

Treatment of Minocycline-Induced Hyperpigmentation With a 755-nm Q-Switched Alexandrite Laser: A Case Report

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Cutaneous hyperpigmentation is a common side effect of long-term minocycline use. Several laser treatments have been successful in treating minocycline-induced hyperpigmentation, including Q-switched Nd:YAG lasers, Q-switched ruby lasers, and Q-switched Alexandrite lasers. This case report corroborates the efficacy of Q-switched Alexandrite lasers in treating minocycline-induced hyperpigmentation. One patient with this disorder on the upper lip was treated with a Q-switched Alexandrite laser at 2-month intervals for a total of 3 treatments. Very minimal residual hyperpigmentation was experienced after the third treatment session, and the overall outcome was cosmetically desirable to the patient. We agree that the Q-switched Alexandrite laser is an effective treatment for minocycline-induced hyperpigmentation, and we advocate its use in clinical medicine.

Minocycline, a semisynthetic derivative of tetracycline, is a broad-spectrum bacteriostatic antibiotic that inhibits bacterial protein synthesis. It has been used against a wide range of gram-positive and gram-negative bacteria, including *Rickettsia*, *Mycoplasma*, *Chlamydia*, *Ureaplasma*, and *Propionibacterium acnes*. Additionally, minocycline has been shown to exhibit anti-inflammatory effects by inhibiting matrix metalloproteinases, which likely contributes to its success in treating acne, rosacea, and other inflammatory dermatoses.^{1,2}

As with many antibiotics, minocycline can produce several systemic side effects, the most common of

which are light-headedness, dissociation, headache, difficulty concentrating, and nausea.³ Minocycline use also has been correlated with several cutaneous adverse events, including exanthematous eruptions, photosensitivity, pruritus, and, most commonly, hyperpigmentation.⁴ The incidence of hyperpigmentation from minocycline use has been reported to range from 3% to 14% in patients with acne^{5,6} and to be as high as 28% in those with rosacea.²

Minocycline-induced hyperpigmentation may present as early as 3 months after the initiation of treatment, but, in some patients, it may take up to 5 years.³ Hyperpigmentation most commonly occurs after a cumulative dose of 50 g or more.⁷ Patients must be closely monitored for hyperpigmentation and other side effects throughout the course of treatment, as initial changes may be subtle or ignored by the patient. The development of adverse effects also may be interpreted by the patient as unrelated to minocycline use, as the negative side effects of minocycline often mimic other processes. Once

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An 83-year-old white woman with faint blue-black hyperpigmentation in a perioral distribution (A). The patient received 3 treatment sessions at 2-month intervals with the 755-nm Q-switched Alexandrite laser. Minimal residual dyspigmentation was experienced after the third therapy session (B).

hyperpigmentation is seen clinically, resolution with current therapies may take years. Results depend on both the degree and duration of pigmentation.⁸

Many patients desire therapeutic intervention for hyperpigmentation because it affects cosmetically sensitive sites and is slow to resolve. Several laser systems have been trialed, with varying success, including 1064-nm Q-switched Nd:YAG lasers, 694-nm Q-switched ruby lasers, and 755-nm Q-switched Alexandrite lasers.⁹⁻¹¹ The following case report demonstrates the effectiveness of the Q-switched Alexandrite laser for the treatment of minocycline-induced hyperpigmentation.

CASE REPORT

An 83-year-old white woman was first seen as a new patient at the University of Iowa Hospitals and Clinics in February 2002 after several years of being treated locally for rosacea. On presentation, her established rosacea treatment regimen of 2 years consisted of minocycline 100 mg twice daily, desonide lotion once daily, and erythromycin gel once daily. The desonide lotion and erythromycin gel were discontinued and metronidazole cream and tretinoin cream were initiated. The patient continued minocycline 100 mg twice daily.

From February 2002 through March 2003, the patient was seen and evaluated at 3- to 4-month intervals. In March 2003, after approximately 3 years of minocycline use and a total cumulative dose near 22 g, the woman presented to the clinic with concern of a faint blue-black hyperpigmentation in a perioral distribution. She was advised to discontinue minocycline. The hyperpigmentation remained stable after cessation of therapy, suggesting minocycline as a likely culprit.

In July 2004, approximately 16 months after discontinuation of minocycline, the hyperpigmentation persisted, and our patient was substantially distressed. Figure A shows the clinical findings of hyperpigmentation. At that time, treatment with the 755-nm Q-switched Alexandrite

laser was discussed. The procedure, associated risks, potential benefits, and possible complications were thoroughly explained to the patient and informed consent was obtained.

Before beginning treatment, a test-dose area on the left side of the upper cutaneous lip was treated with 4 grouped, 50-ms pulse duration, 3-mm diameter pulses of the 755-nm Q-switched Alexandrite laser. Test fluences of 6.0, 6.5, and 7.0 J/cm² were trialed. None of the sites demonstrated any evidence of immediate or delayed cutaneous devitalization.

Subsequently, the clinically evident areas of hyperpigmentation were treated with a 7.0 J/cm² 3-mm diameter beam with closely spaced nonoverlapping pulses. The patient tolerated the procedure well, and no complications were noted.

RESULTS

Treatment began in September 2004, continuing at 2-month intervals for a total of 3 treatment sessions. After 2 treatments, the patient reported substantial improvement in the pigment on the upper lip. The third treatment was performed in January 2005, with continuing improvement in her hyperpigmentation. Very minimal residual dyspigmentation was experienced after the third therapy session. Figure B shows treatment results.

COMMENT

The pathogenesis of minocycline-induced hyperpigmentation remains largely unknown and may be multifactorial. High-performance liquid chromatography performed on lesional skin has isolated minocycline moieties.¹² Theoretically, minocycline could directly cause hyperpigmentation as it oxidizes to a black color when exposed to oxygen. Alternatively, minocycline is a known iron chelator and could indirectly cause hyperpigmentation through the accumulation of electron-dense iron-containing particles in skin. A positive correlation exists between the concentration of these particles in dermal histiocytes and the degree of blue-black skin discoloration.¹³ Lastly, other histologic analyses suggest the possible role of a metabolic derivative of melanin in the pathogenesis of minocycline-induced hyperpigmentation.^{5,6} In summary, the hyperpigmentation that results from minocycline use may be traceable to the deposition of minocycline and its derivatives, iron, or melanin, or any combination thereof.

Three distinct patterns of minocycline-induced cutaneous hyperpigmentation have been described and

Summary of Patient Population and Treatment Characteristics Using the Q-Switched Alexandrite Laser^{11,18}

Age, y	Gender	Duration of Minocycline Use	Treatment Site	Number of Treatments	Average Fluence Used	Results
22	Woman	6 y	Legs	5	6.0 J/cm ²	Complete resolution
52	Woman	8 y	Cheeks, chin, lip, ears	4	6.5 J/cm ²	Complete resolution
83	Woman	3 y	Upper lip	3	7.0 J/cm ²	Near-complete resolution
51	Woman	6 mo	Cheeks	3	7.0 J/cm ²	Complete resolution
53	Woman	1 y	Upper lip	4	7.25 J/cm ²	Complete resolution
44	Man	2 y	Cheeks	4	7.25 J/cm ²	Complete resolution
48	Woman	10 mo	Legs	4	7.25 J/cm ²	Complete resolution
47	Woman	1 y	Cheeks	5	7.5 J/cm ²	Complete resolution

documented in the literature. Type 1 presents as a circumscribed blue-black discoloration at sites of inflammation or scarring, typically on the face. Under light microscopy, the pigment is located within normal dermis and scar tissue and is found both interstitially and within histiocytes. Type 2 is described as a circumscribed blue-gray discoloration found on normal skin, classically on the lower legs and forearms. These areas may be mistaken for bruising. Histologically, pigment of this type is located more deeply, specifically in the dermis and the fat, extracellularly and within macrophages and myoepithelial cells. Type 3 manifests as a diffuse muddy-brown discoloration seen in healthy skin, with accentuation in sun-exposed sites. The histologic distribution of pigment seen in type 3 minocycline-induced hyperpigmentation is more superficial, found within the basilar epidermis as well as within dermal histiocytes.¹⁴

Recently, a new, fourth type of cutaneous pigmentation has been described.¹⁵ Type 4 is seen clinically as a circumscribed blue-gray discoloration occurring in scar

tissue, typically on the back. Light microscopy examination reveals pigment within the dermis and scar tissue, both extracellularly and within macrophages and fibroblast-like cells.

The introduction of Q-switched lasers into clinical medicine has enhanced the clinician's ability to treat pigmented dermatoses. It is presumed that laser treatment causes improvement in hyperpigmentation by inducing pigment fragmentation, subsequent scavenging, and removal by histiocytes. The exact mechanism of action, however, remains elusive.

There are 3 Q-switched lasers that have been documented to improve minocycline-induced dyspigmentation: the 694-nm Q-switched ruby laser, the 1064-nm Q-switched Nd:YAG laser, and the 755-nm Q-switched Alexandrite laser. Q-switching allows shortening of laser pulse duration by virtue of a gating system, minimizing the risk of nonspecific thermal heating and destruction to structures surrounding the target laser chromophore. The Q-switched ruby laser penetrates approximately

1 mm into the skin and is absorbed by melanin and other pigments in the epidermis as well as the dermis. The shorter depth of penetration would theoretically not allow for effective treatment of pigment deposition in the reticular dermis or subcutis. Additionally, because the 694-nm emitted wavelength is absorbed by melanin, undesirable hypopigmentation may occur. In its favor, the Q-switched ruby laser wavelength is minimally absorbed by hemoglobin, thus avoiding vascular damage to the tissues around the treated area. Despite the risks, the Q-switched ruby laser has been judiciously used for minocycline-induced dyspigmentation without resulting hypopigmentation or scarring.¹⁶

The 1064-nm Q-switched Nd:YAG laser, by contrast, is poorly absorbed by melanin, thus decreasing the incidence of hypopigmentation. Furthermore, because of its longer wavelength, the Q-switched Nd:YAG laser penetrates more deeply into the skin (up to 4–6 mm) and thus affords targeting of pigment not only within the epidermis but also within the dermis and superficial subcutis. As a result of the preferentially deep dermis and superficial subcutis energy deposition, the longer-wavelength 1064-nm Q-switched Nd:YAG is perhaps less ideal for the treatment of more superficially located pigment deposition (ie, type 3 minocycline-induced hyperpigmentation). In fact, this laser may be better suited for the treatment of type 1 and particularly type 2 minocycline-induced hyperpigmentation. Effective therapy involving minocycline-induced hyperpigmentation with using the Q-switched Nd:YAG laser has been documented with complete clinical pigment resolution and in the absence of adverse sequelae after 6 treatments.¹⁷

Although both the Q-switched ruby laser and the Q-switched Nd:YAG laser may be used to effectively treat minocycline-induced hyperpigmentation, the 755-nm Q-switched Alexandrite laser may provide the best combination of safety and efficacy. The Q-switched Alexandrite laser, with its intermediate-sized wavelength, has deeper skin penetration than the Q-switched ruby laser. Moreover, because the Q-switched Alexandrite laser poorly targets melanin as a chromophore, there is a decreased risk of hypopigmentation.

Several reports advocate the use of the 755-nm Q-switched Alexandrite laser for minocycline-induced hyperpigmentation.^{11,18} The Table summarizes these results. In general, the reports showed that this disorder totally resolved using an average fluence of 7.0 J/cm² after an average of 4 sessions. Minimal transient side effects (eg, purpura and mild desquamation) were observed, with no evidence of hypopigmentation or scar formation at the sites of treatment. The average age of the patients treated was 49.6 years (range, 22–83 years), and the typical

duration of minocycline therapy was 2.75 years (range, 6 months–8 years). After 3 treatments with the 755-nm Q-switched Alexandrite laser, our patient had near-complete resolution of her minocycline-induced hyperpigmentation without evidence of hypopigmentation or scarring. We agree that the Q-switched Alexandrite laser is an effective treatment for this type of dermatosis, and we advocate its use in clinical medicine.

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