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Review Article

Barriers to the effective management and prevention of post kala-azar dermal leishmaniasis (PKDL) in the Indian subcontinent

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ABSTRACT

Post kala-azar dermal leishmaniasis (PKDL) is a skin disease that usually occurs among individuals with a past history of visceral leishmaniasis (VL). PKDL cases act as a reservoir of parasites and may play a significant role in disease transmission. Hence, prompt detection and complete treatment of PKDL cases are crucial for the control and elimination of VL. The purpose of this review was to highlight the barriers to effective control and prevention of VL/PKDL as well as potential solutions in India. Main obstacles are lack of knowledge about the disease and its vector, poor treatment-seeking behaviours, ineffective vector control measures, lack of confirmatory diagnostics in endemic areas, limited drug choices, treatment noncompliance among patients, drug resistance, and a lack of an adequate number of trained personnel in the health system. Therefore, in order to control and successfully eliminate VL in the Indian subcontinent, early detection of PKDL cases, improved diagnosis and treatment, raising awareness, and effective vector control mechanisms are necessary.

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Introduction

Post kala-azar dermal leishmaniasis (PKDL) is a skin disease caused by obligate intracellular protozoans of the *Leishmania* genus. This is transmitted through the bites of infected female sand flies. The condition is characterized by macular, papular, nodular, or polymorphic lesions all over the body, including the face.[1] The severity and intensity of skin lesions range from mildly depigmented macules to severely disfiguring nodules.[2] Apart from skin lesions, PKDL cases remain otherwise healthy and do not seek treatment generally. Treatment-seeking behaviour in PKDL patients is mainly steered by social stigma, cosmetic depreciation, and/or moderate to severe disfigurement, resulting in significant morbidity.[3] PKDL is generally a sequel to visceral leishmaniasis (VL) although simultaneous presentations of VL-PKDL (para kala-azar dermal leishmaniasis) and cases without a history of VL have been documented.[4,5] Most VL/PKDL infected patients are poor, illiterate, and live in remote rural areas. This disease is endemic in India, Nepal, Bangladesh, Ethiopia, Somalia, and Sudan. The clinical features of PKDL in India, Nepal, and Bangladesh are presented in Table 1. Due to the clinical similarities of its skin lesions, PKDL is often misdiagnosed as vitiligo, leprosy, and other skin diseases and receives erroneous treatment.[6,7] Only a few therapeutic options are available for PKDL. Miltefosine is currently the first-line drug for the treatment of PKDL in the Indian subcontinent. Conventional amphotericin-B and its liposomal formulations are some other available treatment options.

With the coordination of WHO, the governments of India, Nepal, and Bangladesh collectively planned to eliminate kala-azar by 2015, which was extended to 2020,[8] and currently, it is targeted by the end of 2023. The goal of the elimination programme is to reduce the incidence of VL to less than one case per 10,000 population per year at the block/sub-district level in India and Bangladesh and at the district level in Nepal, through early detection and treatment, and to reduce transmission through vector control.[9] Nepal has already achieved its elimination target and is sustaining elimination condition.[9] Significant progress has been made to meet the elimination target in Bangladesh as well as India, but the goal has not yet been achieved.[8] In 2019, only 3128 cases of VL and 817 cases of PKDL were reported in India, indicating a 90% decline in the incidence rate since the kala-azar elimination programme was launched in the year 2005. Besides, the number of endemic regions is also decreasing rapidly. In India, only 37 blocks (6%) remained above the elimination target by 2020.

PKDL is an important reservoir of parasites and may act as a potential source of transmission of disease.[1,10] Hence, PKDL is a major barrier to the kala-azar elimination efforts. Without treatment of PKDL cases, kala-azar elimination will not be achieved. As per the proposed new target of the kala-azar elimination programme, case fatality rate should be less than 1% among primary kala-azar cases.[11] At the block level, the incidence of new and relapse cases should be less than 1 per 10,000 people. Additionally, by 2030, 100% of PKDL cases will have been identified and treated.[11] At this juncture, it is imperative to find out the major obstacles to successful control and prevention of PKDL. In this study, we have reviewed a number of barriers to the control and prevention of PKDL, including treatment adherence, health-seeking behaviour, community awareness, diagnostic difficulties, vector control, and drug resistance. We have also discussed the possible strategies to overcome these barriers.

Health-seeking behaviour

PKDL does not cause any systemic illness, but it has epidemiological significance as a reservoir of the parasites and carries the risk of anthropometric transmission of kala-azar.[1,10] Due to the uncompellingly nonserious nature of the disease, most patients do not seek medical attention easily. Initially, they consult traditional healers, local pharmacies, and rural practitioners, resulting in delayed diagnosis and treatment of PKDL,[3,13] thereby increasing morbidity, expenditure, severity, and transmissibility of disease in the community. Hence, early diagnosis and treatment of PKDL cases are of paramount importance.

There is very little information available about the treatment-seeking behaviour of PKDL patients. A study from the endemic region of India reported poor treatment-seeking behaviour among PKDL patients.[3] The patient delay, that is, the time interval between the onset of PKDL symptoms and the first consultation with a doctor, was reported to be as long as 15 years (ranging from 15 days to 5475 days).[3] The median delay was found to be 285 days. Similarly, due to system delay, the time interval between the first consultation with the doctor and the initiation of definite treatment ranged from 2 to 5475 days. The median system delay was 365 days. This may be one of the reasons for delaying diagnosis and treatment for PKDL. The longer delay was also reported in another study from Bangladesh, in which the patient delay was as long as 13 years (ranging from 10 days to 4745 days) and the median delay was 373 days.[13] Many patients approached traditional, alternative, or quack doctors initially. Visits to traditional or quack practitioners have been linked to system delays, which will ultimately delay receiving a definite treatment.

Table 1 – Key features of PKDL in India, Nepal, and Bangladesh.

The causative agent is *Leishmania donovani*, transmitted by the female sandfly, *Phlebotomus argentipes*. Humans are the sole reservoir of parasites.[1]
Approximately 10–20% of VL cases convert to PKDL within 6 months or more after successful treatment.[5,6]
The disease manifests as painless macular, papular, and nodular skin lesions.[1]
Skin slit smear microscopy, clinical symptoms along with a history of kala-azar, domicile of an endemic area, and rK39 antibody tests are commonly used for diagnosis.[12]
Oral miltefosine is the first-line drug of choice; liposomal amphotericin B or other combination therapies are alternative options.

PKDL affects the poorest of poor people who lives in rural area.[14] Low socioeconomic conditions could be one of the reasons for long patient delays. Therefore, improving the socioeconomic condition of patients may reduce the PKDL incidence in the endemic region. Recently, the National Vector Borne Disease Control Programme of India recognized the involvement of accredited social health activists (ASHA) in the detection of VL cases in rural areas. ASHA are women who live in rural areas and provide incentive-based services for maternal and child health-related issues.[15] They get an incentive of 200 INR for every case registered at a primary healthcare centre and receiving complete treatment. Similarly, ASHA may be trained for the identification of PKDL cases and referred to the higher referral centre for final diagnosis and treatment. This will ultimately reduce the long patient delay and be helpful for achieving the kala-azar elimination goal and maintaining the elimination level. A study has reported a positive impact of ASHA on the detection and treatment of VL cases.[16] The involvement of ASHAs has also had a beneficial effect on a variety of other illnesses, such as human immunodeficiency virus (HIV),[17] nutritional intervention,[18] and malaria.[19] Active case detection through the setting up of camps in the endemic areas is another method to enhance health-seeking behaviour.[20] A multinational study conducted in 50 healthcare centres in India, Nepal, and Bangladesh reported that arranging camps to identify VL and PKDL cases in endemic regions was effective.[20] However, adequate preparation, time, and resources remain the major obstacles to the successful implementation of this strategy.

Diagnosis

The management of PKDL is challenging due to the lack of definitive diagnostic tests. In the primary healthcare centre (PHC), PKDL is diagnosed by clinical signs and symptoms along with a history of kala-azar, belonging to an endemic area, and positive antibody tests. In some areas, PKDL cases are diagnosed by symptoms alone. The hypopigmented form of PKDL lesion is often confused with vitiligo, leprosy, and many other dermatological disorders.[12] Patients are often misdiagnosed and receive the wrong treatment. A study has reported that around 26% of PKDL cases were initially misdiagnosed at primary health centres.[5] Many times, the absence of past episodes of VL in 15–20% of PKDL patients suggests subclinical infection and poses diagnostic challenges.[12]

Laboratory diagnosis is done by skin slit microscopy, immunological techniques, the rapid rK39 enzyme-linked immunosorbent assay (ELISA) test, and molecular methods.[12] All these tests have their own limitations. The selection of appropriate diagnostic methods, however, depends upon the available infrastructure, simplicity, and reliability of the method. Currently, the demonstration of parasites by skin slit smear microscopy is the gold standard for the treatment of PKDL.[21] This method is invasive, requires an experienced clinician, and often lacks sensitivity. Hence, this test is difficult to perform in endemic regions. The reported sensitivity of this technique ranges from 67 to 100% in nodular lesions, 36–69% in papular lesions, and 7–33% in macular lesions.[12] Furthermore, parasite load greatly varies based on the type of lesions, and the refusal rate is also high. The immunochromatographic strip test (rK39) is a rapid, convenient, and useful test for the diagnosis of VL and PKDL in field settings as well as in PHC.[21] The reported sensitivity of the rK39 strip test is 95.6% and 86.3% for polymorphic and macular lesions, respectively.[21] But the major problem associated with this test is that it cannot differentiate between past and present leishmania infection.[21]

The other highly sensitive and specific molecular techniques, such as nested polymerase chain reaction (PCR), qPCR, and restriction fragment length polymorphism (RFLP), are the other diagnostic methods for parasitological confirmation of PKDL.[12] The major drawback with nested PCR is that there is a chance of contamination and that it is time-consuming. qPCR is another highly sensitive diagnostic test that helps in monitoring the progress of treatment outcomes, but the high cost of this technique limits its widespread application in the healthcare system. In view of the above drawbacks, reliable diagnostic techniques are urgently needed for the accurate diagnosis of PKDL andVL, especially at the PHC level. However, newer diagnostic techniques could be a great help for the recent kala-azar elimination programme.

Treatment compliance

Compliance with the therapy is vital for the better management of the disease. However, the importance of compliance in treatment outcomes is often overlooked. PKDL patients receive prolonged therapy, which is further complicated by the adverse drug reaction. This increases the possibility of noncompliance. Another factor that could contribute to noncompliance is wage loss from a protracted course of treatment. Patients who receive partial or incomplete treatment run the risk of relapse, treatment failure, and disease persistence, which in turn will increase the treatment cost and might affect the work and productivity of PKDL patients. Compliance with therapy not only clears the parasites but also reduces the probability of treatment failure and the emergence of drug-resistant parasites.

No study has been conducted on the adherence rate of the antileishmanial drug in the treatment of PKDL. However, in VL, the compliance rate of miltefosine was found to be 83%, and a good compliance rate was observed among educated patients and those aware of the side effects of miltefosine.[22] Many studies from India reported treatment noncompliance with the antileishmanial drugs.[5,23] A retrospective study from India reported that approximately 15% of PKDL patients did not complete the treatment course of miltefosine.[5] Another study by Ramesh et al. reported that out of 86 PKDL patients, 12 received irregular treatment with miltefosine.[23] Noncompliance has also been observed in controlled clinical trials in PKDL patients. A randomized controlled trial (RCT) study by Pandey et al. documented that a total of 6 patients out of 100 were treatment defaulters.[24] Another RCT study by Sundar et al. reported 7 losses to follow-up out of 31 patients recruited.[25] With the limited available data, it is expected that in routine practice outside the studies, the adherence rate of miltefosine in the treatment of PKDL could have been low. A shorter, safe, and tolerable drug may improve the compliance

rate among PKDL patients. As miltefosine is the first-line therapy for PKDL and is used in ambulatory settings, a better understanding of the adherence rate of miltefosine and influencing factors in PKDL is urgently needed for the kala-azar elimination efforts. Besides, this will also improve treatment satisfaction and quality of care for PKDL patients.

In countries with limited resources, well-trained, motivated healthcare staff and adequate counselling regarding the importance of treatment compliance are required. Proper counselling is the best way to improve the compliance rate. Before initiation of treatment, patients should be educated about the drugs, duration of treatment, common possible side effects, and how to deal with them. Besides, patients can be involved in therapy decision-making. In addition, appropriate guidelines need to be provided to health staff so that action can be taken in cases of severe noncompliance. A discharge summary of patients should be accompanied by possible side effects, coping strategies, and the significance of attending follow-up visits. Simultaneously, directly observed treatment with miltefosine has been recommended by many investigators to improve compliance.[26,27]

Drug resistance and treatment failure

Antimonial compounds such as sodium stibogluconate and meglumine antimoniate were the main drugs for the treatment of almost all forms of leishmaniasis for several decades. Sodium stibogluconate is a pentavalent antimony drug, containing about 10% pentavalent antimony (100 mg/ml).[28] In East Africa, SSG is the standard treatment regimen for PKDL.[29] Currently, it has been obsoleted in the Indian subcontinent due to widespread resistance. The most common side effects include cardiac arrhythmias and severe pancreatitis, which can be fatal in certain situations.[28] Due to several toxicities and the longer treatment duration, patients face difficulty tolerating this treatment.

Miltefosine is an alkyl phosphocholine derivative used as a first-line drug for the treatment of PKDL. This drug is not recommended for children less than two years of age and also for pregnant and lactating women because of teratogenicity.[30] Gastrointestinal adverse effects are the major problem associated with this drug. Besides, it has a long elimination half-life; hence, it further carries the risk of drug resistance.[22] A study has reported that the relapse rate of miltefosine in PKDL has increased from 4% to 15%.[23]

Paromomycin is an aminoglycoside antibiotic approved for the treatment of visceral leishmaniasis in a parenteral form. Its effectiveness in the treatment of PKDL is not satisfactory.[25]

Amphotericin B is a polyene group of antibiotics with antifungal and antileishmanial properties. It was also found to be highly efficacious in the treatment of PKDL. A recent study reported that Amphotericin B at 0.5 mg/kg is equally efficacious as 1 mg/kg (cure rate of 95%).[31] Though nephrotoxicity was the common problem associated with both doses,[31] renal toxicity is the major limiting factor for its widespread application in PKDL. Liposomal amphotericin B is a lipid formulation of amphotericin B deoxycholate that has been found to be safe and effective in the treatment of VL and PKDL. This formulation was based on the concept of targeted drug delivery to a specific organ; hence, the incidence of renal toxicity and hypokalemia is substantially reduced. In a recent study, LAmB at a dose of 15 mg/kg given over 15 days in 5 biweekly infusions of 3 mg/kg showed major improvement in 90% of patients, whereas complete cure in 78% of the patients; however, no improvement was noted in 10.3% of patients, and lesions reappeared in 4.8% of patients.[32] Combination therapy was also tried in PKDL. The efficacy of the miltefosine–paromomycin combination for the treatment of PKDL was 83.3%.[33] The combination of miltefosine–liposomal amphotericin B was found to be 100% effective in PKDL in a small number of patients.[34] However, safety and efficacy data for combination therapies in a large sample population are lacking. Therefore, more research needs to be done to explore the efficacy and safety of combination therapy in PKDL. There is no 100% safe and effective therapy for PKDL and available treatments are costly and require prolonged administration. Hence, the search for new, safe, effective, short, and affordable drugs is urgently required for the elimination of kala-azar from the Indian subcontinent.

Awareness and practices

Adequate knowledge, a positive attitude, and good practices are essential for effective control and preventive measures of any disease. Besides, inadequate knowledge of disease and its transmission may lead to poor health-seeking behaviour and treatment delays.[35] Two different studies from the endemic region of India and Bangladesh reported that the majority of PKDL patients had poor knowledge about PKDL and its vector despite having a history of VL in most of them.[3,13] Though a majority of patients showed a positive attitude toward the treatment and vector control for PKDL, a substantial proportion of participants used to sleep outside, and 20–30% of participants sleep without bed nets.[3,13] A similar observation was also observed in VL patients in which community people had inadequate knowledge related to transmission, causes, clinical features of VL, vector, and preventive practices.[35] Sleeping outside, on the ground, or in the vicinity of domestic animals, poor housing (mud walls, cracked walls), earthen floors, and sleeping without bed nets are the risk factors for VL/PKDL.[36] Due to a lack of awareness of PKDL, patients initially mistake the lesions for pityriasis versicolour and ignore them. Seek treatment once symptoms worsen or the patient reaches marriageable age.

Improving the awareness level and knowledge of the community is a prerequisite for the effective control and prevention of diseases. Hence, awareness of VL and PKDL needs to be created among the community living in endemic areas by involving healthcare workers, ASHA, community leaders, community pharmacists, and school teachers. Besides, patients admitted to receive treatment for VL need to be educated regarding the future development of PKDL with the help of trained healthcare staff or pharmacists. Similarly, the policymakers should focus on an appropriate and effective healthcare education programme, especially in the VL/PKDL endemic region without which, control, elimination, and maintenance of the postelimination phase of kala-azar will be far from reality.

Vector control

The main strategy for preventing VL/PKDL in the Indian subcontinent is indoor residual spraying for vector control. Due to the exophagic and exophilic characteristics of the vector *Phlebotomus argentipes*, this technique might not be enough to limit vector density, especially in India.[37] Controlling the outdoor vector population is therefore necessary, especially in locations where people used to sleep outside.[38] Prior to 2015, dichlorodiphenyltrichloroethane (DDT) was the only chemical used to control sandflies, but numerous studies have documented resistance to this insecticide.[39–41] As a result, synthetic pyrethroids have taken the place of DDT. Currently, in India, alpha-cypermethrin in a 5% wettable powder formulation is being used for vector control.[11] According to a study from Bangladesh, there were a number of shortcomings with indoor residual spray (IRS) procedures, such as inadequate training for spray workers, a propensity for supervisors to be absent while spraying, and poor spraying methods.[39] In addition, insecticide spraying is expensive, necessitates specialized equipment and ongoing insecticide resistance monitoring, and is frequently unpopular with the local population. This will ultimately make the vector control method less effective. Therefore, good monitoring and assessment procedures are essential to getting the most out of indoor residual spraying. Additionally, in order to create efficient vector control tools, it is crucial to comprehend vector bionomics and vector behaviours.[40] The COVID-19 pandemic has halted several illnesses' control and prevention efforts, including VL control efforts. The elimination of VL in the Indian subcontinent will be greatly impacted by this.

The other vector control strategy is the use of insecticide-treated bed nets (ITN). Controlling leishmaniasis and malaria with this strategy was successful.[41] According to a study from Bangladesh, the incidence of VL was considerably lower in the ITN intervention cohort as compared to the control group.[42] A similar finding was also found in a Sudanese observational study, which found a 59% decrease in VL occurrences following the use of long-lasting ITN.[43]

Another control strategy involves changing the environment around the house and its surroundings. Housing structure and the surrounding environment are risk factors for VL transmission.[44] Most patients with VL or PKDL live in rural areas, are underprivileged, have poor electricity, live in mud houses with cracks and crevices in the walls, and have mud or brick flooring. Sand flies thrive in these environments, which also carry the risk of parasite transmission through direct contact. Many people expose themselves to the bite of sand flies by sleeping near or inside livestock sheds with animals. In addition, animal waste offers sand flies a good place to relax and breed. Two different studies from the Indian subcontinent reported a significant reduction in the sandfly population after cement plastering of walls of the homes in VL endemic areas.[45,46]

Conclusions

There are several barriers that need to be overcome to achieve control and management of PKDL. Significant progress related to the diagnosis, treatment, and prevention of VL has been achieved, and as a result, the incidence rate of VL has substantially decreased in the past few years. Less attention has been placed on PKDL despite the fact that it is crucial to the transmission of VL. Fighting PKDL cases should be a recent priority for all parties involved in the kala-azar elimination campaign in order to meet the elimination targets.

Disclosure of competing interest

The authors have none to declare.

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