

Mucocutaneous Hyperpigmentation in a Patient With a History of Both Minocycline and Silver Ingestion

Angel Fernandez-Flores, MD, PhD,*†‡ Thao Nguyen, MD,§ and David S. Cassarino, MD, PhD¶

Abstract: Minocycline is a derivative of tetracycline. It has been widely used in dermatology for the treatment of acne and rosacea. One of its adverse effects is pigmentation of various body tissues. Clinically, 3 main distinct types of hyperpigmentation by minocycline have been distinguished: type I, with blue-gray to black pigment on the face in areas of scarring or inflammation; type II, with blue-gray pigment on normal skin of the legs, forearms and on the shins; and type III, with a diffuse muddy-brown discoloration in areas of sun exposure. In the current report, we present the case of a 50-year old man with a history of severe acne treated with minocycline in the past, who currently complained about discoloration of his face. He had also taken colloidal silver supplements for “good health” about 16 years ago. Physical examination revealed gray-blue discoloration on the face, sclera, hard palate and back. Histologic examination showed intracellular pigment deposits in macrophages of the superficial dermis in a perivascular and an interstitial distribution. The pigment stained with Fontana-Masson and von Kossa, whereas it was Perls’ iron negative. This case does not fit well into any of the previously described patterns of minocycline-related hyperpigmentation.

Key Words: minocycline, argyria, silver, hyperpigmentation

(*Am J Dermatopathol* 2017;0:1–4)

INTRODUCTION

Ingestion of minocycline is a well-recognized cause of cutaneous hyperpigmentation.¹ Minocycline is a derivative of tetracycline with both antibacterial and anti-inflammatory properties.¹ It is highly lipophilic, and therefore it has an excellent distribution in all body tissues. A very effective treatment for acne and rosacea, minocycline has been used in long-term treatment regimens historically.^{2,3} However, a well-recognized adverse event is pigmentation of various body tissues including the skin, oral mucosa, teeth, sclera, conjunctiva, nail beds, bones, trachea, tympanic membrane, and thyroid.^{1,4–7}

From the *Department of Cellular Pathology, Hospital El Bierzo, Ponferrada, Spain; †Group of Translational Investigation in Cellular Communication and Signaling (CellCOM-SB), Biomedical Investigation Institute of A Coruña (INIBIC), A Coruña, Spain; ‡Department of Cellular Pathology, Hospital de la Reina, Ponferrada, Spain; §Private Practice, Laser Skin Care Center, Dermatology Private Practice, Long Beach, CA; and ¶Department of Dermatology, Los Angeles Medical Center (LAMC), Southern California Kaiser Permanente, Los Angeles, CA.

The authors declare no conflict of interests.

Reprints: Angel Fernandez-Flores, MD, PhD, Servicio de Anatomía Patológica, Hospital El Bierzo, Medicos sin Fronteras 7, 24411 Ponferrada, Spain (e-mail: dermatopathonline@gmail.com).

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

A rare factor that could modify the clinical presentation of minocycline-related hyperpigmentation is the concomitant intake of metals. In the current report, we present the case of a man with a long-term history of both minocycline and silver ingestion.

Mucocutaneous hyperpigmentation due to silver is known as argyria, and it occurs due to either prolonged contact with or ingestion of silver salts.⁸ Cutaneous manifestations of argyria occur as blue-gray pigmentation most commonly present in sun-exposed areas, which is believed to be the result of the reduction of silver salts to metallic silver by activation with UV light. The ingestion of silver compounds was common in the past for the treatment of certain rheumatic conditions. Although at the present such drugs are no longer used, the incidence of argyria has increased with the popularity of silver as a dietary supplement and a homeopathic medication, and with its availability online.⁹

We have not identified any previous reports of mucocutaneous hyperpigmentation in a patient with a history of both minocycline and silver ingestion.

CASE REPORT

A 50-year-old man complained of a 3-year history of discoloration of the face (Fig. 1A), which was more noticeable on winters. His main activity was landscaping, so he spent a considerable amount of time outdoors. He had a past clinical history of severe acne treated with minocycline 100 mg twice daily for 15 years. He had also taken colloidal silver supplements for “good health” about 16 years ago daily for 2 years. His friend—who started taking the silver supplements at the same time and continues to this day—is now reportedly “very green looking.” The patient had not taken any other medications, apart from ibuprofen intermittently for joint pain.

Physical examination revealed that the patient had skin type 2, with gray-blue discoloration on the face, sclera, hard palate, and back (Fig. 1). The teeth and the fingernails were spared. There was a clinical suspicion of pigmentation due to minocycline. However, the pattern did not precisely fit with any of the 4 main types of clinical presentation typical of minocycline exposure. Therefore, a biopsy from the back was performed to clarify the situation.

Histologic examination showed intracellular pigment deposits within macrophages in the superficial dermis (Figs. 2A, B) in a perivascular and an interstitial distribution. They were accompanied by a mild lymphohistiocytic superficial perivascular inflammatory infiltrate. The pigment seemed to be consistent with melanin because it was strongly stained with a Fontana-Masson stain (Fig. 2C). Perls’ stain for iron was negative. Calcium was also identified on a von Kossa stain (Figs. 2D, E). There were no pigment deposits within or around the eccrine ducts and glands. Therefore, the histopathological findings were consistent with pigmentation due to minocycline only, with no definite histopathological signs suggestive of silver deposits.



FIGURE 1. Clinical presentation with gray-blue discoloration on the face (A), hard palate (B), and back (C). There was also pigmentation of the sclera (not shown).

DISCUSSION

Cutaneous hyperpigmentation is a well-described secondary effect of minocycline ingestion. The pigment deposits identified in biopsies of minocycline-exposed patients are attributed to insoluble complexes of minocycline with iron.¹⁰ Involvement by such complexes has been described in several

organs including the skin,¹ thyroid,¹¹ sclera,¹² heart valves,¹³ nail, bone,⁴ palate,⁴ teeth,⁷ trachea,⁶ and tympanic membrane.⁷

Clinically, 3 main distinct types of hyperpigmentation by minocycline have been distinguished (Table 1). In type I, blue-gray to black pigment occurs mainly on the face in areas of scarring or inflammation associated with acne.¹ This type

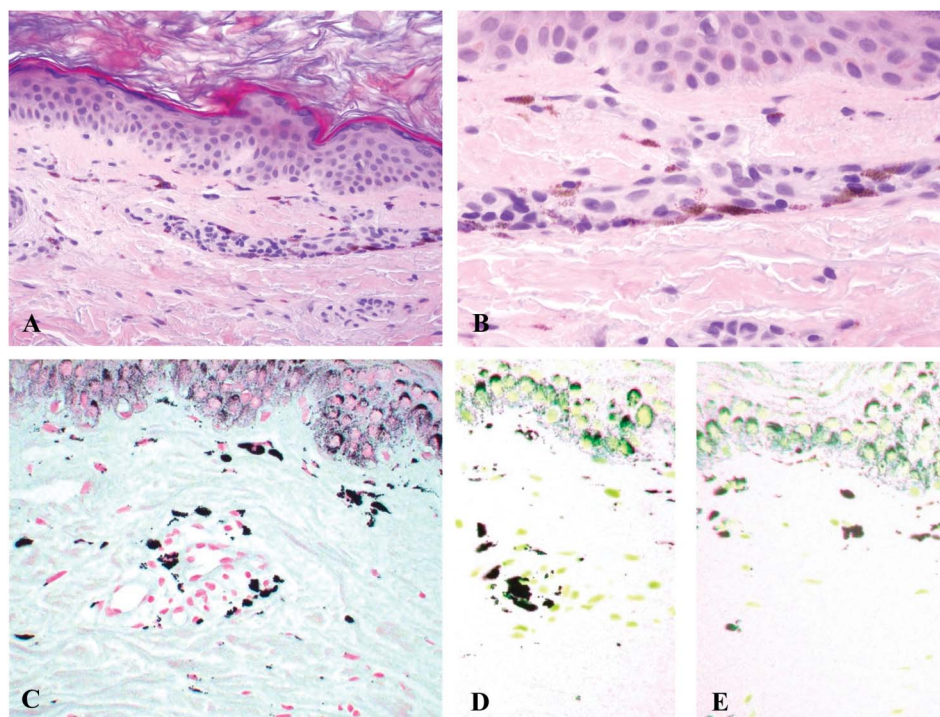


FIGURE 2. Intracellular pigment deposits in macrophages of the superficial dermis (A and B) in a perivascular and an interstitial distribution, accompanied by a mild inflammatory lymphohistiocytic superficial perivascular infiltrate (B). The pigment stained with Fontana-Masson (C) and von Kossa stain (D and E).

TABLE 1. Comparison on Morphological and Clinical Grounds Between the Current Case and the Already Known Cutaneous Forms of Presentation of Minocycline Exposure

	Type I	Type II	Type III	Type IV	Argyria	Current Case
Clinical features						
Color	Blue-gray to black	Blue-gray	Muddy brown	Blue-gray	Gray, brown to black	Blue-gray
Type of skin involved	Previous inflamed skin or scars	Normal skin	Normal skin	Scars	Normal skin and normal mucosae (usually at the sites of topical treatments) Scars with the use of some creams	Normal skin Normal mucosae
Localization	Circumscribed	Circumscribed	Diffuse	Circumscribed	Circumscribed when topical treatments Diffuse in universal argyria	Diffuse
Site(s) involved	Face	Lower legs and/or forearms, shins	Sun exposed skin	Back	Most apparent in sun-exposed areas (forehead, nose, hands) Gums, sclera, nail beds, and mucous membranes. Black tears (rare)	Face, sclera, hard palate, and back
Hematoxylin-eosin						
Pigment location	Dermis	Dermis and hypodermis	Epidermis and dermis	Dermis	Basement membrane of the sweat glands	Dermis
	Areas of previous inflammation or scar	Pigment inside macrophages and myoepithelial cells around vessels and adnexae, and free in the stroma	Increased melanin in basal keratinocytes	Areas of the scar	Connective-tissue sheaths around pilosebaceous structures and nerves	Pigment inside macrophages and free in the stroma
	Pigment inside macrophages and free in the stroma		Pigment also inside the macrophages and free in the stroma	Pigment inside macrophages and fibroblasts-like cells	Elastic fibers	
Histochemistry						
Perls	Positive	Positive	Negative	Negative		Negative
Masson Fontana	Positive	Positive	Positive	Positive		Positive
Melanin bleach	No data	Resistant	No data	Resistant		Not performed

of pigmentation is not related to the time of ingestion or with cumulative doses and the pigmentation can be obvious even after only some weeks of taking the drug.¹⁴ In type II, blue-gray pigment occurs on normal skin of the legs, forearms and on the shins. In type III (the least common), there is a diffuse muddy-brown discoloration in areas of sun exposure.^{15,16} Types II and III are related to long-term administration of the drug ranging from 6 months to 4 years with cumulative doses.^{16–18} A fourth clinical type has also been described,¹⁹ corresponding to blue-gray pigment in areas of scars on the

back. However, some authors believe that this fourth clinical type could just be a variation of type I.¹

Variations in these clinical patterns can occur depending on the intensity and the extent of the pigmentation. For instance, local pigmentation of extrafacial scars after taking minocycline can occur.²⁰

These 3 (or 4) types also show histopathological differences between them.²¹ In types I and II, brown to black granules are evidenced within macrophages along the vasculature and sweat glands. Type I minocycline-induced hyperpigmentation

stains with Perls' reaction, indicating the presence of hemosiderin, ferritin, or iron. Although melanin is usually absent in type I hyperpigmentation, calcium, sulfur, and chlorine may be present. Type II hyperpigmentation stains with Perls' Prussian blue and with Fontana-Masson, indicating the presence of iron and melanin, the latter being also seen extracellularly in the dermis.^{19,22}

In contrast to the histopathological findings described above, type III shows an increase in melanin within basal keratinocytes and in the superficial dermis.

The fourth type described in the literature shows pigment deposits in macrophages and fibroblasts-like cells, and extracellularly in the dermis.¹⁹ The pigment stains with Masson-Fontana and von Kossa, but is negative with Perls' iron.

The case we present herein does not exactly fit into any of these clinical-pathological types so far described in literature. It is debatable if the silver ingestion which occurred in the past of this patient is responsible for the odd pattern of pigmentation evidenced. In fact, argyria presents as diffuse slate-gray discoloration, which may be increased in sun-exposed areas. The discoloration can be localized or widespread. However, the biopsy we took did not show any deposits compatible with what is traditionally seen in argyria (Table 1). In the latter, multiple brown-black granules are deposited in a linear fashion along the basement membrane of sweat glands.²³ Such granules may also be seen in elastic fibers and surrounding pilosebaceous units. None of these features were evidenced in our biopsy, which was taken from the back. It is also debatable if our patient could have features of both conditions (minocycline-related hyperpigmentation and argyria) manifested in different areas of the mucocutaneous surface. Perhaps then, a biopsy of the mucosae could have demonstrated the silver salts deposits. As commented, argyria commonly involves sun-exposed areas of the head and neck and, therefore, the involvement of sclera, palate, and face seen in this patient could potentially have been due to the silver intake, whereas minocycline would be mainly responsible of the pigmentation in the biopsied zone (the back).

The pigment in our case stains with von Kossa. Some authors have previously demonstrated how calcium was present initially in some cases of minocycline deposit; it disappeared after 43 months.¹⁹ Additionally, von Kossa stain is common in deposits from other tetracyclines, such as doxycycline.²⁴

In conclusion, we present the rare and unusual case of a patient with clinically and histopathologically demonstrated cutaneous hyperpigmentation by minocycline ingestion, with a peculiar clinical and histologic pattern which does not fit the typical types described so far in literature. We also raise the possibility that the history of previous ingestion of colloid silver in this patient might be responsible for the peculiar clinical and histologic presentation.

REFERENCES

1. Geria AN, Tajirian AL, Kihiczak G, et al. Minocycline-induced skin pigmentation: an update. *Acta Dermatovenereol Croat*. 2009;17:123–126.
2. Ochsendorf F. Minocycline in acne vulgaris: benefits and risks. *Am J Clin Dermatol*. 2010;11:327–341.
3. Maffei L, Veraldi S. Minocycline in the treatment of acne: latest findings. *G Ital Dermatol Venereol*. 2010;145:425–429.
4. Ayangco L, Sheridan PJ. Minocycline-induced staining of torus palatinus and alveolar bone. *J Periodontol*. 2003;74:669–671.
5. LaPorta VN, Nikitakis NG, Sindler AJ, et al. Minocycline-associated intra-oral soft-tissue pigmentation: clinicopathologic correlations and review. *J Clin Periodontol*. 2005;32:119–122.
6. Asakura T, Nukaga S, Namkoong H, et al. Blue-black trachea as a result of minocycline-induced hyperpigmentation. *Am J Respir Crit Care Med*. 2016;193:e5–e6.
7. Reese S, Grundfast K. Minocycline-induced hyperpigmentation of tympanic membrane, sclera, teeth, and pinna. *Laryngoscope*. 2015;125:2601–2603.
8. McClain CM, Kantrow SM, Abraham JL, et al. Localized cutaneous argyria: two case reports and clinicopathologic review. *Am J Dermatopathol*. 2013;35:e115–e118.
9. Chang AL, Khosravi V, Egbert B. A case of argyria after colloidal silver ingestion. *J Cutan Pathol*. 2006;33:809–811.
10. Gordon G, Sparano BM, Iatropoulos MJ. Hyperpigmentation of the skin associated with minocycline therapy. *Arch Dermatol*. 1985;121:618–623.
11. Attwood HD. A black thyroid and minocycline therapy. *Med J Aust*. 1983;1:549.
12. Sabroe RA, Archer CB, Harlow D, et al. Minocycline-induced discoloration of the sclerae. *Br J Dermatol*. 1996;135:314–316.
13. Sant'Ambrogio S, Connelly J, DiMaio D. Minocycline pigmentation of heart valves. *Cardiovasc Pathol*. 1999;8:329–332.
14. Dwyer CM, Cuddihy AM, Kerr RE, et al. Skin pigmentation due to minocycline treatment of facial dermatoses. *Br J Dermatol*. 1993;129:158–162.
15. Argyi ZB, Finelli L, Bergfeld WF, et al. Minocycline-related cutaneous hyperpigmentation as demonstrated by light microscopy, electron microscopy and X-ray energy spectroscopy. *J Cutan Pathol*. 1987;14:176–180.
16. Schofield JK, Tatnall FM. Minocycline induced skin pigmentation. *Br J Gen Pract*. 1993;43:173–174.
17. Mehrany K, Kist JM, Ahmed DD, et al. Minocycline-induced cutaneous pigmentation. *Int J Dermatol*. 2003;42:551–552.
18. Eisen D, Hakim MD. Minocycline-induced pigmentation. Incidence, prevention and management. *Drug Saf*. 1998;18:431–440.
19. Mouton RW, Jordaan HF, Schneider JW. A new type of minocycline-induced cutaneous hyperpigmentation. *Clin Exp Dermatol*. 2004;29:8–14.
20. Patterson JW, Wilson B, Wick MR, et al. Hyperpigmented scar due to minocycline therapy. *Cutis*. 2004;74:293–298.
21. Bowen AR, McCalmont TH. The histopathology of subcutaneous minocycline pigmentation. *J Am Acad Dermatol*. 2007;57:836–839.
22. Simons JJ, Morales A. Minocycline and generalized cutaneous pigmentation. *J Am Acad Dermatol*. 1980;3:244–247.
23. Granstein RD, Sober AJ. Drug- and heavy metal-induced hyperpigmentation. *J Am Acad Dermatol*. 1981;5:1–18.
24. Böhm M, Schmidt PF, Lödding B, et al. Cutaneous hyperpigmentation induced by doxycycline: histochemical and ultrastructural examination, laser microprobe mass analysis, and cathodoluminescence. *Am J Dermatopathol*. 2002;24:345–350.