

Short Communication

Post-kala-azar dermal leishmaniasis in visceral leishmaniasis-endemic communities in Bihar, India

Rudra Pratap Singh^{1,*}, Albert Picado^{2,3,*}, Shah Nawaz Alam¹, Epcó Hasker², Shri Prakash Singh¹, Bart Ostyn², François Chappuis⁴, Shyam Sundar¹ and Marleen Boelaert²

¹ Banaras Hindu University, Varanasi, India

² Institute of Tropical Medicine, Antwerp, Belgium

³ Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-Universitat de Barcelona), Barcelona, Spain

⁴ Geneva University Hospitals, Geneva, Switzerland

Abstract

We assessed the prevalence of post-kala-azar dermal leishmaniasis (PKDL), a late cutaneous manifestation of visceral leishmaniasis (VL), in 16 VL-endemic communities in Bihar, India. The prevalence of confirmed PKDL cases was 4.4 per 10 000 individuals and 7.8 if probable cases were also considered. The clinical history and treatment of the post-kala-azar dermal leishmaniasis cases are discussed.

keywords Post-kala-azar dermal leishmaniasis, PKDL, *Leishmania donovani*, visceral leishmaniasis, kala azar, Bihar

Introduction

Post-kala-azar dermal leishmaniasis (PKDL) is a late (usually post-treatment) complication of visceral leishmaniasis (VL) caused by *Leishmania donovani*. VL is one of the major neglected tropical diseases and it is especially prevalent among the poorest communities in the endemic areas (Boelaert *et al.* 2009). In East Africa and the Indian subcontinent, the causal pathogen *L. donovani* is transmitted by *Phlebotomus* sand flies. VL is considered fatal if not treated while PKDL is a non-life-threatening cutaneous form characterised by a variety of skin manifestations, from hypopigmented macules to papular or nodular lesions. PKDL is generally linked to a previous episode of VL, and on the Indian subcontinent the lesions tend to appear 2–3 years post-treatment (Zijlstra *et al.* 2003). The risk of developing PKDL seems to be associated with incomplete sodium stibogluconate (SSG) treatment (Uranw *et al.* 2011). But PKDL has also been reported in patients treated with other antileishmanial drugs (i.e. miltefosine, amphotericin B and paromomycin) (Das *et al.* 2009; Kumar *et al.* 2009; Pandey *et al.* 2012) and in individuals with no history of VL (Zijlstra *et al.* 2003). PKDL cases are relevant in the transmission of *L. donovani*, because they can act as reservoirs (WHO 2010). However, except for

cosmetic considerations, PKDL does not cause any physical limitation, and thus, patients do not tend to seek medical care for it. Active case detection is required to ensure adequate identification and treatment of patients (Mondal *et al.* 2010).

PKDL is more prevalent in East Africa, where up to 50% of VL cases develop PKDL, whereas on the Indian subcontinent only 5%–18% of cases develop this cutaneous form (Zijlstra *et al.* 2003). However, the number of studies estimating the burden of PKDL in the Indian subcontinent is limited. There are no estimates on the prevalence of PKDL in Nepal, but a recent study showed that 2.4% of treated VL patients developed PKDL (Uranw *et al.* 2011). In Bangladesh, where the PKDL incidence has been rising (Rahman *et al.* 2010), the estimated PKDL prevalence was 6.2/10 000 (Mondal *et al.* 2010). In India, to our knowledge, only one study reported PKDL prevalence: 48.2/10 000 in 1987 in Uttar Pradesh (Rai *et al.* 1989). However, this estimate, based on 27 of 5,600 individuals with PKDL-like lesions, may be misleading as only one case was confirmed by histopathology. So the actual prevalence of confirmed PKDL cases was 1.8/10 000. Even if the incidence of PKDL seems to be decreasing in India according to surveillance data (Thakur *et al.* 2008), there are no recent studies assessing the burden of PKDL in VL-endemic areas. We report data from a household survey.

*Both authors contributed equally (joint first authorship).

Methods

In June 2010, we surveyed 2020 households from 16 VL-endemic communities in Muzaffarpur district, Bihar. These communities were part of a large bednet trial in the area and were selected based on their high incidence of VL in the previous years. Details on the study population and the results of the trial are provided elsewhere (Picado *et al.* 2010).

A house-to-house survey was used to identify probable and confirmed PKDL cases as defined by WHO (2010). An individual with multiple hypopigmented macules, papules or nodules with no loss of sensitivity was considered a probable PKDL case. Direct observation under microscope of *Leishmania* amastigotes in a slit skin smear (SSS) from the lesions was used to determine confirmed PKDL cases. A three-stage procedure was used. First, during the house-to-house survey, trained field workers used an album with pictures of PKDL patients to identify individuals with PKDL-like lesions. All those subjects were interviewed with a structured questionnaire to collect demographic data and information about the lesions and previous VL episodes (i.e. onset symptoms, treatment). Information about previous VL or PKDL treatment was checked with patients' records when available. In a second stage, these people were revisited by a trained physician to clinically differentiate probable PKDL cases from other skin conditions. Probable PKDL cases were further tested for *Leishmania* antibodies by rK39 immunochromatographic test and referred to the Kala Azar Medical Research Centre (KAMRC) in Muzaffarpur. Finally, at KAMRC, PKDL cases were confirmed by SSS and treated as suggested by WHO (WHO 2010). The prevalence was estimated using probable and confirmed PKDL cases separately.

Written informed consent was obtained from individuals or their guardian for those aged under 18 before enrolling them in the study.

Results and discussion

A total of 11 466 individuals living in the study villages were surveyed. Twenty subjects with PKDL-like lesions were identified by the fieldworkers but only 9 were identified as probable PKDL by the physician. Of the 11 non-probable cases, 8 had other skin disorders and 3 had moved and could not be revisited. The characteristics of the PKDL cases are summarised in Table 1. Five men and four women with a median age of 13 years were identified as probable PKDL cases. All 9 were rK39 positive and referred to KAMRC but only 5 cases were parasitologically confirmed. Of the 4 non-laboratory confirmed cases, 3 did not go to the KAMRC as they had moved and one did

not have a SSS taken. The estimated PKDL prevalence ranged from 7.8 to 4.4 per 10 000 individuals if all (9/11 466) or only confirmed PKDL (5/11 466) cases were considered, respectively. These figures are similar to those estimated in Bangladesh (Mondal *et al.* 2010) but at least 10 times higher than the estimate used in a recent study modelling the epidemiology and control of VL on the Indian subcontinent (Stauch *et al.* 2011). The distribution of PKDL cases was uneven among the study villages; for example, three cases were located in the same village and two of them in the same house. The clustering of PKDL cases had been previously reported in Bihar (Singh *et al.* 2000).

All nine PKDL probable cases had hypopigmented macules and five also had nodules. Skin lesions were found all over the body; face and arms were most frequently affected ($n = 6$ cases). Two PKDL cases had lesions in the face, extremities and trunk. Hypopigmented macules on the face have been reported as the most common skin lesions in PKDL patients in Nepal and Bangladesh (Mondal *et al.* 2010; Uranw *et al.* 2011). All PKDL probable cases had been previously treated for VL with SSG ($n = 6$), paromomycin ($n = 2$) or amphotericin B ($n = 1$). None of the past VL patients was treated with miltefosine. This is remarkable as 7 of them were treated after 2005, when miltefosine was established as the first line treatment for VL in India. Seven cases reported to be cured after VL treatment (no information was available for 2). Two of the confirmed PKDL cases were relapses as they had been previously treated for PKDL. Both cases were first treated with SSG when diagnosed with VL and then with paromomycin for the first episode of PKDL. The median time to develop skin lesions after VL treatment was 30 months (range 9–129 months). This figure is similar to those reported in other studies in the region (e.g. 23 months in Nepal (Uranw *et al.* 2011) or 36 months in Bangladesh (Mondal *et al.* 2010)). Interestingly, 8 of 9 PKDL cases suffered their initial VL episode when they were younger than 13 years. This contrasts with findings in Nepal and Bangladesh, where young VL patients were not at higher risk of developing PKDL than older cases (Mondal *et al.* 2010; Uranw *et al.* 2011). The 6 PKDL cases attending to KAMRC were treated; 3 with amphotericin B and 3 with miltefosine (Table 1) as suggested by WHO (WHO 2010). The lesions disappeared in 5 patients after treatment. One patient treated with amphotericin B had to stop the treatment after 22 days because of increased creatinine levels in serum. One patient stopped the miltefosine treatment after 28 days and the final outcome could not be assessed. Poor treatment compliance of PKDL patients has been reported as a major problem in previous studies.

R. P. Singh *et al.* PKDL prevalence in Bihar**Table 1** Characteristics of the 9 Post-kala-azar dermal leishmaniasis (PKDL) cases identified in the 16 visceral leishmaniasis (VL) endemic villages in Muzaffarpur district, Bihar (India) in June 2010

Village No.	Age*	Sex	Type of lesions	Location of lesions	rk39 test	Date VL Treatment	Past VL Treatment – Drug – Dose – Duration	Past History of PKDL	Time VL treatment to PKDL lesions (months)	Visit to KAMIRC	Slit Skin Smear	PKDL Treatment – Drug – Dose – Duration	Outcome treatment
1	34	M	H, N	F, A	POS	Jan 2006	SSG – 20 mg/kg† – 30 days	No	51	Yes	POS	MILT – 100mg/day – 28 days¶	Defaulter
4	14	M	H, N	F	POS	Aug 2006	SSG – 20 mg/kg† – 60 days	No	38	Yes	POS	MILT – 50mg/day – 84 days	Lesions Regressed
4	9	F	H	F, A	POS	Feb 2008	PAR – 11 mg/kg – 14 days	No	20	No	NA	NA	NA
8	13	F	H	T	POS	Sept 2005	SSG – no info – no info	No	44	No	NA	NA	NA
10	13	F	H	F, A, L, T	POS	Aug 2009	SSG – no info – 7 days	No	9	Yes	Not done	MILT – 100mg/day – 84 days	Lesions Regressed
12	18	M	H, N	F, A, T	POS	Nov 1997	SSG – no info – no info	Yes‡	129§	Yes	POS	AMP – 1mg/day – 22 days** (alternate)	Lesions Regressed
12	10	M	H, N	F, A, L, T	POS	Feb 2004	SSG – 20 mg/kg† – 30 days	Yes‡	30§	Yes	POS	AMP – 1mg/day – 30 days (alternate)	Lesions Regressed
12	12	M	H, N	A, L	POS	May 2007	PAR – 11 mg/kg – 21 days	No	30	Yes	POS	AMP – 1mg/day – 30 days (alternate)	Lesions Regressed
14	7	F	H	T	POS	Feb 2007	AMP – no info – 15 days	No	27	No	NA	NA	NA

H, Hypopigmented macules; N, Nodules; F, face; A, arms; L, legs; T, trunk; SSG, sodium stibogluconate; PAR, paromomycin; AMP, amphotericin B; MILT, miltefosine.
 *Age in years in June 2010.

†Dose estimated as there was no information on the weight of the patient at the time of treatment.

‡Previous PKDL case treated in August 2008 with paromomycin, 11 mg/kg for 45 days, lesions regressed after treatment.

§Time between treatment and PKDL lesions estimated from the first episode of PKDL.

¶Defaulter, stopped treatment after 28 days (84 prescribed).

**Treatment with amphotericin B was stopped after 22 days because of an increase in the creatinine levels in serum.

R. P. Singh *et al.* **PKDL prevalence in Bihar**

For example only 38.9% of PKDL cases completed their treatment in Bangladesh (Mondal *et al.* 2010).

This study confirms that PKDL can develop in VL patients treated with different antileishmanial drugs. Migration of PKDL cases to other villages may expand VL-affected areas.

Acknowledgements

We are grateful to Surendra Uranw for his assistance in preparing the picture album used in the household survey. This work was supported by the European Union [INCO-DEV FP-6015374] and Fonds Wetenschappelijk Onderzoek – Vlaanderen [FWO-1511309].

References

- Boelaert M, Meheus F, Sanchez A *et al.* (2009) The poorest of the poor: a poverty appraisal of households affected by visceral leishmaniasis in Bihar, India. *Tropical Medicine and International Health*, **14**, 639–644.
- Das VN, Pandey K, Verma N *et al.* (2009) Short report: development of post-kala-azar dermal leishmaniasis (PKDL) in miltefosine-treated visceral leishmaniasis. *American Journal of Tropical Medicine and Hygiene*, **80**, 336–338.
- Kumar D, Ramesh V, Verma S, Ramam M & Salotra P (2009) Post-kala-azar dermal leishmaniasis (PKDL) developing after treatment of visceral leishmaniasis with amphotericin B and miltefosine. *Annals of Tropical Medicine and Parasitology*, **103**, 727–730.
- Mondal D, Nasrin KN, Huda MM *et al.* (2010) Enhanced case detection and improved diagnosis of PKDL in a Kala-azar-endemic area of Bangladesh. *PLoS Neglected Tropical Diseases*, **4**, e832.
- Pandey K, Das VN, Singh D *et al.* (2012) Post-kala-azar dermal leishmaniasis in a patient treated with injectable paromomycin for visceral leishmaniasis in India. *Journal of Clinical Microbiology*, **50**, 1478–1479.
- Picado A, Singh SP, Rijal S *et al.* (2010) Longlasting insecticidal nets for prevention of *Leishmania donovani* infection in India and Nepal: paired cluster randomised trial. *BMJ*, **341**, c6760.
- Rahman KM, Islam S, Rahman MW *et al.* (2010) Increasing incidence of post-kala-azar dermal leishmaniasis in a population-based study in Bangladesh. *Clinical Infectious Diseases*, **50**, 73–76.
- Rai RN, Kumar M, Srivastava A *et al.* (1989) Clinico-epidemiological profiles of post-kala-azar dermal leishmaniasis in Varanasi. *Journal of Communicable Diseases*, **21**, 214–217.
- Singh S, Kumar J, Singh R & Dwivedi SN (2000) Hepatitis B and C viral infections in Indian kala-azar patients receiving injectable anti-leishmanial drugs: a community-based study. *International Journal of Infectious Diseases*, **4**, 203–208.
- Stauch A, Sarkar RR, Picado A *et al.* (2011) Visceral leishmaniasis in the Indian subcontinent: modelling epidemiology and control. *PLoS Neglected Tropical Diseases*, **5**, e1405.
- Thakur CP, Kumar A, Mitra G *et al.* (2008) Impact of amphotericin-B in the treatment of kala-azar on the incidence of PKDL in Bihar, India. *Indian Journal of Medical Research*, **128**, 38–44.
- Uranw S, Ostyn B, Rijal A *et al.* (2011) Post-kala-azar dermal leishmaniasis in Nepal: a retrospective cohort study (2000–2010). *PLoS Neglected Tropical Diseases*, **5**, e1433.
- WHO (2010) *Control of the leishmaniasis: report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22–26 March 2010*. WHO Technical Report Series. World Health Organization, Geneva.
- Zijlstra EE, Musa AM, Khalil EA, El-Hassan IM & El-Hassan AM (2003) Post-kala-azar dermal leishmaniasis. *Lancet Infectious Diseases*, **3**, 87–98.

Corresponding Author Albert Picado, Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-Universitat de Barcelona), Roselló, 132, 4th floor, 08036 Barcelona, Spain. Tel.: +34 932 275 706; Fax: +34 932 279 853; E-mail: albert.picado@cresib.cat