Cutaneous Leishmaniasis treated with Terbenafine (Lamasil®) Case Report

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Male patient 44 years old (Asian skin type 4) presented with multiple disseminated oval indurated erythematous ulcerated infiltrated pruritic plaques (10-12 in number) measuring 3-5 cm in diameter and raised 4-5 mm over his exposed parts mainly extremities of one month duration with progressive course, there were smaller synchronous lesions on the shoulder and elbows(Fig.-01& Fig.2), no lymphadenitis detected, all laboratory results within normal limits. Patient is cement field worker, and he is living in Qatar for the last 3 years without traveling to any other countries. Patient did not received any kind of local or systemic therapy, and skin biopsy was preformed from one infiltrated lesions. The histopathological changes showed multiple granulomatous lesions (Fig.03) and leishmania bodies (Fig.04), which confirm the diagnosis of disseminated cutaneous leishmaniasis. Treatment started with terbinafine (Lamasile) Tablets 250mg PO per day for 6 weeks duration without any local therapy to be applied. The patient was regularly followed up every week in dermatological out-patient. The granulomatous lesions started to improved and regress in sizes after the second week of terbinafine therapy and at the end of the third week most of the lesions on his body started to fade

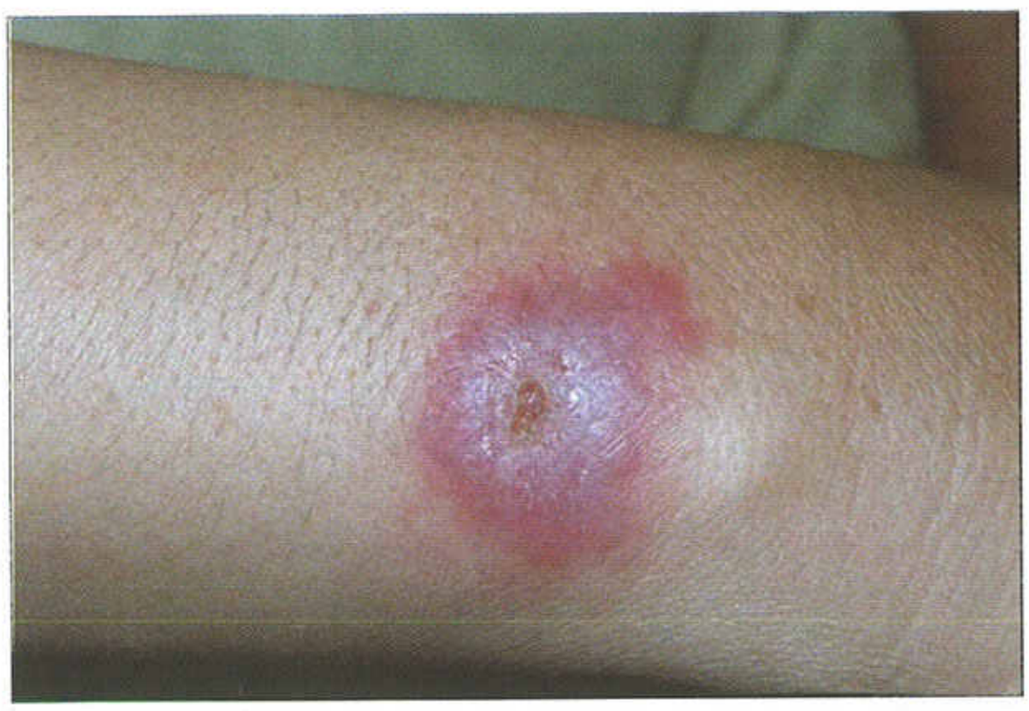

Fig. 01 Cutaneous Leishmaniasis before terbinafine

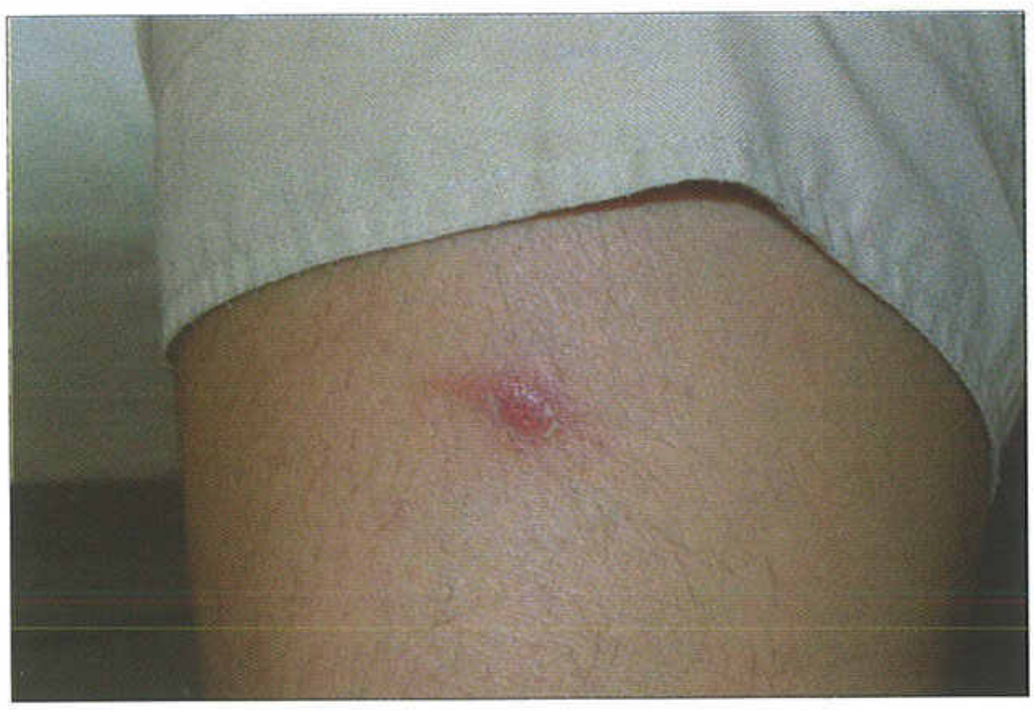

Fig. 02 Cutaneous Leishmaniasis before terbinafine

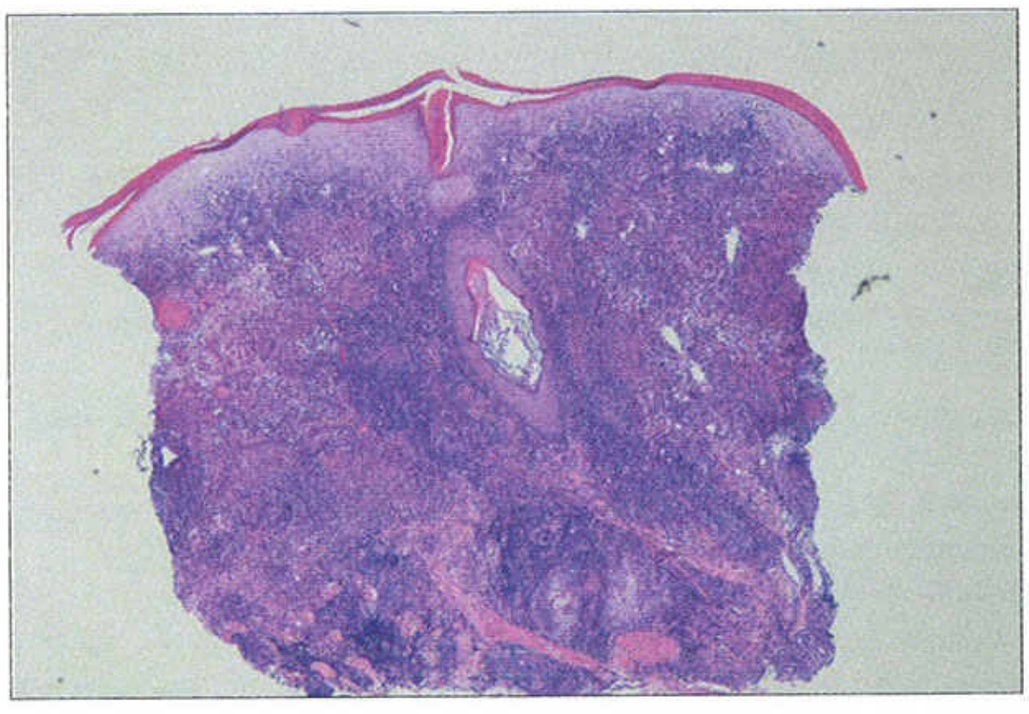

Fig. 03 Multiple infiltrated granulomas

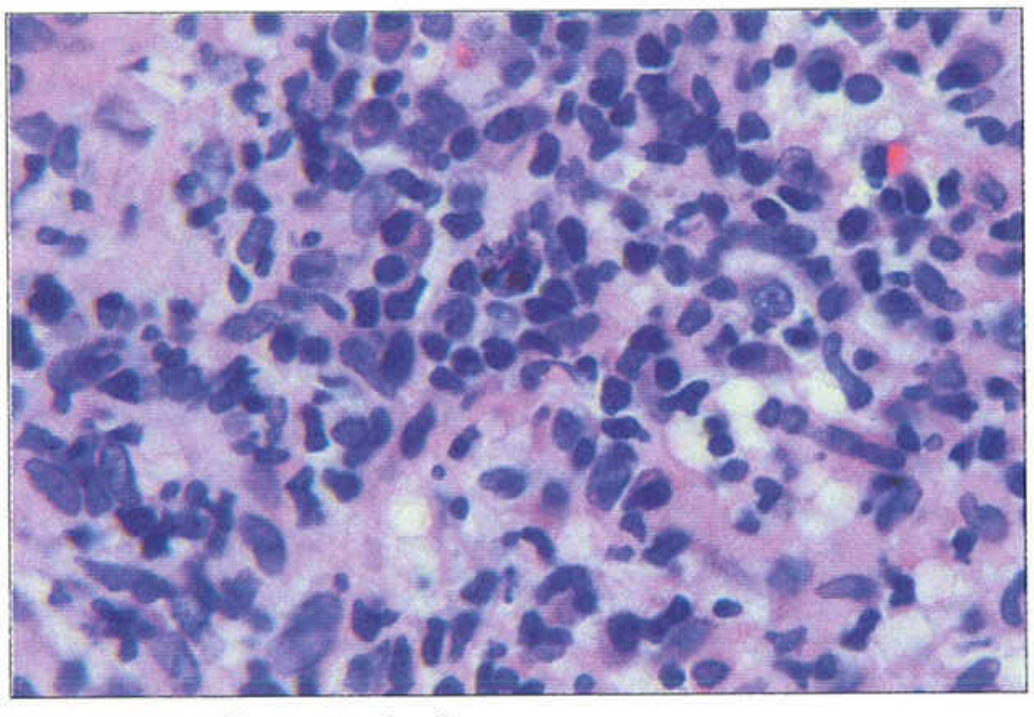

Fig. 04 Leishmanin bodies

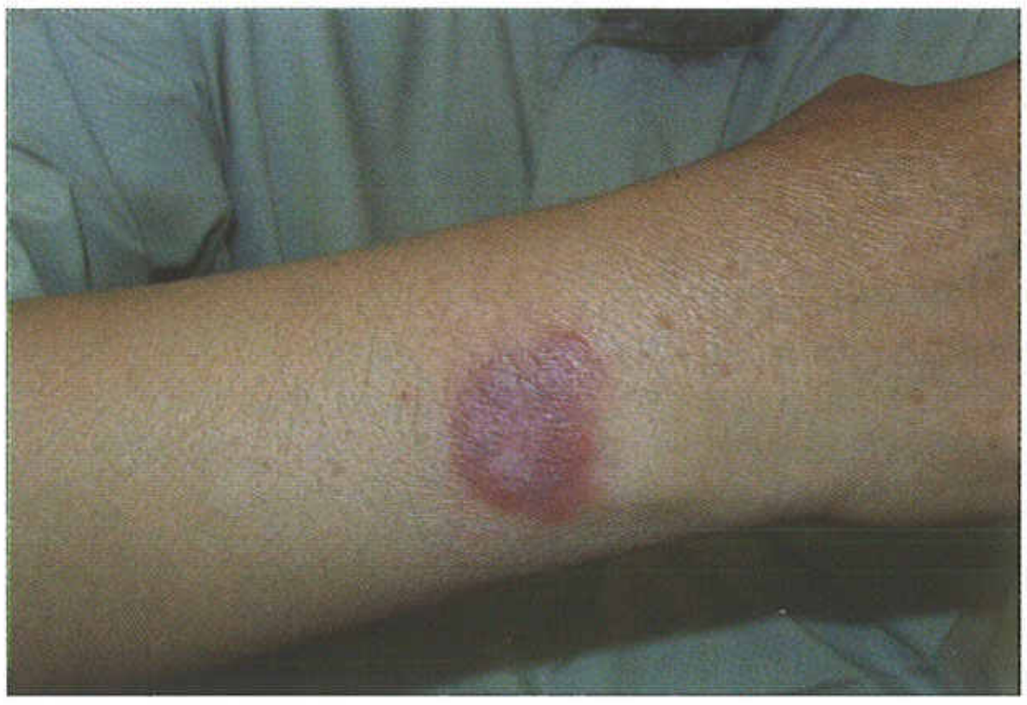

Fig. 05 Cutaneous Leishmaniasis after terbinafine 3 weeks

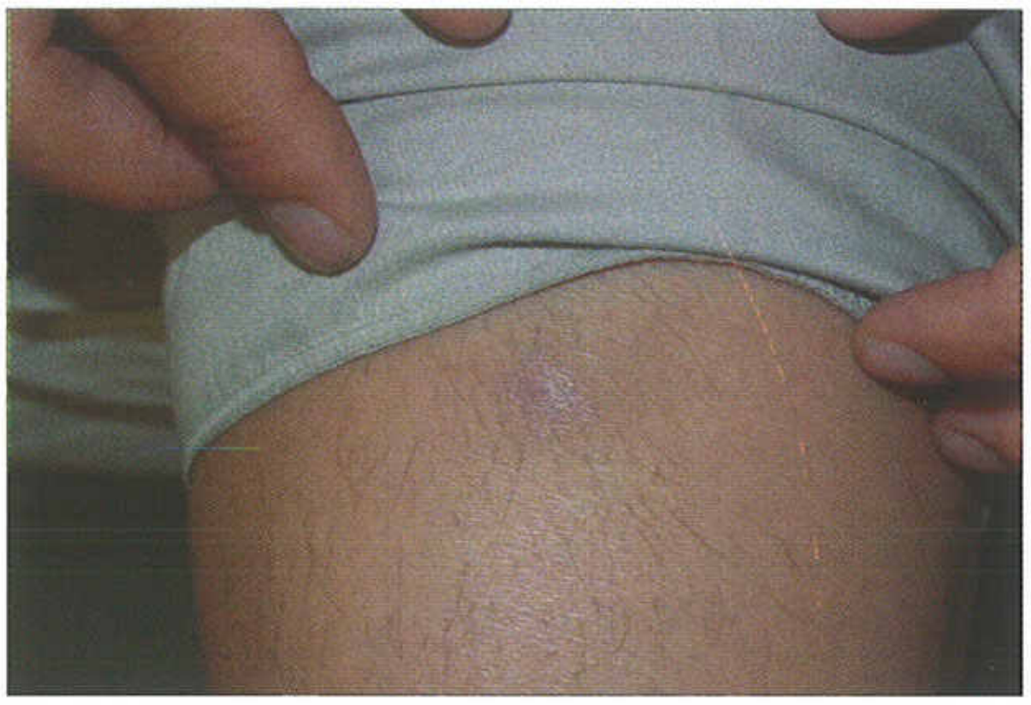

Fig. 06 Cutaneous Leishmaniasis after terbinafine 6th week

away by living mild erythematous patches (Fig.05) and most of the lesions decreased in the diameter to normal skin level, and at the sixth week of therapy patient was full recover from leishmaniasis with residual hyperpigmentation and very minimal scarring in few areas (Fig.06).

Introduction :

Leishmaniasis is a zoonotic infection caused by the protozoa belonging to the genus *Leishmania*. It is named for Leishman, who first described it in London in May 1903. Leishmaniasis is transmitted by sandflies (*Phlebotomus* species), and, in the human host, *Leishmania* are intracellular parasites that infect the mononuclear phagocytes. The spectrum of human disease ranges from self-healing localized ulcers to widely disseminated progressive lesions of the skin, mucus membranes, and the entire reticuloendothelial system.

The *Leishmania* species infecting humans mainly are the *Leishmania donovani* causing visceral leishmaniasis (kala azar) and cutaneous leishmaniasis caused by *Leishmania tropica* and *Leishmania brasiliensis*. Visceral leishmaniasis is distributed all over the world but predominantly is encountered in India, South America, Central Asia, Middle East, and Africa. Cutaneous leishmaniasis caused by *L tropica* is seen mainly along the shores of the Mediterranean, through the Middle East, central Africa, and parts of India. Cutaneous leishmaniasis caused by *L brasiliensis* is confined mainly to Central America and South America.

Leishmaniasis is considered to be endemic in 88 countries (16 developed countries, 72 developing countries) on 5 continents of Africa, Asia, Europe, North America, and South America. A total of 350 million people are at risk. Geographical distribution of leishmaniasis is limited by the distribution of the sandfly, its susceptibility to cold climates, its tendency to take blood from humans or animals only, and its capacity to support the internal development of specific species of *Leishmania*.

Cutaneous leishmaniasis occurs mainly in 2 forms, oriental sore caused by L tropica and American cutaneous leishmaniasis caused by *L brasiliensis*. There is no difference in the pathology of the lesions caused by *L tropica* and *L brasiliensis*. Cutaneous leishmaniasis produces skin lesions mainly on the face, arms, and legs. Although this form is often self-healing, it can create serious disability and permanent scars. After recovery or successful treatment, cutaneous leishmaniasis induces immunity to reinfection by the species of *Leishmania* that caused the disease.

Urban cutaneous leishmaniasis caused by subspecies *L tropica* causes a dry type of cutaneous ulcer in the face and has an urban distribution. Incubation period is approximately 2 months. It is common in Western India, North Africa, Mediterranean area, and Middle East. A similar disease in Mexico, Honduras, and Guatemala is known as the bay sore or chiclero ulcer. It is a chronic lesion occurring at the site of sand fly bite.

Rural cutaneous leishmaniasis is caused by *L tropica* major and has a rural distribution. The moist type of cutaneous lesions are multiple, on the extremities, and are associated with marked local subcutaneous infiltration and regional lymphadenitis. Both lesions are common in Central Asia.

Diffuse cutaneous leishmaniasis is associated with a deficient cell-mediated immunity that enables the parasite to disseminate in the subcutaneous tissues. It starts as a single lesion and spreads slowly over the face, ears, extremities, and buttocks until the whole body is affected. The lesions are neither destructive nor erosive but are disfiguring. The lesions are misdiagnosed as leprosy and are resistant to treatment.

Pentavalent antimonials sodium stibogluconate (Pentostam) have been cornerstone of treatment of leishmaniasis for the last six decades. Acts by interfering with the metabolism of the parasite, dose of 20 mg/kg/d IV/IM for 20 days.

Amphotericin B can be fungistatic or fungicidal used to treat leishmaniasis it binds to sterols (eg, ergosterol) in the fungal cell membrane, causing intracellular components to leak with subsequent fungal cell death. Cure rates of >90% have been observed in various studies. High cost is a disadvantage to its use in areas where visceral leishmaniasis is prevalent. Available as 100 mg/20 mL preparation. 3-4 mg/kg IV qd for 5 days; concentration of IV infusion should be 1-2 mg/mL, also fluconazole ,ketoconazole 600mg/day for 28 days and Itraconazole 200mg 4 times a day for 28 days , Imidazole broad-spectrum antifungal agent; inhibits synthesis of ergosterol, causing cellular components to leak, resulting in fungal cell death had been tried to treat cutenous leishmaniasis. Allopurinol (Zyloprim) — Inhibit xanthine oxidase, the enzyme that synthesizes uric acid from hypoxanthine. Reduces the synthesis of uric acid without disrupting the biosynthesis of vital purines20 mg/kg/d PO divided bid/tid .

Discussion:

Treatment of leishmaniasis is far from satisfactory: Most antileishmanial drugs are toxic and must be used parenterally for prolonged periods, especially for visceral leishmaniasis. In recent years some antifungal drugs such as ketoconazole, fluoconazloe, itracanazole and terbinafine in treating cutaneous leishmaniasis were found to be safe and some showed effectives of the course of the disease. The development of allylamine antifungals (squalene oxidase inhibitor), terbinafine is highly active against a broad spectrum of pathogenic fungi. Clinical studies have shown that terbinafine is effective in the treatment of both cutaneous and lymphocutaneous sporotrichosis, and in several patterns of disseminated and refractory aspergillosis. Patients with chromoblastomycosis, and other mycoses (phaeohyphomycosis, maduromycosis, and mucormycosis), Old World cutaneous leishmaniasis which contain squalene oxidase have also been successfully treated with terbinafine[1]. These results suggest that the therapeutic potential of terbinafine extends well beyond its currently licensed applications to include a range of serious and life-threatening subcutaneous and systemic mycoses. In 1997 the efficacy of terbinafine against cutaneous leishmaniasis was accidentally demonstrated in a human immunodeficiency virus (HIV)- positive patient prescribed 2 weeks of oral therapy for onychomycosis and tinea corporis[1]. however, kalazar , a form of visceral (systemic) leishmaniasis, did not respond to combined terbinafine and itraconazole in nine Sudanese patients[2]. In an open-label pilot study of cutaneous leishmaniasis from Saudi Arabia[3], 14 patients completed a trial of terbinafine, 250-500 mg /day for 4 weeks. Four were cured and six had partial response. For over 100 years, dating back to traditional medicine, it has been known many antifungals also sometimes have antiparasitic properties[4].

Additionally, it has been known for over 50 years that antifungals such as amphotericin B, pentamidine, and ketoconazole have a rule in treatment of leishmaniasis[5]. Recently many studies showed that some compounds act indirectly on the Leishmania as steroidal synthesis regulators: human insulin, human transferrin, and low density lipoprotein (LDL). Both transferrin and insulin are either inhibitors or growth stimulants of human and, possibly also, leishmanial sterol synthesis depending on concentration, Other sterols, synthesized only by the Leishmania and fungi, may act to regulate the host cells (monocyte or macrophage) to prevent parasite killing, e.g. by increasing intracellular Ca.sup.++ level[6&7].

Lipid analysis of several Leishmania spp. revealed that these parasites' membranes contain a high percentage of ergosterol, a sterol found in fungi and

some bacteria, which presents a basis for common mechanism of action of antifungal drugs on leishmania and drugs which interrupt the quantity, transport, or delivery of cholesterol and ergodterol to the parasite would have potential to adversely affect leishmanial survival[8].

Our case with minimal dose of terbinafine 250mg per day responded very well and within three weeks time most of the lesions started to disappear and this improvement confirm that terbinafine can be use safely in higher doses 500mg or more and longer treatment duration and in combination with other antileishmanial drugs which needs further studies in future.

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