ONLINE EXCLUSIVE

Hyperpigmentation of the legs

Was a drug or a comorbidity to blame for this patient's hyperpigmentation?

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A 90-YEAR-OLD MAN was admitted from the Emergency Department (ED) to our inpatient service for difficulty urinating and hematuria. In the ED, a complete blood count (CBC) with differential and a urinalysis were performed. CBC showed a mild normocytic anemia, consistent with the patient's known chronic kidney disease. The urinalysis revealed moderate blood, trace ketones, proteinuria, small leukocyte esterases, positive nitrites, and more than 182 red blood cells—findings suspicious for a urinary tract infection. Computed tomography of the abdomen and pelvis was notable for a soft-tissue mass in the bladder.

He had a history of coronary artery disease (treated with stent placement), atrial fibrillation, congestive heart failure, hypothyroidism, gastroesophageal reflux disease, gastrointestinal bleeding, chronic obstructive pulmonary disease, a 60-pack-per-year history of tobacco dependence, chronic kidney disease, prostate cancer, benign prostatic hypertrophy, peripheral vascular disease, and gout. Medications included digoxin, metoprolol, torsemide, aspirin, levothyroxine, fluticasone, albuterol, omeprazole, diclofenac, escitalopram, and minocycline.

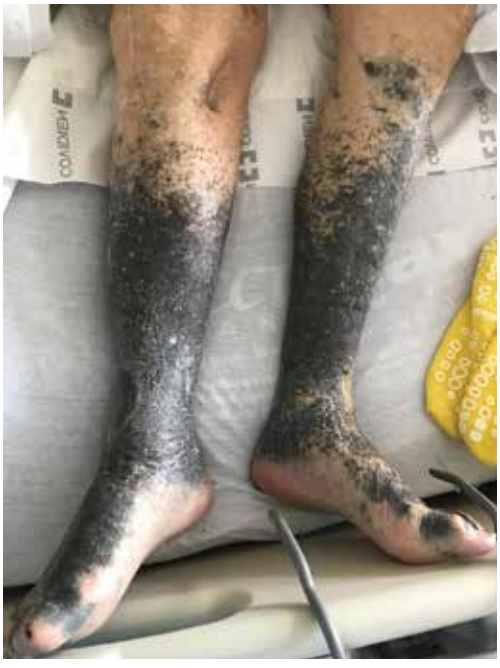
About 5 years earlier, doctors had discovered a popliteal thrombosis that required emergent thrombectomy of the infragenicular popliteal artery, thromboembolectomy of the right posterior tibial artery, graft angioplasty of the right posterior tibial artery, and right anterior fasciotomy for compartment syndrome.

Ten months later, an abscess formed at the incision site. His physician irrigated the popliteal wound and prescribed intravenous (IV) vancomycin. However, the patient developed an allergy and IV daptomycin was initiated and followed by chronic antibiotic suppression with oral minocycline 100 mg bid for about 3.5 years. Skin discoloration appeared within a year of starting the minocycline.

During his hospitalization on our service, we noted black pigmentation of both legs (**FIGURE**). He had intact strength and sensation in his legs, 1+ pitting edema, no pain upon palpation, and 2+ distal pulses. The patient was well appearing and in no acute distress.

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

FIGURE
Black pigmentation of the shins



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Monitor patients taking minocycline for early signs of pigmentation.

Diagnosis: Minocycline-induced hyperpigmentation

The patient's clinical presentation of chronic blue-black hyperpigmentation on the anterior shins of both legs after a prolonged antibiotic course led us to conclude that this was an adverse effect of minocycline. Commonly, doctors use minocycline to treat acne, rosacea, and rheumatoid arthritis. In this case, it was used to provide chronic antimicrobial suppression.

Not an uncommon reaction for a patient like ours. One small study conducted in an orthopedic patient population found that 54% of patients receiving long-term minocycline suppression developed hyperpigmentation after a mean follow-up of nearly 5 years.[1] The hyperpigmentation is solely cosmetic and without known clinical complications, but it can be distressing for patients.

There are 3 types of minocycline-induced hyperpigmentation:

- Type I is a circumscribed blue-black pigmentation that manifests in skin that previously was inflamed or scarred, such as facial acne scars.[2] Histopathologic findings include black pigment granules in macrophages and throughout the dermis that stain with Perls Prussian blue iron.[3]
- Type II (which our patient had) is circumscribed blue-black pigmentation that appears in previously normal skin of the forearms or lower legs—especially the shins.[3] On histopathology, black pigment granules are found in the dermis with macrophages that stain with Perls Prussian blue iron and Fontana-Masson.[3]
- Type III is a diffuse muddy brown hyperpigmentation in previously normal, sun-exposed skin.[2] Histopathologic findings include increased melanin in basal keratinocytes and dermal melanophages that stain with Fontana-Masson.[3]

Types II and III may be related to cumulative dosing, whereas type I can occur at any point during treatment.[2]

Differential includes pigmentation disorders

The differential diagnosis includes Addison disease, argyria, hemochromatosis, and polycythemia vera, which all can cause diffuse blue-gray patches.[4] Brown-violet pigmentation on sun-exposed areas, redness, and itching are more typical of Riehl melanosis.[4]

Diltiazem can produce slate-gray to blue-gray reticulated hyperpigmentation.[5] Other drugs that can induce slate-gray macules or patches include amiodarone, chlorpromazine, imipramine, and desipramine.[5]

Treatment is simple, resolution takes time

The treatment for this condition is cessation of minocycline use. Pigmentation fades slowly and may persist for years. There has been successful treatment of type I and III minocycline-induced hyperpigmentation with the alexandrite 755 nm Q-switched laser combined with fractional photothermolysis.[3,6] Unfortunately, insurance coverage is limited because these treatments are cosmetic in nature.

Given that hyperpigmentation is a known adverse effect of minocycline use, it's important to counsel patients about the possibility prior to initiating treatment. It's also important to monitor for signs of changing pigmentation to prevent psychological distress.

In this case, a biopsy was deemed unnecessary, as the antibiotic was the most likely cause of the pigmentation. The patient's outpatient dermatologist recommended changing therapy if a medically appropriate alternative was available. Doxycycline would have been a reasonable alternative; however, the patient died shortly after his presentation to our hospital due to his multiple comorbidities. JFP

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