

## *Pigmentary and Other Dermatologic Manifestations of Minocycline: a reminder of adverse effects*

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### ABSTRACT

The applications of the tetracycline class of antibiotics extend beyond their antimicrobial activity to anti-inflammatory, immunosuppressive and neuroprotective applications, making it a commonly used class of medication. Minocycline, a second-generation tetracycline, has inherent characteristics that improve absorption and distribution. These benefits promote even more widespread use. This familiarity of usage breeds prescriptive complacency toward the dermatologic complications including hyperpigmentation. The following case explores these adverse manifestations of minocycline use.

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### KEYWORDS

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### INTRODUCTION

Since the 1950s, the broad-spectrum antibiotic tetracycline, a polyketide from the *Streptomyces* genus of Actinobacter,<sup>1</sup> has commonly been used to treat both gram-positive and gram-negative bacterial infections.<sup>2,3</sup> The tetracycline family are bacteriostatic,<sup>2</sup> halting the reproduction of bacterial cells by inhibiting protein synthesis via binding to the 30s-ribosomal subunit.<sup>2-4</sup> In addition to their antimicrobial abilities, tetracyclines demonstrate neuroprotective, anti-inflammatory and immunosuppressive properties,<sup>2,5,6</sup> allowing this class to treat other conditions including rosacea and rheumatoid arthritis.<sup>2,7</sup> Minocycline, along with doxycycline, is a second-generation semi-synthetic tetracycline<sup>1,4,5,8-12</sup> which was developed with improved absorption and lipophilicity allowing both oral and intravenous administration.<sup>3</sup>

Although minocycline specifically has several advantageous properties over other tetracyclines,<sup>2</sup> it has been documented to have a variety of adverse reactions including nausea, vomiting,

dizziness,<sup>1,2,8-10</sup> hepatotoxicity,<sup>1,2,6,9-11,13</sup> vasculitis,<sup>4,6</sup> organ dysfunction<sup>1,8</sup> (including polyarthritis, nephritis, pneumonitis, and pancreatitis), pseudotumor cerebri<sup>5,9,10</sup> and medication-induced lupus.<sup>2,4,5,8-11</sup>

An uncommon yet unfortunate adverse reaction to minocycline, however, is pigmentation related and tends to occur more often when compared to other tetracyclines.<sup>2,7</sup> In this case, these visible risks of minocycline are more closely examined.

### CASE PRESENTATION

At a routine follow up visit for hypertension and hyperlipidemia, a 70-year-old white female with a history of ocular rosacea was noted to have "tanned skin." She denied excess sun exposure and a workup for causes of increased skin pigmentation was unfruitful for any metabolic source. Her medications at that time included doxycycline 100mg daily that had been prescribed for ocular rosacea by her ophthalmologist consistently for 4 years. She was informed of the suspected source of the skin changes and advised to stop doxycycline and discuss



alternative treatment with the prescribing physician.

Three years later, she presented with a six-month history of diarrhea and fatigue. Increased pigmentation on her forehead and cheeks bilaterally was also noted. Physical examination was unremarkable except for generalized hyperpigmentation and blue/black discoloration over the maxillary and temporal areas of her face (Picture 1). The medication review revealed that she had been started on minocycline treatment for ocular rosacea after her doxycycline was discontinued. Evaluation for causes of hyperpigmentation, fatigue, and diarrhea was again negative. She was advised to stop the minocycline. On repeat examinations, not only did her fatigue and diarrhea improve, but the intensity of the hyperpigmentation also minimally improved.

## DISCUSSION

### PHARMACOKINETICS

Compared to the older first-generation tetracyclines, minocycline's pharmacokinetic profile shows some clear advances. Minocycline (7-dimethylamino-6-demethyl-6-deoxytetracycline) differs structurally from tetracycline by the addition of a dimethylamino group at the seventh carbon.<sup>6</sup> Due to its lipid solubility, its absorption rate between the stomach and jejunum is 95-100% in all populations, including the elderly, regardless of food intake.<sup>2-4,7,10</sup> Concomitant iron and antacids containing calcium and magnesium, however, can reduce the absorption.<sup>3</sup> Its lipophilic nature not only promotes wide distribution in tissues, allowing crossing



**PICTURE 1:** Demonstrates the generalized brownish pigmentation to the face, neck, and hand of a Type III reaction (case-patient).



of the blood-brain barrier,<sup>2,3,7,14</sup> but also reduces resistance.<sup>10,15</sup> Three quarters of the medication is protein bound.<sup>3,7</sup> Maximal dose is reached within 2 hours, with a dose-dependent variability and a half-life of 12-18 hours.<sup>2,3,10,12,15,16</sup> The renal clearance of minocycline is 1.2-2.2 ml/min with 5-12% of the drug excreted in the urine and 20-35% eliminated in feces.<sup>3</sup> Minocycline produces six metabolites with antimicrobial activity furthering its effectiveness.<sup>3</sup> This unusual metabolism may also contribute to its unique adverse effects, such as abnormal pigmentation, which is observed in patients with long term minocycline use.<sup>6</sup>

#### PIGMENTARY CHANGES IN MINOCYCLINE USE

Minocycline is routinely prescribed as 100 mg daily with the highest dose recommendations by the Federal Drug Administration being 200 mg daily to avoid side effects.<sup>2,9</sup> Hyperpigmentation is the most common side effect from the cumulative administration of minocycline<sup>7</sup> and is often blamed on its rapid absorption and longer half-life.<sup>15</sup> The classic pigmentation presentation patterns have been classified into four separate types (Table 1). Type 1 demonstrates a blue-black pigmentation primarily around areas of previous scarring or

Hyperpigmentation Type	I	II	III	IV
<b>Presentation</b>	Blue Pigment in areas of previous scarring and inflammation	Blue, black or gray pigment in areas of normal skin usually on the shins, ankles, and arms	Generalized brown pigment in sun-exposed areas diffusely	Blue or gray pigment in areas around the lips or in areas of scarring on the posterior thorax
<b>Histology</b>	Degraded products chelated with hemosiderin and iron. Pigment is seen in perivascular macrophages	Minocycline and oxidation products chelated to iron. Pigment bound in membrane dermis	Minocycline-melanin complex. Pigment bound in basal layer epidermis and papillary dermis	Post-inflammatory from a fixed drug reaction
<b>Onset</b>	Anytime	>100 g cumulative dose	>100g cumulative dose	Anytime
<b>Treatment</b>	Discontinuation of minocycline	Discontinuation of minocycline	Discontinuation of minocycline	Discontinuation of minocycline
<b>Duration</b>	Resolves after months	Resolves after months	Most likely permanent	Resolves after months

**TABLE 1:** Comparison of the different types of cutaneous pigmentary reactions to minocycline. From the large cumulative dose, generalized brownish coloration and lack of significant resolution after discontinuation of the minocycline, the case-patient clearly had a type III reaction.



inflammation.<sup>7,9,12,15</sup> Under microscopy, perivascular macrophages laden with granules of pigment chelated with iron, hemosiderin, and ferritin are seen.<sup>7,15</sup> The pigmentation does not correspond to either duration or cumulative dose of minocycline.<sup>9,15</sup> Therefore, it may be more rapidly seen but also resolves with discontinuation of the medication.<sup>7,15</sup> The Type 2 variant is diffuse, presenting as blue, black or gray discoloration on the shins, arms, and ankles.<sup>7,12,15</sup> It is dose-dependent, associated with a lifetime accumulation of 70g-100g of minocycline. It takes longer to present and months to resolve after discontinuation of the medication.<sup>7,12,14,15</sup> Minocycline oxidative degradation products chelated with iron can be observed microscopically as a membrane-bound pigment collection in the dermis and subcutis or free in collagen fibers.<sup>7,15</sup> Laser treatment can speed resolution by fragmenting both intracellular and extracellular pigments to aid drainage by the lymphatic system. Only mild desquamation and transient purpura are seen as adverse events of this treatment.<sup>12</sup> Type 3 reactions are unique compared to Types 1 and 2 because microscopically the pigmentation is composed of minocycline-melanin complexes.<sup>7,15</sup> This presents as a generalized brown coloration at sun-exposed sites.<sup>7,12,15</sup> This too is a cumulative effect,<sup>7,9,14,15</sup> as is type 2, but it is more likely to be permanent with less efficacy of laser treatments.<sup>7,12</sup> Type 4 pigmentation is similar to Type 1 but has been described as an independent phenotype, appearing as either a bluish

pigmentation of the lips or blue-black pigmented scarring on the posterior thorax. Microscopically it differs slightly in that the pigment seems post-inflammatory from a resolving fixed drug reaction.<sup>7,15</sup>

#### OTHER DERMATOLOGIC MANIFESTATIONS OF MINOCYCLINE

Adverse dermatologic and pigmentary reactions to minocycline can occur outside of these four classic types (Table 2). Multiple cases of hyperpigmentation occurring at the skin,<sup>7,10,14</sup> nail beds,<sup>7</sup> teeth,<sup>7,9</sup> bones,<sup>7,9,14</sup> cartilage,<sup>7,9</sup> mucus membranes,<sup>7,9</sup> thyroid,<sup>7,9</sup> tongue,<sup>7,10,14</sup> sclera,<sup>7,9</sup> cardiac valves<sup>9</sup>, and breast milk<sup>7</sup> have been documented. There are multiple theories pertaining to the cause of hyperpigmentation. These include the formation of insoluble salts from minocycline degradation, siderosis, accumulation of black degradation products at different tissue locations, melanocyte enhancement, and derivatives of minocycline forming complexes chelated to iron, melanin, and calcium.<sup>9,10,12,15</sup> Other non-pigmentary dermatologic changes can occur from minocycline exposure, including urticaria caused by vasoactive amines released from mast cells during a hypersensitivity reaction,<sup>1,2,5,11</sup> subcutaneous nodules and livedo reticularis from polyarteritis nodosa,<sup>4,6,11</sup> vasculitis,<sup>6,11</sup> denudation and hemorrhagic changes of Stevens-Johnson Syndrome,<sup>4</sup> as well as erythema in sun-exposed areas from photosensitivity rashes.<sup>4</sup>

Reaction Site	Mechanism of Disease and/or Clinical Presentation
<b>Bone</b>	Occurs as a result of accumulated deposits chelated with iron, calcium and hemosiderin.
<b>Breast Milk</b>	Lipophilic nature facilitates the accumulation of macrophages with iron complexes.
<b>Cartilage</b>	Occurs as a result of accumulated deposits chelated with iron, calcium, and hemosiderin.
<b>Eyes</b>	Blue-Gray discoloration occurs in the conjunctiva and sclera from a Type III-like hyperpigmentation mechanism.
<b>Mucous Membranes</b>	Rare. Only occurs with minocycline. Areas of trauma demonstrate complexes with iron or calcium.
<b>Nails</b>	Graying of the proximal nailbed by a Type III-like hyperpigmentation pathology. Less common than skin manifestations.
<b>Teeth</b>	Occurs 6% of the time. Permanent blue-gray discoloration. Enamel is etched.
<b>Thyroid Gland</b>	Oxidation by thyroid peroxidase as a result of long-term use.

TABLE 2: Catalogue of the potential pigmentary manifestations of minocycline.



## PATIENT

Interestingly, patients being treated for rosacea have a higher chance of abnormal pigmentation than those being treated for routine acne,<sup>7,15</sup> as they are usually older and have received higher cumulative doses of minocycline than the younger patients treated for acne vulgaris.<sup>7</sup> In this case, the patient was treated for rosacea first with doxycycline, followed by minocycline with an estimated cumulative dose of over 100 grams of minocycline in the three years after the tetracycline was discontinued. Not surprisingly, she developed a Type III reaction from the minocycline cumulative dose. Also, not surprisingly, she has shown very little improvement after discontinuation.

## CONCLUSION

The frequency with which Minocycline is used casts it in a light that makes it seem benign. Whether it is pigment deposition or stimulating a dermatologic process, its effect on the patient can be significant and permanent. Remembering the possible ramifications will allow physicians to better inform their patients during its use.

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