CASE REPORT

Cutaneous leishmaniasis in an overseas Filipino worker who responded favorably to oral itraconazole

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Introduction: Cutaneous leishmaniasis is non-endemic in the Philippines. Antiparasitic pentavalent antimonials are acknowledged as first-line therapy for all forms of the disease. Amphotericin B is the second drug of choice but its use is limited due to side effects.

Case Summary: We present a case of a 32- year-old male overseas Filipino worker who presented with "volcaniform plaques" (nodules and plaques with central crater) and surrounding satellite erythematous papules on the trunk, and extremities after returning from Iraq. A diagnosis of cutaneous leishmaniasis was confirmed by the histopathologic findings of a granulomatous inflammatory infiltrate with round to oval basophilic structures in the cytoplasm of macrophages (Leishman bodies) in the dermis, which were highlighted prominently by Giemsa stain. The patient showed poor response to treatment with 4 weeks of oral Rifampicin 1200 mg daily divided into 2 doses. He was shifted to oral Itraconazole 400 mg daily divided into 2 doses for 6 weeks with dramatic improvement.

Conclusion: This case report highlights the favorable therapeutic response of cutaneous leishmaniasis to oral itraconazole and hence, may be recommended as first-line medication to treat infected overseas workers from endemic areas who seek treatment in the Philippines.

Keywords: Cutaneous, Leishmaniasis, Oral Itraconazole.

INTRODUCTION

Leishmaniasis, a vector-borne disease, is caused by protozoans of the genus *Leishmania* and transmitted via infected female sandflies (*Phlebotomus* and *Lutzomyia*).[1,2]Worldwide, the disease is endemic in more than 90 countries in the tropics, subtropics, and southern Europe. Different *Leishmania* species cause Old World (Eastern Hemisphere) versus New World (American) cutaneous leishmaniasis.[2–5] According to the WHO report in 1990, worldwide prevalence of people infected with leishmaniasis is estimated at 12 million.[5]There is an estimated incidence of 700,000 to 1 million new cases and 20,000 to 30,000 deaths occur annually. [4]

There are 3 main forms of leishmaniasis: (1) visceral (also known as kala-azar and the most serious form of the disease), (2) cutaneous, and (3) mucocutaneous. [5]Cutaneous leishmaniasis (CL) is the most common form of leishmaniasis.[2,4,6]Diagnosis of CL (confirmed case), according to WHO 2014is based on clinical features, and parasitological confirmation of the diagnosis (positive smear or culture).[7]

Overall, there are more than 20 species of Leishmania worldwide and the subtype of disease relates to the species of infecting Leishmania and the interplay of the genetic background and immune status of the host. [8]

Simple cutaneous lesions are most often self-healing within 1 to 2 years but in some cases, such as those caused by *L. panamensis, L. mexicana* and *L. braziliensis*, can progress to involve mucocutaneous tissue. The resolution of cutaneous lesions can often be accelerated by medical treatment.[5]

Pentavalent antimonials is the conventional treatment of choice; however, some cases of resistance have been reported. Amphotericin B is the second-choice therapy. These drugs are expensive and difficult to obtain, especially in the non-endemic area. They must be delivered parenterally, have numerous adverse effects,

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Source of funding: none
Conflict of interest: none
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and many cases of drug-resistant parasites have been reported.[9] Alternative treatment for CL include miltefosine, pentamidine isethionate, antifungal agents (such as, ketoconazole,fluconazole, itraconazole), paromomycin, granulocyte macrophage colony-stimulating factor, and heat therapy or cryotherapy had shown favorable efficacy in some literatures.[2,6,8,9]

CASE REPORT

A 32-year-old male OFW returning from the Middle East presented with a 5-month history of few pruritic erythematous macules and papules whichstarted on the left arm.The lesions increased in size and number after 3 months, evolved into painless ulcerated plaques and nodules, then spreading to the trunk and left leg. He worked in day/night shift as an engineer in a generator company located in the middle of the desert in Iraq and Saudi Arabia for 3 years. Past medical history and family medical history were non-contributory. Review of systems was unremarkable. There were no mucosal lesions. Dermatologic examination showed large reddish-brown to purple "volcaniform" ulcerated nodules and plaques sized 5 x 6 cm to 9 x 11 cm, surrounded by small satellite erythematous papules on the trunk, and extremities. (Figure 1)

A 4-mm skin punch biopsy from the plaque on the back showed scales crusts in the stratum corneum and focal ulceration of the epidermis. The dermis reveals a nodular granulomatous inflammatory inflitrate of histiocytes, lymphocytes and plasma cells. (Figure 2). Round to oval basophillic structures are present in the cytoplasm of macrophages which are better highlighted by Giemsa stain. (Figure 3)

The patient was initially treated with 4 weeks of oral Rifampicin 1200 mg daily divided into 2 doses with no significant improvement. Six weeks of oral Itraconazole 400 mg, divided into 2 daily doses was initiated thereafter, which showed significant improvement, characterized by drying up and flattening of lesions and markedly decreased inflammation (Figure 4). The use of the medication and possible side effects, such as nausea, vomiting, or diarrhea were evaluated every 2 weeks during follow-ups. Routine blood test for liver function abnormalities was determined before treatment and also at 15-day intervals until the end of treatment which revealed normal results.

DISCUSSION

Leishmaniasis is a global term for cutaneous and visceral anthroponotic and zoonotic diseases caused by the

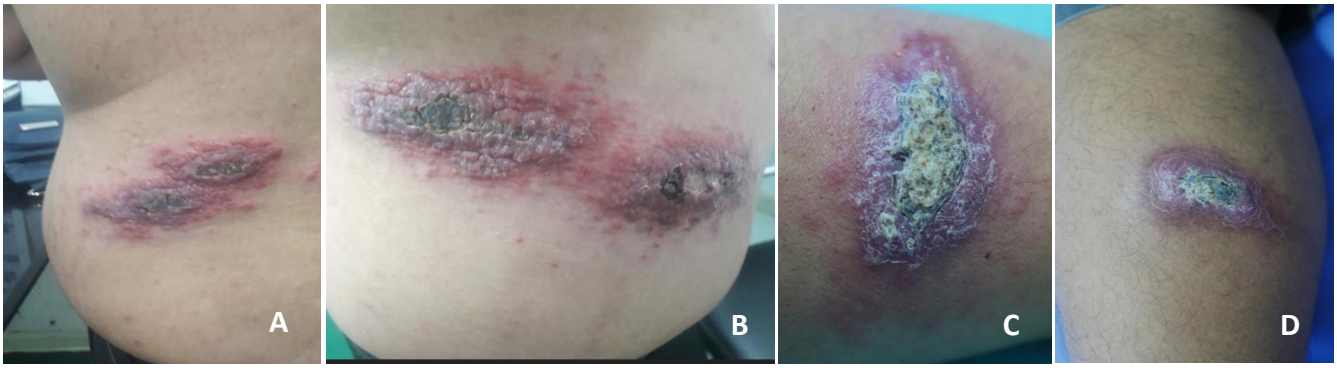

Figure 1. "Volcaniform" ulcerated nodules and plaques surrounded by small satellite erythematous papules on the (A) back, (B) abdomen, (C)left arm and (D) left leg.

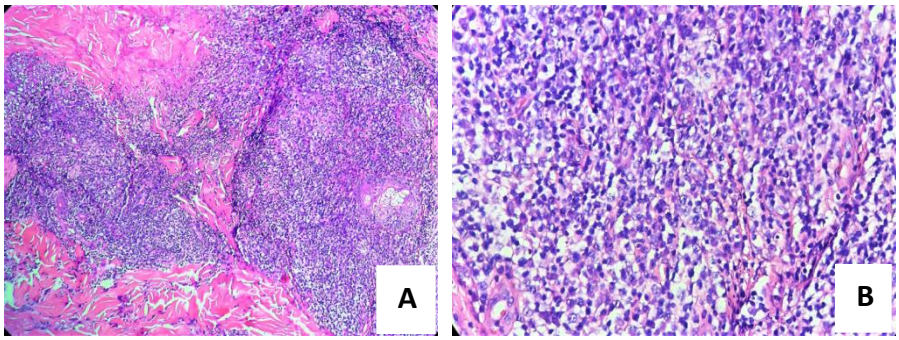

Figure 2. Histopathology of the biopsy specimen: nodular granulomatous inflammatory infiltrate of histiocytes, lymphocytes and plasma cells in the dermis (A) H&E,x40 (B) H&E,x100

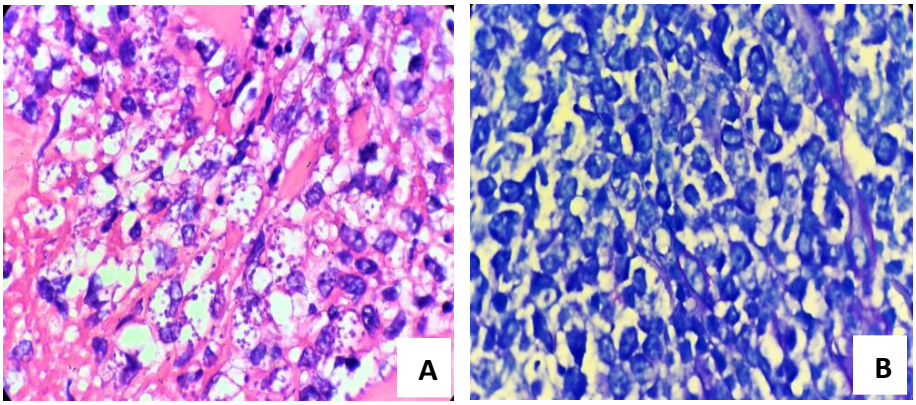

Figure 3. Histopathology of the biopsy specimen: (A) Round to oval basophilic structures are present in the cytoplasm of macrophages (H&E, x100) which are better highlighted by (B) Giemsa stain, x100.

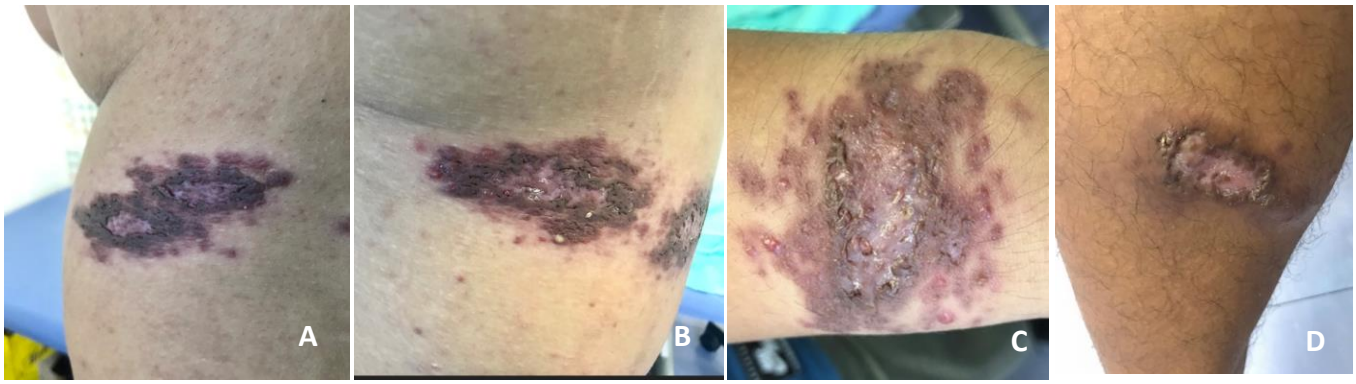

Figure 4. Significant improvement of the lesions with scarring on the (A) back, (B) abdomen, (C)left arm and (D) left leg after 6 weeks treatment with oral itraconazole 400 mg/day.

vector-borne parasites of the genus Leishmania.[1,2] Worldwide, the disease is endemic in more than 90 countries in the tropics, subtropics, and southern Europe. It is usually is more common in rural than in urban areas. Human migration, climate and other environmental changes have the potential to expand the geographic range of the sand fly vectors and the areas in the world where leishmaniasis is found.[2–5] According to the WHO report in 1990, worldwide prevalence of people infected with leishmaniasis is estimated at 12 million.[5] There is an estimated incidence of 700,000 to 1 million new cases and 20,000 to 30,000 deaths occur annually. [4]

The life cycle of the unicellular Leishmania species begins in the gut of the phlebotomine sandfly, which belongs to the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World. In these insect vectors, the parasites are flagellated, found extracellularly, and multiplies in vector's gut then migrating to the salivary glands (promastigote). The parasite enter the host when the female sandfly feeds. It will be ingested by macrophages (amastigote), become intracellular, non-flagellated then triggering host immunologic response.[5]

Experimental studies have indicated that several components of innate and adaptive immunity, including phagocyte cells, NK cells, effector CD4+ and CD8+ T cells, and regulatory T (Treg), T-helper1 (Th-1) and Th-2 cells, are involved in the control of leishmaniasis.[10,11]Treg cells may play a crucial role in controlling Th1 and Th2 responses in vivo.[10]

Cutaneous leishmaniasis is the least severe form of the disease and causes skin lesions, mainly nodules or ulcers, on exposed parts of the body such as the face, forearms and lower legs, evolve over weeks to months, resolving with scars and serious disability.[4,8]Most of CL cases occur in the Americas, the Mediterranean basin, the Middle East and Central Asia. In 2015, over two thirds of new CL cases occurred in 6 countries: Afghanistan, Algeria, Brazil, Colombia, Iran (Islamic Republic of) and the Syrian Arab Republic.[4]

The manifestations of leishmaniasis depend on the responsible species, which have geographic predilections and local ecological characteristics. Old World leishmaniasis (*Leishmania tropica*, *Leishmania major*, *Leishmania aethiopica*, and *Leishmania donovani*) is endemic in Asia, Africa, the Mediterranean region, and the Middle East.[5]*L major* and *L aethiopica* cause cutaneous lesions as well, whereas *L donovani* is implicated in visceral leishmaniasis, also known as kala-azar or black fever. In the Middle East.[5] In New World leishmaniasis (*Leishmania mexicana*, *Leishmania braziliensis*, and *Leishmania guyanensis*) distributed over Central America, most of South America, and southern Texas.[5] *L braziliensis complex, Leishmania panamensis*, and *L guyanensis*can cause the mutilating destructive mucocutaneous leishmaniasis, referred to as espundia. *Leishmania peruviana*, which is part of the *L braziliensis* complex, causes cutaneous and mucocutaneous disease, known as uta.[5]

Leishmaniasis is not endemic, and hence rarely been reported in the Philippines. Retrieving a history of travel and living in endemic countries in a person presenting with "volcaniform" nodules and plaques is necessary and warrants further laboratory investigation.

Several diagnostic methods with a variation in diagnostic accuracy have been described, including direct parasitologic examination (microscopy, histopathology, and parasite culture) and/or indirect test visualizing parasites in tissue by immunologic or serologic methods; culture and detection of parasite DNA are useful laboratory investigation. Parasitologic diagnosis is still considered the gold standard in leishmaniasis diagnosis because of its high specificity. Microscopical diagnosis of CL is performed by the direct identification of amastigotes in Giemsa-stained lesion smears of biopsies, scrapings, or impression smears.[2]Amastigotes appear as round or oval bodies, about 2–4 lm in diameter, with characteristic nuclei and kinetoplasts which is presented also in our patient's histopathologic findings. Culture and PCR testing are technically difficult laboratory techniques that are not currently practical in developing non-endemic countries.[12]

The main purpose of CL treatment is to prevent morbidity and mortality.[6] The objective of treatment is not parasitologic cure, but clinical healing. The interrelated goals of treatment are to minimize local tissue damage, to accelerate cure, reduce scarring, and attempt to prevent dissemination (eg, mucosal disease) or relapse. [6,12]Treatment is especially likely to be given for persistent lesions (≥6 months) or lesions that are located over joints, multiple (5–10 or more), or large (4–5 cm or more).[12] No universally applicable treatment has been identified for CL; the choice of agent, dose, and duration of therapy should be individualized.[6]

Treatment of leishmaniasis can be challenging. Pentavalent antimonial compounds (e.g., sodium stibogluconate and meglumine antimoniate) have been the drugs of choice for the treatment of leishmaniasis for decades worldwide despite their severe side effects (up to 20 injections of moderately toxic drug), and some reported cases of treatment failure and relapse rates.[12,13] Pentamidine and amphotericin B are alternative drugs commonly recommended; however, they may have significant side effects and also require parenteral administration.[9,12] These drugs are expensive and difficult to obtain, especially in the non-endemic area.

One of the alternative treatment that had been reported effective in treating CL is Itraconazole.[9,14] Itraconazole possess antiproliferative effects against *L. amazonensis* promastigotes and intracellular amastigotes.[13]Itraconazole is a known azole antifungal that inhibit ergosterol biosynthesis at the level of sterol C14-α-demetilase (CYP51), an essential enzyme in the sterol biosynthesis pathway in the cellular membranes of Trypanosomatids (*Leishmania spp, and Trypanosoma cruzi*). [13] The inhibition of ergosterol biosynthesis for the cytoplasmic membrane leads to an accumulation of 14-α-methilesterols which break phospholipid chain union and inhibit cell growth.[14]

Response to treatment is assessed by clinical criteria. Repeat parasitologic testing is not recommended if the skin lesion appears to be healing. The healing process may continue after the treatment course is completed, especially for large ulcerative lesions. The first sign of healing is usually flattening of the skin lesion. By 4–6 weeks after treatment, the lesion size should have decreased by >50%, ulcerative lesions should be reepithelializing, and no new lesions should be appearing. Ulcerative lesions are generally fully reepithelialized and clinically healed by approximately 3 months after treatment. Persons with CL should have their skin lesions monitored for 6–12 months after treatment for clinical evidence of therapeutic failure, which is initially seen as recurrence at the border of a healed lesion.[6]

The present case report showed resolution of lesions after receiving oral itraconazole 400 mg/ day, divided into 2 daily doses for 6 weeks. Flattening and decrease in size of the ulcerated nodules and plaques were appreciated in our patient. No new lesions appeared after treatment. These findings show the favorable efficacy of oral itraconazole in CL. All the hematologic parameters for liver function abnormality remained at normal levels.

CONCLUSION

This case report highlights the safety and favorable therapeutic response of cutaneous leishmanisis to orally

administered itraconazole and hence, may be recommended as treatment of choice for infected overseas workers who have returned to the Philippines for treatment. Controlled studies with a larger number of patients are needed to fully evaluate the efficacy and safety of itraconazole in the treatment of this rare and non-endemic disease.

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