Blue-Gray Pigmentation in Trunk and Extremities in a 71-Year-Old Man

Fluoroquinolones are a group of antibiotics widely used nowadays. Gastrointestinal and central nervous system symptoms are its most common adverse effects. Skin reactions are infrequent. We report herein a case of blue-gray pigmentation associated with levofloxacin.

Report of a Case | A 71-year-old man with a history of hypertension, diabetes mellitus, and renal failure was referred to the Dermatology Department for evaluation of long-lasting pruritus that did not respond to antihistamines. Physical examination revealed a blue-gray pigmentation on the back of his hands, the extensor aspect of his forearms, shins, and neck (Figure 1). The patient had undergone internal fixation of a hip fracture 2 earlier. After surgery, the patient complained of fever and pain for several months, but bacterial cultures were performed with negative results. Empirical treatment with rifampicin and levofloxacin was started and continued for 10 months. The patient claimed that the pigmentation began 2 months after he had started this regimen. Drug-induced pigmentation was suspected, and a skin biopsy was performed.

Histopathologic examination showed (1) brown, birefringent, hemosiderinlike deposits in macrophages; and (2) myoepithelial cells and fibroblasts in the superficial and deep dermis, hypodermis, and periadnexal structures (Figure 2A). The pigment stained intensely with both Perls (Figure 2B) and Masson-Fontana stains (Figure 2C). Electronic microscopy showed dense granular deposits inside lysosomes from fibroblasts (Figure 2D). Skin pigmentation associated with levofloxacin was diagnosed, and treatment with the antibiotic was stopped. One year later, the pigmentation remained at lower intensity.

Discussion | Levofloxacin is a third-generation quinolone with broad-spectrum antibiotic action against gram-positive and atypical agents. In osteomyelitis and prosthetic infections, levofloxacin in combination with rifampicin is the first-line treatment. Levofloxacin has a good safety profile; gastrointestinal and neurologic symptoms are its most common adverse effects. Skin adverse reactions are rare, and hypersensitivity reactions are the most common presentation.1 Epidermal toxic necrosis syndrome has also been reported. Pigmentation associated with levofloxacin is extremely infrequent, and to our knowledge, only 1 case has been previously reported in the literature,2 in a 68-year-old woman who showed blue-gray pigmentation in both legs after taking levofloxacin for 4 months. Similar findings have been described in association with other antibiotics, such as pefloxacin3 and minocycline. Minocycline pigmentation is a well-known adverse effect, and 3 clinical forms can be distinguished. In type 1, the pigmentation is...
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.4

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.5

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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.1 After 3 months, the patient’s husband and clinical team noted gray hyperpigmentation predominantly affecting the face (Figure 1A). She had re-