Primary Cutaneous Nocardiosis in a Man Treated With Certolizumab☆

Nocardiosis cutánea primaria en un paciente en tratamiento con certolizumab

To the Editor:

Biologic therapies are increasingly used to treat many inflammatory conditions, including skin diseases. Adverse effects include infections, some of which are potentially serious.[1]

A 53-year-old male livestock worker with psoriatic arthritis, for which he had been treated with leflunomide (5 years) and certolizumab (2 years), presented with an asymptomatic lesion on the wrist that had appeared 15 days earlier and had not responded to a 1-week course of oral clarithromycin (500 mg/12 h) and topical fusidic acid therapy. The patient reported neither fever nor systemic symptoms. Physical examination revealed an indurated, erythematous-violaceous nodule (2 cm in diameter) with a central crust on the dorsum of the left wrist (Fig. 1). A swab sample was collected from the lesion surface for culture and a skin biopsy was taken for culture and histopathology.

The biopsy showed a superficial and deep predominantly neutrophilic inflammatory infiltrate that formed focal dermal abscesses. No nuclear pseudoinclusions were observed. Periodic acid-Schiff (PAS) and silver staining were negative (Fig. 2). The swab culture was negative, but *Nocardia brasiliensis* resistant to clarithromycin and sensitive to trimethoprim/sulfamethoxazole was isolated from the skin biopsy culture (Fig. 3). A basic battery of tests and pulmonary and brain computed tomography (CT) revealed no findings of note. The patient was diagnosed with localized primary cutaneous nocardiosis. After discontinuing certolizumab treatment, he began treatment with trimethoprim/sulfamethoxazole (80 mg/12 h and 400 mg/12 h, respectively), which resulted in complete lesion resolution in 6 months.

Nocardiosis is a rare infection that most often affects immunocompromised patients, and is considered an emerging infectious disease by some authors.[2,3] Cutaneous nocardiosis accounts for up to 25% of cases and can lead to disseminated disease.[4] It is caused by direct inoculation, mainly by *N brasiliensis*. The localized cutaneous form can be indistinguishable from other pyodermas and in one third of cases evolves to a lymphocutaneous form, with formation of nodules along the lymphatic pathway.[5] The differential diagnosis includes bacterial (erysipeloid, tularemia, and anthrax), fungal (sporotrichosis), and viral (Orf and milker's nodules) infections, as well as atypical mycobacterial infections and leishmaniasis. A secondary form of nocardiosis, caused by hematogenous seeding from another focus, can resemble the primary form and can cause significant morbidity and mortality. Diagnosis is established by culture of samples acquired by invasive methods such as biopsy or aspiration of pus. In cases of clinical suspicion of nocardiosis the microbiologist should be notified in advance to ensure culture of the sample in the appropriate medium.[6] Because sensitivity profiles differ between species, it is advisable to perform an antibiogram.[7] Histopathology reveals nonspecific changes and silver staining occasionally enables visualization of the microorganisms.[5,6] In patients with cutaneous nocardiosis, especially immunocompromised patients, systemic disease should be ruled out by pulmonary and cerebral CT.[6]

Tumor necrosis factor α (TNF-α) plays an important role in immunity against intracellular pathogens such as *Nocardia* species.[2] Of the 11 reported cases of nocardiosis in patients receiving anti-TNF therapy, 3 involved patients with primary cutaneous nocardiosis[2–4,8] and none were associated with certolizumab treatment. Singh and coworkers described a case of cutaneous nocardiosis in a 45-year-old patient with Crohn disease who was being treated with prednisone and infliximab.[8] Ali et al reported the case of a 61-year-old Crohn disease patient who was being treated with infliximab.[2] In both cases, the causative species could not be identified. Fabre et al described the

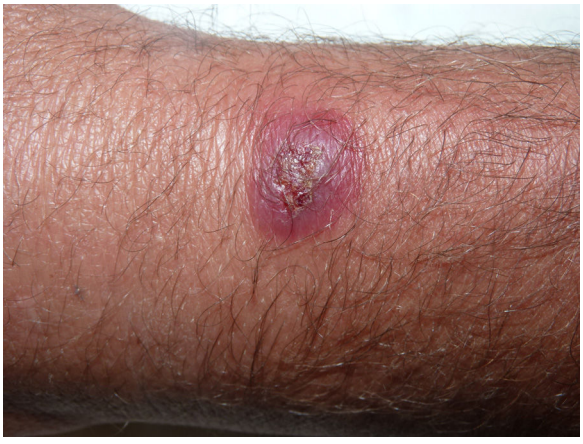

Figure 1 Indurated, erythematous-violaceous nodule with a central crust on the dorsum of the wrist.

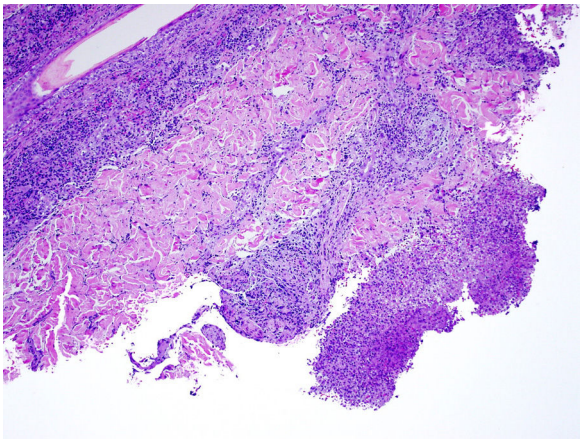

Figure 2 Histology revealing a superficial and deep neutrophilic inflammatory infiltrate forming focal dermal abscesses (hematoxylin-eosin, original magnification ×10).

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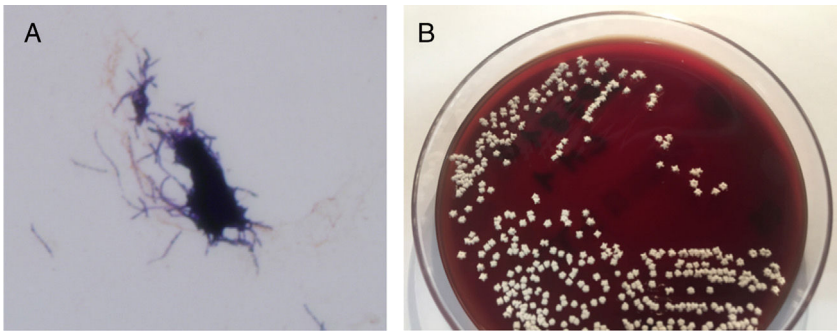

Figure 3 A, Gram staining revealing gram-positive coccobacilli forming branched filaments. B, *Nocardia brasiliensis* colonies growing in blood agar culture.

case of a 70-year-old rheumatoid arthritis patient who was being treated with infliximab, methotrexate, and corticosteroids, and who developed primary cutaneous nocardiosis due to *Nocardia otitidiscaviarum*.[4] In none of the aforementioned cases were systemic symptoms or disseminated disease observed. All patients progressed favorably after discontinuing anti-TNF treatment and beginning treatment with trimethoprim/sulfamethoxazole[2,8] or ofloxacin and clindamycin.[4] Although leflunomide has been associated with the development of intracellular pathogen infections, to our knowledge no cases of leflunomide-associated nocardiosis have been reported. Compared with other disease-modifying antirheumatic drugs, anti-TNF therapy is associated with an increased risk of skin and soft tissue infections.[9] Based on this association and the sequence of clinical events in the current case, we believe that certolizumab was the main determinant of our patient's condition.

While there is currently insufficient evidence to recommend a specific drug regimen and treatment duration, trimethoprim/sulfamethoxazole therapy for 3 to 12 months is considered the treatment of choice, depending on the patient's immune status, and desensitization therapy is recommended in cases of allergy.[3] Localized forms of nocardiosis can be surgically removed to shorten the treatment duration.[6] Immunosuppressive drug treatment should be withdrawn or continued at the minimum dose. A lack of improvement after 2 weeks can indicate resistance, poor tissue penetration, or the need for surgical drainage. It should be noted that clinical suspicion is fundamental for early diagnosis and treatment, and for early withdrawal of anti-TNF therapy.[3,6]

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Levofloxacin-Induced Hyperpigmentation☆

Hiperpigmentación inducida por levofloxacino

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,[1] drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome,[2] fixed drug eruption,[3] and leukocytoclastic vasculitis,[4] 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.[5,6] 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.[7,8] A third report describes a case almost identical to ours that was caused by pefloxacin

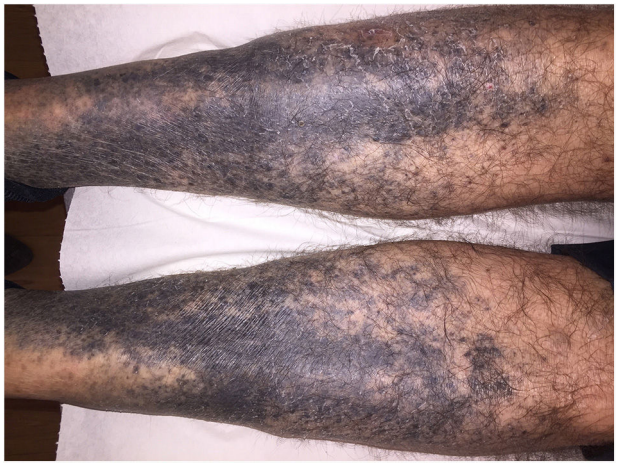

Figure 1 Bilateral, symmetric, blackish pigmentation with irregular borders on the anterolateral aspects of both legs.

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