Type 2 Minocycline-induced hyperpigmentation successfully treated with the novel 755 nm picosecond alexandrite laser – a case report

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Background and Aim: Minocycline therapy for acne vulgaris is associated with the occasional induction of various types of unsightly and often persistent hyperpigmentation, which is frequently resistant to hydroquinone treatment. Pigment-specific lasers have achieved some success with multiple treatment sessions. Recently, the picosecond domain 755 nm alexandrite laser (ps-Alex) has attracted attention in tattoo removal. The present study reports on the successful treatment, in a single ps-Alex session, of minocycline-associated pigmentation.

Subject and method: Subsequent to a course of minocycline, a 28-year-old Asian female developed persistent type 2 minocycline-related pigmentation on the bilateral lower extremities which was recalcitrant to hydroquinone treatment. The patient had a test treatment on a small area with a Q-switched ruby laser and the ps-Alex, following which the ps-Alex was selected for the actual treatment (spot size, 2 mm; fluence, 6.37 J/cm²; pulsewidth, 750 ps) on one leg first, followed later by the contralateral leg.

Results: Rapid clearance of the pigmentation was noted after a single ps-Alex session on both limbs without prolonged post-inflammatory hyperpigmentation (PIH). At one year post-treatment, clearance had been maintained.

Conclusions: Our results in this single case strongly suggest that the novel 755-nm ps-Alex laser is both safe and very effective for the treatment of type 2 minocycline-induced hyperpigmentation even in PIH-prone type IV Asian skin. Further trials with larger patient populations are warranted to confirm this optimistic result.

Key words: Minocycline • type 2 minocycline-induced pigmentation • picosecond alexandrite laser • postinflammatory hyperpigmentation • Asian skin

Introduction

Cutaneous pigmentation associated with minocycline therapy is well-documented. 1, 2) The incidence of minocycline-induced hyperpigmentation is 3-14% of patients. Three different forms of cutaneous minocycline-induced pigmentation have been previously described. Type 1 presents as well demarcated blue-black macules; these apparently develop in areas of previous inflammation and/or scarring. Type 2 presents as blue-gray pigmented macules or with over more diffuse areas, distant from the primary lesion being treated with the minocycline. Reports on the distribution suggest that this is predominantly on the lower legs as well as on sun-exposed
areas. Type 3 presents a diffuse brown-gray discoloration which appears to be accentuated in sun-exposed areas. Types 1 and 2 demonstrate pigment granules in the dermis, within macrophages surrounding the vasculature, and in the eccrine glands in type 2. The pigment is positive for Fontana Masson and Berlin-Blue Iron stain.

The pigment is attributed to insoluble minocycline complexed with iron. Minocycline-induced hyperpigmentation (MIH) is associated with quinine iminium ion and other reactive species which may polymerize to form black pigment. MIH may disappear slowly over months and years after discontinuation of the drug or may persist. Sun exposure accentuates the associated hyperpigmentation. In several case reports, authors have described successful treatment with the 694.3 nm Q-switched ruby laser, the 1064 nm Q-switched neodymium YAG laser, the 755 nm Q-switched alexandrite laser, the 1550 nm nonablative fractional laser, and the 1550 nm nonablative fractional laser in combination with the 755 nm Q-switched alexandrite laser. Almost all treatment cases have comprised type 1 MIH. (Table 1)

Recently, novel picosecond lasers (ps-lasers) have been developed for the treatment of tattoos. Brauer and colleagues demonstrated the successful treatment of green and/or blue tattoos using the 755 nm picosecond alexandrite laser with 75% clearance of pigment after one to two treatments. Since 2013, ps-lasers have been used and reported for clinical treatment of multicolored and recalcitrant tattoos. Application of ps-lasers for the treatment of tattoos was started in the Ohshiro clinic from December 2013. Considering our successful experience regarding tattoo removal with the ps-laser, we hypothesized that it could be a potential alternative treatment for dermal pigmented lesions.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (Years)</th>
<th>Skin Prototype</th>
<th>Duration of Minocycline Treatment</th>
<th>Pigment Location</th>
<th>Laser device</th>
<th>Number of Treatments</th>
<th>Reference number</th>
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<td>59</td>
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<td>10 years</td>
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<td>1 year</td>
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<td>4</td>
<td>Alster (2004)</td>
</tr>
<tr>
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<td>Cheeks, upper lip</td>
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<td>1 year</td>
<td>Forehead, cheeks, chin, nose, temples</td>
<td>FDL QSAL</td>
<td>4</td>
<td>Nisar (2013)</td>
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<tr>
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<td>Upper lip</td>
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<td>11</td>
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<td>27</td>
<td>IV</td>
<td>3 years</td>
<td>Lower legs</td>
<td>PSAL</td>
<td>1</td>
<td>This case report</td>
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</table>

QSRL: 654-nm Q-switched Ruby Laser
QSAL: 755-nm Q-Switched Alexandrite Laser
QSYL: 1064-nm Q-switched Nd: YAG Laser
FDL: 1550-nm Fractional Diode Laser
PSAL: 755-nm Picosecond Alexandrite Laser

Table 1: Laser treatment for minocycline-induced hyperpigmentation
In the present article, we therefore report on the indication of the 755 nm picosecond alexandrite (ps-Alex) laser for unusual blue-gray pigmentation diagnosed as a case of type 2 MIH.

Case Report

A 28-year-old Asian female presented to our clinic with a 3-year history of blue-gray pigmentation on both lower legs. She had been treated for acne vulgaris with daily minocycline during the years comprising the first half of her 20s. Three years prior to presenting at the Ohshiro Clinic, the patient noticed a blue-gray discoloration on the bilateral lower legs and her dermatologist discontinued minocycline. However, after three years’ daily treatment with hydroquinone cream, the hyperpigmentation had persisted without improvement. (Figure 1)

Other significant past medical history was cutaneous hypersensitivity to solar UV radiation. On her initial consultation, the patient was noted to have Fitzpatrick type IV skin, and no abnormal findings were noted on the blood examination. A histological examination was performed on biopsy specimens of the pigmented skin routinely prepared for staining with Fontana-Masson and Berlin blue stain, which demonstrated brown/black pigment granules in macrophages clustered around vessels and the eccrine sweat glands in the reticular dermis. (Figure 2)

The above findings suggested the diagnosis of hyperpigmentation due to minocycline, which had been present on the patient’s legs from 3 years prior to

Fig. 1: A 28-year-old Asian female with a 3-year history of blue-gray pigmentation diagnosed as type 2 minocycline-induced hyperpigmentation on both lower legs. After three years’ treatment with hydroquinone cream daily, the hyperpigmentation was remaining without improvement.
**Fig. 2:** Abnormal pigment stained with H-E: histological examination demonstrated brown/ black pigment granules in macrophages clustered around vessels and eccrine glands in the reticular dermis. The brown/black pigment was recognized as melanin with Fontana-Mason and Berlin blue stain.

**Fig. 3:** Changes of test treatment site

P: ps-Alex
Q: Q-switched ruby laser

The test area of the PSAL became rapid clearance without prolonged post-inflammatory hyperpigmentation (PIH) compared with the QSRL.
her presenting at our clinic. A test treatment was first performed on two small pigmented areas, one treated with a 20 ns 694.3 nm Q-switched ruby laser (Model IB101®, MM&NIIC, Tokyo, Japan) using a 7 mm spot size at 4 J/cm²; and the other with a 755 nm 750 ps ps-Alex laser (Picosure®, Cynosure, Westford, MA) using a 2 mm spot size at 6.37 J/cm². The endpoint was the white change in the epidermis giving a typical frosted appearance of the treated tissue.

At 7 weeks after the test treatment the results were inspected. The test area treated with the ps-Alex laser showed rapid clearance without prolonged post-inflammatory hyperpigmentation (PIH) compared with that treated with the Q-switched ruby laser, and the ps-Alex laser was selected for the resolution of the MIP of the lower legs. (Figure 3)

The actual treatment was first performed on the right lower leg with the 755 nm ps-Alex laser at the parameters used in the test treatment, and one month later the left lower leg was treated. For post-treatment care, the patient was advised to use a vitamin C lotion and a moisturizing gel.

**Results**

Regular follow-up sessions were scheduled, and at 3 months after treatment, very good clearance of the pigmentation was observed, with slight residual erythema and mild PIH (Figure 4). The patient was seen in follow-up at one year post-treatment and almost total

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**Fig. 4**: The actual treatment was performed first on the right lower leg, and after one month on the left leg. The findings are shown at follow-up 3 months later with slight PIH and inflammation being observed in both lower legs.
Fig. 5: No recurrence was recognized in either leg in the follow-up at 1 year post-treatment, with almost total elimination of the MIH being observed in both lower legs.

Fig. 6: No abnormal pigment stained with H/E, Fontana-Masson or Berlin Blue stain could be seen in histological specimens 1 year after irradiation.
clearance of the hyperpigmentation was observed in both lower legs. (Figure 5)

A histological examination was also performed at the post-treatment 1-year follow-up, which revealed hyperkeratosis of the epidermis and slight elongation of the rete ridges with hematoxylin and eosin staining. Melanin pigmentation was recognized in the basal cells. In the upper dermis, slight capillary hyperplasia and mild inflammatory cell infiltration, including lymphocytes, could be observed. Fontana-Masson staining showed scarce positivity for a few melanin-containing cells. On the other hand, staining with Berlin Blue failed to reveal any positive-staining cells (Figure 6).

Discussion

To the best of our knowledge, this is the first case report to demonstrate the complete resolution of MIH in an Asian female using the 755-nm ps-Alex. Blue-gray discoloration related to minocycline use in the lower legs and dorsa of the feet can be a cosmetically and psychologically troubling side effect for young females. We have reported herein on successful and almost complete resolution of blue-gray MIH of the bilateral lower extremities in a 28-year-old skin type IV Asian female with one ps-Alex session, but without PIH formation. Successful outcomes have previously been described in case reports with the use of Q-switched lasers and non-ablative fractional photothermolysis. However, multiple treatment sessions or combined lasers have been required for the complete resolution of this discoloration. There are three types of Q-switched laser treatment for MIH, including the ruby laser at 694.3 nm, the alexandrite laser at 755 nm, and the Nd:YAG laser at 1064 nm. Concerning the irradiation end point in the treatment of this hyperpigmentation with the ns-domain Q-switched lasers in Asians, the immediate whitening phenomenon (IWP), or so-called frosting, caused by epidermal damage after laser irradiation is usually used as the treatment end-point for the clearing of hyperpigmented lesions. In Asians, PIH has usually occurred, lasting from 3 to 12 months after treatment with Q-switched lasers and non-ablative fractional photothermolysis. The combination of an excessive photothermal and some photomechanical effect associated with Q-switched ns-domain lasers can produce undesirable damage to the dermoepidermal junction (DEJ) and superficial blood vessels leading to an inflammatory response. Such a response can in turn alter the activities of the melanocytes residing in the stratum basale above the DEJ resulting in subsequent PIH, particularly in the darker Asian skin phenotypes. Hyperpigmentation of the lower extremities may be the most difficult lesions to deal with because of the vascular hemodynamics and the noted tendency towards PIH. The result of this case demonstrated almost total resolution of the MIH, but without PIH, following a single treatment with the ps-domain alexandrite laser at 755 nm. Theoretically, picosecond-domain laser devices, with more optimal photomechanical effects and better heat confinement, should also work in both epidermal and dermal hyperpigmentation with maximum pigment removal, minimal inflammation and therefore minimal PIH. Histological observations have shown hemosiderin or closely related substances contained in the dermal macrophages associated with cutaneous inflammation in pigmented areas treated with Q-switched lasers, which does not seem to be the case following treatment with ps-domain lasers. Our present case would appear to bear that out with excellent clearance of the MIH at the 1-year follow-up, and no persistent PIH.

Conclusions

Minocycline-induced hyperpigmentation (MIH) has traditionally been hydroquinone treatment-resistant with multiple laser treatments required for clearance, but with the strong potential for PIH in Asian skin. There are a few case reports detailing successful results with the use of non-ablative fractional photothermolysis and Q-switched lasers independently or combined. Pigment resolution in these cases has been achieved with 3-5 treatment sessions spread over one year. This case report suggested that the novel 755-nm picosecond alexandrite laser is most efficacious for the treatment of the type 2 MIH, especially in Asian skin, in a single session. Confirmation of this optimistic result in larger patient populations is warranted.

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest to report with any of the systems used in the present study.
References