

# Chronic Hyperpigmented Patches on the Legs

Tesia C. Kolodziejczyk, DO; Lisa F. Fronek, DO; David Esguerra, DO



A 37-year-old man with a history of cerebral palsy, bipolar disorder, and impulse control disorder presented to the emergency department with breathing difficulty and worsening malaise. The patient subsequently was intubated due to hypoxic respiratory failure and was found to be positive for SARS-CoV-2. He was admitted to the intensive care unit, and dermatology was consulted due to concern that the cutaneous findings were demonstrative of a vasculitic process. Physical examination revealed diffuse, symmetric, dark brown to blue-gray macules coalescing into patches on the anterior tibia (top) and covering the entire lower leg (bottom). The patches were mottled and did not blanch with pressure. According to the patient's caretaker, the leg hyperpigmentation had been present for 2 years.

## WHAT'S YOUR DIAGNOSIS?

- Addison disease
- confluent and reticulated papillomatosis
- drug-induced hyperpigmentation
- erythema dyschromicum perstans
- pretibial myxedema

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Dr. Kolodziejczyk is from Rocky Vista University College of Osteopathic Medicine, Parker, Colorado. Drs. Fronek and Esguerra are from the Department of Dermatology, HCA Healthcare/USF Morsani College of Medicine, Largo Medical Center Program, Florida.

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Correspondence: Lisa F. Fronek, DO (lisa.fronek@hcahealthcare.com).

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## THE DIAGNOSIS: Drug-Induced Hyperpigmentation

**A**dditional history provided by the patient's caretaker elucidated an extensive list of medications including chlorpromazine and minocycline, among several others. The caretaker revealed that the patient began treatment for acne vulgaris 2 years prior; despite the acne resolving, therapy was not discontinued. The blue-gray and brown pigmentation on our patient's shins likely was attributed to a medication he was taking.

Both chlorpromazine and minocycline, among many other medications, are known to cause abnormal pigmentation of the skin.<sup>1</sup> Minocycline is a tetracycline antibiotic prescribed for acne and other inflammatory cutaneous conditions. It is highly lipophilic, allowing it to reach high drug concentrations in the skin and nail unit.<sup>2</sup> Patients taking minocycline long term and at high doses are at greatest risk for pigment deposition.<sup>3,4</sup>

Minocycline-induced hyperpigmentation is classified into 3 types. Type I describes blue-black deposition of pigment in acne scars and areas of inflammation, typically on facial skin.<sup>1,5</sup> Histologically, type I stains positive for Perls Prussian blue, indicating an increased deposition of iron as hemosiderin,<sup>1</sup> which likely occurs because minocycline is thought to play a role in defective clearance of hemosiderin from the dermis of injured tissue.<sup>5</sup> Type II hyperpigmentation presents as blue-gray pigment on the lower legs and occasionally the arms.<sup>6,7</sup> Type II stains positive for both Perls Prussian blue and Fontana-Masson, demonstrating hemosiderin and melanin, respectively.<sup>6</sup> The third form of hyperpigmentation results in diffuse, dark brown to gray pigmentation with a predilection for sun-exposed areas.<sup>8</sup> Histology of type III shows increased pigment in the basal portion of the epidermis and brown-black pigment in macrophages of the dermis. Type III stains positive for Fontana-Masson and negative for Perls Prussian blue. The etiology of hyperpigmentation has been suspected to be caused by minocycline stimulating melanin production and/or deposition of minocycline-melanin complexes in dermal macrophages after a certain drug level; this largely is seen in patients receiving 100 to 200 mg daily as early as 1 year into treatment.<sup>8</sup>

Chlorpromazine is a typical antipsychotic that causes abnormal skin pigmentation in sun-exposed areas due to increased melanogenesis.<sup>9</sup> Similar to type III minocycline-induced hyperpigmentation, a histologic specimen may stain positive for Fontana-Masson yet negative for Perls Prussian blue. Lal et al<sup>10</sup> demonstrated complete resolution of abnormal skin pigmentation within 5 years after stopping chlorpromazine. In contrast, minocycline-induced hyperpigmentation may be permanent in some cases. There is substantial clinical and histologic overlap

for drug-induced hyperpigmentation etiologies; it would behoove the clinician to focus on the most common locations affected and the generalized coloration.

Treatment of minocycline-induced hyperpigmentation includes the use of Q-switched lasers, specifically Q-switched ruby and Q-switched alexandrite.<sup>11</sup> The use of the Q-switched Nd:YAG laser appears to be ineffective at clearing minocycline-induced pigmentation.<sup>7,11</sup> In our patient, minocycline was discontinued immediately. Due to the patient's critical condition, he deferred all other therapy.

Erythema dyschromicum perstans, also referred to as ashy dermatosis, is an idiopathic form of hyperpigmentation.<sup>12</sup> Lesions start as blue-gray to ashy gray macules, occasionally surrounded by a slightly erythematous, raised border. Erythema dyschromicum perstans typically presents on the trunk, face, and arms of patients with Fitzpatrick skin types III and IV; it is considered a variant of lichen planus actinicus.<sup>12</sup> Histologically, erythema dyschromicum perstans may mimic lichen planus pigmentosus (LPP); however, subtle differences exist to distinguish the 2 conditions. Erythema dyschromicum perstans demonstrates a mild lichenoid infiltrate, focal basal vacuolization at the dermoepidermal junction, and melanophage deposition.<sup>13</sup> In contrast, LPP demonstrates pigmentary incontinence and a more severe inflammatory infiltrate. A perifollicular infiltrate and fibrosis also can be seen in LPP, which may explain the frontal fibrosing alopecia that often precedes LPP.<sup>13</sup>

Addison disease, also known as primary adrenal insufficiency, can cause diffuse hyperpigmentation in the skin, mucosae, and nail beds. The pigmentation is prominent in regions of naturally increased pigmentation, such as the flexural surfaces and intertriginous areas.<sup>14</sup> Patients with adrenal insufficiency will have accompanying weight loss, hypotension, and fatigue, among other symptoms related to deficiency of cortisol and aldosterone. Skin biopsy shows acanthosis, hyperkeratosis, focal parakeratosis, spongiosis, superficial perivascular lymphocytic infiltrate, basal melanin deposition, and superficial dermal macrophages.<sup>15</sup>

Confluent and reticulated papillomatosis is an uncommon dermatosis that presents with multiple hyperpigmented macules and papules that coalesce to form patches and plaques centrally with reticulation in the periphery.<sup>16</sup> Confluent and reticulated papillomatosis commonly presents on the upper trunk, axillae, and neck, though involvement can include flexural surfaces as well as the lower trunk and legs.<sup>16,17</sup> Biopsy demonstrates undulating hyperkeratosis, papillomatosis, acanthosis, and negative fungal staining.<sup>16</sup>

Pretibial myxedema most commonly is associated with Graves disease and presents as well-defined thickening and induration with overlying pink or purple-brown papules in the pretibial region.<sup>18</sup> An acral surface and mucin deposition within the entire dermis may be appreciated on histology with staining for colloidal iron or Alcian blue.

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