Short Report: A Series of Case Reports of Autochthonous Visceral Leishmaniasis, Mostly in Non-Endemic Hilly Areas of Nepal

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Abstract. The government of Nepal has committed to eliminate visceral leishmaniasis (VL) by 2015. The expansion of VL into new areas would constitute a major obstacle to achieving this goal. We report a series of autochthonous VL cases from areas currently considered non-endemic, mostly in hilly regions of Nepal.

INTRODUCTION

Globally, visceral leishmaniasis (VL) cases occur > 90% in Nepal, India, Bangladesh, Brazil, and Sudan, and 60% of this burden is estimated to occur in south Asia alone.¹ In Nepal, it is estimated that 1,341 cases are reported annually mainly in the VL-endemic southeastern part of the country in 13 districts adjoining to Bihar state (in India), where VL is highly endemic.^{2,3} The governments of Nepal and India including Bangladesh have committed to collaborative efforts to eliminate VL from south Asia by the end of 2015.⁴ Currently, most of the elimination efforts are being focused on VL endemic areas of Nepal. Nevertheless, there are several challenges to be addressed effectively, before eradication becomes a reality; for example, treatment failure, incidence of co-infections, lack of political commitment to implementation, and the expansion of VL into new areas. Among these, very little is known about autochthonous VL cases beyond the currently considered endemic areas. In a recent study, VL has been shown to be increasingly reported in areas of Nepal previously considered non-endemic; however, whether these cases are imported or the result of autochthonous transmission remains to be elucidated.⁵ Here, we report, for the first time, a series of autochthonous VL cases identified from areas currently considered non-endemic, mostly in hilly regions of Nepal.

METHODS

Sukraraj Tropical and Infectious Disease Hospital (STIDH) serves as a central referral hospital with 100 beds for tropical infectious diseases in Nepal. Patients with suspected VL from endemic and non-endemic areas of the country are referred to this hospital for confirmation of diagnosis and appropriate treatment. Patients with irregular fever more than 2 weeks, weight loss, and splenomegaly, with evidence of amastigote forms of *Leishmania* in bone marrow, and/or positive rK39 (Insure; Inbios, Seattle, WA) antibody tests without history of VL and a positive response to treatment, were defined as VL cases. The VL cases from outside the currently defined endemic areas, with no travel history to an endemic region, were included in this study. Demographic data such as name, gender, age, address, and laboratory investigations were retrieved from the medical records. Personal contact was made with the patients/patient relatives, when additional information was required.

Confirmed VL cases were treated with either Amphotericin B (Amp-B) or Miltefosine (MLF). Amphotericin B was administered at a dose of 1 mg/kg/day for 14 days, whereas MLF was given orally in 50 mg doses twice daily for 28 days. Complete blood count, serum urea, serum creatinine, and liver function tests were performed routinely. Blood transfusion was administered, if hemoglobin concentrations dropped below 8 g/dL. Patients were discharged based on completion of treatment, resolution of fever, improved appetite, and reduction in spleen size.

RESULTS

A total of 39 VL cases were admitted to STIDH, Kathmandu between September 2010 and October 2011. Of these, 11 (28%) were from endemic areas, whereas 28 (72%) were from areas currently thought not to be non-endemic. There were two deaths during treatment. Of the 28 cases, 10 had no history of travel to a known VL-endemic area, and were therefore included in this study (Table 1). The patients' median age was 14 years (range, 3–65 years); all patients were male. The median time from local treatment to VL diagnosis was 20 weeks (range, 4–24 weeks). Of 10 patients, 7 (70%) were admitted from hilly regions, 2 (20%) from Terai, and 1 (10%) from a mountainous region.

The VL was diagnosed by identifying *Leishmania* amastigotes in bone marrow in 2 (20%) patients and by positive rK39 tests in 6 (60%) patients, whereas detection of *Leishmania* parasites in bone marrow by microscopy in association with positive rK39 tests was achieved for 2 (20%) patients. Complete blood counts were available for nine patients, showing leucopenia (a white cell count < 4,000 mm³), and anemia (a hemoglobin count < 10 g/dL) in all patients (data not shown). Five (50%) of 10 patients received blood transfusion during the treatment. Elevated liver enzymes were observed in all patients investigated ($N = 5$). Eight (80%) cases were treated with Amp-B, whereas 2 (20%) were treated with MLF.

DISCUSSION

An increasing number of VL cases reported from areas previously considered non-endemic, is one of the major drawbacks in the effort to control or eliminate the disease effectively worldwide.⁶ Despite the growing number of reported cases from such “non-endemic” areas, very little is known about VL beyond the currently identified endemic areas of Nepal. Until recently, VL was thought to be confined primarily to populations living in rural areas of the southeastern parts of Nepal; therefore, existing research to date has tended

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TABLE 1
Demographic and characteristics of 10 VL patients during 2010–2011, Nepal

Patient	Age (year) and gender	District (region)	Duration, weeks*	Travel history	Spleen size (cm) BLCM(OA-OD)†	Amastigote (BM)	rK39 test	Treatment
1	8, male	Okhaldhunga (hill)	24	No	10–6	ND‡	Positive	Amp-B (Fungizone)
2	13, male	Sindhuli (hill)	20	No	6–4	ND	Positive	Amp-B (Fungizone)
3	15, male	Sindhuli (hill)	20	No	3-ND	ND	Positive	Amp-B (Fungizone)
4	16, male	Nawalparashi (terai)§	4	No	5-ND	ND	Positive	Amp-B (Fungizone)
5	65, male	Nawalparashi (terai)	8	No	ND	Present	Positive	Amp-B (Fungizone)
6	15, male	Surkhet (hill)	24	No	12–8	Present	ND	Amp-B (Fungizone)
7	3, male	Surkhet (hill)	NK¶	No	ND	ND	Positive	Miltefosine (28days)
8	12, male	Pyuthan (hill)	4	No	5-ND	Present	ND	Miltefosine (28days)
9	5, male	Bajura (mountain)	NK	No	5–2	ND	Positive	Amp-B (Fungizone)
10	27, male	Dailekh (hill)	NK	No	7–5	Present	Positive	Amp-B (Fungizone)

*Time from local treatment to VL diagnosis.

†BLCM = below left costal margin, OA = on admission, OD = on discharge; BM = bone marrow.

§Terai = southern lowland plains.

‡ND = not done.

¶NK = not known.

to focus only on this area. To the best of our knowledge, this is the first reported series of autochthonous VL cases from outside these endemic areas.

Most physicians in areas considered to be non-endemic for VL usually do not consider the disease in the differential diagnosis; therefore, treat VL patients for other infectious diseases, which display similar symptoms, resulting in delays of appropriate treatment through misdiagnosis. In our study, seven patients (70%) were initially treated for enteric fever at local hospitals. The time duration between the local treatment and VL diagnosis ranged from 4 to 24 weeks (median, 20 weeks). This result shows there is a substantial delay in VL diagnosis in non-endemic areas compared with endemic areas,⁷ which may

increase the risk of death. There is, therefore, an urgent need for active surveillance in areas previously considered non-endemic, where VL is being reported, and continuing medical education for the physicians working in these areas, is particularly urgently required. An oral drug, such as MLF could be one of the possible causes for delay in the VL treatment in the developing world. The MLF is a relatively new oral drug with a convenient dosing schedule the use of which does not generally require hospitalization. Despite these benefits, insufficient explanation of dosage requirements by physicians may cause patient non-compliance with recommended dosage requirements, which may pose a risk for the development of drug resistance in the long run. Patient 1, for example, had been

FIGURE 1. Geographical distribution of autochthonous visceral leishmaniasis (VL) cases reported prior and during September 2010–October 2011 in Nepal.

treated with MLF following VL diagnosis without hospitalization; however, the patient was not completely cured because of inadequate intake of medicine. Relapse of VL cases because of poor medication adherence have been observed at STIDH soon after the introduction of MLF (data not shown), and are presumed to have occurred (though not identified formally, because of underreporting) in clinical practices elsewhere. In Nepal, the first-line drug recommended for treatment of VL is currently MLF. Given these observations, however, there is a serious concern over improper use of this drug, especially in those areas where people lack adequate education. Directly observed therapy should be applied to overcome this problem. Nonetheless, this issue needs to be brought to the attention of policy makers, and should inform development of alternative strategies to improve medication adherence.

Of even greater concern is the detection of autochthonous VL cases in areas of the country currently considered non-endemic. During the study period, our hospital data shows that 28 VL cases (72%) were admitted from outside the areas currently considered endemic. This finding is in accordance with our earlier observations, which also showed an increasing number of VL cases from “non-endemic” areas of Nepal.^{5,8} The VL cases from non-endemic areas were being admitted to STIDH, while preparing this article. Presently, the reasons for these observations are unclear. Nevertheless, two hypotheses can be put forward to explain our results. First, the VL sandfly vector might be spreading to new parts of the country, although currently it is believed to be restricted to the south-eastern part of Nepal. Deforestation, rapid urbanization, and environmental changes have been found to be highly correlated with shifting the vector’s geographic range worldwide,⁹ and these factors could constitute a possible explanation for vector expansion and leishmaniasis transmission beyond the currently identified endemic areas, as Nepal has been experiencing such events over the last decade.¹⁰ Second, although VL is currently considered an anthroponotic disease in south Asia, several recent studies have indicated that VL may also be a zoonotic disease.^{11,12} A recent study conducted in the eastern part of Nepal, for example, has implicated domestic animals as potential reservoir hosts.¹¹ These emerging indications simply cannot be overlooked, though more research needs to be carried out to confirm the potential for zoonotic transmission of VL disease. It is interesting to observe that the majority of VL patients (70%) in this study were admitted from hilly regions and one patient was admitted from Bajura, a mountainous district of Nepal. Autochthonous VL has been previously reported in the neighboring hilly districts Doti and Accham (Figure 1)^{8,13}, until recently, however, there has been little evidence for the expansion of VL to hilly parts of the country. It would be of interest to determine whether the VL vector has adapted to hilly environments, enabling the disease to spread to this area. We, therefore, highly recommend that future research efforts should focus not only on areas currently considered to be endemic for VL but also on hilly regions of the country.

In conclusion, our study reports on the emergence of autochthonous VL outside the currently defined endemic areas of Nepal, thereby highlighting the need to redefine the boundaries of endemic VL in this country.

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