

Chapter 2

Containing Post Kala-Azar Dermal Leishmaniasis (PKDL): Pre-requisite for Sustainable Elimination of Visceral Leishmaniasis (VL) from South Asia

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Abstract Post Kala-Azar Dermal Leishmaniasis (PKDL) is a chronic dermal manifestation which appears in a small proportion of cases following cure from visceral leishmaniasis (VL) episode, and occasionally in patients with no history of VL. The global prevalence of PKDL is not well studied and the available data are based only on estimates. As per the available reports, the incidence of PKDL varies considerably within endemic countries. PKDL diagnosis remains a challenge more because serology does not have much relevance while parasitological and molecular diagnostic tests show either low sensitivity or are difficult to decentralize in the field. The available treatment options are costly, lengthy and frequently toxic. It is believed that PKDL has a multi-factorial and complex origin combining host and parasite factors and perhaps the treatment rendered in VL treatment. PKDL patients harbor *Leishmania* parasites in the skin, therefore, are considered a durable reservoir of infection that may propagate VL transmission, especially during inter-epidemic periods. Hence, PKDL poses a serious threat to the success of VL elimination program in South Asia and calls for combined and coordinated efforts towards its surveillance and management in India, Nepal, and Bangladesh. In a nutshell, containing PKDL is a must for sustainable elimination of VL from South Asia where VL transmission is anthroponotic.

Keywords Bangladesh • India • Kala-azar • Leishmania • Nepal • Post kala-azar dermal leishmaniasis • Visceral leishmaniasis elimination program • Visceral leishmaniasis

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2.1 Epidemiology

Post kala-azar dermal leishmaniasis (PKDL) is well known to occur in regions endemic for *Leishmania donovani*, with variable incidence in affected countries. Information on global epidemiology of PKDL is fragmentary since only limited studies are available. The highest incidence of PKDL has been recorded from Sudan in East Africa, and in Bangladesh in the Indian subcontinent. More importantly, its distribution predominantly reflects the distribution of visceral leishmaniasis (VL) or kala-azar (KA) caused by *L. donovani*. The factors that predispose apparently cured VL patients to PKDL in an endemic zone are not well understood but appear to be related to age at the time of contracting VL and incomplete treatment course [1]. PKDL is reported to occur not only after treatment of VL with sodium stibogluconate (SSG) [2], but also following treatment with miltefosine, amphotericin B [3] and paromomycin [4]. Longitudinal follow-up studies would help to find out the relation between the type of drug used for VL treatment and the likelihood of patients developing PKDL thereafter. Furthermore, approximately 20 % PKDL cases do not report a history of VL [5] which poses another intriguing question in precise understanding of PKDL pathogenesis.

The first population-based study of PKDL incidence was carried out in Bangladesh [6]. It combined a house-to-house survey (2007–2008) and a retrospective study that included 22,699 people from 4,553 households. In total, 813 cases of VL were detected with 79 PKDL cases (9.7 %) among them. It is noteworthy that 8 of the 79 PKDL cases (10.1 %) reported no history of VL. The median duration between VL episode and PKDL was 22 months. More specifically, 20 % of PKDL cases appeared within 6 months, 40 % between 6–24 months, and 40 % after 24 months. Uncommon events were also reported such as PKDL occurring concomitantly with VL or a VL relapse and spontaneous cure. Subsequent studies suggested that the epidemiology varies widely, even among districts of Bangladesh and showed a prevalence of PKDL of 6–16/10,000 population [7, 8].

In India, PKDL appears in up to 10 % of VL treated cases and usually occurs within 5 years after treatment [9]. In a highly endemic area of Bihar, a three stage house-to-house survey of 2020 households' demonstrated local prevalence of confirmed PKDL of 4.4/10,000 and 7.8 if probable cases were also considered [10].

In Nepal, the incidence of VL is much lower compared to Bangladesh or India. Most of the cases are recorded from 12 endemic districts residing in 25 % of the country's population. In the 1990s, there was an upsurge in the number of VL cases, but the incidence has declined since 2006. The prevalence of PKDL has been estimated to be 2.3 % of patients with history of VL [11]. The prevalence of PKDL may be higher in areas adjacent to Indian border, where SSG resistance has been identified. In 2010, a survey found that the median onset of PKDL following VL episode was 23 months [11]. Patients who received inadequate treatment (<20 injections of SSG) were 11 times more likely to develop PKDL than those who completed full treatment course.

2.2 Clinical Features

PKDL patients are healthy except for their skin rash, therefore, they may not always visit health centres promptly. Unlike VL cases, they do not have fever, splenomegaly or weight loss, and the physical examination looks usually normal. However, severe form of PKDL when present on face can cause significant social and clinical discomfort. Since the initial diagnosis is based on clinical characteristics, the differential diagnosis is very important.

In the Indian subcontinent, the polymorphic form of PKDL is the most frequently encountered: hypopigmented macules, indurated erythematous plaques, papules and nodules are seen in varying proportions [1]. The typical form is that of lesions clustered around the chin and mouth, with discrete to no lesions in the rest of the face or body (Fig. 2.1). At times the lesions may be present on the sides of the cheeks and the ears, leading to potential for confusion with leprosy. Over time, these lesions can coalesce and give rise to large tumor-like plaques which are well circumscribed. Disease progression is nearly always from the face to the rest of the body, including the feet. Approximately 20 % of PKDL cases display mucosal lesions affecting the glans penis and oral cavity. If the outer lips are taken into account, this figure rises considerably since lesions are frequently present in this area. Impact on the mucosa without involvement of the skin is extremely rare and has been observed only occasionally in the highly endemic area of Bihar [12].

Fig. 2.1 Erythematous nodules in the peri-oral area and tongue



Fig. 2.2 Large, irregular and coalescent hypopigmented macules on chest and upper limbs studded with discrete papules and nodules



Similarly, ocular lesions in the cornea and sclera were rarely seen in the distant past. The unusual forms of the disease are those that are often missed and unsuspected. Of these, the macular form of PKDL is the most important. It is more likely to be mistaken for vitiligo rather than leprosy since the degree of pigment loss can be more than that seen in leprosy. Distribution of macular PKDL may be localized, generalized or extensive; such lesions lack a photosensitive evolution and at times the face may be minimally or not affected [13, 14]. Remarkably, hypopigmentation may affect the entire skin surface leaving few areas of normal or hyperpigmented skin, particularly at the flexures (Fig. 2.2). Others have also observed a similar incidence of macular PKDL in their studies [15]. The other presentation of PKDL is the fibroid variety with plaques on the dorsa of fingers and toes, with an appearance like knuckle pads.

African PKDL, mainly concentrated in Sudan, has been increasingly reported and has been reviewed [16, 17]. In contrast to PKDL in Indian subcontinent, which occurs in 5–15 % of those treated for VL [1], Sudanese PKDL appears in as high as 50 % of patients following VL [16]. The distribution of lesions in Sudan is similar to that of Indian form but differs in the ulceration that can occur in severe cases. Lesions typically start on the face as papules, spreading to other parts of the body. The lesions may remain confined to the face or may spread to other parts of the body: first, to the trunk and upper limbs, and subsequently to rest of the body parts. Lesions are generally symmetrical and not itchy. The size of papules may increase, and turn into nodules or plaques, or a combination of these; alternatively, the lesion may be macular. Maculopapular lesions are common; a micropapular form

resembling measles may be seen [1]. Unlike PKDL in the Indian subcontinent, three grades of PKDL severity have been described in Sudan [1]. An interesting study in Sudan showed that the severity of facial involvement was related to ultraviolet B radiation in sunlight that appears to modify the immune system, promoting lesion development [18]. Mucosal involvement in African cases also differs from Indian PKDL in that lesions have been more frequently noted in the eyes or restricted to ocular mucosa [19], giving rise to a number of terms like post-kala-azar ocular or mucosal leishmaniasis. These could well be subsumed under the term PKDL which also covers mucosal lesions, avoiding further confusion.

PKDL is relatively common in HIV-positive individuals and often has atypical presentations, such as large nodular lesions. The typical clinical distribution i.e. the spread from face to other parts of the body is not always followed. The majority of these patients present florid disease with various descriptions including macules, disseminated miliary papules, papulo-erythematous eruption, nodules and plaques, or a mixed picture [20–22]. PKDL in co-infected patients have been reported to be caused by both *L. donovani* and *Leishmania infantum/Leishmania chagasi*; in most cases parasites were easily demonstrated [21–23].

2.3 Diagnosis

The variability of clinical presentations, poor awareness of this otherwise asymptomatic dermatosis, the migration of patients to non-endemic areas and lack of laboratory facilities to confirm diagnosis remain the major impediments in early recognition of PKDL [24]. The diagnosis of PKDL was initially based only on the typical clinical features (macules, papules, and nodules). The most frequent differential diagnoses are leprosy, vitiligo, sarcoidosis and secondary syphilis. However two diseases deserve special mention: neurofibromatosis and leprosy, which can be differentiated by the ulnar nerve thickness and the loss of skin sensitivity on hypopigmented patches. The diagnosis of PKDL is usually supported by the epidemiological background: most cases report a previous VL episode, usually in a focus of anthroponotic transmission, and/or origin from an area endemic for VL. The laboratory methods of diagnosis are immunological and parasitological. Serological methods used for VL diagnosis, such as the direct agglutination test (DAT), rapid rK39 immuno-chromatographic strip test, and ELISA based on recombinant antigens have been applied successfully to PKDL diagnosis [24, 25]. However, a positive antibody test may be the result of the previous VL episode rather than current PKDL. Nevertheless, serology can be helpful when other diseases (for example, leprosy) are considered in the differential diagnosis, or if a history of VL is uncertain. Antigen detection in tissues, blood, and urine is also of some help [26, 27]. However, only parasitological methods are confirmatory. The slit skin smear and culture are the standard methods but lack high sensitivity. In all types of PKDL, the finding of organisms is a bedside aid to diagnosis which the nodular type of lesion is most likely to show *Leishmania*

amastigotes. The likelihood of finding amastigotes diminishes in less indurated type of skin lesions and is the lowest in the macular variety. Molecular methods based on nucleic acid detection, using gene amplification techniques like PCR, provide a reliable means of species-specific diagnosis of the disease. The methods are more sensitive than immunohistochemical or serological methods. Gene amplification is carried out by targeting multicopy sequences like ribosomal RNA genes, kinetoplastid DNA (kDNA), minixon derived RNA genes or genomic repeats [24, 25]. A kDNA based PCR assay developed in India detected the parasite in 45 out of 48 PKDL patients with 93.8 % sensitivity [28]. Different PCR assays are now available: real-time PCR, nested PCR, LAMP PCR, etc. that can detect *Leishmania* parasites in blood or on slit skin aspirates [29]. The LAMP assay in diagnosis of PKDL was demonstrated to be rapid and reliable, with sensitivity of 96.8 % and specificity of 98.5 % [30]. LAMP PCR has several advantages: an easier to run kit is available, no sophisticated equipment needed, the required temperature for DNA amplification is lower (62–65 °C), and the test duration is shorter (1 h only). In addition, the reading is easy (turbidity and color change). It is as sensitive as nested PCR, which is claimed to be more sensitive than traditional PCR. It is also claimed to be a good test of cure as it becomes negative 2 weeks after treatment. However, it is difficult to decentralize the test further than district level. Parasitological confirmation using minimally invasive skin slit aspirate sample demonstrated to have equally reliable results as with tissue biopsy [29] and therefore should be encouraged, as the procedure will reduce discomfort and permanent scarring and thus motivate more patients to come forward for timely diagnosis and monitoring after treatment.

The main limitation is that most of the molecular tests are unavailable or not performed in local institutions. The diagnosis of PKDL at primary health centres when *Leishmania* amastigotes are not demonstrable often rests on the clinical picture and the response to anti-leishmanial therapy. In Africa, PKDL frequently occurs during or soon after the treatment of kala-azar, making the diagnosis relatively easy and with less likelihood of confusion with other dermatoses, unlike the case of PKDL from Indian subcontinent.

2.4 Histopathology

Histopathological examination in PKDL shows several changes that often occur in combination. The epidermal changes include hyperkeratosis, parakeratosis, follicular plugging, focal acanthosis or, rarely, atrophy. Dermis shows mixed inflammatory infiltrate consisting of histiocytes, lymphocytes, and plasma cells [1].

A recent study from India with 88 biopsies from patients of PKDL showed that the dermal infiltrates were arranged predominantly in 3 patterns reflecting the clinical type of lesion; superficial and perivascular in macules, perivascular and perifollicular in some, and the third pattern being diffuse infiltration in those with indurated lesions; *Leishmania* amastigotes were seen in approximately 30 % of the

cases and were better seen in biopsies from mucosal lesions [23]. Anecdotal report from Spain has also shown many parasites in biopsy from the mucosal lesion as compared to none from the skin of the same patient [31].

In African cases, lymphocytes are the predominant cells followed by histiocytes and some plasma cells. Epithelioid cell granulomas were seen in about 20 % of cases and scattered epithelioid cells in about half [17]. Compact granulomas were seen more commonly in nodules than in papules [32]. Neuritis, an unusual finding, has been reported in four of 15 cases and has to be differentiated from leprosy [17]. Parasites are seen in 17–20 % of cases on routinely stained sections; this sensitivity increases to 88 % when a specific monoclonal antibody was used to stain *L. donovani* [33].

2.5 Treatment

Treatment of PKDL is an important component of the kala-azar eradication programme. The pentavalent antimonials which had been at the helm of therapy now stand excluded because of the duration of therapy, toxicity and increasing antimony resistance. Miltefosine and amphotericin B are the current treatments of choice. They can be used separately or combined depending on the severity. Studies for combination therapy are far from complete. The choice of drugs, dose and duration vary from that used in Sudanese PKDL and has been discussed in a separate chapter.

2.6 Pathogenesis

The precise understanding of PKDL pathogenesis is still obscure and, importantly, the immunopathobiology varies between Sudanese and Asian PKDL. PKDL is considered to be immunological triggered, with host, parasite, and drug all perhaps contributing to the pathogenesis.

- Host characteristics are mainly immunological and seem crucial for PKDL development. The host's role is suspected, based on the: (1) high incidence of PKDL in immunosuppressed people (i.e. transplant recipients and patients with HIV/AIDS, tuberculosis, malaria, measles), (2) efficacy of therapeutic vaccines with good and extended immunogenicity, (3) clinical healing associated with a conversion of Leishmanin Skin Test (LST) from negative to positive [34].
- Parasite characteristics are still not well understood. To date, no parasite strain has been associated with one single entity (VL or PKDL) in endemic areas [35, 36]. Molecular studies on genetic typing revealed monomorphism between *L. donovani* isolates from VL and PKDL cases in India [37]. It is clear that PKDL incidence is much higher in *L. donovani* foci than in *L. infantum*. However, there

is still an unanswered question of whether the higher incidence is related to the parasite and/or to the epidemiology. PKDL's higher incidence could be due to the anthroponotic (human-to-human) transmission in *L. donovani* foci compared to the zoonotic (animal-to-human) transmission in the *L. infantum*.

- Drug characteristics may also be important to PKDL development. However, approximately 20 % PKDL cases appear without any previous VL episode [5, 38] and, consequently, prior to receiving any drug treatment. Much of the PKDL reported in the past has been observed after treatment of VL with pentavalent antimonials. The introduction of newer drugs like amphotericin B and miltefosine has led researchers to investigate the relationship between the efficacy of a given drug and the subsequent occurrence of PKDL. Having analyzed cases seen over 35 years from a high endemic area, the authors concluded that the incidence of PKDL declined after the introduction of amphotericin B for VL in areas with high refractoriness to antimonials [39, 40]. It is now established that any drug can lead to PKDL but in variable proportions. PKDL cases after VL treatment with SSG are reported more frequently than with amphotericin B treatment; however this may be because SSG has been the most commonly and extensively used drug over many decades. In recent times PKDL cases have been reported after using miltefosine, amphotericin B and paromomycin for VL treatment [3, 4, 41]. PKDL could be the result of an immunological attack on *Leishmania* parasites which have survived in the skin despite chemotherapy. It is probably not the drug itself which leads to PKDL but the type of cellular immune response induced by the drug (cytokine profile) and the level of *Leishmania* parasite burden remaining in the body after treatment. Sb5⁺ has a specific influence on the immune response through its effects on cell signaling, cytokines and immune complex induced levels of granulocyte macrophage colony stimulating factor (GM-CSF) [42]. Sb5⁺ and amphotericin B have contrasting effects on IL-10 and TGF beta in PKDL patients [43]. Only prospective clinical trials on VL patients treated with different drugs, (Sb5⁺, amphotericin B, miltefosine, paromomycin, and AmBisome) and longitudinal follow up will allow clear and final conclusions on the comparative rate of PKDL induced by each drug [39].

In South Asian PKDL, one of the important effector cell implicated in pathogenesis is CD3⁺CD8⁺ T cells that have been found both in lesions and circulation [44, 45]. The observation of high mRNA expression of FoxP3, CTLA-4, and CD25 at lesion site suggested involvement of Treg cells [46, 47]. Besides, an increased IL-10-expressing CD3⁺CD8⁺ T lymphocytes has been observed in circulation which gets restored to normal post treatment [45]. The cytokine profile at the lesion site show enhanced expression of IL-10, TGF- β , IFN- γ , and TNF- α in both South Asian and Sudanese PKDL. However, the expression of IFN- γ R and TNFR1 was lower in Indian PKDL which was restored following treatment [48, 49]. Similar observations were made in Sudanese PKDL, a genetic polymorphism was found in IFN- γ R [50]. In Sudanese PKDL, expression of IL-10 was considered as an important predictor for onset of PKDL, particularly following VL [17].

Furthermore, high levels of IL-17, its transcription factor ROR- γ t, and IL-22, both in lesions and circulation indicated involvement of Th17 cells in PKDL pathogenesis [51]. Overall, the studies on immunobiology of PKDL suggest that it is a systemic disease rather than localized one.

2.7 Challenges for Sustainable Elimination of VL

In South East Asia, the transmission of VL is known to be anthroponotic; therefore PKDL has a major role as a reservoir of infection, especially during inter-epidemic period [52]. The experimental laboratory work carried out in India, in 1992, demonstrated the infectivity of PKDL cases. One hundred and four laboratory-bred *P. argentipes* sandflies were fed by xenodiagnosis on nodular PKDL cases. Sixty survived and 32 (53 %) were infected as evidence by the presence of *Leishmania* promastigotes in the mid-gut. It was concluded that Indian nodular PKDL cases were highly infective for the sandfly *P. argentipes* and it was extrapolated that PKDL cases can play a role as inter-epidemic reservoir [53]. A few years earlier, in 1988, another study concluded that the presence of as few as 0.5 % durably infectious PKDL patients during an epidemic may cause VL to become endemic [54].

PKDL poses a second challenge: the perception of PKDL by the patients themselves. They consider PKDL as a chronic, cosmetic, non-fatal disease with a stigma only if nodular. Hence the motivation for early diagnosis and treatment is low. The delay between the onset of clinical manifestations and the treatment is usually long and leads to an increased risk of VL transmission to people living in the same household or neighborhood. Another challenge is of PKDL diagnosis: The diagnosis of PKDL is intriguing and the disease is often misdiagnosed especially at primary health centres and/or private clinics, primarily as leprosy, a co-endemic dermatosis with high prevalence in the same areas. In addition, the treatment is long, costly, and frequently toxic. Increasing incidence of drug resistance is another major impediment to deal with to achieve VL elimination.

The presence of asymptomatic VL cases in the endemic areas could be an important issue towards VL elimination. A majority of the *Leishmania* infected human population do not develop into full blown VL cases, and are considered asymptomatic [55–57] and these cases could play an important role in maintaining transmission dynamics of *Leishmania* infection [58]. However, the actual estimate of asymptomatic cases in endemic area is difficult to assess. A few studies have reported the presence of asymptomatic cases in high endemic areas of VL in Bihar in the range of 10–34 % [55, 59, 60] and the conversion rate to symptomatic VL was 17.85 per 1000 persons [59]. These “asymptomatic carriers” could prove an important impediment towards VL elimination program.

2.8 Methods and Strategies to Control PKDL

In 2005, India, Nepal and Bangladesh signed a Memorandum of Understanding to work regionally towards the elimination of VL by 2015; recently extended up to 2017. In order to increase the chances of success of the ongoing VL elimination program in the Indian subcontinent, PKDL has to be addressed more precisely and seriously. In this regard, WHO consultative meeting on the management and control of PKDL made several recommendations [1]. A series of control measures and research activities need to be undertaken quickly and simultaneously:

(I) Control measures

- (I.1) Monitoring of PKDL combining both passive and active case detection (ACD) should be undertaken routinely for a better estimate of PKDL prevalence. Point of care diagnostic testing, adaptable to community-based ACD will enhance surveillance.
- (I.2) PKDL surveillance should be part of the national surveillance system for leishmaniasis or the national communicable diseases surveillance system.
- (I.3) Ensure complete and successful treatment of VL.
- (I.4) Early diagnosis and prompt treatment of PKDL together with an improved referral system.
- (I.5) Greater awareness among the communities based on IEC and BCC campaigns is urgently needed for improved reporting and acceptability of treatment.
- (I.6) Capacity building through institutional strengthening and training at all levels (especially health volunteers, lab technicians and physicians) involving both governmental and private sectors.
- (I.7) Distribution of Long Lasting Nets (LLNs) to limit the infectivity of untreated PKDL cases.
- (I.8) Vector controls measures such as Indoor residual spraying of houses and animal shelters should be undertaken regularly.

(II) Research priorities

- (II.1) Identification of more effective, safe, short-course, affordable, accessible and acceptable treatment regimens for PKDL.
- (II.2) Identification of new treatment regimens (combinations) for VL to prevent the appearance of PKDL.
- (II.3) Post VL-treatment longitudinal follow-up to detect the appearance of PKDL and an assessment of the drug-specific incidence rates.
- (II.4) Evaluate the characteristics of medicines and their capacity to penetrate the skin; modify medicines to target the skin.
- (II.5) Identify immunological markers predictive of PKDL to monitor the immune response after treatment of VL and follow-up for development of PKDL.
- (II.6) Identify serum markers to monitor progression towards cure, and define the end-point of treatment.

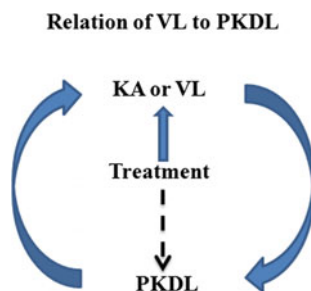


Fig. 2.3 Weak link (*broken lines*) in kala-azar control

In an increasingly global world, it is important for practitioners of tropical medicine to be familiar with PKDL as it can be seen in immigrants residing in the West several years after the episode of kala-azar [61] or in those from non-endemic countries like Japan who return after a period of time in India [62]. The importance of detecting and treating PKDL cases in VL control program is vital (Fig. 2.3). Actions have to be regularly monitored or PKDL cases will remain a major impediment for the VL elimination program. The pace and enthusiasm along with heightened political and financial commitments should be maintained in implementing the above recommendations.

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Current Status and Sustainable Challenges

Noiri, E.; Jha, T.K. (Eds.)

2016, XX, 309 p. 85 illus., 54 illus. in color., Hardcover

ISBN: 978-3-319-43611-1