

# Minocycline-Induced Pigmentation Mimicking Persistent Ecchymosis

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The estimated time to complete this activity is 1 hour.

## GOAL

To understand minocycline-induced pigmentation to better manage patients with the condition

## LEARNING OBJECTIVES

Upon completion of this activity, you will be able to:

1. Distinguish the 3 common patterns of pigmentation based on clinical characteristics.
2. Recognize histologic findings of pigmentation.
3. Discuss the role of the duration and cumulative dose of minocycline on the incidence of pigmentation.

## INTENDED AUDIENCE

This CME activity is designed for dermatologists and general practitioners.

CME Test and Instructions on page 40.

This article has been peer reviewed and approved by Ranon Ephraim Mann, MD, Assistant Professor, Department of Medicine (Dermatology), Albert Einstein College of Medicine. Review date: June 2009.

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*We report an unusual case of minocycline-induced pigmentation mimicking persistent ecchymosis in a patient with persistent (20 months' duration) bluish black discoloration of the medial and lateral aspects of the left ankle following an avulsion fracture. We review the common presentations of minocycline-induced pigmentation as well as some of the more unusual presentations.*

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**M**inocycline is a semisynthetic broad-spectrum antibiotic in the tetracycline family introduced in 1967. Several advantages of minocycline compared to other tetracycline antibiotics have led to its popularity, including rapid achievement of peak serum concentrations, excellent absorption, and long half-life. Furthermore, minocycline is lipophilic, which increases its tissue distribution while decreasing bacterial resistance.<sup>1</sup> These properties have allowed minocycline to be widely used for the treatment of various infections and as a mainstay in the treatment of acne vulgaris. While adverse effects are considered uncommon, even during prolonged treatment, pigmentation has become a well-recognized adverse effect of minocycline therapy. In 1967, Benitz et al<sup>2</sup> reported that the most striking side effect was abnormal pigmentation in the thyroid gland observed in rats, dogs, and monkeys. In 1972, a case of transient hyperpigmented macules on the legs was reported in association with long-term minocycline treatment.<sup>3</sup> Since then, minocycline-induced pigmentation also has been reported to involve the nails, lips, oral mucosa, gingiva, teeth, postacne osteoma cutis, bones, costal cartilage, heart valves, thyroid, prostate, lymph nodes, substantia nigra, atherosclerotic plaques, conjunctival cysts, sclera, and breast milk.

### Case Report

A 21-year-old woman with a medical history of a left ankle fracture and 5 years of treatment with minocycline hydrochloride for acne vulgaris presented with persistent bluish black discoloration of the medial and lateral aspects of the left ankle for 20 months (Figure 1). Her right ankle, however, had no such pigmentation. The onset of the discoloration presented

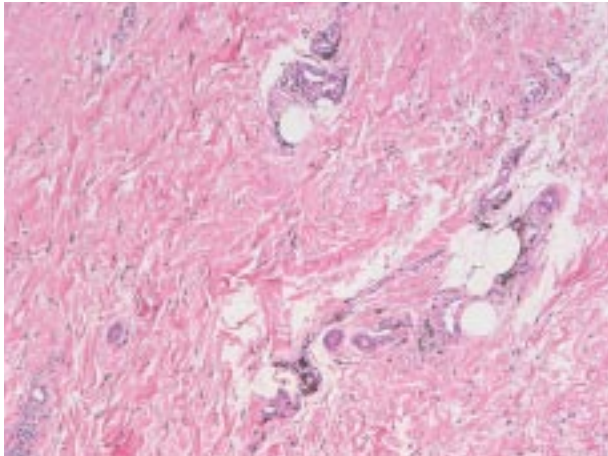
abruptly after she sustained a small medial malleolar avulsion fracture by inverting her ankle while jumping on a trampoline. At that time, she was treated with a cast followed by a walker boot. During a follow-up appointment with the orthopedic surgery department 11 months after the fracture, the patient complained of persistent pain, swelling, and discomfort in the ankle, as well as a sensation of instability. The medical records from that time also described the failure of the bruising and swelling in her ankle to resolve as unusual, noting that according to the patient, the bruising and swelling were not waxing and waning but rather constant and without change in size. The presumed persistent bruising was not related to any new or recurrent injury. X-rays from that time showed that her fracture was healed without disruption of the mortise. Physical examination, however, revealed what appeared to be bilateral tattooing of the skin on the left ankle that resembled a prior hematoma but was not acute in nature.

The orthopedic surgery department recommended consulting the dermatology department for what they deemed was not an active issue of hematoma but rather hyperpigmentation secondary to prior bruising. One month later, the patient underwent a lower extremity duplex Doppler scan to rule out deep vein thrombosis as a cause of her persistent left leg edema. The scan examined both the superficial and deep venous systems in both lower extremities and found no evidence of thrombosis or obstruction. Subsequent magnetic resonance imaging showed findings consistent with a healed avulsion fracture of the medial malleolus without evidence of substantial cartilage injury.

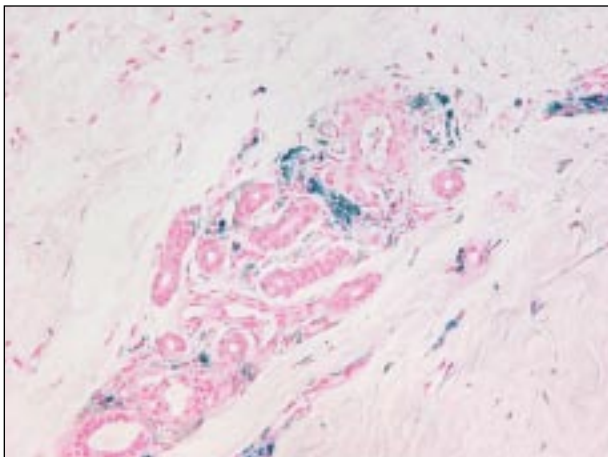
A year and a half after the original injury, the patient was seen in the dermatology department



**Figure 1.** Bluish black discoloration of the medial and lateral aspects of the left ankle.



**Figure 2.** A 3-mm punch biopsy specimen showing mild epidermal acanthosis, numerous pigmented dendritic cells in the underlying superficial and deep dermis, and pigmented perivascular histiocytes (H&E, original magnification  $\times 10$ ).



**Figure 3.** Positive staining for iron (Perls Prussian blue, original magnification  $\times 20$ ).

with bluish black nonblanching patches noted along her left medial and lateral malleoli. Initially, doxycycline hyclate was prescribed to replace minocycline therapy for acne vulgaris, but the patient was unable to tolerate doxycycline because of severe nausea. The patient's current cumulative minocycline hydrochloride dose was 255.5 g, as she had taken 100 mg daily for 3 years and 100 mg twice daily for 2 years. A 3-mm punch biopsy specimen showed mild epidermal acanthosis, numerous pigmented dendritic cells in the underlying superficial and deep dermis, and pigmented perivascular histiocytes (Figure 2). Positive staining for iron with Perls Prussian blue further supported the diagnosis of minocycline-induced pigmentation (Figure 3). Following histologic diagnosis, another trial of doxycycline was attempted and was well-tolerated.

## Comment

Minocycline is a commonly used broad-spectrum antibiotic with a relatively favorable side-effect profile. Skin pigmentation as a sequela of minocycline therapy is a well-documented phenomenon, and incidence has varied from 2.4% to 14.8% in limited longitudinal studies.<sup>4,5</sup> Three common patterns of pigmentation have been categorized and are recognized as types I, II, and III, with clinical and histologic features used to differentiate them.

Type I pigmentation is characterized by blue-black macules that are localized to sites of scarring or inflammation.<sup>6</sup> Some authors, however, have limited type I pigmentation to sites of scarring or inflammation on the face,<sup>7</sup> while others have included contusions, ulcerations, and lacerations, as well as existing scars, as possible sites of type I pigmentation.<sup>8</sup> In type I, pigment granules are not membrane bound within macrophages and are located in the dermis. These granules consist of minocycline or a minocycline degradation product that is chelated with hemosiderin, ferritin, or iron, and stains positive with Perls Prussian blue but not with Fontana-Masson silver.<sup>6,8</sup>

In contrast, type II pigmentation appears as blue-black, brown, or blue-gray pigmentation that develops on healthy skin. While type I typically appears in sites of scarring or inflammation on the face, type II presents primarily on the arms, shins, and ankles. Descriptions of type II pigmentation have varied from diffuse to well-circumscribed. Histologically, pigment granules are found in the dermis and subcutis, often in macrophages, and have been described as variably membrane bound or freely scattered among dermal collagen fibers.<sup>9</sup> Type II pigment-laden macrophages usually stain positive with both Perls Prussian blue and Fontana-Masson silver. While microanalysis has demonstrated the presence of calcium, chlorine, and sulfur, the visible cutaneous pigment is thought to result from insoluble complexes of minocycline or a minocycline oxidation product chelated with iron.<sup>10-12</sup>

Type III pigmentation develops on healthy skin, similar to type II, but type III pigmentation appears muddy brown in hue and the presentation is generalized and symmetric with accentuation in sun-exposed areas. The appearance of the pigment often is compared to a persistent deep brown tan and is thought to result from increased melanin in the basal layer and upper dermis.<sup>1,8</sup> Type III pigmentation usually stains positive with Fontana-Masson silver but not Perls Prussian blue.<sup>8</sup>

Type I pigmentation is thought to be the most common and is unrelated to cumulative or daily dose of minocycline exposure, while type II is less

common and type III is the least common.<sup>13</sup> The incidence of types II and III pigmentation is thought to correlate with the duration and cumulative dose of treatment; both types occur most often when cumulative doses are greater than 100 g.<sup>1</sup> Goulden et al<sup>4</sup> reported that participants taking minocycline 200 mg daily showed a 4% (11/301) incidence in pigmentation compared with 0.4% (2/451) of those participants taking 100 mg daily and 1.1% (4/356) of those participants taking 100 and 200 mg on alternate days. These 3 types of pigmentation, while distinct, are not mutually exclusive, and patients affected by minocycline often demonstrate more than one clinical pattern of pigmentation.<sup>4</sup>

New types of minocycline-induced pigmentation recently have been described. Chu et al<sup>14</sup> proposed a fourth type of cutaneous pigmentation based on a patient who developed dark brown macular pigmentation of the lips. Microscopically, postinflammatory changes consistent with a resolving fixed drug eruption were seen.<sup>14</sup> Mouton et al<sup>7</sup> described a new type in 2 patients with circumscribed blue-gray pigmentation within acne scars confined to the back. While clinically consistent with type I, this new type was found to have calcium, as detected by energy-dispersive x-ray analysis, but no iron.<sup>7</sup>

Several case reports have been published documenting minocycline-induced pigmentation mimicking other conditions. Mooney and Bennett<sup>15</sup> described a case of minocycline-induced pigmentation that presented as a longitudinal pigmented streak of the nail associated with periungual hyperpigmentation mimicking the Hutchinson sign. While minocycline-induced pigmentation k bnerized by sclerotherapy has been documented in the presence of ulceration, Green<sup>8</sup> described both linear and nummular minocycline-induced pigmentation following sclerotherapy in the absence of ulceration. Initially, these cases of pigmentation were attributed to localized cutaneous pigmentation following sclerotherapy, which almost invariably progressively lightens and ultimately disappears. Meyer and Nahass<sup>16</sup> described symmetric blue-gray patches on the dorsal aspects of both feet in a patient who denied any trauma to the area but was an active windsurfer and snow skier. This pigmentation showed a positive reaction to Perls Prussian blue and Fontana-Masson silver stains but also was found to have pigment-laden macrophages between bundles of skeletal muscle.<sup>16</sup> Mehrany et al<sup>13</sup> described a 76-year-old man who sustained a 4-part intertrochanteric fracture that was later followed by an open reduction and internal fixation as well as total hip arthroplasty. The patient later developed blue-gray discoloration of the forearms, which

considerably progressed. When a coronary artery bypass graft was needed, these patches were confused for ecchymosis and possible indication of a bleeding diathesis.<sup>13</sup> Green and Friedman<sup>17</sup> described a 22-year-old woman who had been taking minocycline for acne and was involved in a motor vehicle accident that caused substantial contusions to her anterior legs. She noticed the appearance of pigmentation of her legs within months after the accident but did not consult a physician. Her skin continued to darken over subsequent months. The authors, however, did not clarify the distinction between the contusions the patient initially noted and the pigmentation she reported in the following months that progressively darkened. Presumably, they were distinct entities because the authors distinguish the 2 forms of dyspigmentation as contusions and pigmentation. At the time of the patient's first visit with her dermatologist following the accident (14 months later), she had been taking minocycline hydrochloride 100 mg twice daily for 7 years. She was advised to discontinue use of minocycline and replace it with tetracycline hydrochloride. After discontinuing minocycline therapy, she did not note any spontaneous reduction in the discoloration but also did not note any progressive darkening.<sup>17</sup> Hawfield et al<sup>18</sup> described a case of an 18-year-old woman treated for acne vulgaris with tetracycline hydrochloride for 2 years who presented with a 4-year history of nonresolving, occasionally tender, bruise-like patches on the bilateral lower extremities following episodes of trauma. They also noted that ecchymosis on the upper extremities had resolved in an unremarkable fashion without evidence of pigmentation.<sup>18</sup> Collins and Cotterill<sup>19</sup> described a case of a 55-year-old woman who had been taking minocycline hydrochloride 50 mg twice daily for 14 months for rosacea and developed blue-black pigmentation localized to a site of prior trauma on her right leg but did not give any specifics about the nature of the trauma or the length of time between the trauma and the onset of pigmentation.

The association of minocycline-induced pigmentation and trauma has been well-established. In most reported cases, minocycline exposure precedes the source of injury; however, some invasive intervention initiates the pigmentation. To our knowledge, our patient's presentation is unique in that the onset of her minocycline-induced pigmentation was abrupt, coincided with the fracture of her ankle, and was not associated with any invasive intervention. While other cases of abrupt onset of minocycline-induced pigmentation have been reported, to our knowledge, those cases have all involved invasive instrumentation, as in the patient whose

pigmentation was associated with open reduction and internal fixation as well as total hip arthroplasty,<sup>13</sup> or the patients who underwent sclerotherapy prior to the onset of pigmentation.<sup>8</sup> Other reports of pigmentation following trauma in patients taking minocycline did not clearly differentiate the contusions immediately following the trauma from the pigmentation that occurred later,<sup>17</sup> or did not clarify the nature of the trauma or the length of time between the trauma and the onset of pigmentation.<sup>19</sup>

Our case appears to represent a novel occurrence of minocycline-induced pigmentation. To date, the patient's pigmentation is substantially lighter after 4 treatments with Q-switched Nd:YAG laser therapy for her hyperpigmentation, and she is happy and satisfied with the results. She does not feel further treatment is warranted at this time. Greve et al<sup>20</sup> have demonstrated 90% resolution of pigmentation after 5 treatments with a Q-switched Nd:YAG laser.

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