POST-KALA-AZAR DERMAL LEISHMANIASIS: A MANUAL FOR CASE MANAGEMENT AND CONTROL

REPORT OF A WHO CONSULTATIVE MEETING

KOLKATA, INDIA, 2–3 JULY 2012

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1. INTRODUCTION

Post-kala-azar dermal leishmaniasis (PKDL) is a sequela of visceral leishmaniasis that appears after patients have apparently been cured of visceral leishmaniasis. PKDL has also been reported in patients without a history of visceral leishmaniasis. PKDL appears as a macular, papular or nodular rash, or a combination of these, typically on the face, but it may subsequently affect all parts of the body. PKDL may also affect the conjunctival, nasal, oral and genital mucosa. There is increasing evidence that pathogenesis is largely immunologically mediated.

PKDL is prevalent in all areas where *Leishmania donovani* is endemic (that is, in East Africa especially in Sudan, and on the Indian subcontinent, especially in Bangladesh (*Figure 1*). It does not occur as a sequela of visceral leishmaniasis caused by infection with *L. infantum*, but it has been observed sporadically in patients coinfected with HIV and *L. infantum*. There are differences between the two continents: in Sudan, for example, up to 50% of patients develop the condition after visceral leishmaniasis has apparently been cured, and the severe forms occur mostly in children. In East Africa, PKDL is mostly self-healing. In Sudan, PKDL may occur soon after treatment for visceral leishmaniasis or even concurrently with the disease. On the Indian subcontinent, PKDL occurs after visceral leishmaniasis in about 5–15% of cases, often after a 2–3 year interval; it affects children and adults equally.

The main known risk factor associated with the development of PKDL is previous treatment for visceral leishmaniasis with antimonials; however, PKDL also occurs after treatment with other medicines. The rate of PKDL occurring after patients have been treated with new therapies for visceral leishmaniasis, such as paromomycin or miltefosine, is unknown; patients will need to be followed closely to evaluate the effects of these treatments on the development of PKDL.

Noting this fact, the leishmaniasis control programme at WHO's headquarters collaborated with the vector-borne disease-control programme of the Regional Office for South-East Asia to organize a consultative meeting in July 2012 in Kolkata, India. At the meeting, experts reviewed the epidemiology of PKDL, as well as case-management, prevention and control strategies. They also reviewed recommendations made by the PKDL consortium in June 2012.

1.1 MEETING MINUTES

1.1.1 Opening session

Dr C. Revankar from the vector-borne disease-control programme of WHO's Regional Office for South-East Asia opened the meeting, reiterated the goal of eliminating visceral leishmaniasis from the region and emphasized the potential of PKDL cases as reservoirs of transmission. He highlighted the burden of disease in the sub region; the need to renew the memorandum of understanding signed by Bangladesh, India and Nepal in 2005 as part of a programme to eliminate visceral leishmaniasis, which expired in 2010; and the need to reinvigorate surveillance to improve case detection of PKDL.

1.1.2 Objectives of the meeting

The objectives of the meeting were to:

- review the global burden and epidemiology of PKDL and asymptomatic infections;
- review PKDL case-management guidelines, and strategies for surveillance, control and prevention;
- identify gaps in PKDL control, and make appropriate recommendations for case-management guidelines.

The methods followed to achieve the above objectives included:

- brief presentations on the selected thematic areas;
- breakaway sessions in which participants were split into different working groups;
- plenary discussions, and concluding remarks.

1.1.3 Thematic presentations

The following thematic areas were covered during the presentations:

- importance of asymptomatic infections in the transmission of PKDL;
- the epidemiology and burden of the disease in East Africa and the Indian subcontinent;
- diagnosis, case-management and surveillance;
- the need for additional research and recommendations made by the PKDL consortium meeting during its meeting in New Delhi, India, in June 2012.

1.1.4 Working groups

Three working groups were formed:

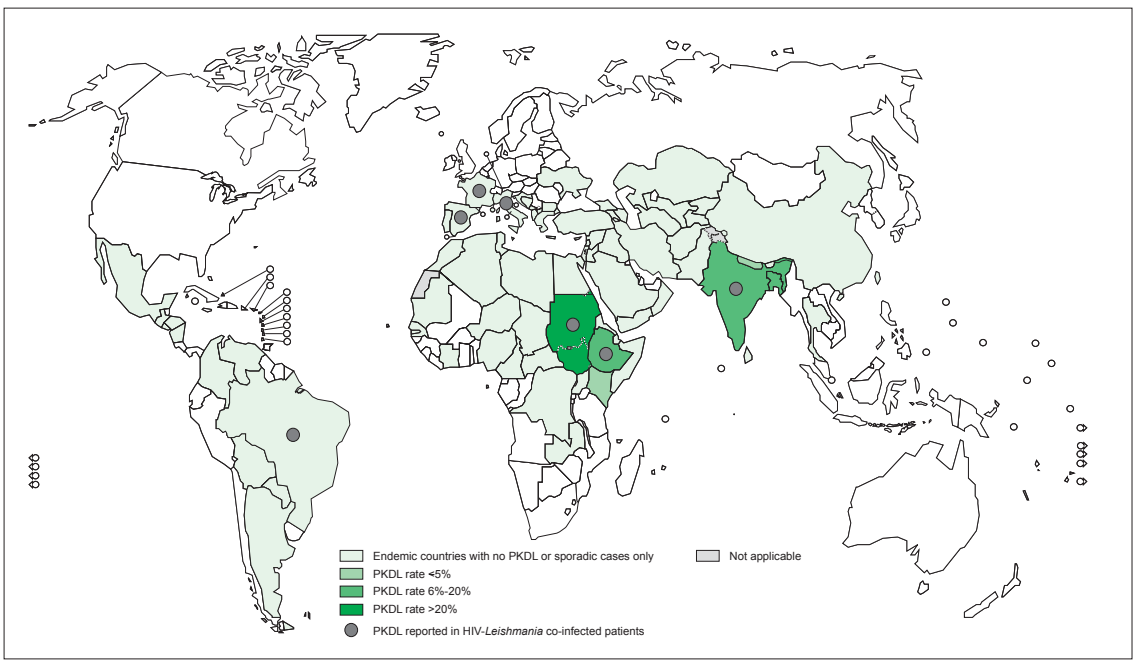
- epidemiology, surveillance and control strategies;
- pathogenesis, clinical features, grading and diagnosis;
- case-management (focusing on regionally specific recommendations).

The working groups discussed and reviewed thoroughly the topics in their thematic areas. At the end of the session, one member presented the findings from each group. These finding were discussed in the plenary session, and recommendations were made.

2. EPIDEMIOLOGY

PKDL occurs in all areas endemic for *L. donovani* but is commonest in Sudan in East Africa, and in Bangladesh on the Indian subcontinent. The frequency is low in other endemic countries, and is reported to be declining in India.

Figure 1. Global distribution of post-kala-azar dermal leishmaniasis, 2005–2010



2.1 TRANSMISSION

PKDL lesions (especially the papular and nodular forms) usually harbour leishmanial parasites, and are potentially infective to sandflies. However, evidence of infectivity is sparse. Xenodiagnosis has shown that vectors can pick up the parasite from nodular, papular and macular lesions, and that the parasites can develop into mature transmissible infections in the vectors, but the relevant studies have been based on an extremely small number of cases.

Patients with chronic PKDL are generally assumed to act as reservoirs for the parasites during interepidemic periods of visceral leishmaniasis. Although transmission of visceral leishmaniasis in Africa is partly zoonotic, in Sudan the interval between epidemic cycles in villages lasts 8–10 years, and patients with PKDL seem to be a human reservoir of infection. In Gedaref State, Sudan, the presence of chronic PKDL cases in 1990 and a low prevalence of visceral leishmaniasis was followed by an upsurge in cases of visceral leishmaniasis in 1991.

On the Indian subcontinent, no animal reservoir host has been identified despite many surveys. Transmission is believed to be only anthroponotic, and patients with visceral leishmaniasis or PKDL, and possibly asymptomatic carriers, are thought to contribute to transmission; patients with chronic PKDL are believed to constitute the main source of parasites during interepidemic intervals.

2.2 GLOBAL EPIDEMIOLOGY

The global epidemiology of PKDL has been insufficiently studied, and data on prevalence are based on estimates. In East Africa and on the Indian subcontinent the distribution of PKDL predominantly reflects the distribution of visceral leishmaniasis caused by *L. donovani*. The factors that increase the risk for PKDL within an endemic zone are incompletely understood but appear to include young age at the time of developing visceral leishmaniasis and an inadequate course of treatment. PKDL has been reported frequently after treatment for visceral leishmaniasis with sodium stibogluconate, but also after treatment with miltefosine, amphotericin B (deoxycholate and liposomal) and

paromomycin; of all these medicines, sodium stibogluconate has been used most extensively. Long-term follow-up data are needed to determine whether treating visceral leishmaniasis with a particular medicine makes it more likely that patients will develop PKDL.

2.2.1 East Africa

In East Africa, visceral leishmaniasis occurs in two distinct ecological settings. The first is the savannah regions in the north where the vegetation is primarily acacia and balanites (Ethiopia and Sudan); in these areas *Phlebotomus orientalis* is the major vector. The second ecological setting is the savannah and forest areas in the south (southern Ethiopia, Kenya and Uganda), where *P. martini* and *P. celiae* are found in association with mounds built by the Macrotermes species of termite.

In areas where *P. orientalis* is the predominant vector, sporadic sylvatic zoonotic transmission of visceral leishmaniasis is well recognized, but sustained peridomestic and domestic cycles in villages have also been identified. Large outbreaks, such as those that occurred during the civil war in southern Sudan in the 1980s and 1990s, are thought to have been caused by anthroponotic transmission during population displacement, coupled with malnutrition, the destruction of health-care infrastructure and increased incidences of other diseases. Seasonal movements of labourers may also spread the disease as migrants return to non-endemic areas; this appears to be to have been occurring in the highlands of Ethiopia since 2000. Specific risk factors for visceral leishmaniasis include the presence of cattle, the person's age and genetic predisposition. Sleeping outside under acacia trees and living in houses constructed of grassy material also appear to increase the risks. Although *L. donovani* infection has been demonstrated in dogs in several foci, their importance in the transmission cycle is uncertain.

In areas where *P. martini* and *P. celiae* are the predominant vectors, the proximity of human dwellings to termite mounds increases risk.

2.2.1.1 Sudan and South Sudan

Sudan is the country with the highest incidence and burden of the disease. PKDL in Sudan is unique and different from PKDL on the Indian subcontinent. (At the time that many studies were done, South Sudan was not independent, so data for Sudan often include what is now South Sudan.) In Sudan, PKDL occurs at a much higher frequency and develops within the first few months after treatment (not after several years as it does on the Indian subcontinent). In Sudan, PKDL occurs after visceral leishmaniasis in 56–62% of cases. Of all PKDL cases, 10% present without a history of visceral leishmaniasis, and 15% present with PKDL at the same time as visceral leishmaniasis (which is known as para-KDL). Usually, patients present with PKDL within 6 months after treatment for visceral leishmaniasis but sometimes they present as soon as 2 weeks after or as long as 13 months after. Using highly effective treatment for visceral leishmaniasis may lead to fewer patients developing PKDL: for example, PKDL developed in 12% of patients treated with sodium stibogluconate monotherapy for visceral leishmaniasis and in 9% of patients treated with paromomycin monotherapy, but it developed in only 6% of patients treated with a combination of sodium stibogluconate and paromomycin. PKDL may resolve spontaneously within 6 months, but if it lasts longer then it becomes chronic and requires prolonged treatment.

2.2.1.2 Ethiopia

In Ethiopia, PKDL occurs at varying rates in different regions and populations of patients. During 1998–1999 in northern Ethiopia PKDL occurred in an average of 13% of patients with visceral leishmaniasis and in 27% of patients coinfected with HIV and visceral leishmaniasis; however, these proportions do not represent the true number of cases since mild PKDL is often not treated and consequently not reported. In southern Ethiopia, the prevalence of PKDL seems lower but there is no published information that includes active follow up of cases.

Limited unpublished data indicate that there are differences among parasites in the northern and southern foci. Those in the south are more similar to parasites seen in India, whereas isolates from northern foci are more variable, and the parasites are often similar to those in eastern Sudan. However, the relevance of this difference for PKDL remains unclear. Differences between northern and southern Ethiopia include a reduced response to treatment in the north, but there are also host differences; in hyperendemic areas in the north malnutrition and high coinfection rates play a part, but in the South, visceral leishmaniasis occurs in a microfocal pattern, and people are generally better nourished.

The reported prevalence of PKDL in Ethiopia is low when compared with Sudan, but it is higher in people coinfected with HIV and visceral leishmaniasis, in whom it often presents atypically. However, during the Libo Kemkem visceral leishmaniasis outbreak (2005–2008), an epidemic that affected mainly children, the incidence of PKDL was higher than seen routinely in Ethiopia.

2.2.2 The Indian subcontinent

In anthroponotic foci in Bangladesh, India and Nepal (with the exception of Bhutan; and Kashmir, Himachal Pradesh and Uttarakhand in India) the general conditions that favour transmission of visceral leishmaniasis are rural areas that are less than 600 m above sea level; a heavy annual rainfall; a mean humidity above 70%; a maximum temperature of 38 °C and a minimum temperature of 15 °C, with a diurnal variation of less than 7 °C; and abundant vegetation, subsoil water, and alluvial soil. Sri Lanka and Thailand are also endemic areas but have few cases annually. Surveillance for visceral leishmaniasis and PKDL should be conducted in all of these areas.

Visceral leishmaniasis occurs in agricultural villages where houses are constructed with mud walls and earthen floors, and cattle and other livestock are kept close to human dwellings. Spatial analyses demonstrate a significant clustering of cases, both at the household level and the community level. Higher densities of the proven vector (*P. argentipes*) are found in cattle sheds than in human dwellings, but the vector takes blood-meals opportunistically from both bovines and humans. Human behaviour, such as sleeping outside or on the ground, may increase the risk of infection, while the use of bednets tends to be associated with lower risk. Risk factors for visceral leishmaniasis include living in the same household as someone who has an active case of the disease or of PKDL and poverty-related factors, such as poor nutrition and housing conditions.

In 2005, Bangladesh, India and Nepal agreed to implement a programme to eliminate visceral leishmaniasis, with the aim of reducing the number of cases at the district or subdistrict level to fewer than 1/10 000 population by 2015. Addressing PKDL will be crucial to achieving this goal.

2.2.2.1 Bangladesh

Visceral leishmaniasis is concentrated mainly in the district of Mymensingh. Studies in the subdistricts of Fulbaria and Trishal showed a prevalence of PKDL of 6–16/10 000 population; one study in Fulbaria found a PKDL incidence of 9.5% of patients treated for visceral leishmaniasis. In a population study in Mymensingh, the incidence of PKDL was found to have increased sharply from 2002 to 2007. This information on the burden of PKDL may not be representative of endemic areas in Bangladesh outside the hyperendemic district of Mymensingh.

PKDL develops within a median time of 21 months (range, 0–120 months) after visceral leishmaniasis, and most often is untreated. The high rate of PKDL may hinder the elimination of visceral leishmaniasis in Bangladesh.

2.2.2.2 India

PKDL is estimated to occur in about 5–10% of visceral leishmaniasis patients within 5 years of onset; it often remains untreated. A 2010 survey of 4 323 households in a highly endemic area in Bihar showed a local PKDL prevalence of 5/10 000 population (Professor Das, personal communication). Visceral leishmaniasis periodically re-emerges in areas considered to be free of the disease; re-emergence is associated with the presence of untreated cases of PKDL cases and changing environmental conditions.

2.2.2.3 Nepal

The number of patients with visceral leishmaniasis in Nepal is much lower than in Bangladesh or India. The majority of cases are reported from 12 endemic districts that account for 25% of the country's population.

In the late 1990s, there was an increase in the number of cases, but since 2006 the case-load has decreased. The prevalence of PKDL has been estimated to be 2.3% of patients treated for visceral leishmaniasis, based on a screening of cases treated by the B.P. Koirala Institute of Health Science in Dharan and by district hospitals. Data on the number of PKDL cases are limited because the disease is not reported by the national elimination programme. The prevalence of PKDL may be higher in districts that are closer to Indian districts, where resistance to treatment with sodium stibogluconate has been identified.

In 2010, a survey found that the median onset of PKDL after visceral leishmaniasis was 23 months. Patients who received only partial treatment (<20 injections of sodium stibogluconate) were 11 times more likely to develop PKDL than those who received the complete treatment series.

3. PATHOGENESIS

PKDL occurs after treatment for visceral leishmaniasis in a proportion of patients, and is considered to be triggered immunologically. In visceral leishmaniasis, the predominant immune response is a Th2 response, whereas in PKDL, there is a mixed Th1 and Th2 response with persistence of interleukin (IL) 10.

It is difficult to predict who will develop PKDL. Inadequate treatment for visceral leishmaniasis (for example, treatment with a low dose of medicine or for a short duration), young age (generally, 5–17 years), malnutrition, HIV infection and antiretroviral treatment all may play a part. There are no proven clinical predictors of PKDL, such as the degree of splenomegaly or hepatomegaly during visceral leishmaniasis. In Sudan, genetic studies have shown decreased expression of the interferon-gamma receptor gene in patients with PKDL; this was not found in patients with visceral leishmaniasis.

PKDL occurs almost exclusively in patients with visceral leishmaniasis caused by *L. donovani*; it is rare in cases caused by *L. infantum*. However, there are marked differences in the rate of developing PKDL among areas where L. donovani is the causative parasite.

In biopsy samples, PKDL in India shows a diffuse dermal infiltrate of macrophages, lymphocytes and plasma cells; in PKDL biopsy samples from Sudan, epithelioid cells are seen but plasma cells are scanty or absent. The inflammatory cells are mainly CD3+ cells; IL-10 is prominent in the lesions; interferon-gamma and tumour necrosis factor (TNF) alpha are found uniformly; and IL-4 is present in varying amounts. Diminished expression of interferon-gamma receptor 1 and TNF-R1 receptors during PKDL may interfere with an effective host response.

Favourable outcomes for patients with PKDL are predicted by a positive leishmanin skin test or when levels of interferon-gamma are higher than levels of IL-10.

4. CLINICAL MANIFESTATIONS

In contrast with visceral leishmaniasis patients, PKDL patients are well except for their skin rash. Therefore, those with a mild rash may not present to a health facility. PKDL patients do not have fever, and the physical examination is usually normal. However, severe forms of PKDL can cause significant social and clinical discomfort. Since diagnosis is based on clinical characteristics, the differential diagnosis of other skin conditions is critical (*Box 1*). WHO has published an atlas that aims to help with the differential diagnosis.[1]

4.1 EAST AFRICA

PKDL lesions typically start on the face as papules around the mouth; they may spread to other parts of the face. The rash may remain restricted to the face or it may spread to other parts of the body: first, to the trunk and upper limbs, and subsequently it may become generalized. Lesions are usually symmetrical and not itchy. The papules may increase in size, and turn into nodules or plaques, or a combination of these; alternatively, the rash may be macular. Combined maculopapular rash is common; a micropapular rash resembling measles may also be found.

[1] *Zijlstra EE, Alvar J, eds. The post kala-azar dermal leishmaniasis (PKDL) atlas: a manual for health workers. Geneva, World Health Organization, 2012.*

In Sudan, three grades of PKDL severity have been described; this clinical grading has also been adapted for case-management in Ethiopia and South Sudan (*Annex 2*). The grades are:

- **grade 1** – scattered maculopapular or nodular rash on the face, with or without lesions on the upper chest or arms;
- **grade 2** – dense maculopapular or nodular rash covering most of the face and extending to the chest, back, upper arms and legs, with only scattered lesions on the forearms and legs;
- **grade 3** – dense maculopapular or nodular rash covering most of the body, including the hands and feet; the mucosa of the lips and palate may be involved.

4.2 THE INDIAN SUBCONTINENT

Most patients on the Indian subcontinent have a polymorphic presentation comprising macular, papular or nodular lesions, with a predilection for the area around the chin and mouth. This presentation can be subdivided into different forms:

- **monomorphic** (macular and nodular);
- **polymorphic or mixed** (both macules and indurated lesions such as papules are present);
- **rare presentations** (for example, erythrodermic).

There is no standard system for grading the severity of PKDL on the Indian subcontinent. The severity may be described as:

- **mild** (very few lesions, usually on the face);
- **moderate** (lesions easily visible and generalized);
- **severe** (dense coverage with lesions and little normal skin remains).

Box 1. The differential diagnoses of post-kala-azar dermal leishmaniasis[a]

- Leprosy
- Pityriasis versicolor
- Pityriasis alba
- Vitiligo
- Measles
- Acne
- Neurofibromatosis
- Lupus vulgaris
- Discoid lupus erythematosus
- Miliaria rubra
- Chronic arsenic poisoning
- Secondary syphilis
- Nutritional deficiencies

[a] The most important differential diagnoses differ according to the epidemiology of the endemic area.

5. DIAGNOSIS

PKDL should be suspected in patients in endemic areas who present with a skin rash combined with previous or concomitant visceral leishmaniasis. The diagnosis can be made using clinical criteria or by identifying the parasite, or both.

Clinical diagnosis is made by assessing the presence of the typical rash, its distribution, whether the patient has a history of visceral leishmaniasis or, because PKDL can occur without previous visceral leishmaniasis, whether the patient lives in an endemic area or has recently travelled to one. In a setting where diagnostic methods are limited, diagnosis will often be based on these clinical criteria and history (*Figure 2*); knowledge of other skin conditions in the area may help with the differential diagnosis (*Box 1*).

Slit-skin smears or samples obtained by biopsy can be used to identify parasites to confirm the diagnosis of PKDL. Studies in India and Sudan have found that smears are more likely to show amastigotes if they are taken from nodular lesions rather than papular lesions; samples are least likely to show amastigotes if taken from macular lesions. Culture can be attempted, but it takes time, and contamination is common.

Skin biopsies may also be examined by histopathology and immunohistochemistry.

Serological tests, such as the direct agglutination test, enzyme-linked immunosorbent assay (ELISA) and the rK39 rapid diagnostic ELISA, are usually positive but are of limited value because a positive result may be caused by antibodies persisting after a past episode of visceral leishmaniasis. Nevertheless, serology can be helpful when other diseases (for example, leprosy) are considered in the differential diagnosis, or if a history of visceral leishmaniasis is uncertain. The rK39 rapid diagnostic ELISA can be used as strong evidence for past visceral leishmaniasis in both Africa and the Indian subcontinent. However, this test is more sensitive in the Indian subcontinent than in Africa; therefore, if negative, it rules out past disease in the Indian subcontinent but not in Africa.

Species-specific polymerase chain reaction (PCR) may be used on skin biopsy samples or slit-skin specimens in well-equipped laboratories. The sensitivity of this test varies depending on the PCR method used and the type of lesions sampled. Quantitative PCR used to assess slit-skin specimens has been shown to be highly sensitive.

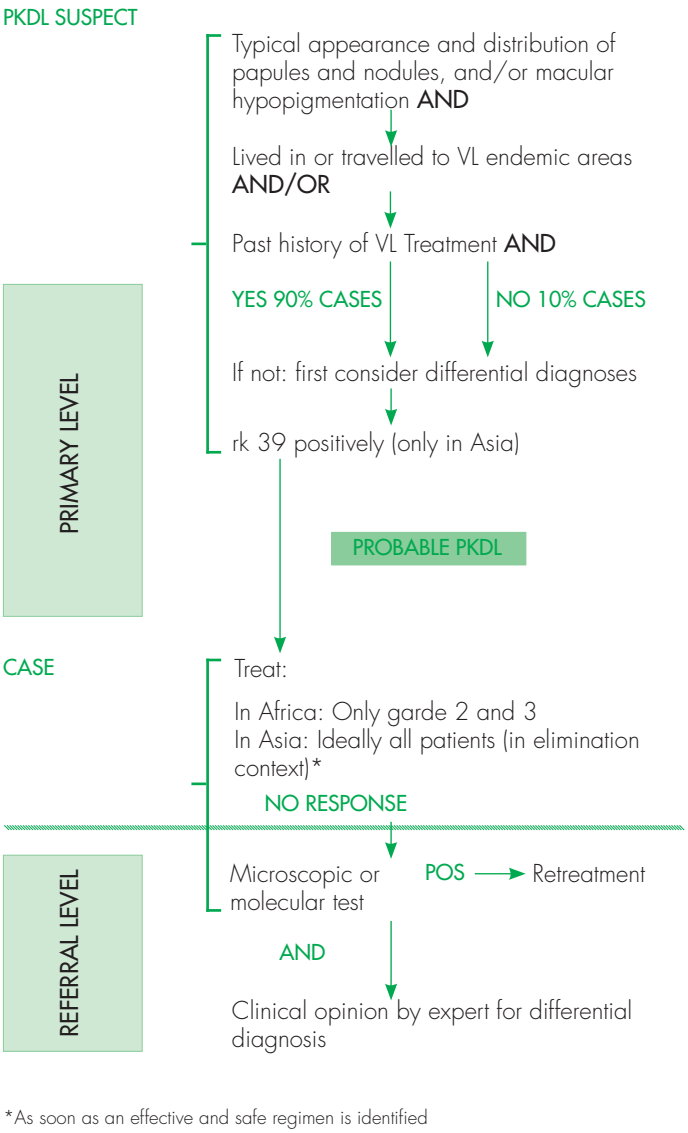
6. TREATMENT AND CASE-MANAGEMENT

PKDL does not cause any physical limitations; therefore, patients ordinarily do not seek treatment unless cosmetic disfigurement leads to problems, such as social exclusion or difficulty in arranging a marriage (this is especially relevant to girls who are at a marriageable age). In addition, treatment with intramuscular injections of sodium stibogluconate is long (2 months in Africa, 4 months on the Indian subcontinent), painful, potentially toxic and cumbersome; as a consequence, only few patients complete treatment, especially on the Indian subcontinent. This is expected to change as new, shorter and more patient-friendly treatment regimens using different medicines become available. However, there is limited evidence about the efficacy of PKDL treatment, and the outcome may depend on the severity of the condition and the duration of symptoms before treatment. Evaluating the efficacy of treatment for macular lesions clinically is not straightforward because repigmentation of lesions may take place long after the goal of parasite clearance has been reached.

Since PKDL usually does not lead to any physical impairment, systematic detection and treatment of PKDL implemented as a disease-control intervention is justified only if the treatment is safe, effective, acceptable to the patient, and if it is not likely to lead to the development of resistant strains when monotherapy is used. Consideration should be given to preventing the development of resistant strains when monotherapy lasting longer than 4 weeks is prescribed. A careful risk–benefit evaluation should be made for each patient.

- Patients must be counselled about the importance of following up if signs of relapse or recurrence are observed. They should also be informed about the importance of completing treatment, the potential side-effects of treatment, and the slow and long healing process.

Figure 2. Algorithm for diagnosing and treating post-kala-azar dermal leishmaniasis (PKDL)



*As soon as an effective and safe regimen is identified

- Pregnant women should not be treated with miltefosine. Women of reproductive age and their partners should be counselled appropriately about the need to use effective contraception during the 12-week course of miltefosine treatment and for 4–6 months after completing treatment.
- Sodium stibogluconate should not be used to treat patients coinfected with HIV, pregnant women, or patients with underlying cardiac disease or renal disease.

It is important that studies evaluate new combinations of medicines, such as liposomal amphotericin B plus miltefosine, miltefosine plus paromomycin, or miltefosine plus sodium stibogluconate.

The medicines and treatment regimens for PKDL discussed here have been graded using standards adapted from Cochrane reviews. The grades used are as follows:

- A – evidence obtained from at least one properly designed randomized controlled trial;
- B – evidence obtained from well-designed trials without randomization;
- C – evidence obtained from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees; and
- D – evidence obtained from expert opinion without consistent or conclusive studies.

6.1 EAST AFRICA

In East Africa, PKDL is not routinely treated since the majority of cases (85%) heal spontaneously within 1 year. The only patients who are treated are those with severe or disfiguring disease, with lesions that have remained for longer than 6 months, with concomitant anterior uveitis, and young children with oral lesions that interfere with feeding. Patients are treated either with sodium stibogluconate (20 mg/kg Sb^{5+} per day) for 30–60 days or with a combination of paromomycin (11 mg/kg base per day) for 17 days plus sodium stibogluconate (20 mg/kg per day) for 17–60 days, or with a 20-day course of liposomal amphotericin B (2.5 mg/kg per day). In Sudan and South Sudan, the end-point of treatment is the flattening of lesions and the improvement of depigmentation.

In a randomized controlled clinical trial in Sudan of patients with persistent PKDL (lasting longer than 6 months), which is difficult to cure with medicines alone, the cure rate with a combined immunotherapy plus chemotherapy regimen was significantly better than the regimen that used chemotherapy alone.

All patients received chemotherapy with sodium stibogluconate (20 mg/kg Sb^{5+}) for 40 days; patients also treated with immunotherapy received a vaccine consisting of a mixture of killed *L. major* adsorbed onto alum plus bacille Calmette–Guérin, given four times at weekly intervals; the evidence for these treatments was graded A. The number of patients included in each group was 15. In the group that received sodium stibogluconate plus vaccine, 87% of patients were cured by day 60 compared with 53% in the group that treated only with sodium stibogluconate.

A small case series (n = 6) showed promising results treating PKDL in HIV-positive patients with miltefosine (100 mg daily) for 28 days; this evidence was graded C.

6.2 THE INDIAN SUBCONTINENT

6.2.1 Miltefosine

A regimen of 12 weeks of continual miltefosine proved successful in adults and the evidence was graded A, but the regimen has not been evaluated for treating children younger than 12 years. Disappearance of the lesion at a 12-month follow-up visit was taken as the criterion of cure, including parasitological as well as clinical cure. This regimen resulted in a final cure rate of 93% of patients (14/15) assessed according to the protocol. There were no serious side-effects. The safety of courses of miltefosine lasting longer than 4 weeks has not been evaluated.

6.2.2 Amphotericin B deoxycholate

Clinical experience with intermittent amphotericin B deoxycholate treatment (20 days on, 20 days off) for up to 4 months was shown to be effective, and the evidence was graded C. All patients in the study (11/11) were clinically cured.

6.2.3 Liposomal amphotericin B

In Bangladesh, a short course of treatment with two doses of liposomal amphotericin B (5 mg/kg per dose) per week for 3 weeks proved successful in a cohort of 406 patients; the evidence was graded C. Most of the patients (96%) had predominantly macular lesions. Altogether, 10% of patients did not respond to treatment; however, 34% of patients had complete repigmentation of their lesions. After 12 months, 56% of all patients showed incomplete repigmentation.

Larger studies are required to validate the use of amphotericin B deoxycholate and liposomal amphotericin B.

The recommended definition of cure is clinical (*Box 2*). The clinical cure of macular lesions is difficult to define because repigmentation occurs over time. However, the duration of treatment for macular, nodular and papular

lesions is the same. If feasible, an attempt should be made to determine whether parasites are still present in lesions that have not healed completely by 12 months after starting treatment.

Box 2. Definitions of cure

Leprosy

Demonstrated by clinical cure of papular and nodular lesions, and complete resolution of macular lesion or repigmentation of macular lesions at 12-month follow-up visit.

Parasitological cure

At the end of treatment and at subsequent follow-up visits, parasites should no longer be present.

Box 3. Treatment options for post-kala-azar dermal leishmaniasis (presented in order of most common use)

East Africa

- Combination treatment: pentavalent antimonials (20 mg Sb^{5+}/kg per day intramuscularly or intravenously) for 17–60 days plus paromomycin (15 mg in 11 mg base/ kg per day intramuscularly) for 17 days when indicated; the evidence for this regimen is graded C.
- Pentavalent antimonial: 20 mg Sb^{5+}/kg per day intramuscularly or intravenously for 30–60 days when indicated; the evidence for this regimen is graded C.
- Liposomal amphotericin B: 2.5 mg/kg per day by infusion for 20 days when indicated; the evidence for this regimen is graded C.
- Miltefosine: 100 mg per day for 28 days may be beneficial in patients coinfected with HIV and PKDL; the evidence for this regimen is graded C.

Bangladesh, India and Nepal

- Amphotericin B deoxycholate: 1 mg/kg per day by infusion, up to 60–80 doses delivered over 4 months; the evidence for this regimen is graded C.
- Miltefosine: 100 mg orally per day for 12 weeks for patients weighing >25 kg; 50 mg orally per day for 12 weeks for patients weighing <25 kg; the evidence for this regimen is graded A.*
- Liposomal amphotericin B: 5 mg/kg per day by infusion two times per week for 3 weeks for a total dose of 30 mg/kg; the evidence for this regimen is graded C.†

* Because the safety of courses of miltefosine lasting longer than 4 weeks has not been evaluated, all patients should be closely monitored for side-effects.

† Although additional evidence is needed, potassium supplementation is recommended for this regimen given in a patient's diet (for all patients) or through intravenous infusion (for those with proven severe hypokalaemia). To prevent serious adverse effects caused by hypokalaemia, patients should be monitored for any related signs or symptoms. Hypokalaemia should be suspected in all patients with general weakness, nausea, myalgia, muscle weakness or cramps occurring during or after treatment.

6.3 PHARMACOVIGILANCE

The safety of the treatments discussed above has not been fully evaluated in patients with PKDL, so it is especially important to collect pharmacovigilance data as part of programmes to control visceral leishmaniasis.

7. SURVEILLANCE

Because patients with PKDL constitute an important residual reservoir, detecting and treating them are important, especially at times of low prevalence. Preventive measures, such as the distribution of bednets, should be implemented in endemic areas, and when a safe and effective treatment regimen has been identified, treatment should be rolled out. Patients with PKDL often do not seek treatment or may default from treatment. Thus, strengthening both passive surveillance and active surveillance is a priority. Because PKDL usually does not lead to physical impairment implementing systematic detection and treatment as a disease-control intervention is justified only if the treatment provided is safe, effective and acceptable to the patient. Surveillance for PKDL should be integrated into the leishmaniasis control programme and become part of the national surveillance system for leishmaniasis or the national communicable diseases surveillance system. PKDL should be included in official reporting systems for visceral leishmaniasis. Surveillance for PKDL should use case-detection methods similar to those used for visceral leishmaniasis and other communicable diseases.

It is important to actively survey for cases because PKDL patients may not seek treatment and may be missed by passive case-detection methods. Passive case detection of PKDL leads to severe underreporting. Health education is an essential component of any active or passive case-surveillance activity. Implementing a campaign that provides intensive public education should be considered in combination with both active and passive case detection. A geographical information system could be helpful in defining microfoci. The detection of cases should be combined with vector control measures if appropriate and possible.

The passive and active case-detection methods used for leishmaniasis surveillance are described below.

7.1 PASSIVE CASE DETECTION

The passive detection of cases is triggered when patients seek care for their illness from clinicians working in fixed health facilities, such as district hospitals. Clinicians who manage a case should notify the appropriate epidemiological surveillance system. It is essential to use standardized case definitions for visceral leishmaniasis and PKDL (*Annex 1*). Most countries where visceral leishmaniasis and cutaneous leishmaniasis are endemic rely on passive surveillance when reporting their disease burden. Such reporting, however, captures only a fraction of the true burden because access to care for these neglected diseases is limited, and cases managed in the private sector are usually not included in surveillance data. Passive case detection results in an underestimate of the incidence of cases and the disease burden.

In a study in India, the actual burden of visceral leishmaniasis was estimated to be 3.7 times higher than the reported burden; in another study, the actual burden was estimated to be 8 times higher. However, no estimates exist for PKDL, and underreporting is likely to be substantially worse for PKDL since most patients do not seek treatment from either the private sector or the public sector.

Providing acceptable treatment increases health-seeking behaviour and thus improves passive case detection; acceptable treatment is patient friendly, with a minimal impact on a patient's life. In Bangladesh, after short-course ambulatory treatment with liposomal amphotericin B was introduced, more PKDL patients presented spontaneously for treatment than had been identified in the community by complementary active case detection.

To ensure that monitoring is sustainable, routine surveillance systems must be improved as health-care systems are strengthened. Passive case detection can be improved by involving the private sector and basic health-care units, where patients with visceral leishmaniasis can be encouraged to voluntarily report PKDL-like lesions. Increasing the public's awareness of PKDL may enhance self-reporting. It should be common practice to engage in long-term follow up of visceral leishmaniasis patients to monitor them for the development of PKDL and at the same time to monitor them also for relapse.

7.2 ACTIVE CASE DETECTION

Although most health systems rely on passive case detection to find leishmaniasis cases, more PKDL cases are detected and reported if active case detection complements passive case detection. Screening by first-line health workers using standard case definitions and well defined risk factors – such as living in an endemic area, living in a family in which someone has had or does have visceral leishmaniasis, having an epidemiological link (such as having had visceral leishmaniasis) – and referring suspected cases to centres where confirmation is possible may contribute to better control of PKDL.

Active case detection (or actively searching for cases) means that health workers reach out to the community and systematically screen the population to identify cases of leishmaniasis. On the Indian subcontinent, active case searches for PKDL, in addition to those for visceral leishmaniasis, should be essential components of the visceral leishmaniasis elimination strategy, provided that appropriate treatment services (that is, those that are safe, effective and acceptable) can be offered to PKDL patients. Active case detection should help reduce disease transmission by shortening a patient's infectious period, which can be several years for PKDL; also, earlier diagnosis and treatment offer clinical benefits. Preliminary data show that active case detection is cost effective in areas where the disease incidence is high; in areas where endemicity is low, the use of focal or cluster surveys may be considered. Since the incidence of PKDL is significantly lower than that of visceral leishmaniasis, a cost-effective strategy would be to combine active case detection for PKDL with that for visceral disease. This seems to be the best way to effectively detect patients with PKDL in the community.

Several active case detection approaches are possible, such as:

- house-to-house searches (or 'blanket screening'), in which a medical team visits each house in a community and screens every member of the household;
- the camp approach, in which a 'medical camp' is organized in a readily accessible place in a village, and the community is invited to attend a screening session, after an awareness-raising campaign;
- the index-case approach (or 'snowballing'), in which a house-to-house search is conducted in the immediate neighbourhood of a recently confirmed case of visceral leishmaniasis or PKDL, or a camp is organized close to the house of the index case;
- an incentive-based approach, in which an incentive or award is given to health volunteers who facilitate case detection.

Operational research has shown that the cost effectiveness of each of these strategies depends on the local epidemiological context.

7.3 PREVENTING TRANSMISSION

The prevention of transmission should be considered from the personal and public-health perspectives. Prevention is best achieved by early diagnosis and complete treatment for visceral leishmaniasis and PKDL, with a 12 month follow-up to detect relapse. Regular active or passive case detection should be combined with the following efforts to prevent transmission:

- blanket indoor residual spraying of houses and animal shelters in highly endemic areas;
- provision of free long-lasting insecticidal nets to patients with PKDL or visceral leishmaniasis, which also encourages self-reporting of PKDL;
- treatment of PKDL, depending on the region and safety of available treatments (*Box 3*).

WHO's recommended case definitions for visceral leishmaniasis and PKDL are given in *Annex 1*.

8. RESEARCH

The priority of future research on PKDL is to provide sound evidence of its infectiousness. As this may take several years, the parallel research priorities are to establish a first indication of infectiousness by xenodiagnosis, validate the criteria for clinical diagnosis to enable active case surveillance and assess the true burden of PKDL, and develop methods to confirm PKDL and a test of cure so that clinical studies become feasible.

8.1 RECOMMENDED RESEARCH PRIORITIES

A meeting of the PKDL consortium was held in New Delhi, India, on 27–29 June 2012 organized by One World Health, a drug development affiliate of PATH, and the Drugs for Neglected Diseases Initiative. The following recommendations were made at the consortium meeting and adopted during the WHO consultative meeting.

8.1.1 Epidemiology

- Measure the exact burden of PKDL by active surveillance (index case) and geographical information systems (mapping).
- Assess and compare the infectiousness of different types of PKDL, visceral leishmaniasis, asymptomatic patients, oligosymptomatic patients, and patients coinfected with HIV and visceral leishmaniasis.
    - o use xenodiagnosis to assess infectivity and its duration.
    - o assess and validate biomarkers to replace xenodiagnosis.
    - o establish when or if patients with PKDL and visceral leishmaniasis become non-infectious after treatment.
- Conduct epidemiological modelling (based on the results of research into infectiousness).

If PKDL is proven to be infectious, it needs to be determined which PKDL patients need treatment and for how long they need treatment; additionally, the best method of prevention needs to be identified (for example, whether using nets treated with long-lasting insecticide is effective or indoor residual spraying, or both).

8.1.2 Diagnosis

- Validate the criteria for clinical diagnosis, compare them with other tests and assess their value for evaluating response to treatment.
- Develop new diagnostic tests (antigen detection) and a test of cure suitable for use in the field.
- Standardize a quantitative PCR method for parasites in different clinical forms and treatment stages of PKDL.

8.1.3 Pathogenesis

8.1.3.1 Short term

- Conduct genetic analysis of host by genome-wide association studies and transcriptome analyses to i dentify markers of susceptibility to PKDL.
- Identify immunological markers predictive of PKDL to monitor the immune response after treatment of visceral leishmaniasis and follow-up for development of PKDL.
- Prepare paired isolates from patients with visceral leishmaniasis or PKDL, a repository of parasites, serum etc.
- Identify serum markers to monitor progression towards cure, and define the end-point of treatment.
- Establish referral laboratories to confirm diagnoses by histopathology and by PCR in suspected PKDL cases negative by microscopy.

8.1.3.2 Medium term

- Complete whole genome sequence analysis of parasites to enable comparison of African and Asian strains of parasites.
- Develop an animal model of PKDL.
- Investigate the mechanism of hypopigmentation in PKDL.
- Prepare antibodies to sandfly components in serum from PKDL and visceral leishmaniasis patients
- Assess the influence of nutritional status on the development of PKDL.

8.1.4 Treatment

- Conduct randomized clinical trials of short-course regimens.
  - In the Indian subcontinent, evaluate a short-course regimen of liposomal amphotericin B in a total dose of 30 mg/kg.
  - In Africa, evaluate new combinations of medicines including:
    - liposomal amphotericin B plus miltefosine;
    - miltefosine plus paromomycin;
    - miltefosine plus sodium stibogluconate;
    - other new combinations.
- Evaluate the use of immunochemotherapy.
- Evaluate the characteristics of medicines and their capacity to penetrate the skin; modify medicines to target the skin.

9. RECOMMENDED PRIORITIES FOR OPERATIONAL RESEARCH

9.1 GENERAL

- The WHO guidelines on PKDL should be updated periodically to include technical advances and experience gained in the field.
- Ethics and equity should be the guiding principles in treating PKDL since it is a disease of poverty.

9.2 SURVEILLANCE

- Awareness-raising in communities and among health workers, as well as capacity building through training, are crucial for improved case detection.
- PKDL surveillance should be part of surveillance for visceral leishmaniasis.
- Active case detection of PKDL is preferable to passive case detection.
- The private sector should be involved in reporting and treatment of PKDL.
- For each reported case of PKDL, previous treatment for visceral leishmaniasis should be recorded.

9.3 TREATMENT

- Control of PKDL should be part of strategies to eliminate visceral leishmaniasis.
- Countries should be encouraged to adopt treatment strategies for PKDL in national protocols for visceral leishmaniasis.
- Capacity-building in treatment facilities for visceral leishmaniasis must be improved in order to provide treatment of PKDL.

9.4 PREVENTING TRANSMISSION

- PKDL should be prevented by ensuring complete and successful treatment of visceral leishmaniasis.

10. FURTHER READING

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ANNEXES

ANNEX 1. WHO'S RECOMMENDED CASE DEFINITIONS FOR VISCERAL LEISHMANIASIS AND POST-KALA-AZAR DERMAL LEISHMANIASIS

These definitions are adapted from *Control of the leishmaniases: report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22–26 March 2010*. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 949).

VISCERAL LEISHMANIASIS

Clinical description

An illness with prolonged irregular fever, splenomegaly and weight loss as its main symptoms. In areas where malaria is endemic, visceral leishmaniasis should be suspected when fever lasts for longer than 2 weeks and no response has been achieved with antimalarial medicines (assuming that drug-resistant malaria has also been considered).

Laboratory criteria for diagnosis

Visceral leishmaniasis is diagnosed when there is:

- positive parasitology (that is, parasites identified on stained smears from bone marrow, spleen, liver, lymph node or blood, or the organism is cultured from a biopsy or aspirated material); *and*
- positive serology by immunofluorescence antibody test, enzyme-linked immunosorbent assay (ELISA), rK39 rapid diagnostic ELISA, or direct agglutination test;
- positive polymerase chain reaction (PCR) or related techniques.

Case classification using WHO's operational definition

A case of visceral leishmaniasis is disease in a person showing clinical signs (mainly prolonged irregular fever, splenomegaly and weight loss) with serological confirmation and/or parasitological confirmation.[1]

POST-KALA-AZAR DERMAL LEISHMANIASIS (PKDL)

Special efforts should be made to trace PKDL in the community, because patients with PKDL have only skin manifestations and usually do not attend clinics or see only skin specialists. PKDL may be confused with paucibacillary or multibacillary leprosy. The skin lesions may also mimic other skin conditions.

Case classification[2]

Probable PKDL: A patient from an area where visceral leishmaniasis is endemic with or without a previous history of visceral leishmaniasis who has a symmetrical macular, papular or nodular rash often starting on the face with further spread to other parts of the body without loss of sensation.

Confirmed PKDL: A probable case as described above with parasite infection confirmed by PCR or a slit-skin smear or biopsy.

[1] *Recommended surveillance standards*, 2nd ed. Geneva, World Health Organization, UNAIDS, 1999 (WHO/CDS/CSR/ISR/99.2).

[2] Indicator tool kit for the visceral Leishmaniasis elimination initiative. New Delhi, WHO Regional Office for South-East Asia, 2010.

ANNEX 2. CLINICAL GRADING AND PHOTOGRAPHS OF CASES OF POST-KALA-AZAR DERMAL LEISHMANIASIS IN EAST AFRICA

In Sudan, three grades of severity for post-kala-azar dermal leishmaniasis have been described; this clinical grading has also been adapted for case management in Ethiopia and South Sudan.

Grade 1: scattered maculopapular or nodular rash on the face, with or without lesions on the upper chest or arms;

Grade 2: dense maculopapular or nodular rash covering most of the face and extending to the chest, back, upper arms and legs, with only scattered lesions on the forearms and legs;

Grade 3: dense maculopapular or nodular rash covering most of the body, including the hands and feet; the mucosa of the lips and palate may be involved

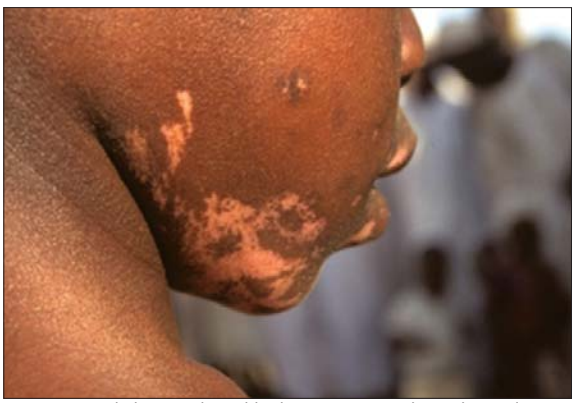

Figure 1: Post-kala-azar dermal leishmaniasis, macular rash, grade 1

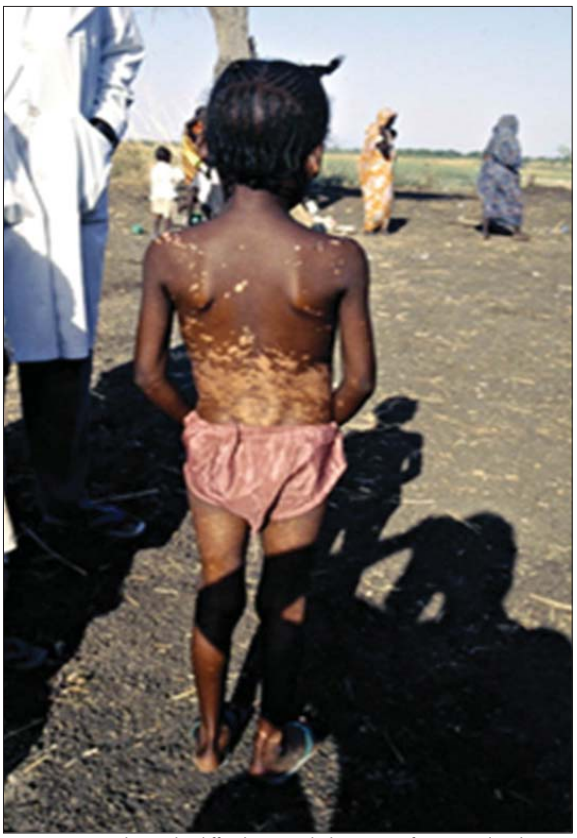

Figure 3: Macular rash, difficult to grade because of uneven distribution

Figure 4: Papular rash, grade 2

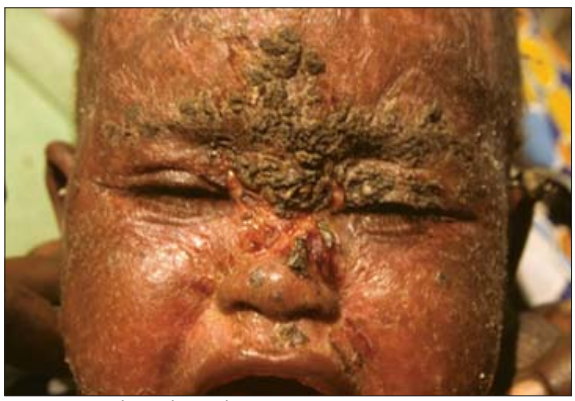

Figure 5: Papular rash, grade 3

Figure 2: Papular rash, grade 1

ANNEX 3. AGENDA OF THE INFORMAL CONSULTATIVE MEETING TO PREPARE THE PKDL CASE-MANAGEMENT AND CONTROL MANUAL, KOLKATA, INDIA, 2–3 JULY 2012

MONDAY, 2 JULY 2012

Chairperson: Professor Be-Nazir Ahmed
Rapporteur: M. den Boer

Time	Activity	Responsible
08:30–09:00	Registration	Participants
09:00–09:30	Opening session	S. Bhattacharya, SAS
•	Opening and welcome remarks	SEARO representative
•	Administrative remarks	
•	Introduction of participants	
•	Group photograph	
09:30–09:40	Objectives of the meeting	J. Alvar, WHO/HQ
09:40–10:00	Tea/coffee break	
10:00–10:40	Status of the kala-azar elimination programme in SEARO	C. Revankar, SEARO
10:40–11:00	Overview of PKDL epidemiology and burden in the Indian subcontinent	C.P. Thakur, Patna Medical College
11:00–11:20	Overview of PKDL epidemiology and burden in East Africa	E. Zijlstra
11:20–12:00	Asymptomatic infections, importance in transmission, prevention and control	C. Bern, University of San Francisco
12:00–12:30	Discussion	Participants
12:30–14:00	Lunch break	
14:00–14:30	PKDL clinical and diagnosis overview	E. Zijlstra, DNDi
14:30–14:50	PKDL case management or treatment overview	K. Ritmeijer, MSF-H
15:00–15:30	Results of PKDL miltefosine trial (WHO/TDR sponsored study in India)	Shyam Sundar, Banaras Hindu University
15:30–16:00	Recommendations on research needs from the PKDL consortium	P. Desjeux. OWH/PATH
16:00–16:30	Tea/coffee break	
	Breakaway sessions	
16:30–17:30	Epidemiology, surveillance and control strategies	Group I
	Pathogenesis, clinical features, grading and diagnosis	Group II
	Case management (region specific recommendation)	Group III

TUESDAY, 3 JULY 2012

Chairperson: Professor N.K. Ganguly
Rapporteur: M. den Boer

Time	Activity	Responsible
	Breakaway sessions (continued)	Group work
09:00–10:30	Epidemiology, surveillance and control strategies	Group I
	Pathogenesis, clinical features, grading and diagnosis	Group II
	Case management (region specific recommendation)	Group III
10:30–11:00	Tea/coffee break	
11:00–11:30	Group work wrap up and preparation for plenary presentation	
	Group work presentation (Chairperson: Professor N.K. Ganguly)	
11:30–11:50	Epidemiology, surveillance and control strategies	Group I
11:50–12:10	Pathogenesis, clinical features, grading and diagnosis	Group II
12:10–12:30	Case management (region specific recommendation)	Group III
12:30–14:00	Lunch break	
14:00–15:00	Plenary discussion and final recommendations	Participants
15:00–16:00	Wrap up and closing	HQ/SEARO

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