Blue-black hyperpigmentation on the extremities

In some cases, diagnosis entails less "what is it?" and more "what caused it?"

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A 68-YEAR-OLD MAN with type 2 diabetes presented with progressive hyperpigmentation of the lower extremities and face over the past 3 years. Clinical examination revealed confluent, blue-black hyperpigmentation of the lower extremities (**FIGURE**), upper extremities, neck, and face. Laboratory tests and arterial studies were within normal ranges. The patient's medication list included lisinopril 10 mg/d, metformin 1000 mg twice daily, minocycline 100 mg twice daily, and omeprazole 20 mg/d.

- WHAT IS YOUR DIAGNOSIS?
- HOW WOULD YOU TREAT THIS PATIENT?

FIGURE
Confluent blue-black hyperpigmentation of the legs

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Diagnosis: Minocycline-induced hyperpigmentation

Hyperpigmentation is a rare but not uncommon adverse effect of long-term minocycline use. In this case, our patient had been taking minocycline for more than 5 years. When seen in our clinic, he said he could not remember *why* he was taking minocycline and incorrectly assumed it was for his diabetes. Chart review of outside records revealed that it had been prescribed, and refilled annually, by his primary physician for rosacea.

Minocycline hyperpigmentation is subdivided into 3 types:

- Type I manifests with blue-black discoloration in previously inflamed areas of skin.
- Type II manifests with blue-gray pigmentation in previously normal skin areas.
- Type III manifests diffusely with muddy-brown hyperpigmentation on photoexposed skin.

Furthermore, noncutaneous manifestations may occur on the sclera, nails, ear cartilage, bone, oral mucosa, teeth, and thyroid gland.[1]

This case underscores the importance of routinely reassessing patients' understanding of their medications and treatment plans.

Diagnosis focuses on identifying the source

Minocycline is one of many drugs that can induce hyperpigmentation of the skin. In addition to history, examination, and review of the patient's medication list, there are some clues on exam that may suggest a certain type of medication at play.

Antimalarials. Chloroquine, hydroxychloroquine, and quinacrine can cause blue-black skin hyperpigmentation in as many as 25% of patients. Common locations include the shins, face, oral mucosa, and subungual skin. This hyperpigmentation rarely fully resolves.[2]

Amiodarone. Hyperpigmentation secondary to amiodarone use typically is slate-gray in color and involves photoexposed skin. Patients should be counseled that pigmentation may—but does not always—fade with time after discontinuation of the drug.[2]

Heavy metals. Argyria results from exposure to silver, either ingested orally or applied externally. A common cause of argyria is ingestion of excessive amounts of silver-containing supplements.[3] Affected patients present with diffuse slate-gray discoloration of the skin.

Other metals implicated in skin hyperpigmentation include arsenic, gold, mercury, and iron. Review of all supplements and herbal remedies in patients presenting with skin hyperpigmentation is crucial.

Bleomycin is a chemotherapeutic agent with a rare but unique adverse effect of inducing flagellate hyperpigmentation that favors the chest, abdomen, or back. This may be induced by trauma or scratching and is often transient. Hyperpigmentation can occur secondary to either intravenous or intralesional injection of the medication.[2]

In addition to medication- or supplement-induced hyperpigmentation, there is a physiologic source that should be considered when a patient presents with lower-extremity hyperpigmentation:

Stasis hyperpigmentation. Patients with chronic venous insufficiency may present with hyperpigmentation of the lower extremities. Commonly due to dysfunctional venous valves or obstruction, stasis hyperpigmentation manifests with red-brown discoloration from dermal hemosiderin deposition.[4]

Unlike our patient, those with stasis hyperpigmentation may present symptomatically, with associated dry skin, pruritus, induration, and inflammation. Treatment involves management of the underlying venous insufficiency.[4]

When there's no obvious cause, be prepared to dig deeper

At the time of initial assessment, a thorough review of systems and detailed medication history, including over-the-counter supplements, should be obtained. Physical examination revealing diffuse, generalized hyperpigmentation with no reliable culprit medication in the patient's history warrants further laboratory evaluation. This includes ordering renal and liver studies and tests for thyroid-stimulating hormone and ferritin and cortisol levels to rule out metabolic or endocrine hyperpigmentation disorders.

Stopping the offending medication is the first step

Discontinuation of the offending medication

may result in mild improvement in skin hyperpigmentation over time. Some patients may not experience any improvement. If improvement occurs, it is important to educate patients that it can take several months to years. Dermatology guidelines favor discontinuation of antibiotics for acne or rosacea after 3 to 6 months to avoid bacterial resistance.[5] Worsening hyperpigmentation despite medication discontinuation warrants further work-up.

Patients who are distressed by persistent hyperpigmentation can be treated using picosecond or Q-switched lasers.[6]

Our patient was advised to discontinue the minocycline. Three test spots on his face were treated with pulsed-dye laser, carbon dioxide laser, and dermabrasion. The patient noted that the spots responded better to the carbon dioxide laser and dermabrasion compared to the pulsed-dye laser. He did not follow up for further treatment. JFP

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