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# Short Report: Clinical Epidemiologic Profile of a Cohort of Post–Kala-Azar Dermal Leishmaniasis Patients in Bihar, India

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*Abstract.* Post–kala-azar dermal leishmaniasis (PKDL) has important public health implications for transmission of visceral leishmaniasis (VL). Clinical and epidemiologic profiles of 102 PKDL patients showed that median age of males and females at the time of diagnosis was significantly different ($P = 0.013$). A significant association was observed between family history of VL and sex of PKDL patients ($\chi^2 = 5.72$, $P < 0.01$). Nearly 33% of the patients showed development of PKDL within one year of VL treatment. The observed time (median = 12 months) between appearance of lesions and diagnosis is an important factor in VL transmission. A significant association was observed between type of lesions and duration of appearance after VL treatment ($\chi^2 = 6.59$, $P = 0.001$). Because PKDL was observed during treatment with all currently used anti-leishmanial drugs, new drug regimens having high cure rates and potential to lower the PKDL incidence need to be investigated.

Post–kala-azar dermal leishmaniasis (PKDL) is a dermatosis caused by *Leishmania donovani* parasites in the skin after apparently successful treatment of patients with visceral leishmaniasis (VL) or those without a history of VL. It is characterized by macular, maculopapular, and nodular lesions in patients recovering from VL who are otherwise healthy.[1] It occurs in nearly 10–20% of patients cured of VL within 1–5 years in India, and in approximately 50% of patients in Sudan within six months.[1–4] In the Indian subcontinent, kala-azar appears to occur at an interval of 10–15 years.[5] Patients with PKDL have immense public health importance because they act as reservoirs of infection.[6] Because there is no animal reservoir of *L. donovani*, in this sub-continent, it is important to detect patients with PKDL and treat them properly to prevent future outbreaks of VL.[7]

It has been reported that a large proportion of VL patients treated with sodium antimony gluconate (SAG) have a high probability of development of PKDL.[8] It is not known whether other anti-leishmanial drugs have a similar post-treatment effect in development of PKDL. Clinical and epidemiologic aspects of PKDL are important for understanding transmission dynamics and defining VL control strategies. Because there is no mechanism currently available to detect PKDL cases at the community level, control strategies currently operational in disease-endemic areas would fail to achieve their goal of elimination. Therefore, we studied a cohort of PKDL cases diagnosed during 2007–2010 to identify clinical and epidemiologic features that are important to public health.

The study was conducted at the Rajendra Memorial Research Institute of Medical Sciences, Indian Council of Medical Research, Patna, India during June 2007–December 2010. A total of 102 confirmed patients with PKDL were enrolled in the study after providing informed consent. A semi-structured questionnaire was administered to each person to obtain demographic characteristics, area of residence, history of VL, relapse of VL, family history of VL or PKDL, month and year of first appearance of lesions, and site of lesions.

All persons were clinically examined by a physician for identification of lesions on the face, trunk, arms, and legs and type of lesions such as macular, papular, nodular, or mixed. Skin snips of patients were collected for detection of *L. donovani* by using a standard microscopic procedure. Only parasitologically confirmed patients were considered patients with PKDL in the cohort. Age and sex distribution of VL patients diagnosed and treated at the center during 2001–2008 were similar to those of patients with PKDL. Data were analyzed by using Epi Info, version 3.2 (Centers for Disease Control and Prevention, Atlanta, GA) and SPSS Version 15 (SPSS, Inc., Chicago, IL).

Of 102 patients with PKDL, 61 (60%) were males and 41 (40%) were females, which was similar to the distribution of VL patients (Table 1). The overall median age of PKDL patients was 23 years (range = 5–60 years), which was significantly different ($P = 0.013$) between males (25 years, range = 6–60 years) and females (16 years, range = 5–51 years). The median ages of male and female VL patients were 18 years (range = 4–56 years) and 13.5 years (range = 2–52 years), respectively. In patients 5–14 years of age, 49% of PKDL patients were female, 42% of patients with VL were female, 18% of PKDL patients were male, and 41% of VL patients were male, which indicated that more female PKDL patients seek early treatment for PKDL. We did not observe any PKDL patients in persons < 1–4 years of age compared with 5% of patients with VL in this age range.

There was no significant association of history of VL with PKDL by sex ($\chi^2 = 0.399$, $P = 0.5273$). Nearly 85 (83%) of PKDL patients had a history of VL, of whom 80 were treated with a single full-course regimen, and 5 received multiple regimens at different times. In the cohort, 38 (37%) had a family history of VL and 64 (63%) did not have a family history of VL. A significant association was observed between family history of VL and sex of patients with PKDL ($\chi^2 = 5.72$, $P < 0.01$). Among 38 PKDL patients with a family history of PKDL, nearly 14 (37%) had more than one case of VL in the past five years. Twenty-nine (28%) PKDL patients had a history and family history of VL, which indicated a possible synergistic effect of these two factors on PKDL.

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TABLE 1

Demographic and clinical dcharacteristics for patients with PKDL, Bihar, India*

| Characteristic | Male (n = 61) | Female (n = 41) | Total (n = 102) | *P* |
|---|---|---|---|---|
| Median age, years (range) | 25 (6–60) | 16 (5–51) | 23 (5–60) | 0.013† |
| Age group, years | | | | < 0.01, $\chi^2 = 16.41$ |
| 5–14 | 11 (18) | 20 (49) | 31 (30) | |
| 15–29 | 28 (46) | 7 (17) | 35 (34) | |
| 30–44 | 13 (21) | 12 (29) | 35 (34) | |
| ≥ 45 | 9 (15) | 2 (5) | 11 (11) | |
| Past history of VL | | | | 0.5273, $\chi^2 = 0.399$ |
| Yes | 52 (85) | 33 (81) | 85 (85) | |
| No | 9 (15) | 8 (19) | 85 (85) | |
| Family history of VL | | | | < 0.01, $\chi^2 = 5.72$ |
| Yes | 17 (28) | 21 (51) | 38 (37) | |
| No | 44 (72) | 20 (49) | 64 (63) | |
| Time (years) between diagnosis and appearance of lesions | | | | < 0.01, $\chi^2 = 1.45$ |
| ≤ 1 | 33 (54) | 27 (66) | 60 (66) | |
| 2–3 | 19 (31) | 9 (22) | 28 (27) | |
| 4–5 | 6 (10) | 3 (7) | 9 (9) | |
| > 5 | 3 (5) | 2 (5) | 5 (5) | |

*Values are no (%) unless otherwise indicated. PDKL = post–kala-azar dermal leishmaniasis; VL = visceral leishmaniasis.
†By Kolmogorov-Smirnov test.

However, we did not observe any significant association between individual history and family history of VL on cases of PKDL ($P = 0.126$, $\chi^2 = 2.342$).

The median time between first appearance of lesions and diagnosis was approximately 12 months (range = 1–144 months). Nearly 59% of persons were given a diagnosis within 12 months after appearance of lesions and 41% were given a diagnosis after one year. Female patients (66%) were given a diagnosis of PKDL comparatively earlier than male patients (54%) within a year after occurrence of a lesion, but the difference was not statistically significant ($P > 0.05$).

The median time of manifestation of PKDL was 24 months (range = 1–192 months) (Table 2). Overall, PKDL developed in 82% of patients within 5 years of successful treatment for VL. However, PKDL developed in approximately 33% of patients within one year of successful treatment for VL. Regarding the distribution of initial occurrence of type of lesions, 41 (48%) of the PKDL patients had macular lesions and 44 (52%) had either papular or nodular lesions. The most prominent site of initial occurrence of lesions in the cohort were the face and arms in 41 (41%) patients; face, arms, and legs in 21 (21%) patients; and face in 12 (12%) patients. A significant association was observed between type of lesions and duration of their appearance after VL treatment ($\chi^2 = 6.59$, degrees of freedom = 2, $P = 0.001$).

Of 85 patients, 62 (75%) showed complete cure after treatment with a full course of SAG, 13 (15.5%) after treatment with amphotericin B, 2 (2%) after treatment with AmBisome, 4 (5%) after treatment with miltefosine, and 4 (5%) after treatment with paramomycin (Table 3). Most (80, 94%) patients received a single drug and only 5 (6%) received multiple drugs. Among VL patients treated with AmBisome, appearance of lesions occurred very early i.e., within 5–13 months, whereas with other regimens, lesions appeared an average of 2 years after cure of VL.

The incidence of PKDL has important public health implications because PKDL acts as the reservoir of *L. donovani* in India and helps trigger transmission of VL in disease-endemic areas.[9] In Indian sub-continent, untreated patients with VL and PKDL are considered to be the only reservoirs that provide a source of exposure by disseminating the causative parasite to unaffected persons living in the same community.[9,10] Of these two reservoirs of *L. donovani*, untreated PKDL continues for years in the community and provides easy access for sand flies to acquire parasites.[8]

It has been documented that *Phlebotomus aregentipes*, the vector that transmits VL in India, has the potential to develop infection by producing promastigotes in the mid gut and is thus capable of transmitting parasites to human by bites.[7,11] In this cohort of patients with PKDL, approximately 52% had either papular or nodular lesions. Among them, 41% had lesions on the face and arms, which are usual exposed areas for bites of sand flies. Because nodular lesions have large concentrations of *L. donovani*, this finding could be one of the reasons for continued sustainability of VL transmission dynamics in disease-endemic regions.

It has been reported that a small percentage of patients treated for VL show development of PKDL within 2–3 years, but PDKL may develop much earlier (i.e., after 6 months) or much later (up to 32 years later).[12] In this study, we observed that the median time of PKDL presentation was 24 months after the end of VL treatment, and in some cases occurred much earlier (within 1 month after treatment) or much later (within 16 years). It was observed that approximately 33% of patients had PKDL within a year after VL treatment, and approximately 49% had PKDL within 2–5 years. Conversely, in Sudan, the time interval between VL and PKDL is short; all cases occur within 0–13 months after treatment, usually within first 6 months.[1] In Bangladesh, nearly 38% of PKDL patients had manifestations within one year after treatment for VL compared with 33% in this study, which showed nearly statistical similarity in two regions of disease-endemic areas of VL in the Indian sub-continent.[13] In comparison

TABLE 2

Time between clinical presentation of PKDL lesions after treatment for VL at the time of diagnosis, Bihar, India

| PKDL after VL treatment (years) | No. (%) macular lesions | No. (%) papular or nodular lesions | Total (%) | *P* |
|---|---|---|---|---|
| ≤ 1 | 17 | 11 | 28 (33) | 0·001, $\chi^2 = 6.59$ |
| 2–5 | 21 | 21 | 42 (49) | |
| ≥ 6 | 3 | 12 | 15 (18) | |
| Total | 41(48) | 44 (52) | 85 | |

PDKL = post–kala-azar dermal leishmaniasis; VL = visceral leishmaniasis.

TABLE 3

Drug use and PKDL presentation in VL-treated cases, Bihar, India

| Anti-leishmanial drug | No. (%) patients | Median time lapse after treatment (months) | Range (months) |
|---|---|---|---|
| Sodium antimony gluconate | 62 (72.9) | 23 | 1–192 |
| Amphotericin B | 13 (15.3) | 29 | 8–106 |
| AmBisome | 2 (2.4) | 9 | 5–13 |
| Miltefosine | 4 (4.7) | 31 | 29–42 |
| Paramomycin | 4 (4.7) | 25 | 19–37 |

PDKL = post–kala-azar dermal leishmaniasis; VL = visceral leishmaniasis.

with Sudan, PKDL among VL-treated cases occurs later in India. This finding is an important distinct feature of PKDL in India, Sudan, and Bangladesh.

Persons with a history of VL seem to be more susceptible to PKDL than persons without a history of VL, which is an important indicator for development of PKDL. It has been reported that 15–20% of PKDL patients had no history of VL suggestive of subclinical infection.[2] In the present study, approximately 17% of patients with PKDL had no history of VL. Causes of development of PKDL without a history of VL need to be investigated.

The type of anti-leishmanial drug used for treating VL patients has an implicit association with PKDL. In this cohort of PKDL patients, of 85 patients with a history of VL, 62 (73%) were treated with SAG, which is the first-line of treatment of VL in Bihar. Brahamchari first described PKDL in India in a patient with kala-azar who was treated with a trivalent antimony compound.[14] It has been reported that most kala-azar patients treated and cured with SAG, but not SAG-resistant cases, showed development of PKDL even after increasing the dose and duration of treatment with SAG.[8,15,16]

In this study, we observed that nearly 15% of patients with PKDL had been treated for VL with a full course of amphotericin B under strict hospital in-door settings during 1999–2007. In the course of follow-up, these patients showed development of PKDL. It has been reported that use of amphotericin B for treatment of VL during the 1990s and 2000s might have resulted in significant decrease in number of cases of PKDL, and inadequate doses of amphotericin B might have caused PKDL.[8] In this study, all patients treated for VL with amphotericin B were given a full dose. This finding indicates that even adequate doses of amphotericin B can cause PKDL in VL patients who were treated and cured. However, our finding supports an earlier observation regarding a significant decrease in PKDL among patients with VL who were treated with AMB. Development of PKDL among patients with VL who were treated with other more potent drugs such as AmBisome, miltefosine, and paramomycin occurred in 2% and 5% of patients. The actual incidence of PKDL among patients with VL who were treated with any of these potent anti-leishmanial drugs can be assessed only by conducting a prospective study over time among a cohort of treated VL patients in disease-endemic areas.

The distribution of PKDL patients is similar to that of VL patients because PKDL patients represent a small subset of VL patients with a higher proportion among males (60%) than females (40%). The median age of occurrence of PKDL was significantly different by sex ($P = 0.013$). The higher proportion of female patients with PKDL in persons 5–14 years of age could be caused by appearance of lesions on face, which are often confused with leprosy, a severe social stigma regarding marriage in communities in India, particularly in rural areas. Because of this finding, parents of unmarried women with PKDL approach health providers seeking diagnosis and treatment comparatively earlier than male patients with PKDL.

The time between appearance of lesions and diagnosis is an important factor in the public health importance of patients with PKDL in terms of transmission of infection in the community. The median time between appearance of lesions and diagnosis was 2 years (range = 1–12 years). A long delay in seeking diagnosis and treatment of PKDL and high densities of *P. aregentipes* could provide opportunities for continuation of transmission of VL in the community. Because development of PKDL was observed in significant proportion of persons who used anti-leishmanial drugs, new drug regimens and/or combination therapy with high cure rates and potential to decrease signs and symptoms of PKDL after VL needs to be investigated.

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