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## Levofloxacin-Induced Hyperpigmentation<sup>☆</sup>



### Hiperpigmentación inducida por levofloxacin

To the Editor:

Among the cutaneous adverse effects associated with drugs used in clinical practice, those caused by antibiotics are particularly frequent. Examples include minocycline-induced pigmentary changes of the skin or mucous membranes. However, these alterations are rarely associated with the use of other antibiotics. We report the uncommon case of a patient who developed blackish lesions on the lower limbs after beginning levofloxacin treatment.

### Case Description

A 72-year-old man with a previous biopsy-confirmed diagnosis of pigmented purpuric dermatosis (PPD) of the legs was seen for darkening of the skin of the lower limbs that had begun 10 months earlier. Two years earlier, the patient had undergone surgery for implantation of a prosthesis in the right shoulder. He had been receiving levofloxacin treatment for several months to treat an infection of the prosthesis. He reported that the skin discoloration appeared a few weeks after beginning levofloxacin treatment. Physical examination revealed very striking diffuse, blackish-gray pigmentation distributed bilaterally and symmetrically on the anterolateral aspects of the legs, from the knees to the toes, sparing the soles (Fig. 1). The mucous membranes were unaffected. The distal pulse was preserved and there were no other signs of ischemia.

A biopsy showed extensive deposition in the superficial and middle dermis of macrophages containing brown granular refractive cytoplasm, and a focal lymphocytic inflammatory infiltrate containing extravasated red blood cells. Perls staining was strongly positive inside the macrophages (Fig. 2A, B). Von Kossa and Fontana Masson staining were negative.

Levofloxacin treatment was suspended, resulting in a striking improvement in the skin pigmentation. Within 4 months, the patient's skin color had returned to normal (Fig. 3).

### Discussion

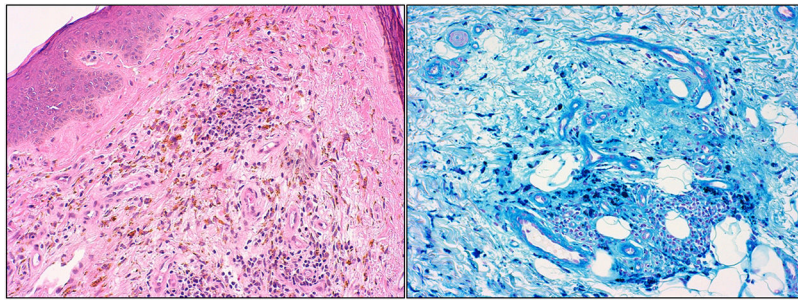
Quinolone treatment has been associated with certain cutaneous adverse effects. Specifically, levofloxacin can cause phototoxicity, toxic epidermal necrolysis,<sup>1</sup> drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome,<sup>2</sup> fixed drug eruption,<sup>3</sup> and leukocytoclastic vasculitis,<sup>4</sup> among other conditions. However, no association between pigmentary disorders and levofloxacin use has been previously reported.

To date, lesions similar to those of our patient have been attributed in almost all cases to minocycline, which causes pigmentation disorders in up to 50% of patients undergoing prolonged treatment.<sup>5,6</sup> We have found only 2 descriptions of patients with blackish-blue lesions similar to those of our patient caused by levofloxacin. In one of those patients, the backs of the hands as well as the legs were affected. In both cases, the histological findings corresponded to those of our patient, and the lesions improved after discontinuation of levofloxacin therapy.<sup>7,8</sup> A third report describes a case almost identical to ours that was caused by pefloxacin

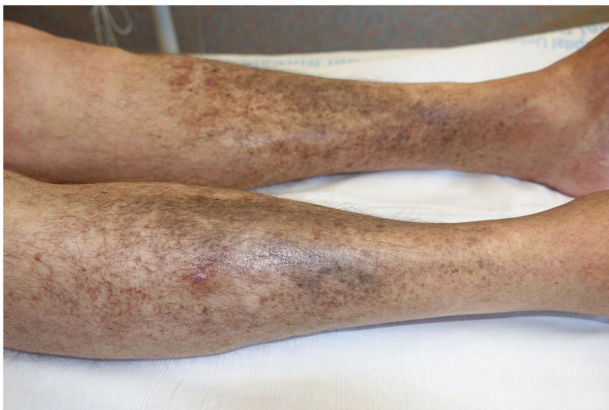


**Figure 1** Bilateral, symmetric, blackish pigmentation with irregular borders on the anterolateral aspects of both legs.

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**Figure 2** A, Abundant siderophages in the deepest areas of the dermis (hematoxylin-eosin, original magnification  $\times 20$ ). Cytoplasm containing slightly refringent golden-brown granules. B, Positive Perls staining (iron), revealing bluish, granular cytoplasm inside the macrophages.



**Figure 3** Significant lesion improvement and decreased pigment intensity after suspension of levofloxacin treatment.

treatment and in which subsequent exposure to norfloxacin resulted in lesion recurrence.<sup>9</sup>

Our patient had been previously diagnosed with PPD, which worsened after beginning levofloxacin treatment. We have found no descriptions in the literature of PPD secondary to treatment with levofloxacin or other quinolones that could explain this disimprovement. Furthermore, Perls staining of the biopsy sample revealed positive staining exclusively inside macrophages, and not in the stroma, as would be expected in PPD. Therefore, we propose that the patient's condition was independent of the underlying PPD and mainly due to levofloxacin treatment.

We believe that this case is of particular interest because it resembles, but is distinct from, pigmentation that typically occurs following minocycline treatment. The mechanism by which these cutaneous pigmentary alterations occur is unclear. In the case of minocycline-associated pigmentation the nature of the pigmented particles within the macrophages is unknown. Depending on the type of pigmentation, of which 3 distinct forms are described, histology shows dermal granules that are either free or located inside macrophages and contain iron and melanin, as revealed by Perls and Masson Fontana staining, respectively. Positive von Kossa staining, indicating the presence of calcium compounds, has been described in some cases.<sup>10</sup> Proposed explanations to account for the presence of these pigmented particles include the deposition of different types of drug metabolites, the presence of iron chelators

within melanophages, and increases in the production of intracellular melanin.<sup>7</sup> In the case of levofloxacin-induced pigmentation it is difficult to draw conclusions owing to the paucity of cases described. Perls staining was positive in our patient and in the 2 previously described cases. Masson Fontana staining was also positive in the case described by Garval and coworkers,<sup>7</sup> but was negative in our patient, as was von Kossa staining, which was not described in either of the 2 published case reports. The study of additional similar cases would help to further our understanding of this unusual entity.

## Conclusion

We report a rare case of striking cutaneous pigmentation caused by levofloxacin treatment. This case underscores the importance of taking changes in the patient's usual medication into account when examining possible skin lesions.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Acknowledgments

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## Pruritic Primary Nonessential Cutis Verticis Gyrata<sup>☆</sup>



### *Cutis verticis gyrata* primario no esencial pruriginoso

To the Editor:

The term *cutis verticis gyrata* (CVG) describes the finding of folds and creases on the top of the scalp, forming patterns reminiscent of those of the surface of the brain.<sup>1</sup>

We report the case of a 25-year-old man who visited our department with pruritis on the scalp that had appeared several months earlier. The patient's past history included immunoglobulin-A (IgA) deficiency, bilateral sensorineural hearing loss, and bilateral diffuse cataracts. Analytical tests and cranial CT scans performed during childhood were normal, and congenital rubella and Alport syndrome were ruled out. The patient's intellectual development and social adaptation were normal.

Physical examination at our department revealed hypertrophy and formation of anteroposterior folds on the scalp, forming furrows and ridges (Fig. 1). The patient presented no desquamation, hair loss, or other skin lesions.

Cranial magnetic resonance imaging revealed slight undulation of the extracranial soft tissue, with no associated involvement of the bone or intracranial tissue (Fig. 2). A skin biopsy of the scalp revealed follicular hypertrophy and hyperplasia, with no other histologic findings of interest (Fig. 3). Blood tests (blood count, glycemia, lipid, hepatic, renal, and thyroid profiles, cortisol, parathyroid hormone, and acromegaly screening) were normal. In light of these

findings, the patient was diagnosed with primary nonessential CVG.

Our patient presented intense pruritis, which had previously been treated with oral antihistamines and topical antipruritics, with no response. Treatment with capsaicin gel 0.075% was instated but the patient's condition worsened; oral gabapentin was then instated with no improvement, and both treatments were therefore suspended. Finally, amitriptyline was prescribed at a dosage of 10 mg per day, and the patient remains asymptomatic to date (5 months).

CVG is a rare morphologic syndrome that presents with hypertrophy and folding of the scalp. Incidence in the general population is difficult to estimate, as the disease is generally asymptomatic.

The primary form has no known cause and may occur in isolation (primary essential CVG) or in association with other neurologic (intellectual disability, deafness, microcephaly, or epilepsy) and/or ophthalmologic abnormalities (cataracts, strabismus, blindness, or retinitis pigmentosa).<sup>1,2</sup> It is more common in males,<sup>1</sup> with onset usually occurring during puberty, and is usually distributed symmetrically, typically affecting the vertex and occipital region,<sup>2</sup> in the form of anteroposterior furrows and ridges that give it the appearance of the surface of the brain.

Secondary CVG is due to the abnormality in the scalp caused by other diseases such as acromegaly, myxedema, fragile X syndrome, Klinefelter syndrome, tuberous sclerosis, psoriasis, eczema, Darier disease, amyloid deposition, extensive nevus or hamartoma, leukemia, Ehlers-Danlos syndrome, or trauma.<sup>1-3</sup>

Study of the patient should initially be guided by past history, the physical examination and the biopsy of the affected area, and associated abnormalities and the diseases that cause secondary forms should be ruled out using different tests and imaging studies.<sup>1</sup>

A typical biopsy of the primary form will reveal hypertrophy and hyperplasia of adnexal structures and increased dermal collagen in skin with no other histologic abnormalities.<sup>2</sup> Secondary CVG shows abnormalities characteristic of the underlying etiology.

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