



Research article

Leishmaniasis in Dhaka Medical College-experience of three years

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ABSTRACT

The People's Republic of Bangladesh has been working to eliminate visceral leishmaniasis or Kala-azar cases since there was a memorandum of understanding signed between neighboring countries in 2005. As a part of the elimination activity, 44 cases of Kala-azar were diagnosed and treated in the regional referral center Dhaka Medical College Hospital (DMCH) during the last three years, which is reported here. Confirmed leishmaniasis cases were included. Patients attending this specialized center with different demographic characteristics and varied presentations with laboratory findings were reviewed and recorded in a structured case record form. Ethical clearance was obtained prior to starting the study. A total of 44 patients with leishmaniasis were reviewed. Approximately 89% (n = 39) were New Kala-azar (NKA), 7% (n = 3) were Relapse Kala-azar (Relapse KA), only one case (2%) was Kala-azar Treatment Failure (KATF) and Post Kala-azar Dermal Leishmaniasis (PKDL) for both. The mean age of presentation was 32 years. Forty percent of patients had houses made by mud, 26% by tin shed, and the rest lived in buildings and semi-buildings. The predominant clinical features were fever (90.9%), pallor (88.6%), splenomegaly (81.8%) and hepatomegaly (68.2%). rK39 was positive in 90.7% of cases, and 94.4% of cases were positive for LD bodies on splenic aspirate. Of all, 90.90% were treated with Inj. Liposomal amphotericin B and 9.10% with the combination of Inj. Liposomal Amphotericin B and Inj. Miltefosine. Moving forward to the elimination of leishmaniasis from Bangladesh, the study highlights the status, characteristics and treatment of the disease in the country.

Author summary

Among tropical diseases, leishmaniasis is a common disease that causes thousands of preventable deaths. The Bangladesh government successfully ran a Kala-azar elimination program, and in 2019, it achieved elimination status from a joint mission report from the WHO. On that ground, Kala-azar cases are relatively rare in this country, and here, we report these clusters of confirmed cases with their clinical and treatment profiles. A total of 44 cases were included in the last 3 years in a regional center for the Kala-azar elimination program.

1. Introduction

Leishmaniasis is a vector-borne parasitic disease caused by protozoan *Leishmania* and is transmitted by female phlebotomine sand flies. Cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL) and

visceral leishmaniasis (VL) is the three common forms of manifestation of this disease. The severity of disease depends on the characteristics of causative *Leishmania* species, biology of the involved vector, host factors and the type of immune response to infection [1]. Visceral leishmaniasis is the most severe form caused by *Leishmania donovani* in Asia and Africa and *Leishmania infantum* in the Mediterranean Basin, the Middle East, central Asia, South America and Central America [2]. On the other hand, cutaneous leishmaniasis is typically limited to a self-curing ulcer that heals over 3–18 months spontaneously but may also lead to formation of scar, disfigurement and stigmatization as disability outcomes [3]. Post-Kala-azar dermal leishmaniasis is another skin manifestation that usually occurs in otherwise healthy people after treatment of visceral leishmaniasis [4].

In 2018, more than 95% of new cases of VL reported to the World Health Organization (WHO) occurred in 10 countries: Brazil, China, Ethiopia, India, Iraq, Kenya, Nepal, Somalia, South Sudan and Sudan, and

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over 85% of new CL cases occurred in 10 countries: Afghanistan, Algeria, Bolivia, Brazil, Colombia, Iran (Islamic Republic of), Iraq, Pakistan, the Syrian Arab Republic and Tunisia. It is estimated that between 700,000 and 1 million new cases occur worldwide annually [5].

Although significant progress has been achieved in the treatment of leishmaniasis in Bangladesh, it still remains one of the most important public health problems with a high frequency of mortality and morbidity in the country [6]. The VL, popularly known as kala azar in this region, is also complicated with a substantial number of cases of post kala azar dermal leishmaniasis (PKDL). Here, reports of sporadic Kala-azar cases were noticed in the 1970s in Bangladesh, which was followed by an outbreak in Pabna district in 1980 [7]. Surveillance data are lacking from that period, but a series of 59 Kala-azar patients diagnosed between 1968 and 1980 in seven districts of Bangladesh was reported in 1983 [8]. From 1993 to 2005, Kala-azar situations have assumed epidemic proportions, with the number of reported cases increasing from 3,978 in 1993 to 8,505 in 2005 [9]. Although Kala-azar was previously reported from 45

districts, the number of affected districts has declined to 26, with a total number of 864 cases in 2016 (New Kala-azar-541, PKDL- 240, Relapse Kala-azar- 73, Kala-azar Treatment Failure- 8) and 459 in 2017 (New Kala-azar- 255, PKDL- 160, Relapse Kala-azar- 37)⁹. The majority of cases were reported from Mymensingh and Tangail [9].

Most of the time, malnutrition, population displacement, poor housing, a weak immune system and lack of financial resources are associated with leishmaniasis as it is linked to environmental changes such as deforestation, building of dams, irrigation schemes, and urbanization [10]. During 5–6 September 2004 in Kurumba Island, Maldives, inter-country meetings of the Ministry of Health of Bangladesh, India and Nepal were held with the aim of eliminating Kala-azar in these countries. A memorandum of understanding (MOU) was performed in the World Health Assembly in Geneva in May 2005 with a target to eliminate Kala-azar by 2015. A regional strategic plan was prepared and endorsed by the WHO South East Asian Organization (SEARO) Regional Technical Advisory Group (RTAG) in October 2006. The objective was a) to reduce

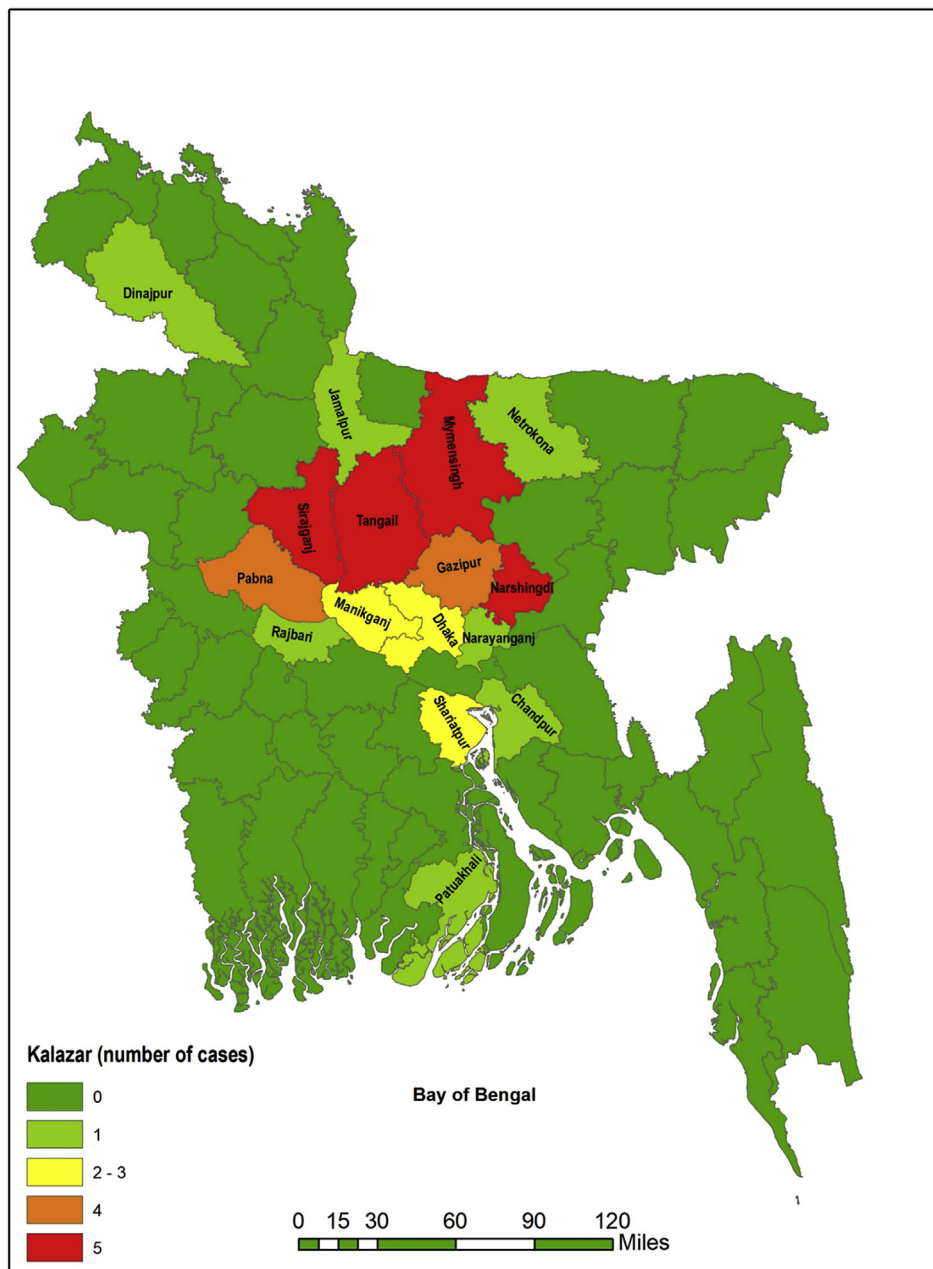


Figure 1. The distribution of patients in different districts of Bangladesh (n = 44).

the incidence of Kala-azar and PKDL per 10,000 population at the sub-district level in Bangladesh and India and the district level of Nepal, b) to reduce case fatality rates from Kala-azar, c) to treat PKDL to reduce the parasite reservoir, and d) to prevent and treat Kala-azar –HIV-TB coinfection. The National Steering Committee for elimination of Kala-azar in Bangladesh was formed on 10 November 2005. The Regional Technical Advisory Group (RTAG) was formed in October 2006 for the implementation of an elimination program. The strategy undertaken was 1) early diagnosis and complete treatment, 2) integrated vector control management, 3) effective disease surveillance, 4) social mobilization and partnership, and 5) operational research (Supplementary figure 1). Thereafter, a “Regional Strategic Framework for Elimination of Kala-azar from the South-East Asia Region: 2011–2015” was adopted with clear goals, targets, indicators and objectives. The Kala-azar elimination target set for the WHO South-East Asia Region in the WHO Neglected Tropical Disease (NTD) road map was 2020 [11,12].

The rarity of cases means the disease may get time to evolve, with patients presenting late in the tertiary care centers undiagnosed. With this assumption and as a part of the elimination strategy, the Government of Bangladesh has established a kala azar regional referral center at different medical colleges of Bangladesh, one of them in Dhaka Medical College, located in the capital city of Dhaka and providing diagnostic and treatment options. From 2016 to 2019, 42 confirmed cases of VL were diagnosed and treated in this regional center. This study was performed to report the diagnosed and treated cases of leishmaniasis in this tertiary care center.

2. Materials and methods

2.1. Design, subjects and procedure of the study

This observational study was conducted in the Department of Medicine and Pediatrics, Dhaka Medical College Hospital (DMCH) for a period of three years covering March 2016–April 2019. Both adult and pediatric cases admitted within the study period were included in the study. Patients of both genders between the ages of 2–70 years with a history of prolonged fever (more than two weeks) living in or travelling to a Kala-azar endemic area and having splenomegaly (palpable spleen) and/or weight loss, anemia, and enlarged liver were considered as Kala-azar cases. The attending physician screened the patients for signs and symptoms of Kala-azar and immediately transferred the patients to the regional center of Kala-azar when suspected. Then, investigations were performed according to the standard guidelines. Clinically suspected kala-azar cases were diagnosed by “rK39 RDT”. The rK39 negative cases were confirmed by splenic aspiration and sometime with the bone marrow examination when the suspicion of kala azar was very high [9]. The parasitic confirmation and density through splenic aspiration was also attempted in positive rK 39 cases unless the patient refuses to give consent. On the other hand, skin biopsies were performed to confirm PKDL [7]. In this study, a total of 44 cases were analyzed. Formal ethical clearance was taken from the ethical review committee of DMC.

Details of demographic features, clinical presentation, and social background were recorded in the printed case record form by doctors of the corresponding unit. Informed written consent was ensured before participation for all adult patients. In case of minors, statement on informed consent were taken from the parents of the participant. Before any invasive procedures, patients were informed about the procedure, advantages and possible complications [8]. All standard precautions were undertaken, and separate written informed consent was undertaken before splenic aspiration. One case of cutaneous leishmaniasis was confirmed by skin biopsy performed by the Dermatologist of Bangabandhu Sheikh Mujib Medical University. Patients were treated according to the national guideline treatment protocol [9]. Liposomal amphotericin B (lipid formulation of Amphotericin B) manufactured by Gilead pharmaceuticals was prescribed according to standard operating procedures (as described in national guidelines) [9], and immediate

adverse reactions were observed, recorded and managed under supervision of the corresponding unit consultant. Follow-ups were performed immediately after completion of the treatment in the hospital and after one and six months after completion of treatment in the regional referral center of Dhaka Medical College Hospital. Systematic analysis of demographic variables and analysis of blood specimens and splenic aspirates were observed by the study team.

Here, cure (initial cure) was defined by improvement of all clinical parameters, including absence of fever, regression of enlarged spleen and return to appetite and/or gain in body weight at day 30, while definitive cure was defined by no fever, reduction of spleen size or not palpable and feeling of general wellbeing compared to day 1. All data were recorded into the case record form (CRF), and separate CRFs were recorded at the end of 30 days and at the end of 180 days.

2.2. Ethical consideration and consent statement

The researcher was duly concerned about the ethical issues related to the study and maintained according to the current declaration of Helsinki. Confidentiality and informed consenting procedure were followed properly. Prior starting the study, ethical approval was taken from the Ethical Review Committee (ERC) of Dhaka Medical College.

2.3. Statistical analysis

After collection of all the required data, these were checked, verified for consistency and then tabulated into the computer using the Statistical Package for Social Sciences 20 (SPSS Inc., Chicago, IL) for Windows 10. Inferential data analysis was carried out to describe the study population by using paired sample t test and McNemar-Bowker test whenever necessary. The results were summarized using frequency or percentage, median with range and depicted in tables and graphs.

3. Results

Overall incidence analysis showed that the highest number of patients ($n = 5$) was referred from Mymensingh, Narshingdi, Sirajganj, and Tangail. The distribution of the location of the Kala-azar cases is described in Figure 1.

A total of 44 patients with leishmaniasis were observed, and among them, approximately 89% ($n = 39$) cases were New Kala-azar (NKA), 7% ($n = 3$) were Relapse Kala-azar (Relapse KA), only one case (2%) was Kala-azar Treatment Failure (KATF) and one case (2%) was Post Kala-azar Dermal Leishmaniasis (PKDL). The mean age of the patients was 32.07 ± 17.45 (SD) years with slight female preponderance ($n = 23$, 52%). Approximately 40% of cases had houses made of mud, 26% had tin shed, 21% had building and rest having semi building as residence (Table 1).

Of all, the predominant symptoms observed were fever for more than 2 weeks (90.9%) and pallor (88.6%) (Table 1). The spleen and liver were palpable in 81.8% and 68.2% patients, respectively. The mean spleen size of the patients was $11.69 (\pm 5.08)$ cm (SD) from the left costal margin with a range from 2 cm to 20 cm. Approximately 90.2% of patients were rK 39 positive, and LD bodies were detected in the splenic aspirate of 94.4% patients (Table 1).

Patients were followed up immediately after completion of treatment, at 1 month after treatment and at 6 months after treatment. A total of thirty patients were included in the follow-up period, while the rest were lost to follow-up. Among the patients who completed follow-up, fever was almost absent at both the one- and 6-month follow-ups (Table 2).

The clinical change in spleen size was also observed before and after treatment, and it showed statistically significant improvement at one and six months after treatment (Table 2).

Injection liposomal amphotericin B (10 mg/kg) single dose (according to national guidelines) was given in most cases (90.9%), while 4

Table 1. Characteristics of study population.

Characteristics	n	%
Age (n = 43)		
<10	5	11.4
10–20	8	18.2
21–30	10	22.7
31–40	7	15.9
41–50	7	15.9
51–60	2	4.5
>60	4	9.1
Mean age (Mean ± SD)	32.07 ± 17.45	
Gender (n = 44)		
Male	21	47.7
Female	23	52.3
Housing (n = 42)		
Mud	17	40.47
Tin	11	26.19
Building	9	21.42
Semi-building	5	11.92
Clinical Symptoms* (n = 44)		
Fever >2 weeks	40	90.9
Pallor	39	88.6
Nausea	10	77.3
Vomiting	4	9.1
Weakness	16	36.4
Skin lesion	3	6.8
Hypopigmented	2	4.5
Papule	1	2.3
Clinical Sign		
	Mean ± SD	Median (Range)
Weight (kg) (n = 43)	40.67 ± 12.67	40 (12–64)
Temperature (Fahrenheit) (n = 33)	101.64 ± 1.41	102 (98–104)
Pulse (beats/min) (n = 30)	82.10 ± 8.46	80 (68–100)
Systolic BP (n = 29)	101.03 ± 14.23	100 (60–130)
Diastolic BP (n = 28)	64.48 ± 14.23	60 (5–85)
Palpable splenomegaly (n = 44)	36	81.8
Palpable hepatomegaly (n = 44)	30	68.2
Investigations		
	Mean ± SD	Median (Range)
Spleen size (cm) (n = 36)	11.69 ± 5.08	12 (2–20)
Hb (g/dl) (n = 42)	8.05 ± 1.87	8.4 (4.7–13.6)
rk 39 (n = 43)	39	90.7
Presence of LD bodies in splenic aspirate (n = 38)	36	94.7
Case distributions		
New Kala-azar (NKA)	39	88.6
Relapse Kala-azar (Relapse KA)	3	6.8
Kala-azar Treatment Failure (KATF)	1	2.3
Post Kala-azar Dermal Leishmaniasis (PKDL)	1	2.3

* Multiple response considered. Spleen span is measured in cm from corresponding costal margins.

patients (9.10%) received a combination of inj. Liposomal amphotericin B (5 mg/kg single dose) followed by miltefosine for seven days (Table 3).

4. Discussion

In these three years, we experienced 44 cases of leishmaniasis, which is alarming, as 1.2 cases every month is slightly high when the country is advocating the elimination of kala azar. These cases are derived from different districts of the country, which means that active surveillance, including active case searches (through different techniques such as snowball, camp, house-to-house search), needs to be highlighted more to capture those cases in primary health care centers [9]. The highest cases

were derived from Narshingdi and Gazipur (close to Dhaka metropolitan), while Mymensingh and Tangail are distant districts from which we also experienced few cases. Mymensingh is the hyperendemic zone for leishmaniasis for a prolonged period, and there is a regional referral center [Surjakanto (SK) hospital] well equipped with a diagnostic and treatment facility. The seven cases derived from that region are surprising, as SK hospitals have provided excellent service for the last few years. This indicates that the different active search techniques should be continued with extra effort in this region to obtain cases for early and appropriate referral to SK hospitals. This also indicates that the existing referral system is porous and that community-based workers need to be enforced to augment elimination activities.

Table 2. Characteristics of the patients before and after treatment (follow up).

Variable	Before treatment	1 st f/u	2 nd f/u	3 rd f/u	P value (BT Vs 1 st f/u)	P value (BT Vs 2 nd f/u)	P value (BT Vs 3 rd f/u)
Temperature, F	101.88 ± 1.39	99.17	99.10 ± 0.97		<.001	0.005	
Pulse, beats/min	78.75 ± 8.41	79.92 ± 3.96	56.29 ± 15.48	83.09 ± 6.59	0.652	0.05	.594
Fever >2 weeks	14 (93.3)	3 (20)	2 (13.3)	0	<.001	<.001	<.001
Nausea	8 (0.5)	1 (6.7)	2 (13.3)	0	.039	.063	<0.001
Vomiting	3 (20)	0	1 (6.7)	0	.25	.50	0.25
Weakness	11 (73.3)	6 (40)	6 (40)	0	.016	.031	<.001
Pallor	12 (80)	4 (26.7)	3 (20)	1 (6.7)	.004	.001	<.001
Hemoglobin, g/dl	7.3 ± 2.19	9.13 ± 1.35			0.014		
Spleen size, cm*	12.90 ± 5.67		2.28 ± 5.71	1.28 ± 1.89		0.001	<0.001

Data is expressed in frequency (percentage) and mean ± SD as needed; Symptom proportion was calculated among fifteen patients.

BT: Before Treatment.

P value was determined by paired sample t test and McNemar-Bowker test as appropriate.

1st f/u: Follow up immediately after treatment.

2nd f/u: Follow up after 1 month.

3rd f/u: Follow up after 6 months.

* Spleen size measured as length (in cm) below left costal margin, only one patient's spleen remained enlarged at 2nd and 3rd follow-up.

Table 3. Type and outcome of treatment among study population.

Variable	n	%
Type of therapy (n = 44)		
Monotherapy (Liposomal Amphotericin B)	40	90.9
Combination therapy (Liposomal Amphotericin B + Miltefosine)	4	9.1
Outcome of therapy (n = 30)		
Cured	29	96.7
Not cured	1	3.3

Twenty-two cases were aged below 30 years, indicating that Kala azar is predominantly a disease of young age group [9, 13] which is consistent with findings of previous studies [13, 14].

Fever and anemia were found to be present in almost all patients. The frequency of fever suggested that there should be less sensitivity of duration of fever in the definition of Kala-azar diagnosis in hyperendemic zones of Bangladesh for making early diagnosis of visceral leishmaniasis (Currently, the guideline suggests fever should be more than two weeks) [11]. More than 50% of cases were anemic, indicating that this should be worked more to see whether any confounding etiology is present or not, and if not, this sign may be incorporated for case definition of VL¹¹.

Splenomegaly is the most common sign, among which most cases had an increase of 5–15 cm in spleen size. Therefore, in the endemic zone, if a patient presents with fever and anemia associated with moderate splenomegaly, the probability of confirming the diagnosis of VL will be very high. Hepatomegaly was also found in nearly half of the cases in this study, indicating the importance of the basic skill of physicians for reaching a convincing clinical diagnosis of VL in Bangladesh.

The surprising news was three relapse cases and one treatment failure case, which indicates there is chance of developing resistance against a single dose of liposomal amphotericin B, as it was the agent predominantly given from the national kala azar elimination programme [14, 15, 16]. Although the national guideline has the option of a combination treatment strategy, it has become the second choice. These four cases of relapse and treatment failure give impulse to think of combination therapy to become the choice rather than single agent therapy. Bangladesh completed the combination RCT, which was published in 2017 by Ridwan *et al.*, and revealed that the cost-effective combination would be liposomal amphotericin B with paromomycin [17]. One case was found refractory to treatment as the patient received two completed treatments, and his splenic aspiration and PCR showed positivity of the LD body. He was later treated in SK hospital with an extended dose of liposomal amphotericin B and an extended dose of the miltefosine

combination for complete cure. One case of Post kala azar dermal leishmaniasis (PKDL) was diagnosed during three years in this regional center, which indicates the rarity of this disease in Bangladesh. The case was also an importer from the Middle East, where cutaneous disease is frequent [4, 18]. Although he was also searched for cutaneous leishmaniasis due to his middle east travel history, the rK 39 positivity and identification of *leishmania donovani* in skin biopsy revealed the case as PKDL rather cutaneous leishmaniasis. The sand fly fauna in Bangladesh is predominantly *Phlebotomus argentipes* which is the proven vector of *L. donovani* causing kala azar in Bangladesh. *Phlebotomus papatasi*, proven vector of *L. major*, is also present but not a common species in Bangladesh [19, 20, 21]. Because of many Bangladeshi workers are frequently travelling to the Middle East countries where CL caused by *L. major* and *L. tropica* is endemic, the presence of *P. papatasi* in Bangladesh may also create a risk for some areas of Bangladesh. The program also needs appropriate steps to diagnose and treat cutaneous leishmaniasis cases. Sodium stibogluconate should not be completely exhausted, and although phased out from the National program, it is highly effective in these cases [4, 9].

More than 95% of cases received a single dose of liposomal amphotericin B (as per national guidelines) and were cured. Only four cases needed combination therapy as they were treatment failure and relapse cases. Combination treatment was highly satisfactory except for one refractory case. Liposomal amphotericin B was found to be safe in most cases except febrile reaction, which was managed easily. However, the drug can be deployed in primary health care centers easily, thus reducing the cost of travel to higher centers [12]. The response of single-dose liposomal amphotericin B was also satisfactory, as 97% of cases remained symptom free at one and six months. These are also seen in previous studies [18, 22]. One of the recent studies performed in ICCDR, B showed that there is a greater chance of developing PKDL in patients who received single-dose liposomal amphotericin B [23]. However, our

regional center, which followed patients up for at 6 months, did not find such positive findings.

In this referral center, the outcome was remarkable, as no death was observed. In the follow-up of cases, there was a remarkable reduction in spleen size as well as improvement in the body built of patients, indicating that the patients were probably cured. However, a definitive announcement of cure warrants a long follow-up, which, according to national guidelines, is up to 5 years of follow-up after treatment.

4.1. Limitation of study

Extensive investigations could not be possible for all patients in this study as individual consultant variation of choice of tests. A prolonged follow-up of patients was outside the scope of this study. PCR-based diagnosis could not be performed due to a lack of facilities in this center.

5. Conclusion

Leishmaniasis cases are still at large in some areas of Bangladesh. New treatment regimens for the disease are successful. Approaches for the prevention, control, and treatment of leishmaniasis in these areas should emphasize the continuation of the elimination status of the disease in the country.

Declarations

Author contribution statement

M. Amin and M. Hasan: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

J. Fardin: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

N. Noor: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

P. Malik: Performed the experiments; Contributed reagents, materials, analysis tools or data.

T. Tabassum: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

M. Khan: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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