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CASE REPORT

AZITHROMYCIN IN THE TREATMENT OF MUCOSAL LEISHMANIASIS

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SUMMARY

This report describes three elderly patients with mucosal form of American tegumentary leishmaniasis associated with chronic cardiopathy. Due to the known toxicity of classical drugs with activity against *Leishmania* sp., the patients received three oral courses of azithromycin therapy in single 500 mg daily dose during ten days, every other month. All lesions healed after the third series. One of the patients relapsed and a new series of azithromycin was prescribed. Azithromycin may be an alternative drug for the treatment of leishmaniasis in special situations due to its optimal mucosal and intraphagocyte concentration, single daily posology, high tolerance and oral administration. The mechanism of this drug on *Leishmania* sp. is unknown at present.

KEYWORDS: Mucosal leishmaniasis; Azithromycin; Chronic cardiopathy.

The pentavalent antimonial (glucantime®) and sodium stibogluconate (pentostam®) are drugs of choice for treatment of American tegumentary leishmaniasis[1,5,11]. However, the therapeutical response in mucosal forms is less than that obtained in the cutaneous ulcers and, usually, several series of antimonial are required for complete clinical healing[2,5,8,9,18]. Amphotericin B and pentamidin therapy is the second choice, because of their toxicity and side effects, although their efficacy is similar to that of those antimonial by-products[14,15,16,20].

Clinical trial with nifurtimox did not show a proper response in the treatment of the mucosal form of American tegumentary leishmaniasis[4], and the use of pentavalent antimonial associated with pentoxiphylin was preliminarly effective in patients with mucosal forms, refractory to antimonial alone[7].

Azithromycin, a macrolide by-product of large use in clinical practice, proved to be experimentally effective against *Leishmania major*[6] and, more recently, in open clinical assay, an efficacy of 85% in 20 patients with leishmaniasis cutaneous forms was reported[13]. Another study in Manaus, Brazil, where *Leishmania viannia guyanensis* is endemic, showed low efficacy in 26 patients that received this drug (unpublished data)[17].

The present work describes three Brazilian elderly patients with mucosal leishmaniasis and associated chronical cardiopathy. Due to the latter condition they received azithromycin.

CLINIC CASE REPORT

Patient 1 - J. P. M., 76 year-old, male, born and resident in São Francisco de Sales, Minas Gerais, an endemic area of leishmaniasis. He presented a-four-year ulcerocrusty lesion in the right nostril and bloody rhinorrhea. Montenegro test was positive (12 mm) and biopsy showed chronical inflammation with giant cells and granuloma formation, presenting necrosis areas and mononuclear cells. No leishmania or other parasites were observed. Because of a previous history of chronical cardiopathy with heart failure, he received dapsone, and during six months his lesion was scarred, after, the lesion relapsed and Amphotericin B was considered. A week later, renal failure developed and this drug therapy was replaced by low doses of pentavalent antimonial. Within a few days, clinical and electrocardiographic examination revealed evidence of antimonial toxicity. The therapy was then discontinued and the patient received oral azithromycin 500 mg/day, during ten days in three series every other month. After 120 days, complete healing of the lesion occurred and at clinical monthly follow-up during one year no relapse was observed.

Patient 2 - C. J. S., 80 year-old, male, born and resident in Porteirinha, Minas Gerais, an endemic area of leishmaniasis. He referred upper and progressive dysphagia for several months. He presented granulomatous pervasive morula-like lesion, jeopardizing hard and soft palate, uvula and oropharynx. The lesion was friable and recovered with a white secretion. Total collapse of the nose had ocurred some years ago alongside chronical cardiopaty. The histopathological oropharynx lesion

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exam showed amastigotes forms of *Leishmania* sp into macrophages. Montenegro test was not performed. Previously, he had irregularly used pentavalent antimonial, unsuccessfully. He received azithromycin 500 mg/day per oral via, during 10 days in three series every other month. His lesions evolved for clinical healing, but six months later, relapse was noticed. Therefore, a new course of azithromycin 500 mg/day during 10 days was required, and remission was observed after three months, but no follow-up was possible, in spite of several patient recalls.

Patient 3 - E. F. O., 76 year-old, female, born and resident in Araçuaí, Minas Gerais, an endemic area of leishmaniasis. She presented ulcerovegetative lesions in the upper lip, hard and soft palate and oropharynx for eighteen months. She referred upper and progressive dysphagia, easy bleeding of lesions at minimal traumatisms and weight loss due to the dysphagia. Clinical exam revealed edema, infiltration and remarkable protraction of the upper lip, and together with total collapse of the nares, which had occurred several years ago. Besides, the patient referred chronical heart failure. Montenegro reaction resulted positive (14 mm) and lip ulcer biopsy showed chronical inflammation characterized by perivascular infiltrate with limphocytes, plasmocytes and histiocytes, and scattered granuloma formation. No amastigotes or other microrganisms were observed. She received azithromycin 500 mg/day per oral via, during 10 days, in three courses every other month. There was complete regression of the lesions in the fourth month of treatment, normal nourishing and weight. Gain. At 12 months follow-up she was asymptomatic.

COMMENTS

The treatment of the mucosal form of American tegumentary leishmaniasis presents some problems regarding the variable response to antimonials which, like other classical drugs, are all administered by parenteral via for long periods, and frequently have toxic and side effects, mainly nephro and cardiotoxicity[1,3,11]. This fact becomes more evident in old patients, since they often present cardiopathies and other underlying diseases. Therefore, contraindications to use these drugs are common and patient hospitalization is often needed[2,7,10]. In such cases, other anti-leishmania therapeutic alternatives become relevant. A favourable clinical response to azithromycin was described to the cutaneous forms of American tegumentary leishmaniasis caused by *Leishmania viannia brasiliensis*[13]. The authors treated 20 patients who received 500 mg of azithromycin daily per oral via for 3, 5 or 10 days or 1,000 mg daily for two days. Similar courses were repeated when necessary, until full re-epitelization. Healing time ranged from 60 days in six (30%) of patients to 120 days in four (20%) of them[13].

These results supported the use of azithromycin in these three elderly patients with chronic mucous lesion suggestive of American tegumentary leishmaniasis. Besides, they presented chronic cardiopathy and had been receiving anticongestive therapy for a long time.

Only one of three patients had leishmaniasis diagnosis confirmed by biopsy. The others presented suggestive clinical lesion together with a Montenegro positive test and successful response to treatment with this drug. Nevertheless, other diseases might be considered although no other microrganisms were seen at histopathological examination.

Despite the early good response, six months later, patient 2 presented clinical relapse, and a new course with azithromycin healed the lesions. No side effects were observed in these cases and similar results were previously reported[13]. These authors used the same dosage for a short time. On the other hand, TEIXEIRA (2003)[17] observed diarrhea in 60% of the cases, abdominal pain in 28%, and headache and nauseas in 12% of 26 patients with cutaneous leishmaniasis receiving azithromycin during 20 days (unpublished data).

A favorable response obtained in these cases may support the anti-leishmania activity of this macrolide on mucosal leishmaniasis, especially if considering some outstanding advantages of it: therapeutical response observed over ten years of its use for several infectious diseases, good tolerance, high levels of drug into mucosae and phagocytes, and a single daily oral dose[10,12,19].

In accordance with KROLEWIECKI *et al*.[6], the azithromycin's mode of action against *Leishmania* sp is unknown at present. It might be through either direct effect on parasite or by immune and inflammatory modulation response. Nevertheless, clinical randomized and controlled studies are necessary to evaluate the azithromycin efficacy in mucosal and other clinical presentations of American tegumentary leishmaniasis.

RESUMO

Azitromicina no tratamento da leishmaniose mucosa

O presente relato descreve três pacientes idosos com leishmaniose mucosa de longa evolução, os quais eram portadores de cardiopatia crônica. Pela alta freqüência de efeitos secundários e tóxicos dos medicamentos utilizados no tratamento clássico, esses pacientes receberam azitromicina. Este medicamento foi administrado pela via oral, em dose única diária de 500 mg, durante dez dias, em três séries com intervalo de um mês. Em todos, houve cicatrização das lesões depois da terceira série. Um dos pacientes apresentou recidiva após seis meses e uma nova série de azitromicina fez regredir novamente o quadro. Azitromicina pode ser uma alternativa para o tratamento das leishmanioses, principalmente pela concentração adequada em mucosas e nos fagócitos, posologia única diária, boa tolerância e administração oral.

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