5–7 days).

RA-HQ treatment accelerates the removal of accumulated melanosomes in the epidermis and replaces them with much less pigmented cells. QS ruby laser irradiation not only reduces dermal melanosis and melanocytosis, but

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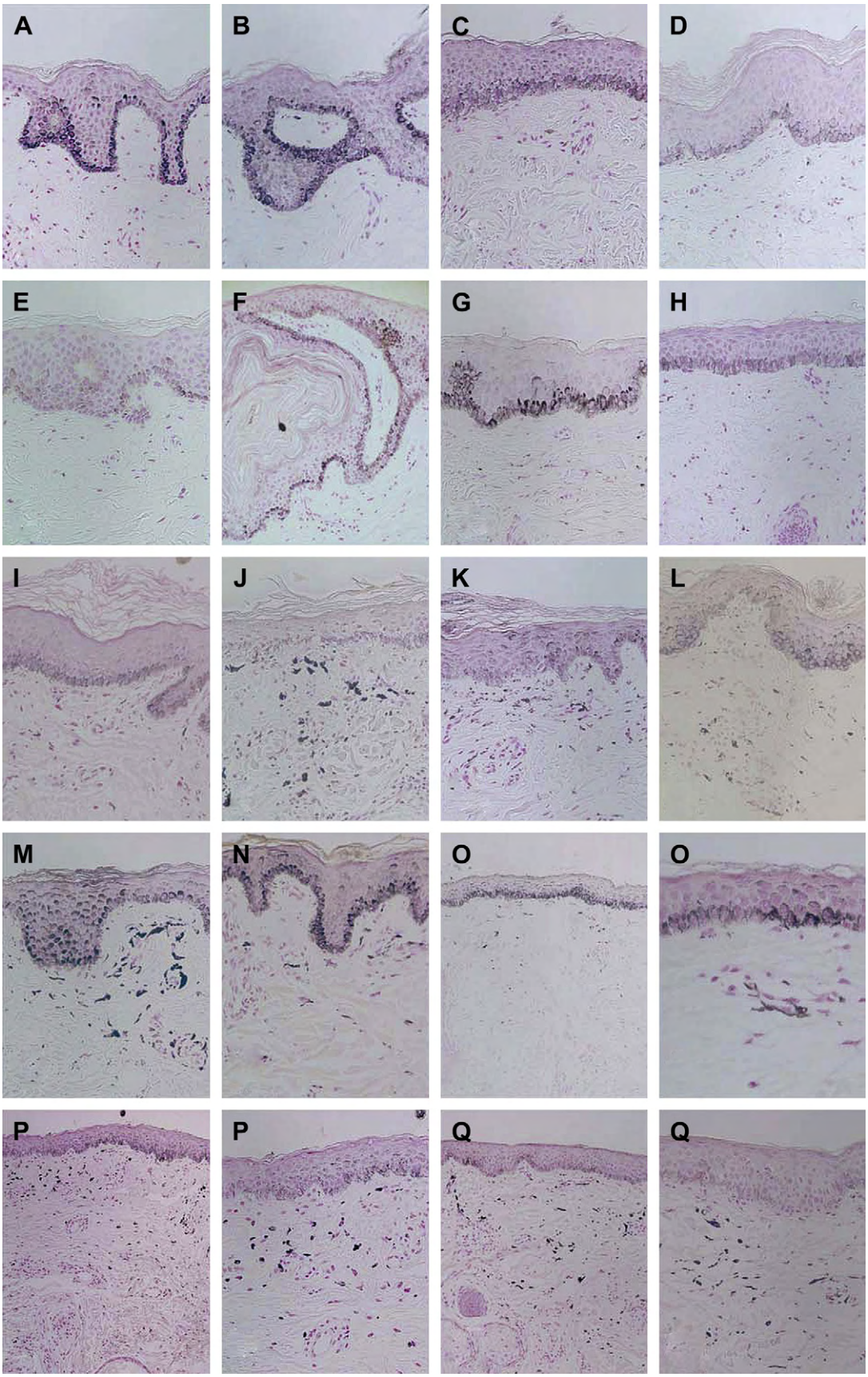

Figure 2 Hyperpigmented lesions in Asians: histological findings. Specimens were obtained from lesions A—Q shown in Fig. 1. Original magnification ×100; alongside O, P and Q are corresponding images at ×200 magnification.

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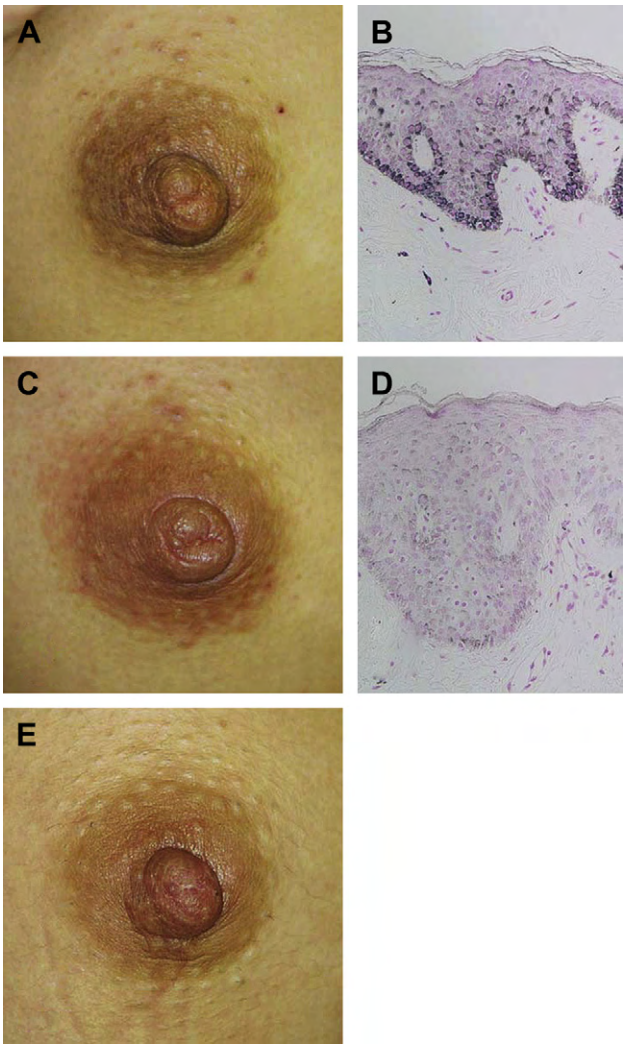

Figure 3 A 26-year-old woman with PNAC. (A) At baseline, the NAC showed dark-brown hyperpigmentation. (B) Histological examination revealed epidermal pigmentation. (C) Two weeks after starting bleaching treatment with 0.2% tretinoin and 5% hydroquinone, the hyperpigmentation had improved. Some tretinoin-associated erythema was observed. (D) Histological examination revealed hyperplasia of the epidermis. Epidermal pigmentation was highly reduced. (E) Eight weeks after starting treatment (final result). For 4 weeks, 0.2% tretinoin was used together with 5% hydroquinone, followed by treatment with 5% hydroquinone alone for 4 weeks. Pigmentation improved and no post-inflammatory hyperpigmentation was observed.

also removes the pigmented and hyperkeratotic epidermis associated with solar lentigines. The former can also be accomplished using a QS Alexandrite laser, and the latter can be accomplished with other lasers, such as a QS Nd:YAG laser. A CO_2 laser was used to treat lesions with excessive hyperkeratosis (Category I lesions) which could not be effectively treated with a QS ruby laser. Hyperkeratotic lesions need to be treated with lasers; because the thickened horny layer prevents percutaneous absorption of topical ointment, RA-HQ therapy does not work.

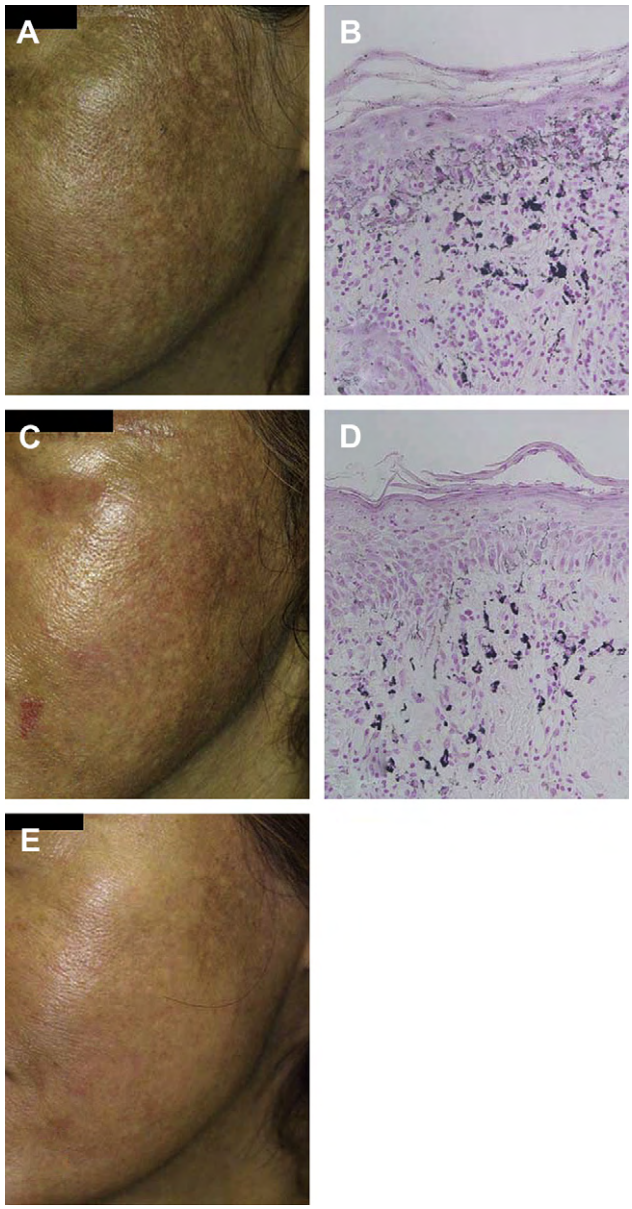

Figure 4 A 56-year-old woman with pigmented contact (cosmetic) dermatitis. (A) At baseline, the patient showed dark-brown or dark-grey macules distributed symmetrically on a wide area of the face. (B) Histology at baseline. The dermo-epidermal junction was severely damaged and a number of melanosomes were found in the upper dermis (pigmentary incontinence). (C) At 8 weeks, just after topical bleaching treatment with 0.1% and 0.4% tretinoin and 5% hydroquinone, pigmentation was reduced with slight erythema, but the macules still had a greyish color. (D) Histology at 8 weeks. Epidermal pigmentation was significantly improved, while the dermal melanocytosis appeared not to have changed at all. (E) Clinical appearance at 20 weeks. QS ruby irradiation was performed to reduce dermal melanosis at 8 weeks. Four weeks later, RA-HQ therapy was performed again: 4 weeks of bleaching phase and 4 weeks of healing phase.

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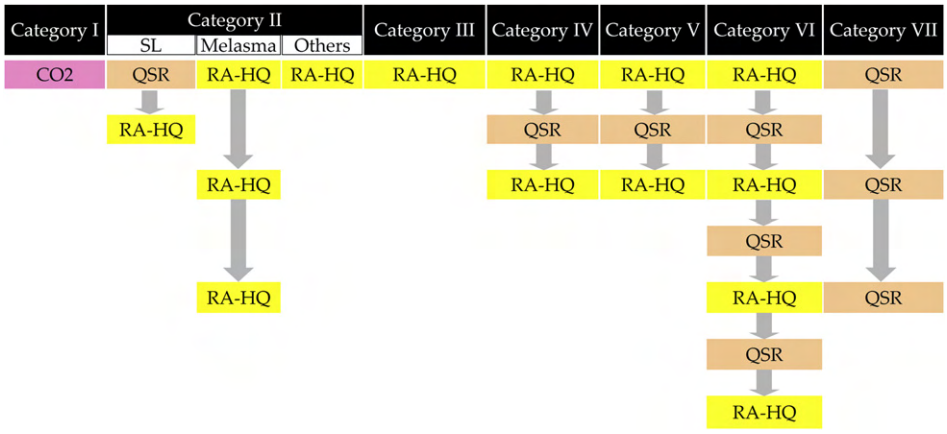

Figure 5 Schematic summary of our therapeutic strategy for pigmented lesions. A treatment protocol is suggested for lesions in each Category (I—VII) except for Category II, which was divided into three subclasses: solar lentigines (SL), melasma and others. SL frequently has a thicker horny layer, so is initially treated with a QS ruby laser (QSR) followed by RA-HQ therapy for post-laser hyperpigmentation. Melasma sometimes requires two or three sessions of RA-HA. Category IV—VI lesions require combination protocols using QSR and RA-HQ therapy, while Category VII can be treated with QSR alone.

Lesions in Categories II and III are treated only with topical RA-HQ therapy, except for solar lentigines with hyperkeratosis. The treatment usually needs to be performed repeatedly for melasma.[4] PIH-S does not recur after treatment, but ephelides, lentigo simplex and nevus spilus (café-au-lait macules) tend to reappear within a few months unless topical hydroquinone is used for post-treatment maintenance. Although RA-HQ cannot be used to treat dermal pigmentation and hyperkeratotic lesions, it can be used as a pre-treatment for QS ruby laser irradiation of Categories IV—VI lesions. RA-HQ can also be used after QS ruby laser treatment, because it is quite effective for treating the PIH frequently seen after QS ruby laser treatment of darker coloured skin.

A critical difference between lesions in Category IV—VI and those in Category VII is the extent of epidermal pigmentation, which determines the beneficial and adverse effects of QS ruby laser on dermal pigmentation. If the lesion has only dermal melanocytosis (Category VII), it can be effectively treated with repeated sessions of QS ruby laser irradiation alone.[10,11] The sole use of QS ruby laser irradiation failed in the treatment of morbidities with both epidermal and dermal pigmentation (Categories IV—VI), resulting in a high frequency of PIH and/or depigmentation.[12—14] We believe that, in these morbidities, epidermal melanin deposits obstruct laser irradiations to dermal pigmentation as competing chromophores. Laser irradiation thus induces considerable inflammation in the epidermis and, consequently, severe PIH results, especially in patients with darker coloured skin.[6] To overcome these problems, we propose that topical bleaching be performed prior to QS ruby laser therapy. The pretreatment can be applied not only to ADM, but also to other skin conditions with both epidermal and dermal pigmentation, such as friction melanosis, pigmented contact (cosmetic) dermatitis and RHAD (lesions in Categories IV—VI; Fig. 4). For Category VI lesions (dermal melanocytosis), the combination of RA-HQ treatment and QS ruby laser may need to be performed two or three times, while only one QS ruby session is usually needed for treating lesions in Categories IV and V (dermal melanosis).

We refined a strategy for treating hyperpigmentation by studying lesion histology and by reviewing our extensive clinical experience in treating Asian skin. The histology-based treatment principles may be helpful for establishing a standardized treatment algorithm for hyperpigmented skin lesions, especially in Asians.

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