Topical Treatment of Cutaneous Leishmaniasis: A Case Treated with A Glucantime-Based Lotion Experienced in Ecuador and A Mini Review

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ABSTRACT

A 1.5-year-old male patient living in a remote community in the southeast of Manabí province of Ecuador was diagnosed as cutaneous leishmaniasis (CL) caused by *Leishmania (Viannia) guyanensis.* He was treated with a lotion, meglumine antimoniate Glucantime plus Merthiolate chloride, applying four to five times a day during eight weeks. The complete cure of lesion was obtained. This childhood-CL case did not respond against systemic therapy with Glucantime for the first cycle of regimen administered before the current topical treatment. Although systemic administration of pentavalent antimonials still remain as the first choice of treatment, it may often cause severe side effects, in addition to various disadvantages, such as painful injections, long-term regimens, difficulty to access health centers for patients living in remote/mountainous endemic areas. Therefore, as the alternatives, effective, easy-applicable and patient-compliant treatment is urgent need, especially for childhood-CL patients, who are highly vulnerable for toxic, systemic administrations of the drug. The current Glucantime plus Merthiolate lotion could be recommended as a future topical therapy of CLs, because of several advantages, easy-application, already-used drug as systemic therapy for the disease for a long time, more than 70 years.

Keywords: *Cutaneous Leishmaniasis, Topical Treatment, Meglumine Antimoniate, Ecuador*

Introduction

Leishmaniasis is a vector-borne disease that is transmitted by the bite of infected female of a tiny blood-sucking insect phlebotomine sand fly in tropical and subtropical areas of 98 countries and territories in the world (Alvar *et al*., 2012; WHO, 2018). The disease is principally divided into three clinical manifestations, cutaneous (CL), mucocutaneous (MCL), and visceral (VL), the fatal form if not treated (Alvar *et al*., 2012; WHO, 2018). Nearly 350 million people are at the risk of infection and 12 million are affected by the disease worldwide; among them, CL is the most prevalent and approximately

0.7 to 1.2 million cases occurring each year (Alvar *et al*., 2012; WHO, 2018).

In Ecuador, CL is the most predominant, followed by few numbers of MCL, 5-7% of the total cases, and other atypical clinical forms such as diffuse-CL, disseminated-CL, recidiva cutis, sporotrichoid-CL/pian-bois, and etc. (Hashiguchi and Gomez, 1990; Calvopiña *et al*., 2004, 2006, 2013a,b, 2014; Hashiguchi *et al*., 2016, 2017); no VL case is available. The disease is prevalent in 22 of the country's 24 provinces at both sides of the Andes, Pacific and Amazonian regions, including Andes valleys where Andean-CL exists, and it remains as one of the important public health concerns (Hashiguchi *et al*., 1991, 2017, 2018).

In the 2016 outbreak in Manabí province, Ecuador (Molares, 2017), an infantile patient presented to a rural health center of the Ministry of Health and he was diagnosed as CL. The patient received systemic therapy with meglumine antimoniate Glucantime; however, no improvement was observed, suggesting a resistant case for the systemic therapy of the drug. Thus, childhood-CL are frequently resistant against systemic therapy with antimonial compared to adult-CL (Layegh *et al*., 2011a; Aksoy *et al*., 2016). This study describes a complete healing of a childhood-CL case which was resistant for systemic therapy with Glucantime, and then treated topically with a lotion of Glucantime plus Merthiolate.

Besides, paromomycin ointment/cream was recently shown to be effective for the treatment of both Old World and New World CL caused by *L. (L.) major* and *L. (V.) panamensis*, respectively (Ben-Sarah *et al*., 2013; Sosa *et al*., 2013, 2019).

A Case Experienced In Ecuador: Clinical Images

A 1.5-year-old male patient presented to a rural health center of the Ministry of Health, with a crusted ulcer lesion (20 mm x 15 mm) on the left cheek very close to the mouth (Fig, 1A). The patient was parasitologically and microscopically diagnosed as CL in the health center, by observing *Leishmania* amastigotes on smear specimen taken from the ulcer lesion, in addition to the typical clinical manifestation. His primary lesion appeared six months before as mosquito-bite-like papule that gradually ulcerated. The patient received intramuscular Glucantime injection for 21 consecutive days without any improvement, thereafter the patient's parents refused to continue further cycle of regimens of the systemic treatment at the health center, because of different reasons, such as various side effects and painfulness of the injections, remoteness of patients dwelling site, etc. We searched for the patient living in a remote and newly established community surrounded by dense forest where no health services are available. The patient's parents gave informed consent, to participate in the current topical treatment, because of daily worth and advanced evolution of their baby's lesion. A comprehensive

clinical history was taken by LVN, Ministry of Health, and a physical examination was performed by EAG, Ministry of Health, under the parent's informed consent. Before commencement of the current treatment, for the aim of determination of the causative *Leishmania* species, residual tissue materials were taken from the ulcer margin and spotted onto FTA Classic Card, Whatman Newton Center, MA. Using the clinical FTA samples, the parasite was identified as *L. (Viannia) guyanensis* by a polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) and cytochrome *b* (*cyt* b) analysis (Kato *et al*., 2019). The patient received topical treatment of a lotion of Glucantime mixed with white Merthiolate chloride, half and half concentration four to five times a day for eight weeks at his house (Calvopiña *et al*., 2013a,b). The lesion improved remarkably (Fig. 1B) and healed completely leaving scars (Fig. 1C, D).

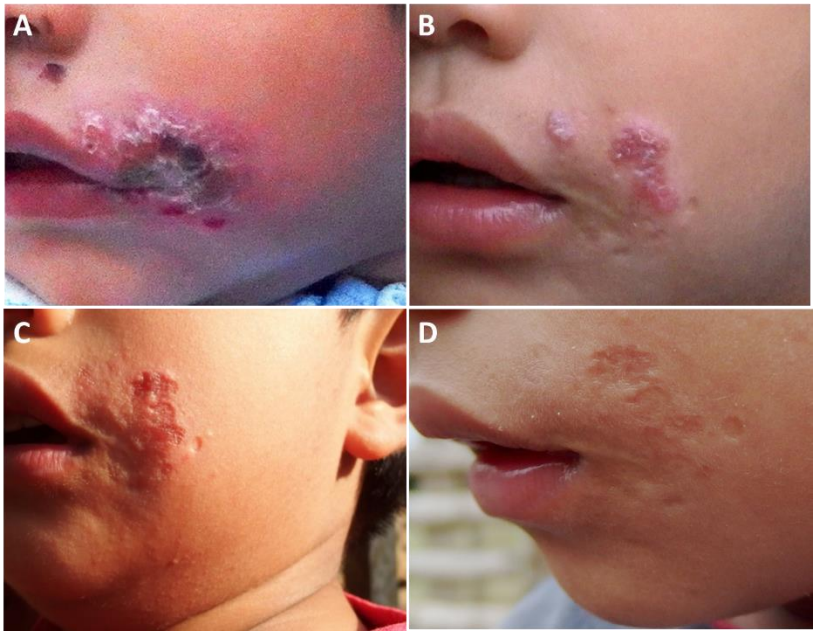

Figure 1: Childhood cutaneous leishmaniasis (1.5-year-old male patient) and its topical treatment with a lotion of Glucantime plus Merthiolate chloride lotion **A.** Severe, profound and advanced stage of the lesion as of our first examination, before the treatment with the lotion. (Photo: 2017.10.05.). **B.** Partly healed lesion, during the topical treatment (6 weeks of application), the lesion improved remarkably but still leaving papules at the periphery; the treatment continued further two weeks (8 weeks in total). (Photo: 2017.11.16.). **C.** Two months of follow-up of B, complete cure was observed, but unexpectedly leaving typical scars of CL, probably due to severe, profound and advanced stage of the lesion as seen in A. (Photo: 2018.01.12.). **D.** Five months of follow-up of C, complete cure was observed, leaving depressed, depigmented and retracted scars typical for CL. (Photo: 2018.06.09).

Unfortunately, however, this case leaved an unexpectedly large scar typical for CL, probably because of the severity and profoundness of the primary lesion which could be caused by; 1) careless attending for a long time after unresponsiveness of the patient to the systemic antimonial therapy, 2) thereby, hesitation of the patient's parents to search for further treatment; and living in a remote area

surrounded by dense forest (Personal communication: Drs. LVN & EGL). Therapeutic response of the present case was in agreement with our previous cases which were also resistant against systemic therapy with Glucantime, before topical treatment with the same lotion (Calvopiña *et al*., 2013a, b).

Thus, the current topical lotion may be one of the alternative therapies for CL, even in those cases unresponsive to the systemic injection of Glucantime, lack of medical care systems, lower age groups impossible to tolerate for a long course of systemic regimens, etc. The current patient received half and half concentration of Glucantime per Merthiolate for eight weeks in total. However, this concentration of the lotion would be able to modify depending on the disease and/or patient conditions, such as sizes, numbers, sites, evolution times of lesions, patient's ages, etc (Calvopiña *et al*., 2013a,b). Besides, this is an interesting and noticeable case of childhood-CL in which the lesion located very close to the mouth, the initial site of infection; the sand fly's bite site; the lesion involved gradually labial mucosa. Such a case, especially in the progressed stage, is frequently diagnosed as mucosal leishmaniasis (ML) or erroneously MCL in the New and Old Worlds.

A Brief Review on The Available Topical Treatment

Systemic pentavalent antimonials, or meglumine antimonite Glucantime or sodium stibogluconate Pentostam, remain the standard therapy for CL including other clinical forms of the disease in the world, though the alternatives include amphotericin B, pentamidine, and miltefosine depending on the causative *Leishmania* species and clinical manifestations (Reithinger *et al*., 2007; Rosal *et al*., 2010). However, the systemic therapy with antimonials reveals serious side effects or toxicity such as musculoskeletal pains, renal failure, hepatotoxicity and cardiotoxicity, frequently requiring admission to hospital (Blum *et al*., 2004). Therefore, under the standard protocol of treatment with antimonials, many patients fail to complete the full course of treatment with poor compliance, in addition to yearly increase of non-responsive cases against the drugs (Croft *et al*., 2006; Reithinger *et al*. 2007; Rosal *et al*., 2010). Other factors such as a long course of painful injections, remoteness of patients' dwelling sites to medical care systems are also roles as reasons of poor compliance of the systemic therapy (Croft *et al*., 2006; Reithinger *et al*., 2007). Besides, the cure rate of CL-cases with the recommended regimens is not necessarily acceptable; thus, further limiting the patients from completing a full course of the administration of antimonials (Gasser *et al*., 1994; Sosa *et al*., 2019). For these reasons, different topical treatments of CL have been conducted against the patients from the Old and New World endemic areas. Topical and oral formulations, topical paromomycin, topical niosomal zinc sulphate, and oral terbinafine are also prescribed, because of absence of pain and more or less acceptable efficacy (Reithinger *et al*, 2003). In the rural endemic areas of CL, however, these drugs are not easy for the patients to access. Under such circumstances, more effective, easy applicable and patient-compliant topical treatment is an

urgent need especially for childhood-CL patients who are highly vulnerable for the available therapy. In this brief review, we focus on the topics of the available topical treatment of CL cases, especially on those performed in the New World.

Intralesional Infiltration

Intralesional antimonial therapy remains the gold standard of treatment for CL-patients including childhood-CL cases. However, this intralesional injection is also suffering pain in the same way as systemic therapy, because of repeated, multiple shots, and may result in poor patient-compliance; therefore, the patients and/or physicians may prefer a single intramuscular dose/shot (Aksoy *et al*., 2016). Intralesional injections of antimonial have been administered frequently for CL-patients in both the New and Old Worlds, obtaining a good or acceptable/tolerable result. Notably, such a topical treatment has been recommended to use only in geographical regions where CL causing *Leishmania* species have low potential for mucosal spread (Rosal *et al*., 2010). Recently, however, an important and interesting comment was given, addressing the question of whether the risk of developing ML/MCL warrants systemic treatment in all patients with New World CL or whether local treatment might be an acceptable alternative (Blum *et al*., 2012). The results were given as follows: local treatment might be considered as a valuable treatment option for subjects suffering from the New World CL, provided that there are no risk factors for developing ML/MCL such as multiple lesions, big lesions (>4 cm^2), localization of the lesion on the head or neck, immunosuppression or acquisition of infection in the high Andean countries, notably Bolivia (Blum *et al*., 2012). To answer the question of whether the risk of developing severe, metastatic MCL appears or not, it is important to know the *Leishmania* species or genotypes circulating in given endemic areas of the New World CL, performing molecular- and clinico-epidemiological studies, including other MCL-causing factors; *Leishmania* RNA virus may control the severity of MCL (Ives *et al*., 2011). Besides, here an important note have to be given on this intralesional infiltration, that this treatment should be avoid or prohibited, when the CL-lesions localized on the face especially close to the eyes. The antimonial infiltration to such a lesion could cause serious toxic side effects affecting visual sight, finally losing eyesight (Hashiguchi *et al*., 2007a).

Ointment/Cream Treatment

As topical treatment of CL, more effective, easy-applicable and patient-compliant methods are urgent need for the localized self-limiting clinical forms. Considerable numbers of topical treatment of CL, such as paromomycin-gentamicin ointment, have been reported in both the New and Old Worlds until now (Ben-Sarah *et al*., 2013; Sosa *et al*., 2019). Trial of topical treatment was first implemented for the Old World CL in which the causative *Leishmania* parasites belong to the subgenus *L. (Leishmania)*

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which mainly causes simple and self-limiting CL. On the other hand, the trial for the New World CL was postponed, because of different species of the causative parasites which belong to the subgenera *L. (Leishmania)* and *L. (Viannia).* Among them*, L. (L.) mexicana,* and *L. (L.) amazonensis* belong to the former, and *L. (V.) braziliensis, L. (V.) guyanensis, L. (V.) panamensis* and *L. (V.) peruviana,* to the latter causing more severe ML and/or metastatic MCL clinical forms in the New World. Very few trials have been conducted for the New World CL caused by *L. (L.) amazonensis* and *L. (L.) mexicana* (Hendriksen and Lende, 1983; El-On *et al*., 1985, 1986).

At the early phase of trials of topical CL treatment using ointments/creams, some were found to be effective in healing the CL-lesions. Those were chlorpromazine ointment against diffuse-CL due to *L. (L.) aethiopica,* and paromomycin plus methylbenzethonium chloride against recurrent- or advanced-CL caused by *L. (L.) major* or *L. (L.) aethiopica* (El-On *et al*., 1985, 1986; Weinrauch *et al*., 1987). Lipid formulations of amphotericin B could also be useful as a topical treatment for Old World CL in children (Zvulunov *et al*., 2003), and topical treatment with nanoliposomal amphotericin B reduces early lesion growth but fails to induce cure in an experimaental model of cutaneous leishmaniasis caused by *L. (L.) mexicana* (Varikuti *et al*., 2017). Among these, a pioneering study on the topical treatment of CL using ointment was noted, that a preparation of antibiotics of the aminoglycoside class, paromomycin, using 15% paromomycin sulphate and 12% methylbenzethonium chloride in a hydrophobic base, was employed for the treatment of CL caused by *L.* (*L.*) *major,* proposing the possibility that the topical formulation could be an alternative method for the disease (El-On *et al*., 1986). However, it is still remain problems that need to be investigated, such as low penetration of most compounds through the human skin, though the transdermal transport of drugs against CL-lesions has many advantages over other routes of administration (Rossi-Bergmann *et al*., 2011). Nowadays, two paromomycin ointments especially for the Old World CL are commercially available but the use is limited due to toxicity or lack of remarkable efficacy (Ben-Sarah *et al*., 2013; Sosa *et al*., 2019). Several topical formulations have been in clinical trials, but many results have still been equivocal, and no major breakthroughs have been achieved yet (Garnier and Croft, 2002). Under such a circumstance, a randomized, hydrophilic vehicle-controlled trial of topical treatments containing 15% paromomycin, with and without 0.5% gentamicin, for ulcerative CL caused by *L. (L.) major* was conducted in Tunisia (Ben Sala *et al*., 2013). The results revealed that either formulation was an effective treatment for the disease by 20 days medication, without showing superiority of paromomycin-gentamicin combination. Recently, the two formulations, paromomycin-gentamicin and paromomycin alone, were also tested for the New World CL caused by *L. (V.) panamensis* in Panama, demonstrating similar results to those reported in Tunisia, and the previous results reported with systemic antimonial therapy (Sosa *et al*., 2019).

Lotion/Solution Treatment

Topical treatment with a lotion for CL could be desirable alternatives especially for infantile, childhood-CL, because of its easy and non-invasive natures, increasing accessibility and patient's adherence and satisfaction, thus resulting in a higher cure rate of the disease (Ben-Sarah *et al*., 2013; Sosa *et al*., 2019). Efficacy of topical treatment for CL with ethanolic lipid amphotericin B was reported (Vardy *et al*., 2001). In Israel, furthermore, a 1.5-year-old infant who did not respond to repeated courses with paromomycin-containing ointment, then the patient was treated with topical ethanolic lipid amphotericin B, applied twice daily, one drop to each lesion, for three weeks, resulted in cure of the CL-lesions, with no local or systemic side effects; in the case three months after the treatment, no signs of recurrence were observed (Zvulnov *et al*., 2003). Furthermore, one of such topical trials provided that liposomal amphotericin B solution had the same efficacy as intralesional Glucantime infiltration in the CL-cases caused by *L. (L.) tropica* and *L. (L.) mexicana* (Layegh *et al*., 2011b).

Cryotherapy and Thermotherapy

Cryotherapy was compared with intralesional Glucantime infiltrations for childhood-CL treatment in Iran (Layegh *et al*., 2009). The results revealed that 1) cryotherapy is an effective treatment for the CL, 2) no serious post-treatment side effects were observed in either group, 3) at six months of follow-up, no recurrence of disease was observed in cured patients in either group, 4) because of its simplicity, lower cost, low rate of serious complications and greater tolerability, and thus, 5) cryotherapy should be recommended as an appropriate alternative treatment for childhood-CL. The efficacy of thermotherapy for the treatment of 401 CL-patients with a single lesion due to *L. (L.) tropica* was tested in a randomized, controlled trial in Kabul, Afghanistan, comparing the treatment with sodium stibogluconate (SSG) (Reithinger *et al*., 2005). The results of thermotherapy/SSG comparison revealed that no statistically significant difference was observed in the odds of cure in comparison of intralesional SSG and thermotherapy treatments, and the time to cure was significantly shorter in the thermotherapy group than in the intralesional SSG or intramuscularly SSG group, and concluding that thermotherapy is an effective, comparatively well-tolerated, and rapid treatment for CL, and it should be considered as an alternative to antimony treatment. Recently, this was further evaluated that thermotherapy can be considered as a therapeutic alternative in localized cutaneous leishmaniasis, especially in cases of single cutaneous lesions and with formal contraindications to conventional treatment with pentavalent antimonials (Goncalves and Costa, 2018).

Topical Treatment in Ecuador

Intralesional Infiltration

In Ecuador, topical treatment by using antimonial (Glucantime) intralesional infiltration against CL-patients was carried out countrywide until now. As seen in other leishmaniasis-endemic countries, intralesional injections of Glucantime to CL-patients were performed for a long time in the country, depending on the patient's conditions. It is noteworthy to mention that during the 1984 and 1985 outbreaks of CL, after El Niño phenomena, a lack of antimonials was occurred in the country, and the outbreaks forced the use of this topical treatment; the method resulted in several advantages, with much low dose and undesired side effects, shorter treatment period, etc., together with its good and acceptable result (Gomez and Hashiguchi, 1990; Hashiguchi *et al*., 2017). Recently, this intralesional, topical treatment was applied to recidiva cutis type of CL-lesions and resulted in an excellent result with a high cure rate (Calvopiña *et al*., 2017). However, as mentioned above, this topical treatment should be considered more seriously or prohibited, when the CL-lesions localized on the face especially close to the eyes, because the antimonial infiltrations cause severe and/or toxic side effects affecting visual sight; for example, we reported one case who lost her right eyesight after receiving intralesional infiltration on the lesions located on her right cheek, losing eyesight (Hashiguchi *et al*., 2007a).

Ointment/Cream Treatment

Paromomycin (PM) ointment as a monotherapy for CL with clinical cure of 10%-54% patients (Nonaka *et al*., 1992); topical PM plus methylbenzethonium (MB) for CL with 85% cure rate with 9% cure in placebo (Krause and Kroeger, 1994); topical PM-MB and PM-urea ointment for CL with clinical cure in 79.3% and 70% respectively (Armijos *et al*., 2004). Topical treatment with nitric oxide donor was shown for CL with 100% cure (Lopez-Jaramillo *et al*. 1998), but disappointingly resulted in low cure rate and local adverse reaction in another trial (Davidson *et al*. 2000).

Lotion/Solution Treatment

Topical treatment with a lotion, Glucantime diluted with saline solution, was for the first time administered in the Andean type of CL-endemic areas, where the causative agent is *L. (L.) mexicana* and the lesions are small and superficial ulcers mostly in children less than 5-year-old (Hashiguchi *et al*., 1991; Nonaka *et al*., 1992). In these patients, usual systemic injection of Glucantime was not effective for the CL lesions, in addition to strong adverse reactions for the infant patients. Then, the lotion was prepared and applied directly to the lesions, in order to avoid painful injection and systemic adverse reactions, resulted in an excellent cure. Recently, two clinical cases of CL in Ecuador, both were quite resistant for the repeated Glucantime systemic injections, were treated by the lotion, and the results showed excellent healing, suggesting a future alternative treatment (Calvopiña *et al*., 2013a,b). Those cases are briefly summarized as follows. The first one is a 7-year-old female with four small crusted

papules in the periphery of a large central scar on her cheek, diagnosed as CL (recidiva cutis) due to *L. (V.) guyanensis*; she received intramuscular antimonial (Glucantime) for 15 consecutive days but no improvement was observed, and finally treated with a topical lotion comprised of Glucantime plus Merthiolate (half and half concentration), healing completely after two months of application (Calvopiña *et al*., 2013a). The other one is an 18-year-old female case with a severe ulcerative lesion on her right ear. Her ear was edematous and erythematous with a large, painless ulcerative lesion covering a third of the pinna and satellite papular lesions on the posterior. She was diagnosed with chiclero's ulcer demonstrating abundant *Leishmania* amastigotes in smear specimens. Because of preferences of the patient and the large volume (21 mL or 4 ampoules/day) of antimonials against her weight for systemic therapy needed, we recommended topical treatment with a lotion of Glucantime mixed half and half with white Merthiolate. After applying the lotion three to four times a day for six weeks, the lesion healed completely (Calvopiña *et al*., 2013b).

Thermotherapy, Cryotherapy and Other Treatment

Topical thermotherapy was applied to Andean type of a CL case with excellent healing without resurgence (Hashiguchi *et al*., 2007b). Topical cryotherapy treatment with nitrogen liquid is also used in limited private hospitals or research projects (Gomez *et al*., 2007). Besides, there exist many traditional medications for CL. In a subtropical area endemic for CL, about 150 therapies were reported (Weigel *et al*., 1994). These included the indigenous plants, chemicals, acids, antibiotics, heat treatments or petroleum byproducts, and some of these treatments could have clinical value. Almost 70% of the subjects with a past or present CL history were treated solely by traditional methods; notably, only 12% received a full course of systemic therapy with Glucantime, and the premature drug discontinuance was frequent in the CL endemic areas of Ecuador (Weigel *et al*., 1994; Weigel and Armijos, 2001).

Discussion

In this study, a childhood-CL case was treated with a lotion composed of Glucantime plus Merthiolate and resulted in complete cure. The case was no responder for systemic therapy with Glucantime. Although systemic and/or intralesional administration of the drug remain as the first choice of CL treatment, but these therapies need repeated painful injections, long-term regimens, various side or toxic effects, and etc. Therefore, an effective, easy-applicable, and patient-compliant treatment is urgent need especially for infantile, childhood-CL patients who are highly vulnerable for systemic or intralesional administrations of the antimonials. Recently, paromomycin ointment/cream was shown to be effective for the treatment of both Old World and New World CL caused by *L. (L.) major* and *L. (V.) panamensis*, respectively (Ben Sarah *et al*., 2013; Sosa *et al*., 2013, 2019).

On the other hand, there is no recommended treatment for childhood-CL less than two years of age yet (Tuon *et al*., 2008). Limited therapeutic options and increased incidence of childhood-CL force the development of more effective treatment for this vulnerable population (Askoy *et al*., 2016; Castro *et al*., 2017). Topical treatment including intralesional antimonial infiltration has been recommended to use only in geographical regions where CL-causing *Leishmania* species have low potential for mucosal spread (Rosal *et al*., 2010). However, topical/local treatment might be considered as a valuable treatment option for those people suffering from the New World CL, provided that there are no risk factors for developing ML/MCL (Blum *et al*., 2012). For obtaining precise information on these potential factors or risks, it is important to know the causative *Leishmania* species or genotypes circulating in given endemic areas of the disease, performing molecular- and clinico-epidemiological studies, including other MCL-causing factors.

In Ecuador, for example, only 5% to 7% of all the CL cases were found/reported countrywide (Hashiguchi and Gomez, 1990; Hashiguchi *et al*., 2017). Furthermore, our retrospective studies demonstrated that any case of MCL was detected, except one or two ML but not MCL cases in the Amazonian CL endemic areas for 27 years (1986-2012) (Olalla *et al*., 2015). Besides, in the Ecuadorian Andes regions, there exist Andean childhood-CL caused by *L. (L.) mexicana* mainly affecting children less than 10 years of ages (Hashiguchi *et al*., 1991). Those childhood-CL cases are mostly resistant for systemic antimonial therapy but susceptible for the lotions (Glucantime plus Merthiolate or Mercury chrome) applied directly onto the lesions (Hashiguchi, Gomez and Nonaka, unpublished data). Under such a situation of the disease, it could be possible to consider topical treatment in the areas where no MCL or more severe cases are reported. Regarding intralesional antimonial infiltrations, again, it should be avoided or prohibited, when the CL-lesions localized on the face especially close to the eyes, causing serious toxic side effects affecting visual sight, losing eyesight (Hashiguchi *et al*., 2007a).

Our previous trials using the lotion of Glucantime plus Merthiolate resulted in a good or complete cure of CL lesions in Ecuador (Calvopiña *et al*., 2013a,b), similarly as observed in the current clinical case. Thus, the topical treatment with Glucantime plus Merthiolate lotion could be one of the alternative therapies for CL, even in those cases unresponsive to conventional systemic antimonial injection, especially for childhood-CL patients impossible to tolerate for a long course of systemic regimens etc. The current patient received half and half concentration of Glucantime plus Merthiolate. However, this concentration would be able to be modified depending on the disease conditions, including other combinations than Merthiolate as anticeptics. Further studies are needed to get more precise information on the current Glucantime lotion, based on randomized research protocols. In addition, combination with nanoparticles (NPs) could enhance local skin accumulation of the drugs (Espuelas *et*

al., 2016). Recently, nano-deformable liposomes (NDLs) for the dermal delivery of sodium stibogluconate (SSG) against CL was tested, indicating that the targeted delivery of SSG could be accomplished by using topically applied NDLs for the effective treatment of CL (Dar *et al*., 2018). Those are useful information for the development of future ideal topical treatment of CL prevalent worldwide as serious health concerns.

Conclusions

The current Glucantime-based lotion could be able to recommend as a future topical therapy of CL, because of the following advantages: 1) it needs very small amount of Glucantime, in comparison with systemic injection or intralesional infiltration, 2) there exist no side effects, 3) it is easy to apply at patient's house or working place in remote endemic areas, 4) the drug itself has been used for a long time as the first choice of the treatment of different clinical forms of leishmaniasis in the world, and etc. Thus, more ideal and efficient combinations of the drugs for CL should be developed, employing NDLs or others, especially for infantile, childhood-CL.

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