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Research Article

Cure of post Kala-azar dermal leishmaniasis with paromomycin/sodium stibogluconate combination: a proof of concept

Younis BM, Mohammed HAA, Dafalla MMM, Adam AOA, Elamin MY, Musa AM, El-Hassan AM, Eltahir Awad Gasim Khalil*

Department of Clinical Pathology & Immunology, The Leishmaniasis Research Group/Sudan (LRG/Sudan), Institute of Endemic Diseases, University of Khartoum, P.O. Box 45235, Khartoum-11111, Sudan

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***Correspondence:**
Dr. Eltahir Awad Gasim Khalil,
E-mail: eltahirk@iend.org, eltahirgasim@yahoo.ca

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ABSTRACT

Background: Post kala-azar dermal leishmaniasis (PKDL) is a recognized dermatologic complication of successfully treated visceral leishmaniasis (VL). PKDL lesions are suspected to be important reservoirs for VL transmission in Sudan. Prolonged treatment schedules, feeling of general well-being and the social stigmata of PKDL prevent most patients seeking treatment. The mainstay of treatment is cardiotoxic sodium stibogluconate (SSG) for 60-120 days. Recently, liposomal amphotericin B (Ambisome®) and immunochemotherapy gave promising results. Ambisome® is expensive and difficult to prepare under field conditions. Paromomycin/SSG combination has been shown to be safe, efficacious and can save time in VL treatment. This study aims to prove that Paromomycin/SSG combination can cure and reduce PKDL treatment duration.
Methods: We are reporting nine cases of patients with PKDL lesions of ≥6 months duration who were diagnosed by clinical signs, histopathological/immunohistochemical and PCR.
Results: Patients' mean age was 11.7 ± 4.3 years. A third of the patients (3/9; 33.3%) who failed previous SSG treatment of 2-3 months duration responded completely to 40 days of paromomycin/SSG combination. The majority of patients (5/9; 55.6%) responded completely to 30 days of the combination. One patient (1/9; 11.1%) relapsed following 30 days paromomycin/SSG combination.
Conclusion: It was concluded that paromomycin/SSG combination for 30 days is time-saving, safe and efficacious for PKDL treatment.

Keywords: Short course, Paromomycin/sodium stibogluconate combination, PKDL

INTRODUCTION

Visceral Leishmaniasis (VL) is a major health problem in the Sudan where children are mostly affected. A considerable number of successfully treated patients develop a dermatosis called post Kala-azar dermal leishmaniasis (PKDL).[1-3] The disease has been reported with lower frequencies from India.[4] PKDL rash usually takes 0-6 months to develop and can be macular, maculo-papular or nodular in sun-exposed parts of the body. The rash usually heals spontaneously after a few weeks in the majority of cases, but in 15% of patients lesions persist for long periods.[3]

The lesions can constitute a social stigma and can easily be confused with leprosy.[5] PKDL is mainly restricted to leishmaniadonovani-endemic areas with few reports from L. infantum/chagasiareas. In Sudan, persistent PKDL cases are considered possible culprits for anthroponotic VL transmission.[2,6-8]

There is increasing evidence that the pathogenesis of PKDL is immunologically mediated, with a number of cytokines playing pivotal roles. The role of inadequate treatment and the effect of UVB have also been highlighted.[3,9-15]

The diagnosis of PKDL is mainly clinical with a previous history of VL, characteristic distribution and appearance of the rash and good response to treatment. Other dermatological conditions especially leprosy must be meticulously sought and excluded. Clinical diagnosis could be further supported by a reactive DAT and/or Leishmanin Skin Test (LST). Although parasitology of the smears is of low sensitivity, monoclonal antibodies and PCR may detect parasites in more than 80% of cases with added expense and lack of availability in remote endemic areas.[2,3,5,14]

The treatment of PKDL is protracted, difficult, and costly and uses potentially cardio/nephro toxic drugs. Safe and effective drugs that can be given over a short period of time would be the ideal to cure patients and resolve the transmission issue.[9,16] Only a hand-full of controlled studies on the management of PKDL exist, most data was generated from small case series.[17-20] Sodium stibogluconate (SSG) is given at 20 mg/kg for 2 months in Sudan and for 4 months in India.[9,14,21] Experience with amphotericin B in the treatment of PKDL is limited.[22] Liposomal amphotericin B (Ambisome®) was shown to be safe and effective, but the cost is prohibitive.[17,20] Immunochemotherapy showed some promise in Sudan, where a randomized and controlled clinical trial showed that a combination of alum-precipitated autoclaved leishmania major (Alum/ALM) vaccine + BCG and sodium stibogluconate (SSG)) is safe and efficacious.[23] Itraconazole/terbinafine combination failed to cure PKDL lesions.[24]

Miltefosine is safe, efficacious and has the advantages of being an oral treatment of a shorter duration.[25] Recently, paromomycin/SSG combination was proven to be safe, efficacious for VL treatment. The combination can reduce treatment duration significantly.[26]

In this case series a 30 days course of paromomycin/SSG combination was shown to cure persistent lesions of PKDL.

METHODS

Nine PKDL patients presented to our hospital with ages ≥5 years, rash of ≥6 months duration and no concurrent chronic disease (HIV, diabetes mellitus, chronic renal disease etc.). Four patients failed prolonged trial of treatment with SSG alone and five patients did not received prior treatment. Due to the shortage of ambisome at that time and paromomycin/SSG combination was approved by the Sudan Ministry of Health to be the first line treatment for visceral leishmaniasis and following informed consent from guardians a trial of paromomycin/SSG combination was tried. All patients were diagnosed clinically for having past history of parasitologically confirmed VL, characteristic distribution and appearance of skin rash, previous SSG treatment, hepatospelnomegaly and lymphadenopathy. The rash was graded according to distribution and severity. Grade 1 PKDL was considered when lesions mainly involve the face, head, arms chest and back. Grade 2 when lesions are on the head, scalp, forearm upper legs and upper chest but not on the hand and legs. When the lesions affect the whole body including the hand and legs the case was considered grade 3. Each grade was further sub-graded into 1, 2 and 3 sub grades depending on the lesions proximity to each other. Sub grade 1 is when the lesions are scattered; grade 2 is when the lesions are in close proximity; grade 3 is when the lesions are dense and confluent.

Grade 8:8 means no PKDL lesions.[2,20,23] Leishmanin Skin Test (LST) was performed by injection of 0.1 ml of Leishmanin antigen (Pasteur Institute, Tehran, Iran) on the volar aspect of the right forearm. The LST was read 48-72 hours later using the point-ball pen technique.

Hematological and biochemical tests were carried out before recruitment and weekly till end of treatment. Skin biopsy in formalin-buffered saline for H&E sections for parasites and histopathological features that are consistent with PKDL (hyperkeratosis, parakeratosis, acanthosis, follicular plugging and liquefaction degeneration of the basal layer of the epidermis; varying intensities of inflammation in the dermis with leshmania parasites and a cellular infiltrate of mainly lymphocytes; macrophages and epithelioid cells and discrete granulomas).[2] Skin biopsies taken in lysis buffer for parasite DNA by PCR. (Promega, Madison WI, USA & Inqaba Biotechnical Industries (Pty) Ltd, South Africa).

RESULTS

Nine PKDL cases aged 5, 12, 13, 8, 16, 17, 11, 16 and 7 years with a mean age of 11.7 ± 4.3 years (median 12.0 years) and a M:F ratio of 1:3. All patients fulfilled the criteria of having a parasitolgically confirmed past history of VL, characteristic appearance and distribution of PKDL rash (Figure 1-4). The mean PKDL lesions durations was 16.9 ± 6.5 months (range 6-28 months). Eight patients (8/9) were treated for VL with 30 days of SSG, while the ninth was treated with paromomycin/SSG combination for 17 days. All patients had a parasitological negative test of cure bone marrow samples after VL treatment. Three patients had their PKDL treated previously with SSG for 60-90 days without success; one of these patients had in addition a course of ambisome. All patients had histopathological features consistent with PKDL and PCR confirmed the presence of L. donovani DNA. Patients looked generally well, not pale or jaundiced and no organomegaly was detected. The majority of PKDL was of grade 2:1 (5/9 cases) with 2 cases of grade 1:1, one

case of grade 1:2 and one had grade 3:3. LST was non-reactive in the majority of cases (7/9; 77.8%) (Table 1).

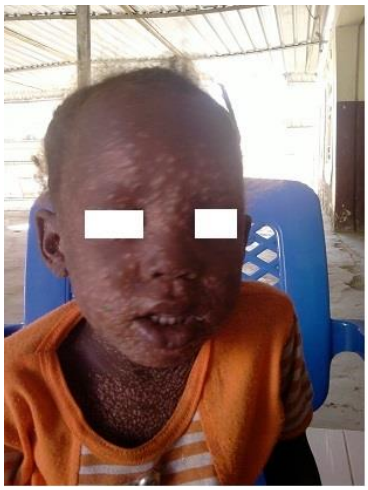

Figure 1: PKDL skin lesions before treatment, patient's ID No. 1.

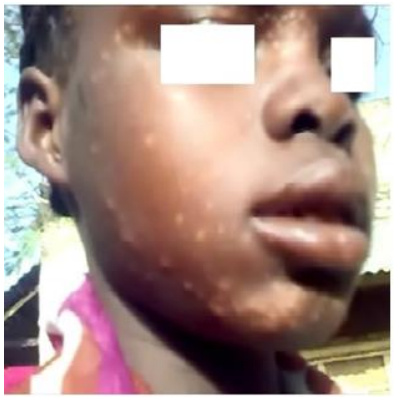

Figure 2: PKDL skin lesions before treatment, patient's ID No. 2.

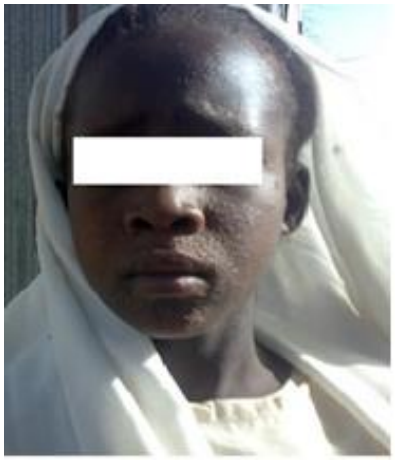

Figure 3: PKDL skin lesions before treatment, patient's ID No. 3.

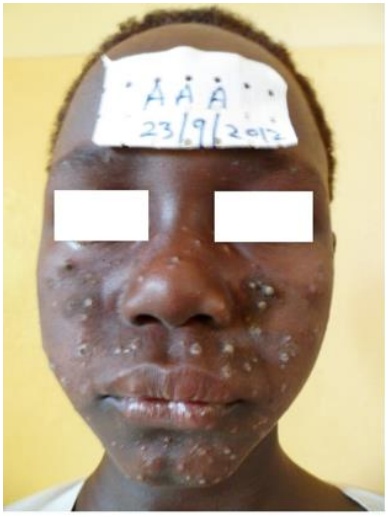

Figure 4: PKDL skin lesions before treatment, patient's ID No. 4.

Table 1: Baseline characteristics, PKDL grade, type and dose of treatments received and PM/SSG treatment outcome of the study patients.

ID #	Age (years)	Sex	Baseline LST size	Baseline PKDL grade	Lesion duration	Follow up duration	PM/SSG treatment	
							Duration	Outcome
1.	5	F	00 mm	3:3	13 months	18 months	40 Days**+	Cure
2.	12	F	08 mm	1:1	14 months	13 months	40 Days**	Cure
3.	13	F	00 mm	2:1	19 months	14 months	40 Days**Ω	Cure
4.	08	M	00 mm	1:2	24 months	09 months	30 Days**	Cure
5.	16	M	00 mm	2:1	28 months	08 months	30 Days*	Cure
6.	17	M	00 mm	2:1	22 months	10 months	30 Days*	Cure
7.	11	F	00 mm	2:2	12 months	06 months	30 Days*	Relapse
8.	16	M	00 mm	2:3	14 months	10 months	30 Day*	Cure
9.	07	M	05 mm	1:1	06 months	10 months	28 Days*	Cure

*No previous treatment for PKDL, **Previous treatment with SSG for 60 days, **+Previous treatment with SSG for 90 days, **ΩPrevious treatment with SSG for 60 days plus 20 days ambisome. LST = Leishmanin skin test. PM = Paromomycin.

Hematological and biochemical parameters were within normal ranges at admission. No biochemical or haematological adverse events were reported during treatment. Pain at the injection sights was reported by all patients. The PKDL rash was completely cleared on discharge (Figure 5-8).

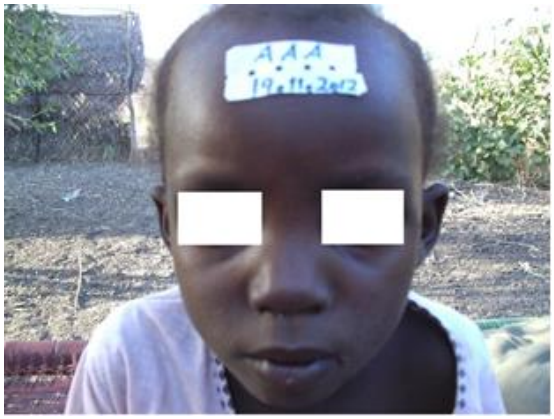

Figure 5: Disappearance of PKDL lesions after treatment, patient's ID No. 1.

Figure 6: Disappearance of PKDL lesions after treatment, patient's ID No. 2.

Figure 7: Disappearance of PKDL lesions after treatment, patient's ID No. 3.

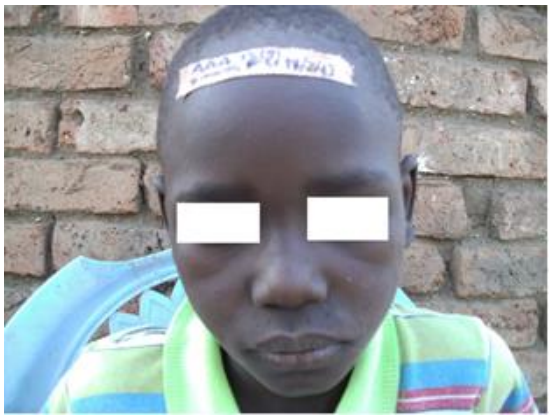

Figure 8: Disappearance of PKDL lesions after treatment, patient's ID No. 4.

DISCUSSION

The most important impediment to VL control in Sudan is the failure to definitely identify a reservoir for the parasite. Tentative reports of rodents and other animals are not supported by solid scientific proof. Anthroponotic transmission from persistent PKDL has been suggested as an important mode of VL transmission. This seems more logical in the face of the fact that most successfully treated VL patients in the Sudan develop PKDL. The lesions although heal spontaneously in the majority, lesions stay active for some time for the sand fly to pick up the parasite from patients' skins. Previously, we have shown than L. donovani parasites can be demonstrated in the skin of VL and PKDL patients.[10,14] Only a small number of PKDL patients come forward for treatment since the complaints are not major and the treatment course is lengthy, painful and costly with some economic burden on patients and families. In addition, PKDL lesions constitute a social stigma, since it resemble leprosy in a number of cases in areas where leprosy and PKDL co-exist.[5] In Sudan, treatment of PKDL cases has never been practiced to control VL may due to causes mentioned previously.

Recently, paromomycin/SSG combination for 17 days has been introduced with marked success in East Africa for the treatment of VL. The main objectives of the combination treatment were to shorten treatment duration and to stem the development of resistance in the region.[27]

Treatment of asymptomatic L. donovani infections and PKDL cases has been suggested as control strategies to eliminate VL from the Indian subcontinent. To achieve such a mammoth goal, cheap and short-course of treatment can help in areas where anthroponotic transmission is prevalent.[28,29]

Based on its efficacy in treating VL patients this report aimed to show that a 30 day combination of paromomycin/SSG can effectively treat PKDL lesions

with reduced cost and minimum side-effects. It was shown clearly that the combination is safe even in three patients who were previously unresponsive to ambisome and SSG. These patients were given a 40 days course of the combination. This prolonged course probably reflected bias on the physicians' side towards initially unresponsive patients. The rest of the patients responded completely to 28-30 days of the combination except one patient who had no previous history of treatment for PKDL and relapsed one month after treatment. This patient was treated with 40 days SSG monotherapy but unfortunately refused longer treatment and was discharged with partial improvement. This combination will definitely reduce hospital stay, reduce the risk of toxicity and may encourage PKDL patients to forward for treatment.

CONCLUSION

Paromomycin/SSG combination for 30 days is safe, efficacious and probably reduces toxicity and cost of PKDL treatment.

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Ethical approval: The study was approved by the institutional ethics committee

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