

Photodynamic treatment of cutaneous leishmaniasis

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Summary

Leishmaniasis is a widespread arthropod-borne protozoan zoonosis caused by more than 21 *Leishmania* species. Vectors are sandflies of different genera. The disease is classified into „Old World“ versus „New World“ leishmaniasis and further subclassified in cutaneous, mucocutaneous and visceral forms. Most therapeutic approaches are not evidence-based. We report a patient with facial cutaneous *Leishmania tropica* infection which proved to be resistant to various therapeutic regimes. Excellent results were achieved with photodynamic therapy.

Keywords

Leishmaniasis – photodynamic therapy (PDT)

Case report

A 57-year-old patient presented with an erythematous papule on his left cheek that had progressed for four months and eventually ulcerated. There was no history of relevant associated disease. He reported vacationing in the Maldives in 2000, a visit to Mauritius in 2003, and a vacation in Italy in 2004.

The patient initially received treatment for suspected pyoderma, consisting of a four week course of amoxicillin followed by four weeks of oral doxycycline. The lesion failed to heal and the patient came to our clinic after it continued to expand (Figure 1a). A biopsy sample was taken from the affected area – the first biopsy taken in the four months since the lesion appeared. Histologic analysis and PCR to identify the pathogen yielded a diagnosis of cutaneous Leishmaniasis caused by *L. tropica*. Infection was presumed to have occurred while the patient was in Italy (Tuscany), 10 weeks before the lesion appeared.

After confirming the diagnosis, topical treatment consisting of 15 % paromomycin in petrolatum and an additional 2 months of adjuvant therapy with oral itraconazole (4 × 50 mg) was administered but failed to produce any effect (Figure 1b).

Because the lack of response, the patient was then given a total of 7 intramuscular injections of pentamidine (Pentam[®]), an aromatic diamine, at a dosage of 2 mg per kg every other day. This was supplemented by 5 sessions of cryotherapy. Eight weeks after stopping this therapy, the lesion was still erythematous and had flattened but not changed in size

(Figure 1c). Because of its location on the face, the lesion was considered cosmetically unacceptable by the patient, so we initiated photodynamic therapy (PDT) with Metvix[®] cream as a photosensitizer. Treatment consisted of 2 applications of light, administered at a one week interval (Waldman PDT 1200 L; 100 J/cm²), with a third session after four weeks to ensure treatment success. The lesion healed rapidly after photodynamic therapy with a good cosmetic result (Figure 1d).

Discussion

Leishmaniasis is an anthroponosis caused by numerous *Leishmania* spp. Its name is derived from that of the British tropical medicine specialist W. B. Leishman (*1865, †1926). The insect vector responsible for transmitting the protozoa is the sandfly (*Phlebotomus* spp. and *Lutzomyia* spp.). Leishmaniasis has been divided geographically into “Old World” versus “New World” disease as well as clinically into cutaneous, mucocutaneous, or visceral forms [1, 2]. About 12 million people are affected by the disease worldwide with 400,000 to 2 million new cases each year [2, 3], the majority of which occur in the “Old World.” Cutaneous leishmaniasis predominantly affects exposed areas of the skin such as the face, arms, and lower legs. After an incubation period of up to 3 months a small papule develops at the site of the sandfly bite. The papule later develops into a plaque or nodule that may eventually ulcerate. Smaller satellite nodules may form in the surrounding area or in nearby lymphatics. Lesions typically heal spontaneously after several months or years, leaving an atrophic scar. Patients who heal spontaneously generally develop immunity to the infecting *Leishmania* spp. This is a particularly important factor in endemic regions as observation may be appropriate if the lesion is not located in a cosmetically sensitive site [2, 3]. Because precise speciation is essential for prognosis and therapy, a sample biopsy should be taken to confirm infection and PCR performed for speciation [4, 5].

The appropriate therapy for leishmaniasis is determined by the causative species and the form of disease. While there are case reports on the results of various therapeutic approaches, evidence from larger, controlled studies is often

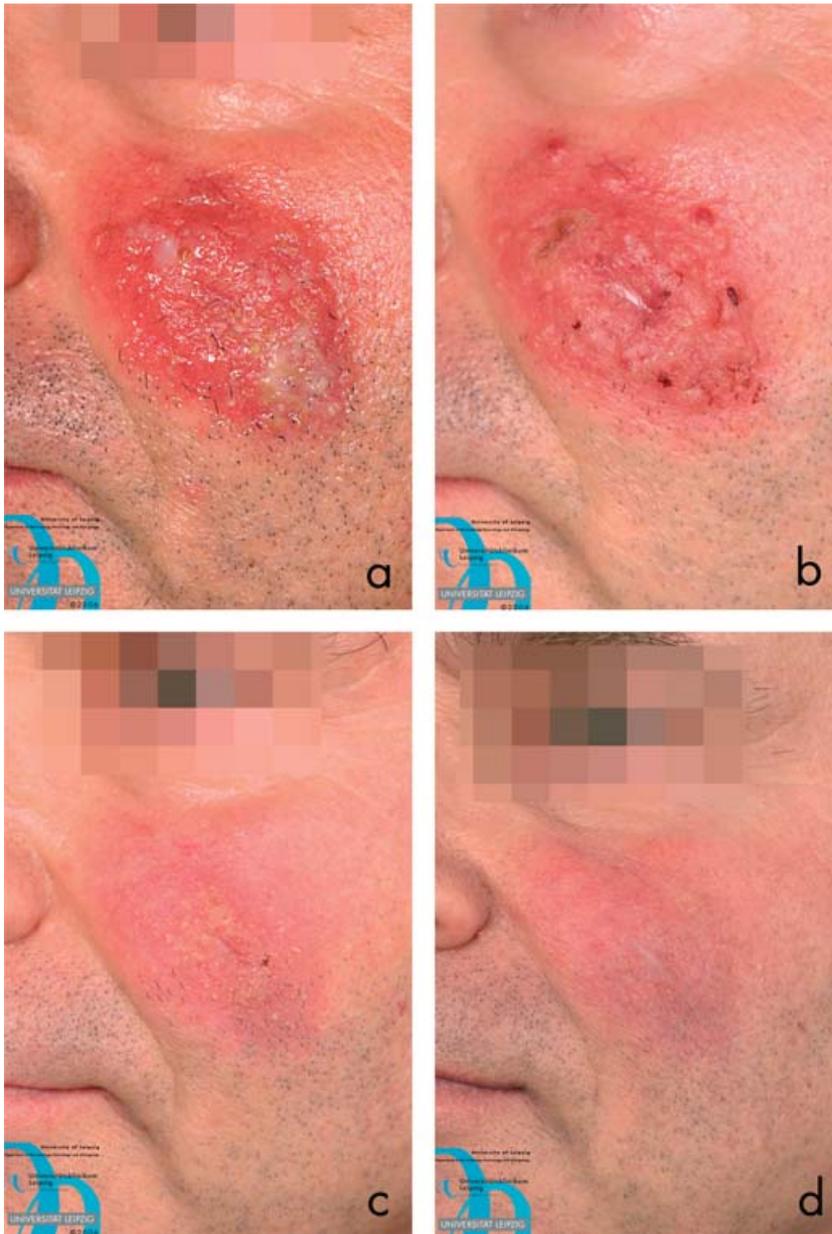


Figure 1: Biopsy-proven cutaneous *Leishmania tropica* lesion on the face of a 57-year-old patient. (a) Appearance 4 months after onset of primary skin changes. (b) After topical treatment with 15 % paromomycin in petrolatum for 4 months and an additional 2 months of oral itraconazole (4×50 mg) (c) After intramuscular injection of pentamidine (Pentam[®]) at a dosage of 2 mg/kg (7 injections) and 5 sessions of local cryotherapy. (d) After 3 cycles of photodynamic therapy (PDT).

unavailable. This presents a challenge when selecting an appropriate therapeutic strategy, as some approaches described in the literature have been limited to select species. Yet, not all species are equally sensitive to a given therapy. Drug resistance is well documented and the necessity of trying alternative treatment strategies is apparent [2]. Solitary lesions caused by „Old World“ *Leishmania* spp. are typically self-limited and delayed treatment may be prudent; mucocutaneous

and visceral forms should be treated systemically [2, 3].

Systemic treatment approaches that have already been in use for decades include pentavalent antimony preparations such as sodium stibogluconate (Pentostam) and meglumine antimoniate (Glucantime). An alternative therapy is the aromatic diamine Pentamidine isethionate (Pentam[®]). Use of itraconazole, ketoconazole, amphotericin B, and IFN- γ has also been reported [6, 7].

Topical agents that may be used to treat cutaneous leishmaniasis include 15 % paromomycin in petrolatum and intraleisional sodium stibogluconate (Pentostam). Surgery, cryotherapy, and hyperthermia treatment have also been used [8]. Recent studies have described effective use of photodynamic therapy (PDT) with a good cosmetic outcome [2, 9, 10]. Photodynamic therapy also achieved a good result in our patient. Whether or not delaying treatment, even for a longer period of time, would have resulted in resolution of the lesion is uncertain. In the future, PDT could be tried prior to pentamidine isethionate therapy.

The mechanism underlying the effect of photodynamic therapy on leishmaniasis is not well understood. Its main effect presumably lies in prior application of a topical ointment containing δ -aminolevulinic acid or its ester (Metvix[®]) which leads to accumulation of excessive amounts of intracellular protoporphyrin IX (PP IX) related to heme synthesis. Activation of PP IX by light of the appropriate wavelength induces the release of singlet oxygen, which is thought to have a toxic effect on *Leishmania* spp. While this mechanism has generally been described with keratinocytes [11] rather than macrophages – the host cells for the parasites – or *Leishmania* spp. itself, studies have demonstrated an antimicrobial effect of PDT [12]. It is also entirely possible that the effect is in large part due to the occlusive effect of application of porphyrin-based topical agents. It is well known that protozoa of the Trypanosomatid family, including *Leishmania* spp., have a metabolic defect in biosynthesis of heme [13]. *Leishmania* spp. can only grow in vitro on media containing heme or protoporphyrin IX. In higher concentrations, however, such as arise with PDT, protoporphyrin IX has been shown to have an anti-leishmanial effect [14]. In addition, the use of PDT with an incoherent light source produces local heating of tissue, albeit as a side effect. Hyperthermia treatment of leishmaniasis has also been described in the literature [3, 8]. Almost certainly several of these mechanisms contribute to the effectiveness of PDT in treating cutaneous leishmaniasis.

Conflict of interest

None.

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