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Minocycline-Induced Pigmentation
Incidence, Prevention and Management

Drore Eisen[1] and *Miriam D. Hakim*[2]

1 Dermatology Research Associates of Cincinnati, Cincinnati, Ohio, USA
2 University of Cincinnati Medical Center, Cincinnati, Ohio, USA

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Summary

Pigmentation is a well recognised adverse effect of minocycline therapy. Various body sites, most notably the skin, nails, bones, thyroid, mouth and eyes are affected and the pigmentation may appear at multiple sites. In general, pigmentation results from long term administration of minocycline at cumulative doses greater than 100g, although cutaneous or oral mucosal pigmentation may appear, regardless of dose or duration of therapy. When the skin is involved, the blue-black pigmentation develops most frequently on the shins, ankles and arms. Other patterns of skin involvement include pigmentation that is either generalised and symmetrical, or that develops at sites of inflammation. The bones of the oral cavity are probably the most frequently affected sites of pigmentation affecting greater than 20% of patients taking minocycline for more than 4 years. In contrast, the oral mucous membranes and teeth are infrquently pigmented from minocycline. Ocular, thyroid and visceral pigmentation is also relatively uncommon and usually develops only with high doses and long term minocycline use. Whereas pigmentation of the skin and oral mucosa is generally reversible when the drug is discontinued, the pigmentation is often permanent when other sites are involved. Although minocycline-induced pigmentation is not harmful, the drug should be discontinued when the adverse effect is recognised. All patients receiving minocycline, especially those treated for longer than 1 year, require screening for the development of pigmentation.

1. Tetracyclines

The tetracyclines, antibacterials with antimicrobial, anti-inflammatory and immunosuppressive properties, are widely employed for the treatment of acne, rosacea and a variety of other dermatological conditions.[1] Although once considered the antibacterials of choice for selected Gram-positive and Gram-negative infections, their broad antimicrobial spectrum make them valuable for the treatment of many infections such as atypical pneumonias, sexually transmitted diseases, traveller's diarrhoea, rickettsial infections, periodontal disease and methicillin-resistant *Staphylococcus aureus* (MRSA) colonisation.[2] In addition, a double-blind study has confirmed efficacy in rheumatoid arthritis.[3]

1.1 Minocycline

Minocycline is a semi-synthetic broad-spectrum tetracycline antimicrobial agent that was introduced in 1967. It is a popular member of the tetracycline class because of several advantages the drug has compared with other tetracyclines. In addition to achieving peak serum concentrations within several hours after administration, it is well absorbed and possesses greater antimicrobial activity than other tetracyclines.[4] Also, orally administered minocycline hydrochloride is highly bound to plasma proteins and is lipid soluble, thus facilitating penetration into body fluids (such as saliva, bile and breastmilk) and tissues (including the skin, brain, thyroid, fat and liver).[4,5] Bacterial resistance to minocycline is minimised by the high liphophilicity of the drug. Minocycline resistance is mediated through chromosomally located Tet genes, and occurs less frequently than resistance to tetracycline which is mediated through Tet genes within a plasmid locus.[6]

1.2 Pigmentation

Pigmentation is a well recognised adverse reaction associated with all tetracyclines, with the exception of doxycycline. For example, methacycline, a tetracycline used infrequently in the treatment of acne, may, with prolonged administration, result in grey-black pigmentation of nails, conjunctiva and sun-exposed skin.[7,8] Tetracycline hydrochloride has also been reported to cause pigmentation of teeth and nails[9,10] and osteoma cutis.[11]

However, of all of the tetracyclines, minocycline is most often associated with the adverse effect of pigmentation, potentially affecting various organs and body fluids (table I). Although minocycline is a yellow crystalline material, its black degradation product may be deposited in various tissues.[12] The accumulation of high concentrations of minocycline at various sites may, in part, explain the pigmentation that results with its use.

Although the safety of long term high-dosage (200 mg/day) minocycline for the treatment of acne has recently been demonstrated, cutaneous pigmentation was the most frequently observed adverse reaction.[13] Failure to recognise this relatively common cause of pigmentation of the skin and other body sites may lead to unnecessary test-

Table I. Minocycline-induced pigmentation: sites of involvement (after Dummett and Barens,[44] with permission)

Cutaneous
Skin
Nails
Oral cavity
Teeth
Mucous membranes
Alveolar bone and hard palate
Ocular
Sclerae
Conjunctiva
Skeleton and cartilage
Vertebrae
Costal cartilage
Parietal bone
Alae nasi
Viscera and body fluids
Thyroid
Substantia nigra
Aortic and mitral valves
Atherosclerotic plaques
Breastmilk

ing and confusion with other causes of pigmentation.

2. Minocycline-Induced Pigmentation

As mentioned in section 1.2, minocycline can be associated with the development of pigmentation in a number of body areas.

2.1 Skin

2.1.1 Types of Pigmentation

Minocycline-induced pigmentation of the skin is readily identifiable and 3 patterns of involvement have been well described (type I, type II and type III).

Type I

Type I cutaneous pigmentation is characterised by blue-black macules that are localised to sites of scarring or inflammation.[14] Although the pigmentation appears predominantly on the face within acne scars (fig. 1), it has also been reported at other sites of inflammation on the chest and legs. This distribution was emphasised by Fleming et al.[15] who described a patient with lepromatous leprosy who developed multiple blue-black lesions at various sites of inflammation.

Pigmentation from minocycline following sclerotherapy has also been reported, highlighting the localisation of type I pigment to sites of inflammation.[16] Additionally, minocycline, like tetracycline, may cause pigmentation of post-acne osteoma cutis.[17] These osteomas, which represent metaplastic bone formation, are rare complications of chronic acne and typically develop on the face.

Microscopically, pigment granules in type I pigmentation, free within macrophages, have been identified in the dermis and consist of minocycline or a minocycline degradation product chelated with haemosiderin, ferritin or iron.[14]

Type II

Type II cutaneous pigmentation appears as blue-black, brown or slate-grey pigmentation and develops on healthy skin, primarily the skin of the shins, ankles and arms (fig. 2). The staining may appear to be either well circumscribed or diffuse.

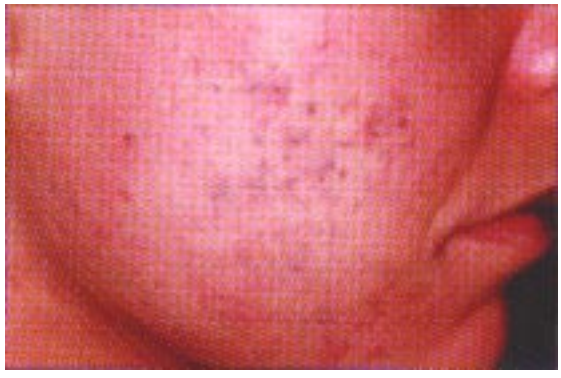

Fig. 1. Minocycline–induced type I cutaneous pigmentation develops most commonly on the face within acne scars.

The pigment is found in the dermis and subcutis, often in macrophages, where it may be membrane bound or freely scattered among dermal collagen fibres.[18] Although microanalysis has revealed the presence of sulphur, chlorine and calcium, the cutaneous pigment is thought to consist of insoluble complexes of minocycline or a minocycline oxidation product chelated to iron.[19-21]

Type III

Type III cutaneous pigmentation appears as muddy-brown in hue and develops on healthy skin in a generalised and symmetrical pattern, accentuated in sun exposed areas.[22] The pigment resembles a persistent, deep brown tan and may result from increased melanisation of the basal cell layer. Melanin or a minocycline-melanin complex without iron may be demonstrated microscopically in the epidermis and papillary dermis.[22]

Additional Types

A fourth type of cutaneous pigmentation has been proposed by Chu and Van,[23] who described a patient taking minocycline who developed dark brown macular pigmentation of the lips. Microscopically, post-inflammatory changes were consistent with a resolving fixed drug eruption. Ridgway and Reizner[24] observed similar clinical and microscopic features in a patient taking minocycline.

Pigmentation can also be classified according to its distribution as either: (i) local, corresponding to

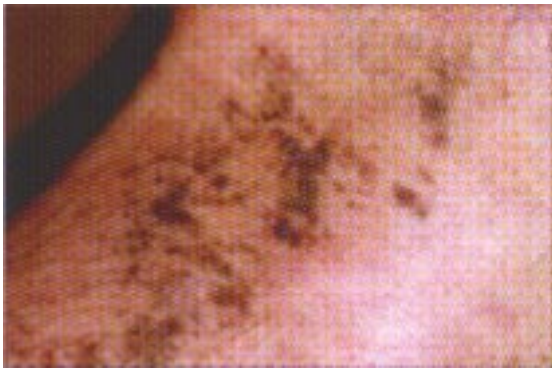

Fig. 2. The ankle is a common location for the development of type II cutaneous minocycline-associated staining.

Pigmentation can also be classified according to its distribution as either: (i) local, corresponding to type I; or (ii) diffuse, which typifies types II and III. Patients may display features of several types at a given time, and cutaneous pigmentation may also be accompanied by pigmentation involving other organs.

2.1.2 Incidence

The incidence of pigmentation resulting from minocycline appears to be related to several factors. Whereas the duration of therapy and total cumulative dose do not influence the onset of type I pigmentation, types II and III pigmentation develop predominantly in patients who are treated for prolonged periods with high dosages of the drug.[25] This is evidenced by reports of type I pigmentation developing after only a few weeks of minocycline therapy.[15,16] In contrast, types II and III pigmentation generally do not develop until patients have received a cumulative dose of minocycline exceeding 70 to 100g.[26,27] The intensity of the pigmentation does not appear to correlate with the total dose of minocycline or the duration of treatment.

Patients treated for rosacea develop pigmentation from minocycline more often than those treated for acne.[25] This may be related to the older age of patients with rosacea, who demonstrate greater age-related solar elastosis and receive higher cumulative doses of minocycline than patients with acne. In the study by Dwyer and Cuddihy[25] of 54 patients treated with minocycline for a mean duration of 17 months for acne or rosacea, approximately 15% (8 patients) developed pigmentation. Six of the 8 identified patients were treated for rosacea and the remaining 2 for acne. These figures are in agreement with others who have reported an incidence of pigmentation of 3% in patients with acne who were treated with minocycline for prolonged periods.[28]

2.1.3 Management

Patients undergoing therapy with minocycline should be informed of the possible adverse effect of cutaneous pigmentation and should be appropriately screened for its development. This is especially true for patients treated for extended periods of time with cumulative doses greater than 100g.

Fortunately, both type I and II pigmentation is harmless, but it may be unsightly and darken significantly if the drug is not withdrawn. In almost all cases, the pigmentation resolves after the drug is stopped; however, several months may elapse before complete resolution is achieved. In contrast, the diffuse muddy brown pigmentation observed with type III pigmentation may persist indefinitely,[25,29] although, based on paucity of reports in the literature and our own observations, this type is the most rare.

Successful treatment of minocycline-induced pigmentation without scarring or hypopigmentation has been reported with a Q-switched laser.[30] Management of pigmented osteoma cutis involves surgical removal of the epidermal nodules or the use of tretinoin cream for dermal osteomas.

2.2 Nails

Nail pigmentation caused by minocycline is unusual and far less common than skin involvement. Although a number of colour changes have been reported, a slate-grey discoloration of the proximal nail bed appears to be the most frequent type (fig. 3).[31] Even more rare are longitudinal melanonychia, diffuse nail pigmentation and photoonycholysis.[32,33]

Generally, nail pigmentation develops concomitantly with other sites of involvement and it is rarely an isolated finding. Stimulation of nail matrix melanocytes with increased melanin deposition in the nail plate has been described as the cause of pigmentation in longitudinal melanonychia.[34] This is similar to the mechanism in type III cutaneous pigmentation.

Pigmentation of the nail may persist for prolonged periods despite withdrawal of the drug. The recognition of these changes may avoid unnecessary biopsy.

2.3 Oral Cavity

Minocycline may cause pigmentation of the teeth, the oral mucosal surfaces and the underlying bones of the oral cavity.

2.3.1 Teeth

Although the incidence of tooth discoloration in the erupted permanent dentition has been reported to be as high as 6% in 1 retrospective study,[35] our own experience and that of others reveal a much lower rate.[36] In fact, we have only observed this type of pigmentation in a few cases after treating several hundred patients with minocycline, and only when therapy was administered for an extended period of years. When present, the discoloration is greyish-blue. Unlike staining caused by tetracycline, which primarily affects the proximal third of the tooth, minocycline staining is most evident in the middle portion of the tooth and occasionally involves the lower incisal third. The blue pigmentation is generally permanent, unless it appears shortly after the initiation of minocycline therapy and the drug is promptly withdrawn.[37]

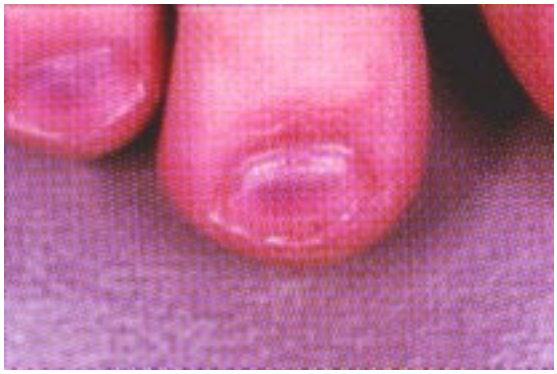

Fig. 3. Minocycline–induced slate-grey pigmentation of the proximal nail bed.

Some have suggested that the pigmentation of the teeth may be caused by either demineralisation and etching of the enamel by minocycline resulting in a persistent extrinsic stain[38] or deposition of minocycline in dentin which becomes visible through the enamel.[39] Since the concentration of systemically administered minocycline in the gingival fluid is 5 times that of serum,[40] pigmentation near the gingival margin would be expected. Additionally, after the teeth erupt, dentin formation is greatly reduced. Thus, both theories are insufficient to explain why minocycline but not tetracycline cause erupted teeth to discolour.

Staining of the roots of teeth has been well documented.[41,42] Indeed, our oral surgeons have frequently observed this during extraction of third molars (wisdom teeth) from patients with acne who were treated with minocycline during root development.

2.3.2 Oral Mucosal Surfaces

Reports of minocycline-induced pigmentation affecting the oral mucous membranes are equally rare and have included the buccal mucosa, gingiva, lips and tongue.[36,43,44] Although minocycline is the only tetracycline associated with oral mucosal pigmentation, its cause remains unknown. It has been suggested that either a minocycline-metabolite complex or melanin, iron and calcium-containing granules are the source of the pigment.[41] We have observed that the oral pigmentation develops at sites predisposed to oral trauma such as the tongue and buccal mucosa. The pigmentation appears to be unrelated to the duration of minocycline therapy or the cumulative dose, and resolves completely when the drug is discontinued. These features are identical to those described for type I cutaneous pigmentation (see section 2.1.1).

2.3.3 Bones of the Oral Cavity

Without question, almost all cases of intraoral pigmentation represent minocycline staining of the

underlying bones without involvement of the overlying oral mucosal surfaces. As we recently reported, the incidence of intraoral bone pigmentation from minocycline, at dosages of 100 to 200 mg/day, is 10% after 1 year of therapy.[45] The incidence increases to 20% in patients taking minocycline for 4 years.

Based on these results, it is apparent that intraoral bone represents the body site most often affected by minocycline-induced pigmentation, but that it is also perhaps the most overlooked. Distinct blue or blue-black bone pigmentation, also known as black bone disease,[46] is most evident beneath the semi-translucent maxillary and mandibular anterior alveolar mucosa (fig. 4). To visualise these areas properly, the lips should be fully retracted and the alveolar mucosa inspected. Involvement of the hard palate and lingual alveolar bone, however, is also frequently observed. The pigmentation of the bone is probably irreversible in most patients because of the formation of insoluble salts from minocycline degradation.[47] When the drug is discontinued, the intensity of pigmentation does, however, reduce significantly over a number of years.

2.3.4 Management

The recognition of minocycline-induced pigmentation in the oral cavity may avoid unnecessary testing and confusion with systemic diseases that may also result in pigmentation. Like cutaneous pigmentation, oral pigmentation of the mucous membranes or bones is innocuous. Although some authors have advocated testing of renal and hepatic function to exclude the possibility of impaired excretion of minocycline in patients with black bone disease,[46] we do not feel this is necessary based on our personal experiences with such patients who have undergone laboratory testing without detection of abnormalities.

2.4 Thyroid and Other Viscera

The development of a black discoloration of the thyroid gland associated with long term minocycline therapy has been reported by many investigators.[48-50] According to Landas et al.,[49] a black pigment, which can best be described as neuromelanin, accumulates normally in the thyroid with advancing age. Minocycline may accelerate the onset of black pigmentation of the thyroid. It has been postulated that minocycline may cause melanosis either by acting as a premelanin substrate concentrated in thyroid tissue, or by altering the amount of oxidative activity or oxidative products in thyroid epithelium.[51]

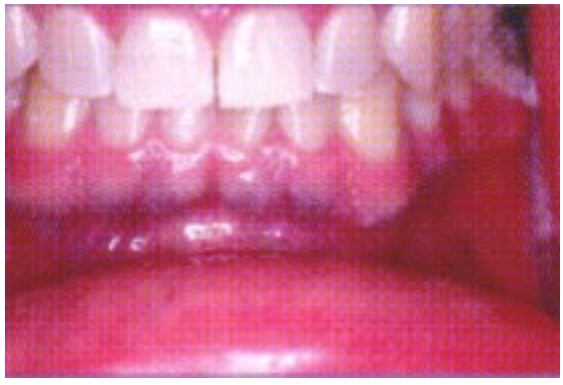

Fig. 4. Minocycline–induced oral pigmentation of the underlying alveolar bones visible through the semi-transparent alveolar mucosa. The mucous membranes are uninvolved.

In 1993, Enochs et al.[52] further characterised the black thyroid pigment as a polymeric product of the *in vivo* oxidation of minocycline by thyroid peroxidase. Taurog et al.[53] recently confirmed the role of thyroid peroxidase in the production of minocycline–induced black pigment and, of far greater significance, demonstrated the potent antithyroid effects of minocycline *in vitro*. These data, coupled with those of Alexander et al.,[54] who reported a patient with minocycline–induced black thyroid and clinical and laboratory evidence of thyroid hypofunction, prompted several investigators to suggest a need to monitor patients receiving long term minocycline therapy for thyroid function. Although these have been the only studies that have implicated minocycline-induced pigmentation as potentially harmful, it may be prudent to investigate thyroid studies in patients treated long term with this drug.

In addition to the thyroid gland, minocycline-associated pigmentation has been reported in the substantia nigra and atherosclerotic plaques,[49] as well as in aortic and mitral valves.[55] In all of these cases, pigmentation was found incidentally, and additional information regarding any harmful effects of the pigmentation was not reported.

2.5 Breastmilk

Because of its lipophilic nature, minocycline is highly soluble in body fluids and may be excreted in breastmilk. We know of only 2 cases that report black galactorrhoea in patients taking minocycline.[56,57] The first patient developed galactorrhoea from phenothiazine, and after 4 years of taking minocycline 200 mg/day developed black breastmilk. The second patient, who had completed breast feeding 18 months prior to her presentation, had been treated for only 4 weeks with minocycline at a dosage of 150 mg/day before she noted small amounts of black milk. The milk of both patients demonstrated macrophages containing particles that stained positive for iron. It was postulated that the pigmentation consisted of an iron chelate of minocycline or one of its derivatives.[56]

2.6 Skeleton and Cartilage

Rumback et al.[58] reported a case of blackened thoracic vertebrae discovered incidentally during an elective neurosurgical procedure, without evidence of pigmentation elsewhere. The pigmentation occurred in a woman who had a cumulative ingestion of minocycline of greater than 220g. Other patients who had been administered smaller cumulative doses were noted to have pigmented bones, usually in association with pigmentation of the skin and nails.[59]

Minocycline-staining involving other portions of the skeleton, including costal cartilage, parietal bones and alae-nasi, were reported in a single patient.[48] These findings occurred simultaneously after treatment with minocycline 200 mg/day for over a year and were found concurrently with a uniformly black thyroid.

The dark pigment in bone may represent a degradation product or a drug complex, and has been shown to consist of a deposit containing iron and calcium and resemble haemosiderin.[58,60]

The effect of minocycline on bone metabolism is unknown, although no adverse effects of minocycline on the structure or function of bone have been reported. Tetracycline is known to chelate calcium phosphate and bind loosely to polypeptides in bone, but despite considerable accumulation of the drug in adult bone, no adverse consequences have been noted.[61] The metabolic effects of minocycline on bone require further investigation.

2.7 Ocular

Minocycline staining of the ocular structures including the conjunctiva and the sclera has been reported by several investigators.[18,62-64] Distinct pigmented changes involving the sclera include a blue-grey, 3 to 5mm band starting at the limbus, which is usually enhanced in the palpebral aperture.[65] Diffuse blue discoloration of the sclera has also been observed.[18] It has been noted that almost all patients who report scleral pigmentation also display pigmentation of the nails. Furthermore, in addition to taking high dosages of minocycline for prolonged periods (exceeding 2 years), all patients exhibited type III, diffuse muddy-brown cutaneous pigmentation.

Subconjunctival, densely pigmented spots located on the inferior tarsal plate, hypothesised to be conjunctival cysts, have also been noted in patients taking minocycline.[18,66] These pigmented abnormalities have been reported in both the presence and absence of skin changes.

Pigmentation involving the ocular structures may resolve within years or it may persist indefinitely. Fortunately, no harmful effects of the pigmentation have been reported.

3. Conclusion

Minocycline has been demonstrated to cause dark pigmentation of various body sites, most prominently the skin, nails, bones, thyroid and

Table II. An overview of minocycline-induced pigmentation

Organ involvement	Clinical features of pigmentation	Effects of dose and duration of drug therapy
Skin		
type I	At sites of inflammation on face, chest and legs	Does not influence onset
type II	On healthy skin of shins, ankles and arms	Cumulative dose >70-100g
type III	Generalised, symmetrical on sun-exposed areas	Cumulative dose >70-100g
Nails	Slate-grey discoloration of the proximal nail bed	Usually with prolonged therapy
Oral cavity		
teeth	Middle of tooth, occasionally the incisal third	After years of therapy
mucous membranes	Sites predisposed to trauma, e.g. tongue and buccal mucosa	Does not influence onset
alveolar bone	Beneath the semitranslucent maxillary and mandibular alveolar mucosa, and hard palate	Evident after 1 year of therapy; incidence increases with prolonged therapy
Thyroid	Black discoloration of the thyroid gland	Usually after long term therapy
Skeleton/cartilage	Thoracic vertebrae, costal cartilage, parietal bones and alae-nasi	Usually after long term therapy
Ocular	Blue-grey scleral pigmentation and subconjunctival pigmented spots	After high doses for extended periods

eyes. Table II provides an overview of this adverse effect.

In general, with the exceptions of type I cutaneous pigmentation and intraoral mucous membrane pigmentation which develop independent of dose or duration of therapy, all other minocycline-induced pigmentations develop after long term administration of the drug and high cumulative doses. Multiple sites of pigmentation are frequently detected. Since almost all cases of pigmentation develop in patients with acne and rosacea who have been treated long term, minimising the cumulative dose of minocycline by discontinuing the drug after 6 months will avoid this common adverse effect.

The pigmentation may lead to confusion if not properly recognised and may result in unnecessary testing to exclude other causes of pigmentation. All patients receiving minocycline therapy should be carefully screened for the development of pigmentation. In addition to a twice yearly examination of the skin, nails, eyes and oral cavity, some authors advocate thyroid function testing for those patients treated with minocycline for longer than 1 year, or for those receiving cumulative doses of greater than 100g. Additional research on the effects of minocycline on thyroid function is required before routine testing can be recommended.

Once pigmentation has been identified, the drug should be promptly discontinued and substituted with an alternative antibacterial. Pigmentation of the skin usually resolves within months or years, although pigmentation of other body sites is more likely to be permanent.

With proper monitoring, minocycline remains an invaluable drug for the treatment of acne and a variety of other conditions.

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Correspondence and reprints: Dr *Drore Eisen,* Dermatology Research Associates of Cincinnati, 7691 Five Mile Road, Cincinnati, OH 45230, USA.