Two Cases of Cutaneous Leishmaniasis Treated with Itraconazole

Byoung Chan Park, M.D., Hee Jae Chae, M.D., Jong Yuk Yi, M.D.,
Baik Kee Cho, M.D., Won Houh, M.D., Dong Jin Kim, M.D.*, Won Young Choi, M.D.*

Department of Dermatology and Parasitology, Catholic University Medical College, Seoul, Korea*

Two patients with cutaneous leishmaniasis were treated with itraconazole. One patient was a 24-year-old man who had several erythematous papulonodules on the extremities for 1 month, which revealed cutaneous leishmaniasis, histopathologically. He was treated with itraconazole (200 mg/day) for 2 months. After treatment he showed clinical healing and the biopsy specimens no longer showed leishmania organisms. The other patient was a 27-year-old female who had several erythematous papulonodules on the face and neck for 3 months. The skin lesions revealed leishmania organisms in the tissue sections and culture media. She was also treated with itraconazole (200 mg/day) for 2 months. After treatment she also showed satisfying clinical healing and the biopsy specimens revealed no leishmania organisms.

No specific side effects were encountered in both patients during the treatment. From these results, itraconazole is considered to be one of the promising anti-leishmanial drugs.

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Leishmaniasis is an endemic disease in the Middle East, Africa, Southern and Central America, and the Mediterranean countries. The disease is caused by *Leishmania*, which is transmitted by species of sandflies belonging to the genera *Phlebotomus* (Old World) and *Lutzomyia* (New World)[1].

Since the first Korean case was reported in 1978[2], it is not so rare to find cutaneous leishmaniasis among the Koreans who went abroad for work or travel in endemic areas[3].

Chemotherapeutic treatment for leishmaniasis is often difficult. The presently available first choice (pentavalent antimonials) and second choice (amphoterecin B, Pentamidine) drugs are toxic and expensive and can be administered only parenterally[4, 5]. Attempts at nonpharmacological treatment using cryosurgery, surgical excision, or radiotherapy have been reported, but all of these treatments have their limitations[4, 5].

Recent trials with ketoconazole[6-9] and itraconazole[10-12] have led to promising results in the therapy of cutaneous leishmaniasis. Itraconazole is a newer synthetic triazole dioxolane derivative with antimycotic properties. Itraconazole is safer than ketoconazole, particularly regarding hepatic toxicity. Itraconazole interferes with the biosynthesis of the fungal cell wall by inhibiting the 14 alpha-demethylation of lanosterol thus preventing the synthesis of ergosterol. The antileishmanial effect of itraconazole appears similar to be fungal cell wall inhibition[10-12].

Here we present two patients in whom cutaneous leishmaniasis were successfully treated with itraconazole.

REPORT OF CASES

Case 1: A 24-year-old man was first seen at our hospital in September 1990 with several erythematous papulonodules on the right arm and left leg, which had appeared after travelling to Israel, an en-

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Reprint request to: Byoung Chan Park, M.D., Department of Dermatology and Parasitology*, Catholic University Medical College, Seoul, Korea.

demic area of cutaneous leishmaniasis, 2 months ago.

Physical examination showed several, linearly arranged, erythematous and edematous papulonodules with central ulceration and crust on the right arm and left leg (Fig. 1). The lesions slowly increased in size and became slightly painful. Laboratory examinations including complete blood cell count, urinalysis and blood chemistry were within normal limits. Skin sections taken from the ulcerated nodules showed epidermal necrosis and heavy inflammatory cell infiltration, predominately histiocytic, in the dermis. Numerous nonflagellate forms of leishmania organisms (amastigotes) were found within the cytoplasm of histiocytes (Fig. 2). A diagnosis of cutaneous leishmaniasis was made.

Itraconazole was given, 200 mg daily for 2 months. The patient was seen every two weeks to evaluate the clinical efficacy. Clinical improvement in the form of reduced erythema and lesion size was noted as early as 2 weeks of treatment. After 1 month of treatment, a second skin biopsy was performed in an area adjacent to the first biopsy site. No leishmania organisms were found in the cytoplasm of the histiocytes. After 2 months of treatment most of the lesions were healed leaving slight redness and atrophy (Fig. 2). The patient tolerated the treatment well, and no side effects were observed except nausea. No laboratory abnormalities were detected at the end of the treatment. An additional improvement was noted, with only slight redness and atrophy 1 month after completion of treatment.

Case 2: A 27-year-old female presented with several erythematous papulonodules on the face and neck in October 1990. The lesions had appeared after travelling with 'Case 1' to Israel 3 months prior.

Physical examination showed several erythematous papulonodules with central ulceration and crust on the face and neck (Fig. 4). The lesions slowly increase in size and became slightly painful. Even though the number of leishmania organisms identified in the histologic sections was very few, culture was successful by using Nicolle-Novy-MacNeal (NNN) media at 20°C. After 7 days numerous flagellate forms of leishmania (promastigotes) were grown in NNN culture media (Fig. 5). Complete blood cell count, liver and kidney function tests were within normal limits.

Itraconazole (200 mg/day) was given for 2 months. Protozoal culture and repeated skin biopsy 1 month after beginning the treatment gave negative results. At that time the size of lesions and erythema were markedly reduced. After completion of the treatment the lesions healed leaving only slight redness and atrophy (Fig. 6).

The patient tolerated the treatment well without side effects or laboratory abnormalities observed at the end of the treatment.

DISCUSSION

Cutaneous leishmaniasis has been sporadically seen in nonendemic areas. Several of these patients like our cases and other reported Korean cases[2, 3] have contracted the disease in endemic regions such as Saudi Arabia, Jordan, Iran, Iraq and Israel while working or travelling[13].

Although diagnosis of cutaneous leishmaniasis can be suggested by the clinical and histopathologic features, definitive diagnosis rests on isolation of the organisms in smears and cultures or their identification in tissue sections[1, 5]. We performed leishmanial cultures on the second case using NNN media and obtained positive results demonstrating flagellate forms of the organism.

Cutaneous leishmaniasis is of clinical importance because of its chronicity and its potential for local destruction and disfigurement. Unfortunately however, no satisfactory systemically administered drug against the disease has been developed. Reliance has been placed on a few

Legends for Figures

Fig. 1. Erythematous papulonodules with central ulceration and crust on the right arm before treatment.

Fig. 2. Numerous amastigotes of leishmania are present within the cytoplasm of histiocytes (H&E stain, ×1,000).

Fig. 3. After 2 months of treatment the lesions of the right arm healed leaving some redness and atrophy.

Fig. 4. Erythematous papulonodules with central ulceration and crust on the face before treatment.

Fig. 5. Electron micrograph of promastigotes of leishmania which possesses a nucleus(N) and distinct flagellum(F) (×10,000).

Inset: Aggregate of promastigotes of Leishmania sp(Giemsa smear, ×400).

Fig. 6. After 2 months of treatment the facial lesion healed leaving only slight redness and atrophy.

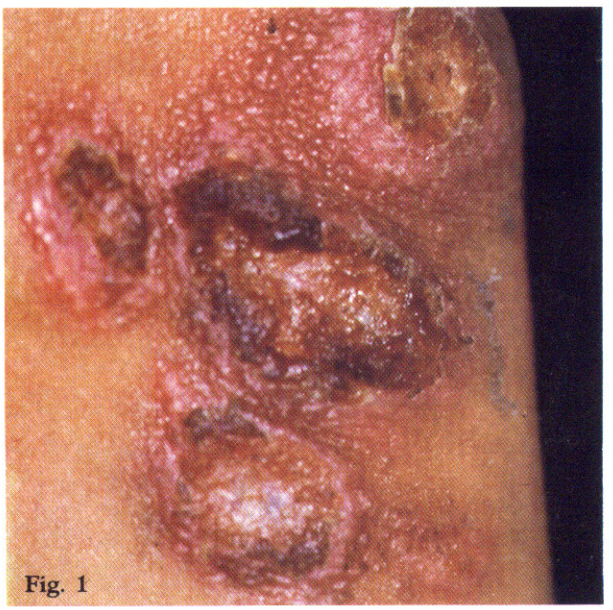
Fig. 1

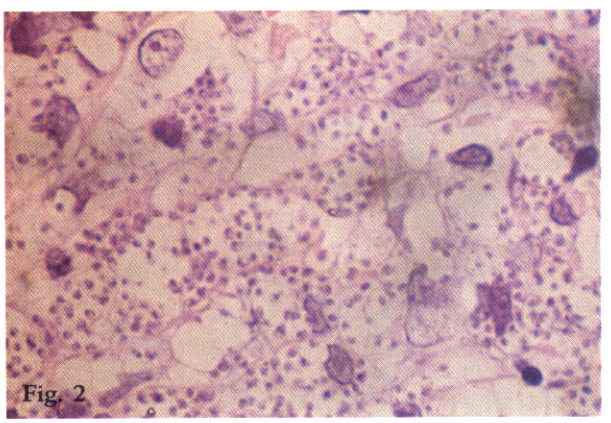
Fig. 2

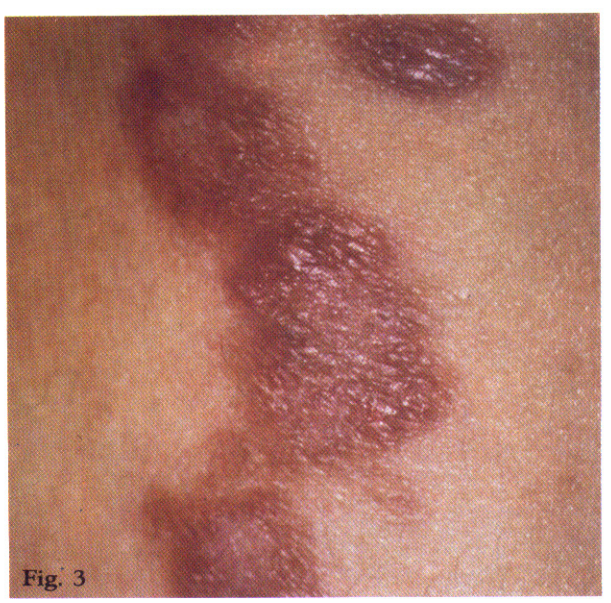
Fig. 3

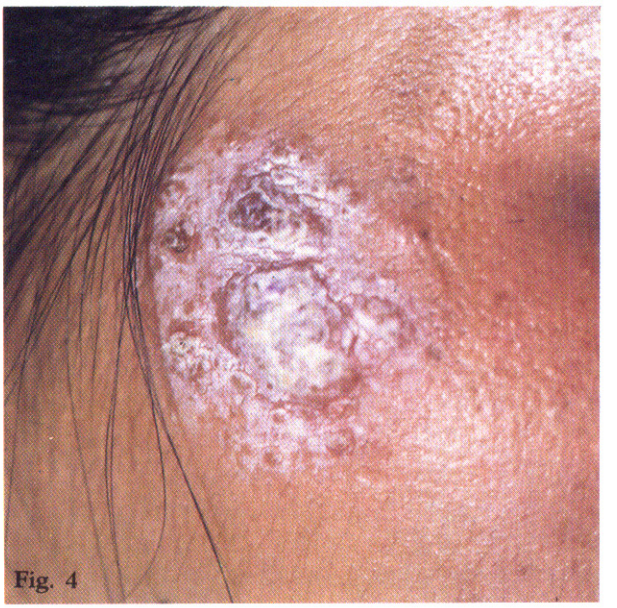
Fig. 4

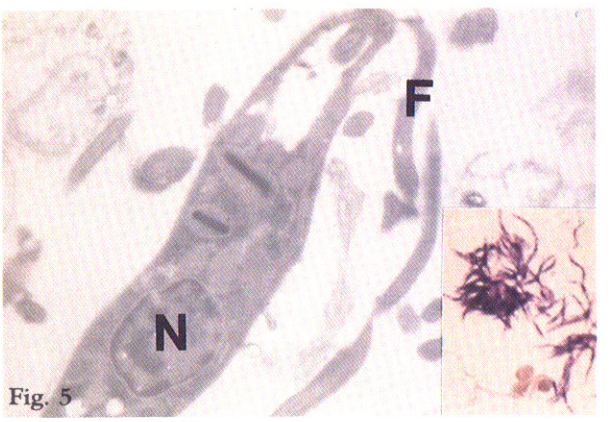

Fig. 5

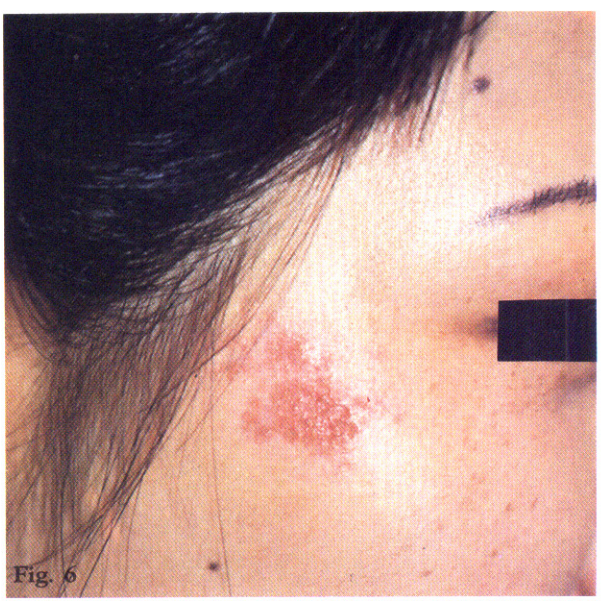
Fig. 6

drugs which are sometimes ineffective and may have associated side effects[1, 4]. Efficacious, more easily administered, and less toxic antileishmanial agents are required. In 1982, Urcuyo et al.[6] reported the successful treatment of six cases of cutaneous and primary mucocutaneous leishmaniasis caused by *Leishmania braziliensis*, using 400 mg ketoconazole daily for 12 weeks. Thereafter Weinrauch et al.[7], Jolliffe[8], and Kubba et al.[9], respectively, reported the clinical efficacy of ketoconazole in the treatment of leishmaniasis. Ketoconazole, an orally active imidazole derivative, has a wide spectrum of antifungal activity which is, at least in part, a result of its ability to interfere with sterol biosynthesis within fungal cell membranes. The antileishmanial effect of ketoconazole seems to be associated with the fact that leishmanial membranes also have high ergosterol content[4, 8, 9]. Recently, the newer and more effective antifungal agent, itraconazole, a synthetic dioxolane derivative, has been used in the treatment of cutaneous leishmaniasis with considerable success. Borelli[10], Albanese et al.[11] and Dogra et al.[12], respectively, reported the successful treatment of leishmaniasis using itraconazole (100-200 mg/day) for 1 to 2 months without demonstrable side effects. The therapeutic effect of itraconazole for leishmaniasis appears similar to that of ketoconazole as both drugs antifungal activity is due to the same mechanism. In our cases, both patients responded well and tolerated itraconazole. Definite clinical improvement was observed as early as 2 weeks following initial treatment. At the end of 2 months of therapy, both patients were relatively cured both clinically and histopathologically without side effects. The assessment of treatment in cutaneous leishmaniasis is difficult due to the fact that spontaneous healing is frequent. The time period required for this spontaneous healing is ill-defined[1, 5]. In this regard, we decided to limit treatment to 2 months so as to avoid superimposition of spontaneous involution.

To date there is no definitive treatment for leishmaniasis. Surgical and physical modalities such as excision, electrosurgery, cryotherapy and X-ray therapy are destructive and lead to scarring. Surgery has a limited value applicable only in the treatment of the early or single lesion. On the other hand, itraconazole, with its demonstrated effectiveness, safety and bioavailability, in our opinion, is a promising alternative to the treatment of cutaneous leishmaniasis.

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