Itraconazole Can be Effective in the Treatment of Sporotrichoid Leishmaniasis

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Leishmaniasis represents a diverse group of diseases caused by protozoan parasites that are transmitted to humans by the bite of phlebotomine sandflies. Three major clinical forms can be recognized, visceral, cutaneous and mucocutaneous, which are widespread in tropical, subtropical and temperate areas. Data on the incidence of cutaneous leishmaniasis in travelers are scarce. In fact, constant parameters (time of exposure, kind of travel, burden of outdoor activities, rural or urban setting) are necessary to determine this incidence. Studies performed in defined groups such as military personnel in the Middle East showed an incidence of about 8/1,000 persons.

Cutaneous leishmaniasis is sometimes associated with sporotrichoid spread. Sporotrichoid leishmaniasis is characterized by the development of subcutaneous, nontender, slightly erythematous nodules, often associated with lymphangitis, that progress, starting from the mother lesion, along dermal and subcutaneous lymphatics. In sporotrichoid cutaneous leishmaniasis, amastigotes may be found in both primary lesions and subcutaneous nodules.

Sporotrichoid spread is more frequently associated with New World cutaneous leishmaniasis, particularly Leishmania braziliensis, although it can be observed also in association with Old World cutaneous leishmaniasis (L. major).

The factors that trigger lymphatic dissemination are unclear. Some data suggest that both antileishmanial treatment and the host immune status could influence the dissemination.

The diagnosis of cutaneous leishmaniasis is often made clinically on the basis of a typical lesion together with a history of exposure. Confirmation can be obtained by the direct detection of amastigotes during histologic examination of the biopsy of the lesion.

The identification of Leishmania spp. is done traditionally through isoenzyme analysis and requires parasite culture. PCR is a suitable and quick tool for the diagnosis and identification of the different species.

In the differential diagnosis of sporotrichoid infections, we have to consider, apart from Leishmania spp., infections caused by Sporotrich schenkii, Mycobacterium spp., Nocardia spp. and Francisella tularensis.

Case Report

In March 2002, a 63-year-old man complained about the presence of two cutaneous lesions that had appeared 3 months before, one on the posterior side of the left leg and the other on the right side of the thorax. These lesions had progressively increased in size and, by the time of our observation, they presented as two ulcers with a central depression, raised, indurated borders, and fibrin covering the bottom. The diameter of each lesion was about 3 cm.

The patient was a frequent traveler, and the last trip had been 6 months before, when he had traveled to Tunisia and Morocco.

A cutaneous biopsy of the lesions was performed, and the histologic examination revealed the presence of Leishmania parasites.

Parasites were identified as L. major by means of PCR analysis and PCR–restriction fragment length polymorphism (RLFP) analysis, as described elsewhere.
Intralesional treatment with meglumine antimoniate was started, with an initial dosage of 0.5 mL per lesion, which was subsequently increased to 1.5 mL.

After nine administrations (3 weeks), the lesion on the thorax healed with scarring and pigmentation, while the lesion on the leg was unchanged. Perimalleolar edema and signs of cutaneous inflammation of the left leg, together with omolateral inguinal lymphoadenopathy, was noted. Treatment with meglumine antimoniate was stopped, and progressive improvement of the edema and adenopathy was observed. A new biopsy was performed for both lesions, and the microscopic evaluation showed no evidence of parasites in either lesion; the PCR analysis for the detection of Leishmania parasites gave negative results regarding the lesion on the thorax, whereas the results for the lesion on the leg were still positive.

One month later, a new nodular lesion of about 2 cm in diameter was noted proximally to the lesion on the leg in the popliteal area. Numerous minor nodules could be seen, with the appearance of a beaded cord, and extended from the dominant lesion proximally to the thigh (fig.).

Systemic treatment with itraconazole given orally (400 mg q.d.) was started, and after 1 month of therapy a significant improvement was noted: the diameter of the nodular lesion of the popliteal cave was reduced (1 cm), and fewer satellite nodules could be seen. Itraconazole was continued at a lower dosage (200 mg q.d.) for another 4 weeks.

Six weeks after the end of therapy, complete healing of the primitive lesion and the disappearance of the sporotrichoid form were noted. A last biopsy, performed on the leg, gave negative results on PCR analysis. To date, after 2 years of follow-up, the patient has not suffered any relapse.

Discussion

Cutaneous leishmaniasis may heal spontaneously, although this can take years. Treatment is recommended for large, multiple, disseminated lesions, for lesions localized on the face, and for lesions in the immunocompromised host. Cutaneous lesions caused by Leishmania from the New World should be treated because of the low rate of spontaneous healing and the potential risk of developing mucosal disease. Mucosal metastases may appear years after the onset of the first cutaneous lesions if they had been treated incompletely or not treated at all.

The decision about whether and how to treat a patient depends on the species of Leishmania, the types of lesion, the localization, and the characteristics of the affected patient.

The pentavalent antimony compounds (sodium stibogluconate and meglumine antimoniate), given systemically, are still considered to be the drugs of choice. Pentavalent antimony compounds can also be given by intralesional administration, and this therapy is generally indicated for patients who present with one or with a limited number of localized lesions, or who cannot receive intravenous therapy.

Amphotericin B deoxycholate and pentamidine isethionate are used as second-line drugs. Data on the efficacy of the lipid formulation of amphotericin B are insufficient to determine its usefulness in the treatment of cutaneous leishmaniasis.

Studies have been performed to determine the efficacy of the azole compounds, but the results are controversial. These antifungals include two different classes: imidazoles (ketoconazole) and triazoles (fluconazole and itraconazole). They share the same antifungal spectrum and mechanism of action, but triazoles are more slowly metabolized, have less effect on human sterol synthesis and are less toxic than imidazoles. In some studies, ketoconazole has shown cure rates of up to 70% in patients affected by L. major or L. mexicana, but its activity against L. tropica, L. aethiopica and L. braziliensis seems to be substantially lower. Some authors consider the drug to have modest activity against L. mexicana and L. panamensis, and its usefulness against L. major is still not confirmed. Studies performed on the efficacy of itraconazole taken orally gave variable results, although they demonstrated that itraconazole is better tolerated than ketoconazole. Two double-blind studies evaluating the efficacy of itraconazole compared to placebo were performed; one included 131 patients and the other included only 10 patients. The former demonstrated a low rate of response to the drug, whereas the latter showed a higher efficacy of itraconazole compared to placebo. The main difference between the two studies was the duration of administration of the azole compound: 3 weeks in the trial
where itraconazole showed low efficacy, and 6 weeks in the study where the drug was effective. This suggests that the outcome of therapy with itraconazole may depend on the duration of administration.

Neither of the two studies included cases of sporotrichoid spread.

Fluconazole, another triazole, showed promising results in the treatment of noncomplicated forms of cutaneous leishmaniasis due to *L. major* in a trial conducted in Saudi Arabia.\(^{19}\)

One single case report describing a sporotrichoid form reported successful healing after treatment with itraconazole.\(^{6}\) The patient received intralesional pentavalent antimonials, since cutaneous leishmaniasis caused by *L. major* does not usually develop into mucosal disease. Although parenteral therapy is more effective and results in faster healing, it may lead more frequently to toxic adverse events.\(^{11}\)

When the patient developed complicated sporotrichoid dissemination, we decided not to start treatment with a parenteral and more toxic treatment with pentavalent antimonials, and we gave him oral itraconazole. Even though the patient complained about minor adverse effects (modest nausea and diarrhea), itraconazole was generally well tolerated and the treatment resulted in complete healing of the lesions and the disappearance of the sporotrichoid dissemination. To date, after 2 years of follow-up, the patient has not suffered any relapse.

Although the description of one case is of little help in evaluating the efficacy of a specific therapy, we believed that it was interesting to report the healing of a disseminated form of *L. major* leishmaniasis, treated with itraconazole, that did not respond to first-line treatment with pentavalent antimonials. In the literature, a case of sporotrichoid dissemination treated successfully with itraconazole has been previously reported.\(^{6}\) This suggests the possibility of the use of azole compounds in the treatment of disseminated forms of cutaneous leishmaniasis caused by *L. major*.

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**Declaration of Interests**

The author is on the speakers’ bureau for GSK.

**References**