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Efficacy of fluconazole therapy for cutaneous leishmaniasis. A case report and review of literature.

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ABSTRACT

Cutaneous Leishmaniasis is endemic in the western province of Libya, including the Zliten countryside, despite its self-limited nature, many cases may run a chronic course and resist ordinary treatment, causing disfigurement or even deformity. Our case is a 47-year-old black Libyan man presented to us 2 years ago, with an ulcerated plaque in his left leg and infiltrated plaque in his right ear due to cutaneous leishmaniasis. While the leg ulcer healed with a small scar after a 6-week course of intra-lesional sodium stibogluconate, the lesion on the ear failed to heal by local treatment. Furthermore, parenteral antimony was stopped by a cardiologist. By time, nodules had developed inside the infiltrated lesion. After 18 months, the case was reevaluated by skin slit smear and histopathology, which both showed amastigotes in the lesion. We tried 150 mg of fluconazole daily for 45 days after appropriate investigations. Unfortunately, without success. Our paper details the clinical, parasitological and pathological findings of this case, in addition to literature review on the efficacy of oral fluconazole in treating cutaneous leishmaniasis.

KEYWORDS: Cutaneous leishmaniasis, Fluconazole, *Leishmania major*, Sodium stibogluconate.

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INTRODUCTION

Cutaneous leishmaniasis (CL) is a protozoan disease caused by the genus Leishmania, which belongs to the family Trypanosomatidae. The vectors of CL are female sand flies of the genus Phlebotomus in the "Old World" and Lutzomyia in the "New World". Rodents, dogs, or other mammals act as reservoirs while humans are accidently infected (1, 2). There are 350 million individuals at risk of CL in nearly 100 endemic countries (3).The new cases of CL are estimated to range from 0.7 to 1.2 million annually (4). Leishmania major (L major) and Leishmania tropica (L tropica) are responsible for most cases of CL in northern Africa. CL may be presented with an ulcerative nodule, a warty lesion, or a lupoid form, among others (5).

Pentavalent antimonials continue to be the principal treatment agents for leishmaniasis. However, there has been a vigorous search for alternate therapy, including oral drugs for CL, due to the severe side effects of antimony and their need for parenteral delivery (6). Azoles are among the possible oral drugs for CL, as they display in vivo and in vitro anti-Leishmania effects. Azoles cause inhibition of 14α-lanosterol demethylation. Thus, it results in 14αmethyl sterol accumulation, which blocks ergosterol synthesis, which is the principal Leishmanial sterol. Fluconazole is thought to be the best azole for this use because of its benefits, which include a lengthy half-life, high concentrations in the skin, and mild side effects (7, 8). Fluconazole, a hydrophilic bis-triazole, is well absorbed through the gastrointestinal tract and its toxicity is low (3).

Here, we reported a case of a rare clinical presentation of CL (lupoid form) treated unsuccessfully with oral fluconazole, followed by a review of the literature.

CASE REPORT:

A 47-year-old black Libyan man from Zliten city, presented to the dermatology out-patient department at Zliten Medical Center, 2 years ago, with asymptomatic ulcerated lesion in his left leg and reddish swelling in his right ear. The patient was otherwise normal. both lesions began as minute papules that enlarged slowly. On examination; there were oozy ulcerated erythematous plaque in the left leg and crusted infiltrated erythematous plaque in the right ear (figure 1). Patient was not feverish and lymph nodes were normal. The clinical diagnosis of wet type CL was made and confirmed by skin slit and smear test which demonstrated plenty of leishmania amastigotes inside and outside macrophages. Complete blood counts, renal function tests and liver function test were all within normal range. Patient was treated by intra-lesional pentostam once weekly for 6 weeks, while the leg ulcer healed with small scar, the swelling of the right ear failed to heal. We tried cryotherapy for other 6 weeks without benefit when we started intramuscular sodium stibogluconate which unfortunately was stopped by cardiologist due to abnormal ECG changes. After 18 months, the patient presented again to us with multiple nodules inside the erythematous infiltrated plaque in the right ear (figure 2).

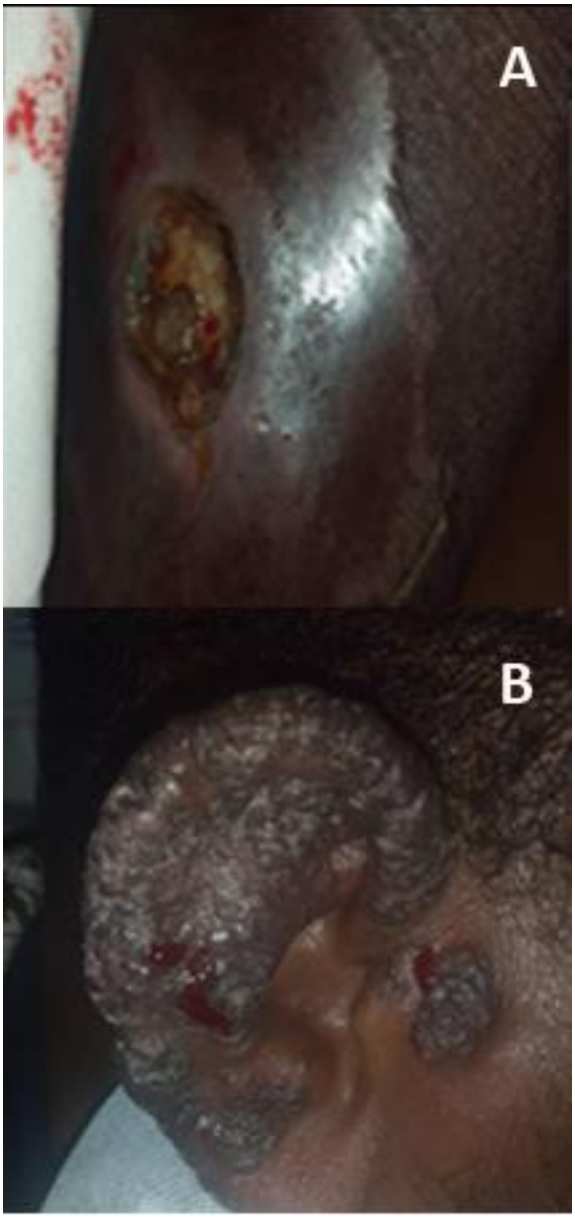

Figure 1: Two years ago; A. An oozy ulcerated erythematous plaque on the Lt leg. B. A large crusted erythematous and infiltrated plaque, extending over most of the right ear.

The case was reevaluated by skin slit smear, which showed extracellular and intra-macrophagic leishmania amastigotes (figure 3). Furthermore; histopatholgical analysis of biopsy from the lesion of the ear showed a granulomatous changes with giant cells and extracellular and intra-macrophagic leishmania amastigotes. At that moment the diagnosis of lupoid CL was confirmed. All lab investigations including complete blood count, liver function and renal function tests were normal. we started oral fluconazole 150 mg daily for 45 days and the patient was followed up fortnightly to detect any lab abnormalities and evaluate the clinical prognosis. Unfortunately, after 6 weeks there was no clinical improvement at all. on the other hand; neither considerable side effects nor lab abnormalities were noticed.

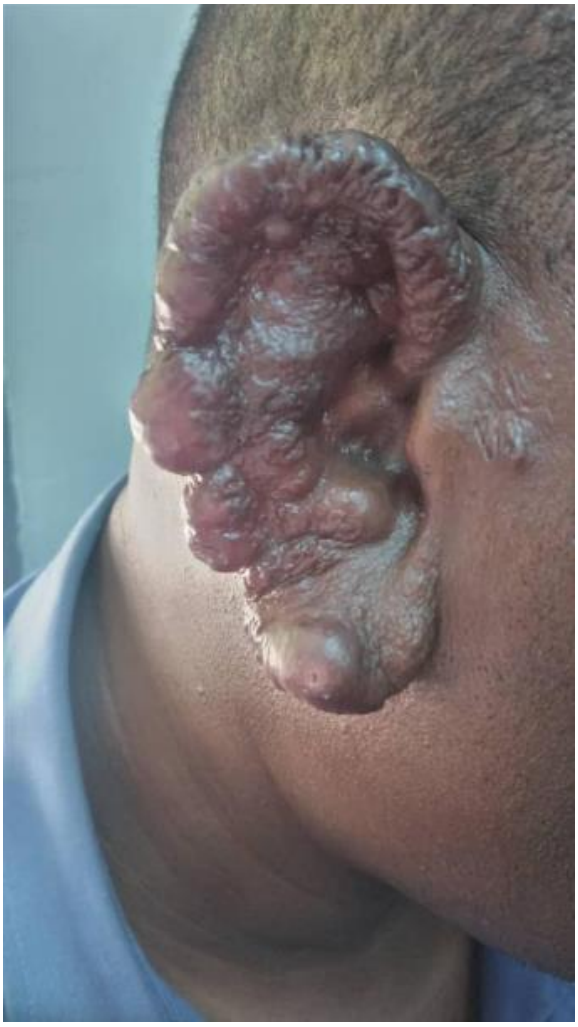

Figure 2: After 18 months, the patient presented again with nodules inside the infiltrated erythematous plaque in the right ear.

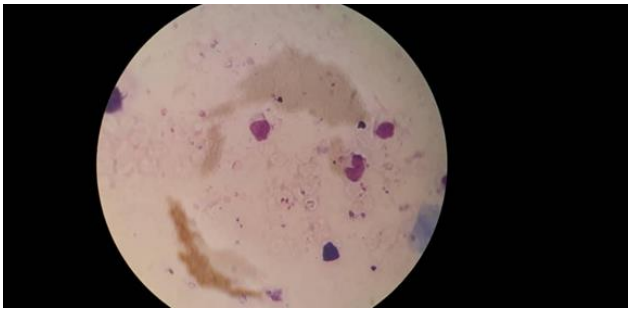

Figure 3: Skin slit and smear showed Leishmania amastigotes in and outside macrophages.

DISCUSSION:

The Western province of Libya is an endemic area for CL. The incidence of CL in Libya is more than thousands of patients annually. *L. major* causes greater than 90% of the recorded CL patients. *L. major* is primarily responsible for wet rural CL . *L. tropica* is responsible for dry urban CL (9). Despite the fact that CL is usually a self-limited disease, it may cause ugly scars and result in deformity and restriction of joint movement. Hence, therapy might be required to avoid such sequelae (10).

In our case the intralesional antimony failed to cure the ear lesion. Furthermore; the intramuscular antimony caused ECG changes made the cardiologist to stop the drug administration.

It is well-known that parenteral antimony may cause severe side effects such as hypotension, cardiac arrhythmia, thrombocytopenia (11). At that point we decided to use oral fluconazole for management of our case. Data concerning the efficacy of fluconazole in treating CL is variable. Many case reports and few studies showed that oral fluconazole was effective and safe. Khan and Zakai found that 200 mg of oral fluconazole for 45 days resulted in a good cure rate with insignificant lab abnormalities in liver function tests and creatinine (12). Khaled *et al.* reported that a middle-aged Tunisian lady with CL was healed by oral fluconazole at a daily dose of 200 mg for 45 days (13). In 2002, Alrajhi *et al.* from Saudi Arabia described a safe, complete healing for 63/80 (79%) of patients treated for 6 weeks with 200 mg daily of oral fluconazole, compared to only 22/65 (34%) of those on placebo (6). From Australia, Sklavos *et al.* reported an imported case of CL due to *L. major* in the limbs and face of a toddler for 3 months and noticed that all lesions were completely healed with cribiform scarring after a course of 150 mg fluconazole daily for 6 weeks. Therefore, they concluded that oral fluconazole seemed to be effective in treating CL, especially in children (14). Toubiana *et al.* described a complete cure for a girl with CL due to *L. major* after a 3-week course of oral fluconazole at a dose of 5 mg per kg daily without side effects (15). Tan *et al.* noticed a cure rate of 80% in a child with CL due to *L. tropica* after treatment with oral fluconazole at a dose of 6–9 mg/kg daily for 3 months (16). *Michelerio et al.* reported a safe, complete resolution with minimal scarring of CL lesions due to L. major or *L. tropica* in 3 children aged between 3 and 6 years after 6 mg/kg/d of oral fluconazole for 45 days (4). Benzaquen *et al.* found that a Tunisian old man with sporotrichoid CL (a rare presentation) due to *L. major* for one year was completely cured with fluconazole 200 mg twice daily for 2 months without complications or recurrence (5). Daly *et al.* reported a case of CL due to *L. viannia* that was recalcitrant to ordinary treatment but healed after a course of oral fluconazole (17). Sousa *et al.* found that oral fluconazole at a dose of 8 mg per kg daily was tolerable, cost-effective, and effective in treating CL caused by *L. braziliensis* (18). Veraldi *et al.* reported 4 Caucasians with recalcitrant CL due to *L. braziliensis* who were fully cured with fluconazole 400 mg daily for 6–11 months, with mild side effects, negligible lab abnormalities, and no relapse during several years of follow-up (8). Yaich *et al.* described a complete healing of CL lesions in a kidney transplant case with a 2-month course of oral fluconazole and allopurinol without recurrence for more than 3 years (19). Mixed results had been detected by Nepal *et al.* who treated 3 children with CL due to *L. Mexicana* with 6–12 mg per kg per day of oral fluconazole for 6–10 weeks. Two of them healed with fluconazole, but the third did not (1). Moreover; Stewardson *et al.* found that a six-week course of oral fluconazole 200 mg daily resulted in a complete healing of multiple lesions of CL due to *L. major* in a middle-aged Australian lady who returned from

Morocco, and at the same time, they noted a self-healing of a clinically diagnosed CL lesion in another woman (20).

On the other hand; Chacko *et al.* described a failure of a 2-month course of fluconazole at a dose of 100 mg/day in treating a toddler with CL from an endemic area of *L. tropica* (21). Also Morizot *et al.* prescribed 200mg of oral fluconazole daily (for children; 2.5 mg per kg per day) for 45 days and they found that the cure rate among the cases of CL due to *L. major* was 44.4% (12/27) which was similar to those of the placebo groups of other trials carried out on cases of CL due to *L. major*. They questioned the efficacy of fluconazole in treating CL due to *L. major* (22). Furthermore, Prates *et al.* carried out a study on 53 cases and concluded that a 4-week course of oral fluconazole at a dose of 6.5 to 8.0 mg per kg per day was not a suitable treatment for CL caused by *L. braziliensis* (7). After using oral fluconazole 450 mg daily for a month to treat 20 cases of CL caused by *L. guyanensis*, Francesconi *et al.* discovered that only one patient (5%) recovered. They concluded that 450 mg of fluconazole per day was ineffective in treating CL caused by *L. guyanensis* (3). In 2024, Parhizkar *et al.* found that the addition of 6 mg/kg/d fluconazole for 6 weeks to patients on cryotherapy (n = 28) did not provide statistically significant therapeutic value to those on cryotherapy alone (n = 24) in the treatment of CL (23).

The failure of fluconazole in curing our case may be due to the low dose of fluconazole used (200 mg/day) in treating the case. Fluconazole at high doses and long courses seems to be safe and tolerable. Despite the fact that fluconazole has been found to be ineffective in our case, we think that it may be useful in treating recalcitrant cases at higher doses and longer courses than ours. A further large study is advisable to evaluate the efficacy of fluconazole therapy for recalcitrant CL.

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