

THE CLINICAL PICTURE

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Minocycline-induced hyperpigmentation



FIGURE 1.

doi:10.3949/ccjm.83a.16058

A 64-YEAR-OLD WOMAN had a remote history of generalized fatigue, tightness of the hands, tingling and numbness of the face, joint stiffness, and bluish discoloration of the fingers that worsened with cold weather. Laboratory testing at that time had revealed an antinuclear antibody titer over 1:320 (reference range < 1:10), anti-Scl-70 antibody 100 U/mL (< 32 U/mL), and thyroid-stimulating hormone 10.78 mIU/L (0.4–5.5). Pulmonary function testing showed a pattern of restrictive lung disease. She was diagnosed with hypothyroidism, Raynaud phenomenon, and scleroderma. She was referred to a rheumatologist, who prescribed levothyroxine and penicillamine.

Despite treatment, she continued to feel fatigued, and she requested the addition of minocycline to the scleroderma treatment after seeing a report on television. Minocycline 100 mg twice daily was prescribed. She reported improvement of her symptoms for the next 2 years but was then lost to follow-up with the rheumatologist. She continued to take penicillamine and minocycline as prescribed by her primary care physician.

She presented to our clinic with bluish discoloration (**Figure 1**) that had started 1 year before as a small area but had spread to involve the entire face, fingers, gums, teeth, and sclera, and included a dark discoloration of the neck and upper chest. She had been taking minocycline for nearly 9 years. We referred her to a dermatologist, who diagnosed minocycline-induced hyperpigmentation. Her minocycline was stopped. Skin biopsy was not done, as the dermatologist was confident making the diagnosis without biopsy. At 1 year later, she continued to have the widespread skin pigmentation with no improvement at all.

DIFFERENTIAL DIAGNOSIS

Hyperpigmentation is the darkening in the natural color of the skin, usually from increased deposition of melanin in the epidermis or dermis, or both. It can occur in different degrees of blue, brown, and black (from lightest to darkest). Less frequently, it may be caused by the deposition in the dermis of an endogenous or exogenous pigment, such as hemosiderin, iron, or heavy metal.¹ The hyperpigmentation can be circumscribed or more diffuse.

The differential diagnosis of diffuse skin pigmentation includes Addison disease, hyperthyroidism, hemochromatosis, erythema dyschromicum perstans, cutaneous malignancies, sunburn, and drug-induced hyperpigmentation.^{1,2} Medications commonly cited as causing hyperpigmentation include minocycline, amiodarone, bleomycin, prostaglandins, oral contraceptives, phenothiazine, and antimalarial drugs.^{1,3} In Addison disease, the pigmentation is typically diffuse, with accentuation in sun-exposed areas, flexures, palmar and plantar creases, and areas of pressure or friction.² The bronze discoloration of hemochromatosis is from a combination of hemosiderin deposition and increased melanin production.¹ Erythema dyschromicum perstans presents with brownish oval-shaped macules and patches. Early lesions may have thin, raised, erythematous borders that typically involve the trunk, but they may spread to the neck, upper extremities, and face.⁴

The role of minocycline in the treatment of scleroderma is controversial. Early reports

involving a small number of patients showed a benefit of minocycline in decreasing symptoms,^{5,6} but these findings were not achieved in a larger multicenter trial.⁷

Types of minocycline-induced hyperpigmentation

Three types of minocycline-induced hyperpigmentation occur^{3,8}:

- Type 1—blue-grey coloration on the face in areas of inflammation
- Type 2—blue-grey coloration on normal skin on the skin of the shins and forearms
- Type 3—the least common, characterized by diffuse muddy brown or blue-grey discoloration in sun-exposed areas, as in our patient.

The prevalence of minocycline-induced hyperpigmentation varies between 2.4% and 41% and is highest in patients with rheumatoid arthritis.^{3,9} Type 1 pigmentation is not correlated with treatment duration or cumulative dose, while type 2 and 3 are associated with long-term therapy.⁸ In type 3, changes are nonspecific, consisting of increased melanin in basal keratinocytes and melanin-only staining dermal melanophages. Types 1 and 2 may resolve slowly, whereas type 3 can persist indefinitely.^{3,8,10}

TREATMENT

Treatment involves early recognition, discontinuation of the drug, and avoidance of sun exposure. Treatment with pigment-specific lasers has shown promise.^{8,10}

Type 3 minocycline-induced hyperpigmentation is diffuse, affects sun-exposed areas, and can persist indefinitely

REFERENCES

1. **Stulberg DL, Clark N, Tovey D.** Common hyperpigmentation disorders in adults: Part I. Diagnostic approach, café au lait macules, diffuse hyperpigmentation, sun exposure, and phototoxic reactions. *Am Fam Physician* 2003; 68:1955–1960.
2. **Thiboutot DM.** Clinical review 74: dermatological manifestations of endocrine disorders. *J Clin Endocrinol Metab* 1995; 80:3082–3087.
3. **Geria AN, Tajirian AL, Kihiczak G, Schwartz RA.** Minocycline-induced skin pigmentation: an update. *Acta Dermatovenerol Croat* 2009; 17:123–126.
4. **Schwartz RA.** Erythema dyschromicum perstans: the continuing enigma of Cinderella or ashy dermatosis. *Int J Dermatol* 2004; 43:230–232.
5. **Le CH, Morales A, Trentham DE.** Minocycline in early diffuse scleroderma. *Lancet* 1998; 352:1755–1756.
6. **Robertson LP, Marshall RW, Hickling P.** Treatment of cutaneous calcinosis in limited systemic sclerosis with minocycline. *Ann Rheum Dis* 2003; 62:267–269.

7. **Mayes MD, O'Donnell D, Rothfield NF, Csuka ME.** Minocycline is not effective in systemic sclerosis: results of an open-label multicenter trial. *Arthritis Rheum* 2004; 50:553–557.
8. **James WD, Berger TG, Elston DM.** *Andrews' Diseases of the Skin: Clinical Dermatology*. 11th ed. London, UK: Saunders/Elsevier; 2011:125–126.
9. **Roberts G, Capell HA.** The frequency and distribution of minocycline induced hyperpigmentation in a rheumatoid arthritis population. *J Rheumatol* 2006; 33:1254–1257.
10. **Vangipuram RK, DeLozier WL, Geddes E, Friedman PM.** Complete resolution of minocycline pigmentation following a single treatment with non-ablative 1550-nm fractional resurfacing in combination with the 755-nm Q-switched alexandrite laser. *Lasers Surg Med* 2016; 48:234–237.

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