Minocycline-Induced Hyperpigmentation Involving the Oral Mucosa After Short-term Minocycline Use

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Practice Points

- There are 4 types of minocycline-induced hyperpigmentation that vary by clinical presentation, resolution, and light and electron microscopy features.
- Awareness and early detection are important because resolution may occur months to years after termination of treatment.

Minocycline is a semisynthetic broad-spectrum tetracycline used for its bacteriostatic and anti-inflammatory properties in the treatment of moderate to severe acne vulgaris. Minocycline-induced hyperpigmentation (MIH) is a well-recognized phenomenon documented to involve a wide array of anatomic locations including the skin and nails, the sclera and conjunctiva, the oral cavity, and the skeleton and cartilage, as well as within viscera and body fluids. Oral involvement typically includes the hard tissues (eg, alveolar bone, roots, crowns of teeth). We present a case of MIH of the labial, gingival, and lingual oral mucosa after only 2 weeks of treatment. Our case is unique because of the short course of minocycline treatment.

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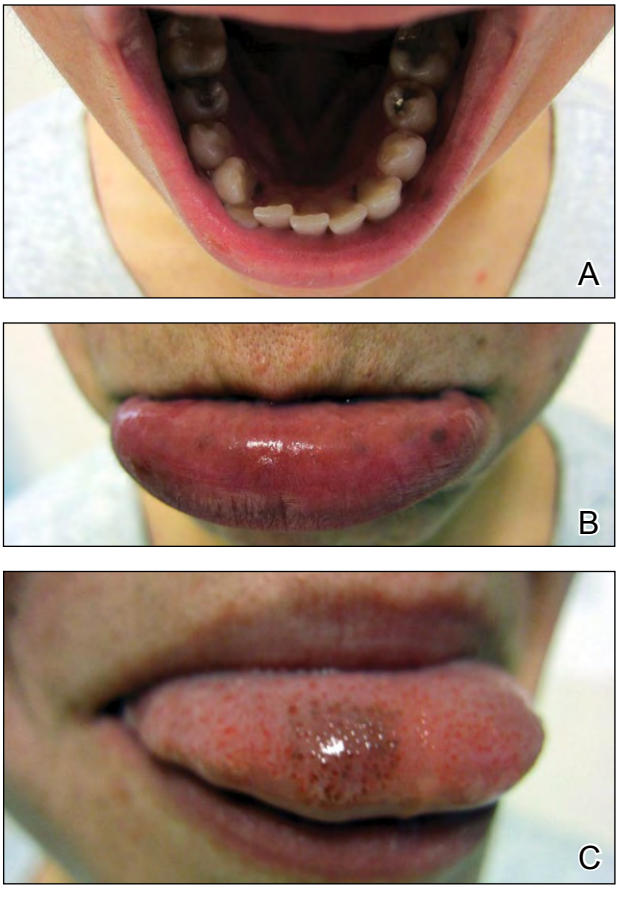
Minocycline-induced hyperpigmentation (MIH) has been documented in a wide array of anatomic locations including the skin and nails, the sclera and conjunctiva, the oral cavity, and the skeleton and cartilage, as well as within viscera and body fluids.[1] We present the case of a patient who developed gingival, labial, lingual, and scar-localized MIH after a 2-week treatment (100 mg orally twice



Minocycline-induced hyperpigmentation of the oral mucosa involving the gingiva (A), lower lip (B), and tongue (C).

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daily). This case is unique for 2 reasons. First, the majority of reports of oral MIH described in the literature involve the hard tissues (eg, alveolar bone, roots, crowns of teeth), and cases that note mucosal involvement often are interpreted as such because of pigmentation of bone seen through translucent overlying mucosa.[2,3] Second, true instances of hyperpigmentation of the oral soft tissues involving the tongue, lips, gingiva, and/or buccal mucosa have been more rarely documented and typically occur after longer durations of treatment and higher cumulative doses than presented here.

Case Report

A 22-year-old woman presented to our dermatology clinic for a 1-month follow-up after starting treatment with spironolactone for moderate inflammatory acne vulgaris of the lower face and jawline. She stopped taking the spironolactone within 1 week of initiation, citing the development of a "small bumpy rash" over the shoulders and face. Prior therapies included over-the-counter topical treatments and tretinoin cream 0.1%. She then was started on oral minocycline (100 mg twice daily). The proper use and risks were discussed with the patient and she was asked to return for follow-up in 3 months. Two weeks later, the patient contacted our clinic to report "dark spots" on the lips, gums, tongue, and existing scars on her bilateral knees. She was advised to stop taking the minocycline and come in for evaluation. On physical examination (Figure), inspection of the oral mucosa revealed hyperpigmented macules on the tip

Minocycline-Induced Hyperpigmentation Patterns

	Pattern Type			
Characteristics	**I**	**II**	**III**	**IV**
Clinical Highlights				
Color	Blue-gray	Blue-gray	Muddy brown	Blue-gray
Skin predilection	Scarred skin	Normal skin	Normal skin (sun exposed)	Scarred skin
Pattern	Circumscribed	Circumscribed	Diffuse	Circumscribed
Localization	Face	Forearms/ lower legs	Accentuated over sun-exposed areas	Back
Dose dependence	−	+	+	−
Resolution with time	+	+	−	−
Light Microscopy				
Pigment location	Dermis (extracellular or within macrophages)	Dermis/ subcutaneous fat (extracellular or with macrophages and myoepithelial cells)	Epidermis/dermis (extracellular or within macrophages and basal keratinocytes)	Dermis (extracellular or within macrophages and fibroblasts)
Histochemistry	Perls Prussian blue stain (iron), +	Perls Prussian blue stain (iron), +; Masson-Fontana ammoniac silver stain (melanin), +	Masson-Fontana ammoniac silver stain (melanin), +	Masson-Fontana ammoniac silver stain (melanin), +; von Kossa stain (calcium), +
Electron Microscopy				
Pigment location	Free within macrophages	Free and membrane bound with macrophages and myoepithelial cells	No information	Free and membrane bound with macrophages and fibroblasts

Abbreviations: −, not present; +, present.

of the tongue, the inside of the gingiva, and on the vermilion border of the lower lip. Inspection of the lower extremities revealed dark brown macules superimposed on existing scars on the bilateral knees. The patient was informed that the hyperpigmentation likely was due to the minocycline and was instead given oral doxycycline (100 mg twice daily). The patient subsequently was lost to follow-up.

Comment

True instances of MIH arising on the oral mucosa are uncommon. Our case is unique because the eruption developed after a short course of treatment. Lingual hyperpigmentation has been described after approximately 5 months of acne treatment with minocycline (approximate total cumulative dose, 19–24.5 g).[4,5] Pure labial and labial-gingival involvement previously have been described after approximately 4 and 6 months of acne treatment with minocycline at approximate total cumulative doses of 13 and 33.6 g, respectively.[3,6] Anecdotally, a 61-year-old woman with rosacea who was being treated with minocycline developed lingual hyperpigmentation after only 4 weeks of treatment (approximate total cumulative dose, 2.8 g).[4] In our case, lingual and labial hyperpigmentation occurred within an even shorter treatment duration of 2 weeks.

Four unique patterns of cutaneous MIH have been proposed and have been shown to vary in their clinical characteristics, light microscopy, immunohistochemistry, and electron microscopy features (Table).[7] Types I, II, and IV share a similar morphology including well-circumscribed, blue-gray macules. Type III typically is associated with a muddy brown color and a diffuse distribution.[7,8] Types I and II are believed to be caused by minocycline-iron chelation products, while types III and IV do not involve iron. Instead, type III MIH is believed to be caused by either minocycline-induced melanization or a minocycline-melanin complex, and type IV is due to either a calcium-minocycline or melanin-minocycline complex.[7,9] In types I and IV, there is a predilection for scarred or inflamed skin, and hyperpigmentation has been less clearly related to a total cumulative dose or duration of treatment but has been reported after only a few weeks. In contrast, for types II and III there is a predilection for normal skin, and incidence has been shown to vary according to total cumulative dose, duration of treatment, and condition being treated.[1,10-12] Complete pigment resolution in types I and II almost invariably occurs several months to years after terminating minocycline treatment. Types III and IV do not appear to resolve with time.[1,7] Although they have not been formally named, other MIH patterns also have been described, including postinflammatory pigment alterations associated with a fixed drug reaction.[6,13]

Our patient ultimately declined a biopsy, making it difficult to state for certain which MIH pattern was involved in our case, as identifying the exact type of dyspigmentation is contingent on biopsy and immunohistochemical analysis; however, our patient's short treatment duration and small cumulative dose tend to suggest a type I or IV pattern. She also displayed scar-localized MIH on the bilateral knees, which also indicates a type I or IV pattern. Because our patient does not fit perfectly within a single pattern, our case represents a mixed-pattern presentation, which is not an uncommon phenomenon.

REFERENCES

1. Eisen D, Hakim MD. Minocycline-induced pigmentation. incidence, prevention and management. *Drug Saf*. 1998;18:431-440.
2. Siller GM, Tod MA, Savage NW. Minocycline-induced oral pigmentation. *J Am Acad Dermatol*. 1994;30 (2, pt 2):350-354.
3. 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.
4. Meyerson MA, Cohen PR, Hymes SR. Lingual hyperpigmentation associated with minocycline therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1995;79:180-184.
5. Tanzi EL, Hecker MS. Minocycline-induced hyperpigmentation of the tongue. *Arch Dermatol*. 2000;136:427-428.
6. Chu P, Van SL, Yen TS, et al. Minocycline hyperpigmentation localized to the lips: an unusual fixed drug reaction? *J Am Acad Dermatol*. 1994;30(5, pt 1):802-803.
7. Mouton RW, Jordaan HF, Schneider JW. A new type of minocycline-induced cutaneous hyperpigmentation. *Clin Exp Dermatol*. 2004;29:8-14.
8. Bowen AR, McCalmont TH. The histopathology of subcutaneous minocycline pigmentation. *J Am Acad Dermatol*. 2007;57:836-839.
9. Simons JJ, Morales A. Minocycline and generalized cutaneous pigmentation. *J Am Acad Dermatol*. 1980;3:244-247.
10. Goulden V, Glass D, Cunliffe WJ. Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol*. 1996;134:693-695.
11. Roberts G, Capell HA. The frequency and distribution of minocycline induced hyperpigmentation in a rheumatoid arthritis population [published online ahead of print June 1, 2006]. *J Rheumatol*. 2006;33:1254-1257.
12. Gordon G, Sparano BM, Iatropoulos MJ. Hyperpigmentation of the skin associated with minocycline therapy. *Arch Dermatol*. 1985;121:618-623.
13. Ridgway HB, Reizner GT. Acquired pseudo-mongolian spot associated with minocycline therapy. *Arch Dermatol*. 1992;128:565-566.