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【 CASE REPORT 】

Failure of Liposomal-amphotericin B Treatment for New World Cutaneous Leishmaniasis due to *Leishmania braziliensis*

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Abstract:
Liposomal-amphotericin B (L-AmB) is used for cutaneous leishmaniasis (CL); however, its treatment failure has not yet been described in detail. A 58-year-old man returned from the Republic of Venezuela with a cutaneous ulcer on his left lower leg. The causative pathogen was *Leishmania braziliensis*. We started L-AmB 3 mg/kg/day for 6 days; however, the ulcer did not resolve. The patient was successfully retreated with a higher dose L-AmB 4 mg/kg/day 9 times (total, 36 mg/kg). If L-AmB fails to treat CL and other therapeutics cannot be used, increasing the L-AmB dose is a viable option.

Key words: cutaneous leishmaniasis, *Leishmania braziliensis*, liposomal-amphotericin B

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Introduction

Leishmaniasis, a protozoan disease transmitted by sandflies, is classified into cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (ML), and visceral leishmaniasis (VL) according to the clinical presentation. Leishmaniasis contracted in the North and South American continents is called new world leishmaniasis. Approximately 1-10% of new world CL (NWCL) can develop into ML (1). These new world leishmania species, e.g. *Leishmania braziliensis*, are mainly distributed in South and Central America.

In the endemic areas, self-limited NWCL is well-recognized, and systemic therapy is not always administered. Conversely, in nonendemic areas (the United States and Europe) systemic treatment is recommended for NWCL, particularly cases caused by *L. braziliensis* (2, 3), as ML is a concern and CL causes cosmetic and functional damage and secondary bacterial infection (3). As a systemic treatment, liposomal-amphotericin B (L-AmB) is currently a treatment option for NWCL caused by *L. braziliensis*. Favorable results (high therapeutic effects and short treatment durations) have been reported in practical reviews (1, 4); however, the optimal therapeutic dose and duration of L-AmB for NWCL remain unclear. Furthermore, there have been no detailed reports concerning retreatment with L-AmB for CL caused by *L. braziliensis* in immunocompetent hosts.

We herein report a case of NWCL caused by *L. braziliensis* with a poor response to L-AmB and oral fluconazole. We successfully retreated the patient with an increased dose of L-AmB. We describe the clinical course in detail and discuss how to treat cases of CL with L-AmB primary failure.

Case Report

A 58-year-old Japanese man traveled to the Bolivarian Republic of Venezuela to make films about the nature of the Guiana Shield twice during the past year. The first visit was 6 months earlier and had lasted for 30 days; his more recent visit had been approximately one month before visiting our outpatient clinic and lasted for 17 days. He did not perceive

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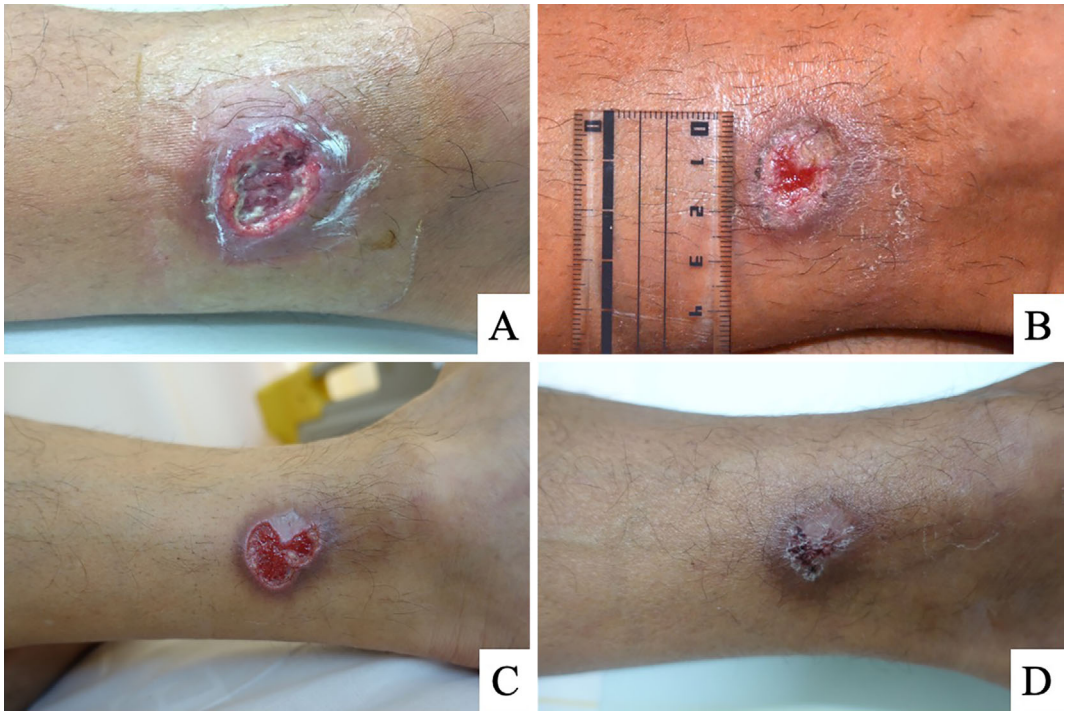

Figure. Therapeutic response of L-AmB for cutaneous leishmaniasis caused by *L. braziliensis*. A: Before treatment. B: One month after usual-dose L-AmB therapy, the ulcer seemed shallow. C: Before retreatment, the ulcer had expanded. D: One month after high-dose L-AmB therapy, the ulcer had healed.

any bug bites during these trips. During the latter half of the recent trip, however, he noticed a nodule on his left lower leg that gradually broke and ulcerated. He visited a local hospital and received a clinical diagnosis of NWCL; however, he returned to Japan without receiving treatment. On his return to Japan, he visited our hospital for the further assessment and treatment.

The findings of a physical examination were normal, except for a single, round ulcer with a well-defined raised border 2.5 cm in diameter on his left lower leg (Figure A). There were no signs of secondary infection and no mucosal symptoms suggestive of ML. His medical history included hypertension. His vaccine status was fully covered. The laboratory data were as follows: white blood cell count, 12,500/μL, hemoglobin count, 13.2 g/dL; platelet count, 314,000/μL, urea nitrogen level, 20 mg/dL; serum creatinine level, 1.1 mg/dL; and serum C-reactive protein level, 0.68 mg/dL. NWCL was strongly suspected based on the patient's recent history of travel to South America and the unhealed ulceration typical of CL. The wound culture was negative for bacteria and mycobacteria. We tested exudates from the ulcer for the polymerase chain reaction (PCR) target on the *cytochrome b* gene of leishmania parasites, and the PCR product was sequenced using direct-sequencing method, which confirmed *L. braziliensis* (5).

We initiated L-AmB (3 mg/kg/day; AmBisome®; Sumitomo Dainippon Pharma, Osaka, Japan) for 6 consecutive days (total, 18 mg/kg) of hospitalization. He was discharged without remarkable adverse events. However, the lesion was not completely cured even three months after the initial treatment (Figure B). The patient desired additional treatment in the outpatient setting; therefore, we prescribed him 300 mg/day of oral fluconazole (5 mg/kg) for 28 days.

After 3 months, the ulceration had increased by 3 cm (Figure C), and the patient agreed to short-term hospitalization. We initiated increased-dose L-AmB therapy (4 mg/kg/day) on days 1-5, 10, 17, 24, and 31 (total, 36 mg/kg) with reference to the dose for immunocompromised patients because the lesion was unresponsive (or refractory) to the L-AmB dose usually used for immunocompetent patients. During the treatment course, his serum creatinine level gradually increased from 1.5 to 2.5 mg/dL (day 31). We skipped the dose on day 31; on day 38, we confirmed that his serum creatinine level had decreased to 1.5 mg/dL and administered the last dose.

The ulceration healed well during the second treatment course compared with the primary treatment (Figure D). One month after the second treatment, his serum creatinine level recovered to 1.1 mg/dL. At the time of follow up, one year after the second treatment, the ulcer had disappeared. There were no signs of ML throughout the patient's two-year clinical course.

Discussion

CL is actually rare in Japan, and only 22 imported cases were reported from 1980-1995 (6). The treatment options in nonendemic countries are controversial. Some drugs cause

adverse reactions, and systemic treatment is not always recommended for CL. To decide who should receive systemic treatment, a stepwise approach for assessing risk factors leading to ML has been suggested (7). In the present case, the lesion was not potentially disfiguring or disabling, and the size was <4 cm; however, the causative species (*L. braziliensis*) indicated systemic treatment according to the stepwise approach. He did not notice any bug bites during these trips. Given that the incubation period of CL is typically more than two weeks, we believed that his previous travel was therefore likely responsible for the development of CL.

Identifying the causative species is important because drug susceptibility primarily depends on the leishmania species, and the risk of progression to ML differs by species. Our present case was definitively diagnosed using PCR and direct sequencing (8). These methods are less invasive and more specific than a biopsy. The limitation of the report is that the drug resistance test was not performed. L-AmB resistances are reported in VL cases caused by other leishmania species (9). It is difficult to separate parasites form CL lesions and, as a result, no drug resistance test method for CL has yet been established (10). The findings from the present case suggested that *L. braziliensis* has dose-dependent resistance to L-AmB.

L-AmB is currently considered a first-line therapeutic agent for NWCL in nonendemic countries because of its high cure rate and short therapeutic duration (11). Previous studies and the present case have suggested that a high cumulative dose of L-AmB may provide clinical benefits for the treatment of NWCL. Solomon et al. reported that L-AmB was effective for NWCL when the cumulative dose was >18 mg/kg (12). In a case series of CL including immunocompromised patients treated by L-AmB, the total dose varied from 15 to 600 mg/kg (13). Treatment guidelines suggest a total of 18-21 mg/kg of L-AmB for CL; however, there is no standard regimen based on randomized controlled trials (3). To determine the appropriate L-AmB dosage for CL, a sensitivity test method should be established, and randomized controlled trials should be conducted.

There are no detailed reports on CL cases initially treated by L-AmB and retreated with an increased L-AmB dose. Our present case shows that treatment failure can occur even in small lesions with systemic L-AmB treatment. We used a high-dose L-AmB regimen typically used for immunocompromised patients with VL (3) as a reference for our secondary treatment. There were two advantages to this treatment: we were able to monitor the healing process on a weekly basis as well as check for adverse effects. Harms et al. reported that healing occurred within one month in all patients who responded to the initial treatment (14). In our study, the healing after one month of high-dose therapy had markedly progressed compared to usual-dose therapy; the wound recovery at one month after L-AmB therapy may be a point of reference. To avoid nephrotoxicity, additional weekly doses were carefully adjusted by monitoring the serum creatinine levels.

Pentavalent antimony (sodium stibogluconate) and miltefosine are often used as a first- or second-line treatment in endemic and some nonendemic countries. However, these agents should be used as a last resort in cases where these drugs are not approved. The tolerability of sodium stibogluconate is quite low because of its adverse effects (fatigue and fever, injection cite local reactions, and severe arrhythmia) (15). Miltefosine was more effective than sodium stibogluconate in a randomized controlled trial in Brazil. The incidence rate of adverse reactions from miltefosine was equivalent to that of sodium stibogluconate (16). Unfortunately, these drugs are not approved in some nonendemic countries, including Japan, reducing their clinical use.

Azoles are another easily accessible therapeutic agent. Sousa et al. reported the effectiveness of high-dose oral fluconazole (6.5-8 mg/kg/day) for CL caused by *L. braziliensis* (17). However, Prates et al. conversely reported the ineffectiveness of oral fluconazole (6.5-8 mg/kg/day) for 28 days in a randomized controlled trial (18) that was reported soon after our patient underwent 28 days of treatment. The cure rate was much lower in the study by Prates et al. (92.8-100% vs. 22.2%, respectively). Azole therapy requires a much longer healing time than L-AmB therapy (14, 18). There are few reasons to use fluconazole as a first-line treatment, and it should not be a substitutional therapy.

In summary, L-AmB is the optimal treatment for NWCL in nonendemic countries. Our experience shows that even L-AmB can cause treatment failure of NWCL caused by *L. braziliensis*. If other treatment agents cannot be used, increasing the L-AmB dose is another option for treatment failure of L-AmB.

Consent for publication was obtained from the patient, as recorded in the electronic medical record.

The authors state that they have no Conflict of Interest (COI).

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