Hyperpigmented Scar Due to Minocycline Therapy

James W. Patterson, MD; Barbara Wilson, MD; Mark R. Wick, MD; Candrice Heath, MD

GOAL

To understand the varieties of hyperpigmentation that can be induced by minocycline therapy, including hyperpigmented scars

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the types of hyperpigmentation associated with minocycline therapy.
2. Explain the possible mechanisms of minocycline hyperpigmentation.
3. Discuss the differential diagnosis of hyperpigmented scars.

CME Test on page 304.

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A 20-year-old woman presented with a heavily pigmented scar on the left lower abdomen following excision of a benign compound nevus. Reexcision showed an organizing scar with pronounced hemosiderinlike pigment deposition and no residual melanocytic lesion. Results of further histopathologic workup showed positive staining with both Perls stain for iron and Fontana-Masson stain. These findings led to further questioning of the patient, which revealed a history of minocycline therapy—information that had not been provided during her initial evaluation. Hyperpigmented scars may result from minocycline ingestion. We present a review of the literature, with particular regard to the possible mechanisms of minocycline hyperpigmentation and the differential diagnosis of hyperpigmented scars.

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From the University of Virginia School of Medicine, Charlottesville. Dr. Patterson is Professor of Pathology and Dermatology. Dr. Wilson is Edward P. Cawley Associate Professor of Dermatology. Dr. Wick is Professor of Pathology and Dermatology. Dr. Heath was a medical student.

Reprints: James W. Patterson, MD, Department of Pathology, University of Virginia Health System, PO Box 800214, Charlottesville, VA 22908-0214 (e-mail: jwp9e@virginia.edu).

Scars may become pigmented for a variety of reasons, including the persistence and/or recurrence of an incompletely removed melanocytic nevus. However, development of an intensely hyperpigmented scar not long after a surgical procedure, in the absence of a clear explanation, would be a distinctly uncommon event. We recently encountered such a lesion in an otherwise healthy 20-year-old patient. In this case, the histopathologic findings led to further questioning of the patient and revealed a cause that had not been previously suspected.

Case Report

A 20-year-old woman was seen for evaluation of a lesion on the left lower abdomen. Six weeks earlier, the lesion had been shave excised by an outside physician; pathology results were not initially available. The patient reported that the lesion had quadrupled in size and darkened considerably since the time of the excision. Her grandmother had died of malignant melanoma. She reported that her only medication was birth control pills. On physical examination, there was a 13×8-mm brown-black nodule with discrete but irregular borders (Figure 1). The clinical impression was recurrent nevus in a shave excision scar. However, because of the rapid growth, dark color, and family history of melanoma, there also was concern about the possibility of an atypical nevus or malignant melanoma. Therefore, an elliptical excision was performed. A report of the initial biopsy specimen was received, with the interpretation benign compound nevus.

Results of histopathologic evaluation of the reexcision specimen showed no residual melanocytic lesion. There was a prominent pigmented, cellular scar occupying the superficial to mid dermis in the central portion of the specimen. The pigmented material consisted of refractile, golden brown granules within macrophages and extracellularly, having a resemblance to hemosiderin (Figure 2). These granules stained positively with Perls stain for iron and with Fontana-Masson stain (Figure 3). Fontana-Masson staining was negative when performed after a bleaching procedure that employed potassium permanganate solution at a concentration of 3 g/L.

The staining results suggested the possibility of minocycline-related hyperpigmentation. Subsequent questioning of the patient revealed that she had been taking minocycline 100 mg twice daily during the 2 years prior to her clinic visit.

Comment

Pigmented scars can arise occasionally because of a number of factors. The sites of persistent and/or recurrent nevus are often pigmented. This pigment, confined to the scar, often shows irregular borders and may have a mottled appearance.[1] Pigmented scars also are observed in spontaneously regressing malignant melanoma.[2] In a related phenomenon called tumoral melanosis, sheets of melanophages may accompany either a regressed melanoma or epithelial neoplasm.[3,4] Pigmentation of scars related to hemorrhage also could occur, eg, following postsurgical trauma or in association with clotting abnormalities, though it is difficult to find literature directly addressing this problem. Other reported associations with hyperpigmented scars include leishmaniasis,[5] chickenpox,[6] burns,[7] Addison disease,[8] and hemosiderin-related pigmentation in endometriosis arising in cesarean scars.[9] Among other agents that cause cutaneous pigmentation and could potentially produce hyperpigmented scars are heavy metals (eg, gold) and drugs such as amiodarone, phenothiazines, and antimalarials.[10,11] Biopsy results of oral hyperpigmentation due to long-term antimalarial therapy have shown macrophages that contain melanin and ferric iron,[12] findings resembling those reported here. None of these causes was pertinent to our case.

Figure 1. Clinical appearance of a scar on the left lower abdomen showing dark brown-black pigment with an irregular border.

Minocycline first became available for clinical use in 1967. An association between minocycline administration and black discoloration of thyroid gland follicles in animals was reported that same year.[13,14] As early as 1972, Velasco et al[15] reported a macular pigmentation of the legs in patients receiving minocycline for the treatment of venereal disease. Since that time, there have been a number of

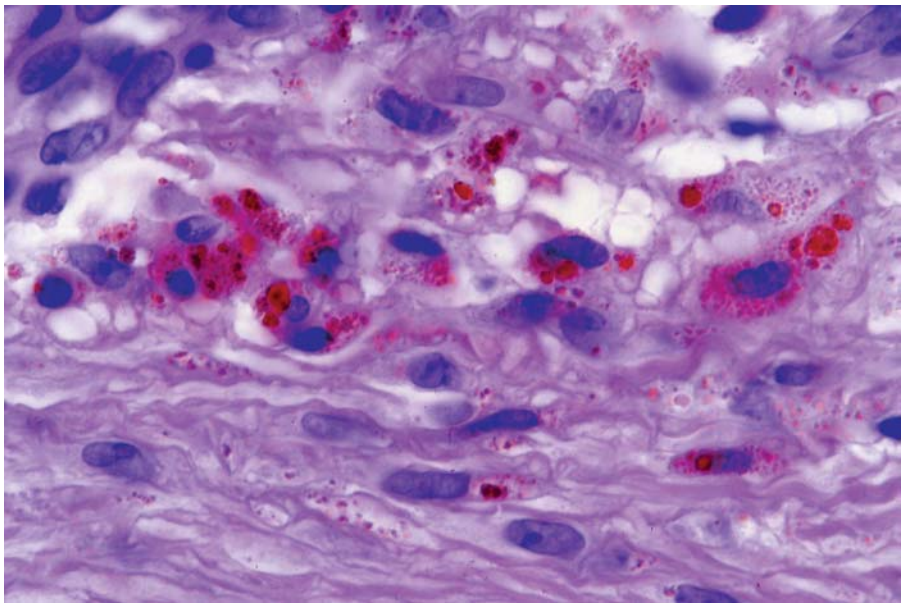

Figure 2. Scar containing abundant golden brown granules resembling hemosiderin (H&E, original magnification ×40).

reports of minocycline-induced pigmentation of skin and mucous membranes. Journal articles and textbooks usually divide minocycline-related cutaneous pigmentation into 3 major types. The first, type I, is a blue-black pigmentation that develops in areas of inflammation and scar[13,16-19]; this is the type that we report here. The second, type II, is a blue-gray pigmentation that develops particularly over otherwise normal-appearing skin of the arms, legs, or face.[18,20,21] The third, type III, is usually described as a diffuse or generalized "muddy brown" pigmentation,[13,22-25] though in one report this type of pigmentation was actually described as dark blue-gray.[24] The Table provides a summary of the clinical and histopathologic changes associated with the 3 major types of minocycline pigmentation. Pigmentation of the nails and nail beds also occurs[19,26] and has coexisted with diffuse cutaneous and scleral pigmentation.[25] A fourth type of pigmentation that is not specific to minocycline results from fixed drug eruption, as described by Chu et al[27] and possibly also represented by the case of Tanzi and Hecker.[28] Minocycline also has been associated with discoloration of teeth,[23] pigmented conjunctival cysts,[29] and black galactorrhea,[30] as well as pigmentation of internal organs such as cardiac valves.[31,32]

The duration of treatment and total dose required for minocycline to produce cutaneous pigmentation is difficult to determine. Although data on duration and total dose are often provided in reports, these figures typically reflect the totals at the time the patients present to their physician, rather than the time of actual onset of pigmentation, which is much more difficult to determine. Localized pigmentation at a site of tissue injury does not appear to be directly related to the duration of treatment[18] and has been reported to occur as rapidly as 1 to 3 months following the onset of minocycline therapy.[16,19] The evidence suggests that the diffuse type of pigmentation is more dependent on total dose and duration of therapy; reported patients have been on minocycline for about 3 years, with total doses ranging from 130 to 144 g.[24,25]

As generally described, there are differences among the microscopic features of the 3 major types of minocycline pigmentation. In type I, the dermal pigment is present in macrophages and stains positively for iron in a manner similar to hemosiderin.[13,16,17] Type II pigmentation stains for iron and also is reactive with Fontana-Masson.[10,20,33] Type III pigmentation has shown an increase in basilar melanin and brown-black pigment in macrophages that stains positively with Fontana-Masson and negatively for iron.[24] However, staining results are not always distinctive among the 3 types. For example, in our patient's scar and in the inflammatory lesions of Ozog et al[19] (examples of type I pigmentation), there was dermal pigment that stained positively both for iron and with the Fontana-Masson method. Patients also may have more than one type of cutaneous minocycline pigmentation. In the case of Pepine et al,[25] there were areas of blue-black pigmentation, as well as muddy brown discoloration in sun-exposed areas. Biopsy results showed black pigment deposition in perivascular and periadnexal areas, though it is not entirely clear whether these specimens were obtained from blue-black or muddy brown areas.[25] Electron microscopy in cases with blue-gray or blue-black

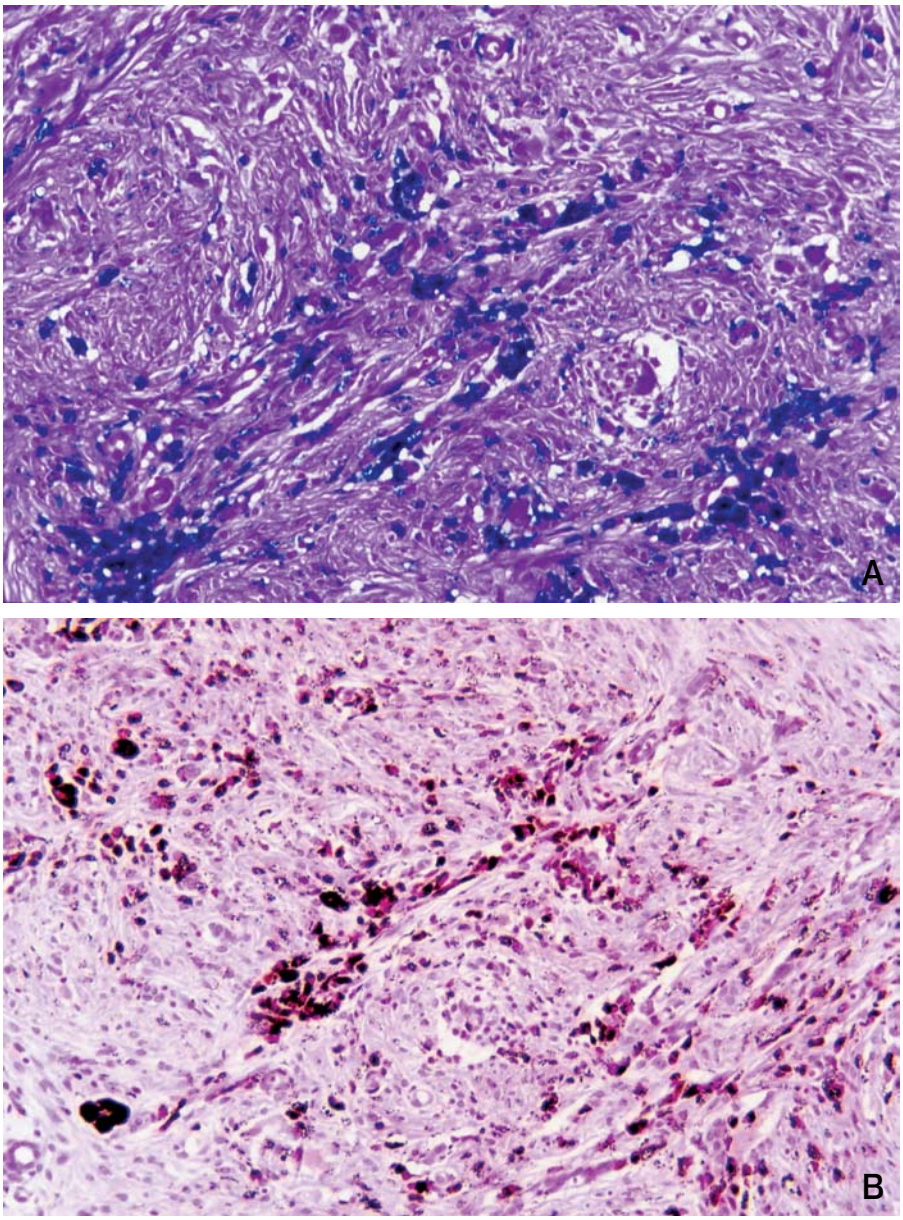

Figure 3. The same areas stained positively with Perls stain for iron (A) and with Fontana-Masson stain (B) (original magnifications ×20).

pigmentation has shown electron-dense particles in macrophages or extracellularly. Some intracytoplasmic granules are present within lysosomes, while others, including fine dustlike particles consistent with ferritin, are not bound by lysosomal membranes.[10,17,20,25] Energy dispersive x-ray microanalysis has shown that the granules mostly contain iron, with lesser amounts of calcium.[21,26]

The Fontana-Masson staining method is routinely employed to demonstrate the presence of melanin in tissue sections. Therefore, positivity in instances of minocycline pigmentation has suggested to some that melanin is at least partly responsible for the changes. This idea has been supported by one ultrastructural study showing melanosome complexes in siderosomes in a case of minocycline-related hyperpigmentation.[21] However, melanosomes have not been identified in other studies.[10] It is reported that iron may give positive reactions with Fontana-Masson staining.[20] Furthermore, the black staining of Fontana-Masson results from the action of a reducing substance on ammoniated silver nitrate; that reducing substance is not necessarily melanin.[10] The failure of the pigment to bleach, in contrast to the case with melanin, has been used to support the idea that the pigment in question does not contain melanin.[10] However, reported results with bleaching have been variable. Successful bleaching or partial bleaching has been observed in examples of cutaneous minocycline pigmentation,[19] as well as minocycline pigmentation of the thyroid gland[34]

The 3 Classic Types of Minocycline Pigmentation

Type	Clinical Appearance	Location	Duration of Treatment and Dose	Histopathologic Characteristics of Dermal Pigment
Type I	Blue-black	Areas of inflammation and scar	Not related to duration; occurred after <3 mo of therapy	Pigment in macrophages; stains positive for iron
Type II	Blue-gray	Otherwise normal skin (arms, legs, face)	Duration 11–35 mo; total dose 22–104 g	Pigment stains positive for iron and reacts with Fontana-Masson
Type III	Muddy brown	Diffuse or generalized	Dependent on total dose and duration; duration ~3 y; total dose 130–144 g	Increased basilar melanin; brown-black pigment in macrophages negative for iron, positive with Fontana-Masson

and heart valves.[32] This also is true of our case, because Fontana-Masson staining became negative when preceded by a bleaching procedure. Because past studies have employed several bleaching agents—hydrogen peroxide and potassium permanganate—and because the concentrations used in bleaching and other technical details are rarely provided, in our view, one cannot rely on the results of bleaching alone as proof of the presence or absence of melanin.

The evidence suggests that most examples of minocycline pigmentation—particularly types I and II—are due to cutaneous deposits of the drug or a metabolite thereof, chelated with iron.[10,17,26,35] Clues to the mechanism of pigment deposition are provided by the studies of thyroid pigment by Enochs et al.[36] Their in vitro modeling studies using electron paramagnetic resonance spectroscopy suggest that the pigment is a polymer caused by the in vivo oxidation of minocycline by thyroid peroxidase, which produces a melaninlike pigment.[36] This pigment also contains significant amounts of iron, tightly bound in situ. A related phenomenon could well occur in the skin. Then, as suggested by Argenyi et al,[10] the metabolite could act as a reducing substance, explaining the frequent positivity with the Fontana-Masson stain. It is possible that minocycline also may stimulate melanin production, accounting for the diffuse muddy brown type III pigmentation,[17] but further studies are needed to clarify this point. The good news is that minocycline pigmentation resolves after cessation of therapy, though this may be a gradual process.[17,19,25,37]

Conclusion

Minocycline therapy should be included in the differential diagnosis of hyperpigmented scars. Careful history taking and even repeated questioning may be necessary to elicit an accurate medication history. The pigmentation is most likely due to a minocycline metabolite, bound to iron; Fontana-Masson positivity may result from the action of reducing agents other than melanin. Slow resolution of the pigment can be expected following discontinuation of the drug. Nevertheless, biopsy is indicated when, as in this case, an atypical pigmented skin lesion raises concerns about malignant melanoma.

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