

## Blue Legs in a 60-Year-Old Gentleman

### Case Report

A 60-year-old bread seller with a background history of diabetes mellitus, hypertension and a previous unidentified abdominal surgery (which may have been an abscess) was seen by the orthopaedic team for chronic right big toe ulceration. A wedge biopsy of the ulcer was done and showed acute-on-chronic inflammation with fungal organisms. However, the orthopaedic team noted an incidental finding of hyperpigmentation over his lower limbs and referred him to dermatology.

The patient noted a pruritic dark discolouration over his feet for the past 6 years and also had hyperpigmentation over his face. He denied applying anything on his skin. On examination of his lower limbs, he had dark bluish hyperpigmented patches on his legs and feet (Fig. 1). There was a similar but milder hyperpigmentation over his right and left periauricular regions and nails (Fig. 2).



Fig. 1. Bluish-grey hyperpigmentation over the legs and feet.

What is your diagnosis?

- A. Postinflammatory hyperpigmentation
- B. Drug-induced hyperpigmentation
- C. Alkaptonuria
- D. Haemochromatosis
- E. Addison's disease

A skin biopsy was done. Histopathological examination noted hyperkeratosis with dense infiltrates of predominantly lymphocytes and plasma cells in the upper dermis and periadnexal areas. There were collections of melanophages in the upper dermis, containing coarse granules of melanin (Fontana stain positive) admixed with iron (Perl's stain positive), associated with an interrupted band-like infiltrate of lymphocytes and plasma cells (Fig. 3). Eosinophilia was not a feature, distinguishing this from a drug-induced inflammatory reaction. There was no degeneration of the epidermis. The melanophages were CD68 positive, indicating their macrophage nature. They were negative for HMB45, indicating that they were not melanocytes. The overall impression was a lichenoid inflammatory reaction with postinflammatory hyperpigmentation.



Fig. 2. Involvement of the finger nails.

Answer: B

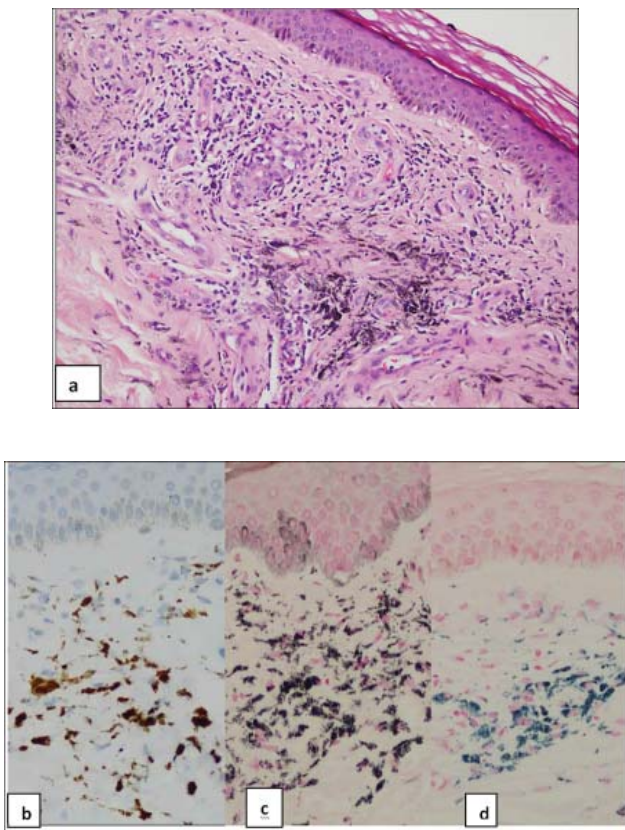


Fig. 3. Photomicrographs showing (a) hyperkeratosis of the epidermis and dense collections of melanophages in the upper dermis, containing coarse granules of dark pigment associated with infiltrates of lymphocytes and plasma cells. H&E x 200; (b) The melanophages are immunopositive for CD68. IHC CD68 x 400. (c) Pigment in melanophages and basal layer of epidermis stain positive for melanin. Masson Fontana x 200; (d) Some pigment are positive for iron (blue). Perl's stain x 200.

On further history taking, the patient had been consuming ampicillin/sulbactam for the past 1 year and minocycline for the past 30 years. He was unsure of the reason why he had been originally prescribed the antibiotics, merely stating that the pills were used for an “infection”. His doctor had prescribed him with minocycline 30 years ago and since then, he had continued buying minocycline over-the-counter from the pharmacy on his own.

## Discussion

Minocycline is a semi-synthetic second generation tetracycline which binds to the 30S ribosomal subunit, blocking transfer RNA binding to the messenger RNA-ribosome complex and thus inhibiting bacterial protein synthesis. Minocycline-induced hyperpigmentation is a well known disfiguring side effect with prolonged usage of the antibiotic which may occur in up to 36% of patients.<sup>1</sup> Here, we present the case of an elderly gentleman who presented

with bluish hyperpigmentation over his legs, nails and face after use of minocycline for 30 years.

There are 3 recognised types of minocycline-induced hyperpigmentation. Type I minocycline-induced hyperpigmentation presents with blue-black or grey pigment on areas of scarring or acne-related inflammation on the face which stain iron and melanin extracellularly and within dermal macrophages. Type III presents with persistent diffuse muddy-brown discolouration in areas of sun exposure and there is non-specific increased melanin in basal keratinocytes and dermal macrophages staining for melanin. Mouton et al proposed a fourth type with circumscribed blue-grey pigmentation on the thorax within scar tissue which remained unchanged after 43 months of follow-up. This type was previously thought to be a variant of Type I. Histopathologically, pigment is present within dendritic cells and extracellularly throughout the dermis.<sup>2</sup>

Hyperpigmentation may also affect the nails, lips, oral mucosa, gingivae, teeth, bones, costal cartilage, postacne osteoma cutis, substantia nigra, atherosclerotic plaques, conjunctival cysts, sclera and breast milk.<sup>2</sup> In this case, the patient's clinical presentation is suggestive of type II minocycline hyperpigmentation which presents with blue-grey pigment on normal skin of shins and forearms, and which can also affect other sites besides the legs, namely the face and nails. The aetiology of minocycline-induced hyperpigmentation is postulated to be related to polymerised reactive metabolites, insoluble chelation products and lengthy treatment durations.<sup>2</sup>

The patient was advised to cease minocycline therapy. Topical clobetasone butyrate 0.05% and oral antihistamines were prescribed in view of the pruritus. On follow-up a year later, the hyperpigmentation had improved markedly upon discontinuing minocycline as advised with fading of the bluish discolouration over the legs and near-resolution over the upper shins and forefeet.

Besides that, sun protection should be advised. Q-switched laser therapy has been used to treat minocycline-induced hyperpigmentation, with the Alexandrite 755 nm more effective than the Nd:YAG infrared 1064 nm and the Ruby 694 nm.<sup>3</sup> Type I and II minocycline-induced hyperpigmentation was found to have better response to laser therapy compared to type III.<sup>3</sup>

In this patient's case, he had continued buying minocycline from the pharmacy. He was unsure regarding the reason the medication was initially prescribed and was unsure whether he should continue taking the medication. As such, it is important for prescribers to educate the patients regarding the indications and the duration of treatment for medications prescribed in order to prevent adverse effects and complications from misuse of medications. Patients should also be advised to follow up with their doctors

instead of self-medicating.

## Conclusion

Minocycline-induced hyperpigmentation is an important adverse effect to consider while choosing antibiotic therapy in clinical practice. Prolonged minocycline use can be a cause of blue-grey pigmentation over the lower limbs, and may also affect the face, teeth, nails and sclera. Patients should be advised to cease the drug, use sun protection and Q-switched laser therapy, in particular with the Alexandrite 755 nm, may be offered. Prescribers should educate and counsel patients regarding the indications and duration of medications so that patients will use their medications as prescribed.

## REFERENCES

1. Fay BT, Whiddon AP, Puumala S, Black NA, O'Dell JR, Mikuls TR. Minocycline-induced hyperpigmentation in rheumatoid arthritis. *J Clin Rheumatol* 2008;14:17-20.
2. Mouton RW, Jordaan HF, Schneider JW. A new type of minocycline-induced cutaneous hyperpigmentation. *Clin Exp Dermatol* 2004;29:8-14.
3. Nisar MS, Iyer K, Brodell RT, Lloyd JR, Shin TM, Ahmad A. Minocycline-induced hyperpigmentation: comparison of 3 Q-switched lasers to reverse its effects. *Clin Cosmet Investig Dermatol* 2013;31:159-62.

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