confined to scars or sites with previous inflammation or trauma. In type 2, blue-gray pigmentation occurs within previously normal-appearing skin, especially in the lower legs and forearms. Type 3 is characterized by the presence of diffuse brownish discoloration of sun-exposed areas. Histopathologically, types 1 and 2 demonstrate pigment granules in the dermis, concentrated around vasculature within macrophages, and, in type 2, around myoepithelial cells as well. Perls staining is positive in type 1. In type 2, both Perls and Masson-Fontana stainings are positive. In type 3, there is increased melanin in basal keratinocytes with subjacent dermal melanophages without the presence of iron. Only Masson-Fontana staining is positive in this type.

Ultrastructural observations have confirmed that the clinical coloration is a result of a minocycline derivative chelated with iron that is stored within the lysosomes of macrophages. To our knowledge, there are no reports of cutaneous pigmentation due to rifampicin. Our patient’s symptoms and the histologic findings were similar to those described for minocycline pigmentation type 2 and previous cases associated with levofloxacin and pefloxacin.

The course of the pigmentation is unknown, but it tends to fade if levofloxacin treatment is discontinued. Months or years are necessary to achieve resolution, although in some cases the pigmentation can be permanent. Treatment with Q-switched laser has been reported with successful results.

Mónica Lorente, MD
Adrián Ballano, MD
Adriana Juanes, MD
Maria Antonia Pastor, MD
Jesús Cuevas, MD

Author Affiliations: Department of Dermatology, Hospital Universitario de Guadalajara, Spain (Lorente, Ballano, Juanes, Pastor); Department of Pathology, Hospital Universitario de Guadalajara, Spain (Cuevas).

Corresponding Author: Mónica Lorente, MD, Donantes de Sangre s/n, E-19002 Guadalajara, Spain (m.lorente.luna@gmail.com; mlorentel@sescam.jccm.es).


Conflict of Interest Disclosures: None reported.

Additional Contributions: Special thanks to Miguel Angel Martínez, MD, Hospital 12 de Octubre, Madrid, for ultrastructural study.


Eltrombopag-Associated Hyperpigmentation

We report 2 cases of cutaneous hyperpigmentation with eltrombopag, a novel thrombopoietin receptor agonist.

Report of Cases | Case 1. A 69-year-old white woman with refractory acute myelogenous leukemia (AML) was referred to dermatology for skin graying. Treatment with eltrombopag, 300 mg/d, was initiated in a clinical trial. After 3 months, the patient’s husband and clinical team noted gray hyperpigmentation predominantly affecting the face (Figure 1A). She had re-
ceived cytarabine and daunorubicin 10 weeks prior to eltrombopag and sirolimus and mitoxantrone 5 weeks prior to eltrombopag. The hands, nails, sclera, and mucosa were uninvolved. Histopathologic examination of preauricular skin demonstrated mild inflammation and focal dermal pigment that stained positive with Fontana-Masson and weakly positive with Prussian blue (Figure 1B-D). The pigmentation remained stable over the subsequent 8 months during eltrombopag treatment.

Case 2. A 66-year-old woman of mixed white, African, and Native American descent with refractory AML developed darkening of her skin during treatment with eltrombopag. She had received cytarabine and daunorubicin 3 months prior to initiating a clinical trial with eltrombopag. Two months after starting eltrombopag therapy, the dermatology consult team was called to evaluate subcutaneous nodules clinically suggestive of Sweet syndrome. At that time she was noted to have a diffuse dusky complexion involving her face, arms, and legs. A biopsy of a subcutaneous nodule on her leg was performed. In addition to deep neutrophilic inflammation, there was prominent pigment deposition in the mid to deep dermis staining positive with both Fontana-Masson and Prussian blue stains (Figure 2). The pigmentation remained stable 3 months into eltrombopag therapy. The patient, her husband, and the oncology team believed that she was notably darker than before beginning eltrombopag treatment, and on comparison with a family photograph, the patient’s skin was believed to be darker than baseline by the dermatology team.

Discussion | Ertrombopag is a novel, nonpeptide thrombopoietin receptor agonist approved for treatment of chronic idiopathic thrombocytopenic purpura (ITP). It has also recently been approved for the treatment of hepatitis C associated thrombocytopenia and is currently being used in clinical trials for AML and myelodysplastic syndromes. Reported cutaneous adverse effects have been minimal. Pruritic exanthema have been reported in 3 patients taking eltrombopag, 25 to 50 mg/d, for ITP. In vitro studies suggest a theoretical phototoxic effect
of eltrombopag; however, a clinical study of eltrombopag, 300 mg/d (75 mg 4 times daily) for 6 days, failed to show increased photosensitivity.4 To our knowledge, this is the first report of cutaneous hyperpigmentation associated with eltrombopag.

Numerous medications are associated with drug-induced hyperpigmentation, including minocycline, amiodarone, and chemotherapeutic agents including novel targeted therapies.5,6 The pathogenesis behind medication-associated hyperpigmentation remains unclear. Some attribute increased melanin deposition (measured by Fontana-Masson staining) to increased melanin production stimulated directly by the medication or indirectly by inflammation related to the medication. Likewise, hemosiderin deposition (seen with Prussian blue staining) is postulated to arise from red blood cell leakage (1) from direct vessel damage caused by the drug, (2) secondary to inflammation related to the drug or (3) due to deposition of specific pigments related to the drug.6

Although some of the other chemotherapeutic agents used previously in the patients have been associated with hyperpigmentation, the onset of the clinical graying in our patients occurred more than 10 weeks after discontinuing treatment with those agents. Additionally, the lack of inflammation or erythema in the skin, along with the presence of both hemosiderin and Fontana-Masson-positive material, supports a drug-associated hyperpigmentation rather than postinflammatory hyperpigmentation. The hyperpigmentation in case 1 appeared photodistributed, which, along with the superficial pigmentary deposits, may implicate phototoxic effects in the pathogenesis.

We describe the novel finding of cutaneous hyperpigmentation associated with eltrombopag and the associated pathologic findings. Further investigation is needed to better characterize this phenomenon.

Inbal Braunstein, MD
Karolyn A. Wanat, MD
Rosalie Elenitsas, MD
XiaoWei Xu, MD, PhD
Noelle Frey, MD
Misha Rosenbach, MD

Author Affiliations: Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Braunstein, Wanat, Elenitsas, Xu,
Becker Nevus of the Leg With Lipoatrophy

Becker nevus presents most commonly as a patchy hyperpigmentation with dark hairs on the upper arms or the shoulder girdle of male patients. Its prevalence has been determined at 0.52 percent in a large cohort of male French military recruits between the ages of 17 and 26 years.\(^1\) The male to female ratio of Becker nevus has been approximated to be about 4:1, although it may well be underdiagnosed in women owing to less intense pigmentation and milder or even absent hypertrichosis. An association with soft-tissue defects is common, manifesting most frequently as breast hypoplasia. Danarti et al\(^a\) defined a Becker nevus syndrome as the coincidence of Becker nevus and ipsilateral breast hypoplasia, scoliosis, spina bifida, or ipsilateral limb hypoplasia. Becker nevi of the lower extremity are exceedingly rare.

**Report of a Case**

We report the case of a 31-year-old woman from the United Arab Emirates who presented with a lesion that had been present since birth but darkened during adolescence. Following a cesarean section 1 year before presentation, she observed a reduction in girth of the left leg. She also complained of pain on exercise. Examination showed hyperpigmentation and lipoatrophy involving the entire left lower extremity, extending from the left lumbar region to the ankle (Figure). The lesion's margins were irregular with satellite macules, reminiscent of an archipelago. The circumferences of the left and right thighs were 56 and 68 cm, respectively. There was only minimal hypertrichosis, and that was restricted to the ventral aspect of the left thigh. The patient underwent 7.5-MHz sonography, which revealed thinning of the subcutis of the left side (1.04 cm) compared with the right side (2.57 cm). Histopathologic analysis showed increased melanin production with pronounced pigmentation of the basal cell layer.

The patient desired to improve the cosmetic appearance of the affected leg, which required extensive plastic surgery. This, again, was declined by the patient, and she was lost to follow-up for 3 years.

**Figure. Dark Pigmentation and Lipoatrophy Extending From the Hip to the Ankle**

A, Front (A) and posterior (B) views.