Leishmaniasis in Sri Lanka: atypical cutaneous disease by an unusual parasite species

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Abstract

Though clinical outcome of human leishmaniasis is multi factorial, it mainly depends on the causative species. Sri Lanka is now considered as a new focus of human cutaneous leishmaniasis. Over 2500 cases have been investigated by us during past several years. Main clinical entity seen in the country is cutaneous leishmaniasis while it is caused by the usually visceralizing species *L. donovani*. Furthermore, the local *L. donovani* variant is genetically different from other members of *L. donovani* complex. Mismatch of a visceralizing parasite with a dermatological condition has led to several clinical and epidemiological concerns that need to be addressed without delay.

Visceralization or dissemination of primary skin infection and recurrence of treated lesions of *L. donovani* are dangerous possibilities. Clinical outcomes and treatment response patterns of the local parasite may be different from other known cutaneous variants of Leishmania parasites. Early case detection and management is the mainstay of *L. donovani* control as there are no known animal reservoirs. In depth clinical and epidemiological characterization and scientifically defined treatment protocols that suits the local setting and availability of diagnostic services in the hospital settings are necessary in this regard. Few clinical trials carried out locally, under limited resources have shown encouraging results and need to be actively pursued. Phlebotomus argentipes, the vector of *L. donovani* is widely prevalent in the country. Regional differences in transmission characteristics and preliminary evidence showing a potential animal reservoir in Sri Lanka, further complicate the decision making process in defining control strategies.

Parasite virulence is known to increase during an epidemic of leishmaniasis. Few cases of MCL and VL have already been reported locally. Preventive and control activities are required to be put in place urgently to minimize the spread of this potentially deadly species. Leishmaniasis was made a notifiable disease in Sri Lanka in 2008. Action plan for its control was drawn up in year 2008 with the involvement of all stake holders including the Ministry of health and the scientists in Universities. To achieve the defined objectives, a considerable amount of information is already available, and further research in all the fields is needed to fill in the essential gaps.

The disease leishmaniasis

Leishmaniasis is a vector-borne protozoan disease caused by several species of parasites of the genus Leishmania. Though clinical outcome of this infection is diverse and the underlying mechanisms are multi-factorial, the ultimate clinical outcome mainly depends on the causative parasite species and take one of the three main clinical forms (i.e., cutaneous (CL), muco-cutaneous (MCL) or visceral (VL) leishmaniasis). In Sri Lanka the disease has changed from being categorized as an imported disease in the 1990s[1,2,3] to a locally transmitted fast-spreading health problem in the following decade[4]. In year 2008, leishmaniasis was made notifiable in the country and a national action plan was developed for leishmaniasis control[5].

Parasite in the clinical setting

CL remains the main clinical entity seen within the island up to date. Interestingly, it is caused by a new variant of *L. donovani*[4]. This species results in visceral leishmaniasis in other endemic sites in the world and usually it is the most virulent among its member species. Other forms i.e., CL and MCL caused by *L. donovani* are only occasional[7,8,9].

L. donovani infection itself carries much significance with regard to the patient management due to its virulent nature and the high level of associated mortality and morbidity. Mismatch of a visceralizing parasite with a clinical picture of CL in Sri Lanka has left the treating clinicians, public health officials and the scientists with many uncertainties.

Normally in CL, primary skin infections completely heal spontaneously or with treatment, leaving immunity and resistance to re-infection by homologous Leishmania species[10]. However, an important point to be remembered is that though clinical manifestations improve, achieving a simultaneous parasitological cure can be difficult in leishmaniasis. Remaining dormant parasites can give rise to full-blown leishmaniasis when conditions become favourable (eg: immune suppression or other concurrent illnesses). CL causing species are known

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to cause recurrence of disease in about 1% of patients[10]. *L. donovani* skin infections are also known to recur in other parts of the world[11]. Local variant of *L. donovani* has already shown its ability to infect different sites (skin, mucosa and viscera) and to diverse skin manifestations in addition to the observed typical CL skin lesions[12,13,14,15,16]. The dangerous possibility of visceralization of *L. donovani* in Sri Lanka need to be urgently and adequately studied with careful follow up of patients over a reasonable period of time. Recent reports of VL and MCL in the country already points towards this possibility. There is historical evidence to support the presence of visceral leishmaniasis even 100 years ago in this island. In a recent study, CL patient's sera had tested negative for rk39 while MCL and VL had shown a positive response[16]. rk39 is the standard serological diagnostic assay used for VL confirmation. However, number of VL and MCL cases may be grossly under diagnosed in Sri Lanka, due to low transmission levels of VL, asymptomatic nature of early infections and lack of clinical suspicion[17,18].

Confirmation of *L. donovani* infection

Timely case detection and treatment is considered as the mainstay of *L. donovani* control as there are no known animal reservoirs involved in transmitting this species. In the context of diverse clinical outcomes associated with *L. donovani* infection in Sri Lanka, the dermatologist as well as the physician, ENT surgeon and the dental surgeon need to consider the possibility of leishmaniasis in the relevant settings. Early disease confirmation through laboratory means is strongly advocated as advanced lesions with or without therapy and treated lesions can produce false negative results. There are no pathognomonic clinical features in leishmaniasis and clinical patterns can be misleading and diverse[10,17,18], complicating the decision making procedure for the clinicians. Therefore early and pre-treatment laboratory confirmation through light microscopy, in-vitro cultivation, PCR or rk 39 serological assay[16,19] as the case may be, play a major role in proper patient management in the local setting.

***L. donovani* and treatment response**

Known VL and MCL infections require specific and vigorous treatment while self limiting parasite forms causing CL could be left to self cure[10,17,18,20] though this view remains debatable. Host immunity levels are promoted during natural elimination of Leishmania parasites (and therefore healing of the lesion) while treatment can downregulate these mechanisms, facilitating visceralization or further local spread of parasites[21,23]. Furthermore, inappropriate drug regimens, and substandard formulations are known to result in drug resistance[22]. *L. donovani* parasites in India has already shown over 60% drug resistant rate for pentavalent antimonials mainly due to factors associated with its usage[22].

On the other hand, untreated skin lesions can remain as a source of infection to the vectors, therefore increasing the reservoirs of infection which in turn promote disease spread. In the local setting this argument alone may justify the need for early confirmation of diagnosis and treatment which is further strengthened due to reports that indicate great variability in the treatment response patterns of *L. donovani* induced CL at different epidemiological settings. Clinical improvement, late onset recurrence and recurrence after treatment of first recurrence are possibilities[11,23]. Therefore, management of a case of CL caused by *L. donovani* is not straight forward. It is always advisable to carefully monitor the treatment response patterns of local parasites before establishing or adopting treatment practices. Limited and irregular availability of specific anti-leishmanials in the curative sector is a major drawback in this regard (personal communication with dermatologists). Few drug trials carried out under limited resources in the clinical sector in Sri Lanka has shown encouraging results and such efforts need to be actively encouraged[24].

Parasite in the epidemiological setting

Presence of this potentially virulent species in Sri Lanka calls for urgent preventive and control activities for many reasons. There is a widening of case distribution in the country to include more and more districts during the past, though in general, clinical and demographical features of *L. donovani* infection has remained nearly the same as reported earlier[16,25,26,27,28]. However the factors that affect *L. donovani* transmission have shown to be regionally different[16,29], further complicating the picture.

Phlebotomine sandfly ("Hohaputuwa" in local language) is the incriminated vector for *L. donovani* and it is prevalent in Sri Lanka since long[30,31]. Vectorial status of these insects in Sri Lanka is not known. Sandfly control will be necessary in future, but irrational introduction of insecticides can be rather harmful which can result in re-emergence of the disease probably in greater proportions as evidenced in leishmaniasis history in India[32].

Integrated vector management that combines multiple methods such as long lasting impregnated bed nets (LLIN) and indoor residual spraying (IRS) has been increasingly adopted for disease control during the recent past[18,32].

In contrast to the general belief that *L. donovani* transmission does not involve an animal reservoir, there is preliminary evidence for a potential animal reservoir host in Sri Lanka[33,34]. Reservoir host aspects also need to be studied further and might need to be considered in future control plans based on evidence.

The way forward

WHO targets for complete elimination of VL by year 2020 through 100% detection and effective management[35]. Early case detection and treatment, vector control (managing the sand flies that transmit the parasite) and communication and education within the endemic communities are the three main WHO strategies for this task[35]. It is an urgent need to identify locally appropriate preventive and control strategies in an evidence-based manner. It may be necessary to define transmission characteristics and anti-leishmanial measures on a regional basis, as a single control programme for the whole island may not be appropriate in the presence of different transmission characteristics that appear to prevail regionally, and potential zoonotic/animal reservoirs. Increase in parasite virulence levels, non-immune status of the indigenous population with increased vulnerability and free movements of people, lack of awareness, poor self referrals and under diagnosis at clinical settings may lead to quick establishment of more virulent forms of disease within this country.

A multidisciplinary approach including improved and appropriate case management, field preventive and control activities, continued surveillance and effective dialogue among administrative, research, clinical and preventive authorities, backed up by correct scientific data will ensure successful control of leishmaniasis in this island.

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References

1. Naotunne T de S, Rajakulendran S, Abeywickrema W, *et al.* Cutaneous leishmaniasis in Sri Lanka – an imported disease linked to the Middle East and African employment boom. *Trop Geogr Med* 1990; **42**: 72-4.
2. Athukorale DN, Seneviratne JKK, Ihalamulla RL, Premaratne UN. Locally acquired cutaneous leishmaniasis in Sri Lanka. *J Trop Med* 1992; **95**: 432-3.
3. Senevirathne JKK, Siriwardena S, Rathnathunge N, Wijesundera Mde S. Locally acquired leishmaniasis from Central Sri Lanka: a case report. *Kandy Medical Journal* 1995; **4**(2): 54-6.
4. Siriwardana HV, Noyes HA, Beeching NJ, Chance ML, Karunaweera ND, Bates PA. Leishmania donovani and cutaneous leishmaniasis, Sri Lanka. *Emerg Infect Dis* 2007; **13**(3): 476-8.
5. International Colloquium on Leishmaniasis in Sri Lanka. In: Abstracts and National Action Plan 2009.
6. Karunaweera ND, Pratlong F, Siriwardane HV, Ihalamulla RL, Dedet JP. Sri Lankan cutaneous leishmaniasis is caused by *Leishmania donovani* zymodeme MON-37. *Trans R Soc Trop Med Hyg* 2003; **97**(4): 380-1.
7. Harms G, Schonian G, Feldmeier H. Leishmaniasis in Germany. *Emerg Infect Dis* 2003; **9**: 872-5.
8. Ben-Ami R, Schnur LF, Golan Y, Jaffe CL, Di T, Zeltser D. Cutaneous involvement in a rare case of adult visceral leishmaniasis acquired in Israel. *J Infect* 2002; **44**(3): 181-4.
9. Sethuraman G, Sharma VK and Salotra P. Indian mucosal leishmaniasis due to *Leishmania donovani* infection. *New Eng Journal of Med* 2008; **358**(3): 313-5.
10. Dedet JP, Pratlong F. Leishmaniasis. In: Gordon Cook and Alimuddin Zumla. (Eds). Manson's Tropical Diseases (21st ed). Saunders 2002; 1339-64.
11. Mebrahtu YB, Van Eys G, Guizani I, *et al.* Human cutaneous leishmaniasis caused by *Leishmania donovani s.l.* in Kenya. *Trans R Soc Trop Med Hyg* 1993; **87**(5): 598-601.
12. Siriwardana HVYD. Clinical epidemiology of leishmaniasis in Sri Lanka and the molecular identification of the causative organism. PhD thesis 2008.
13. Rajapaksa US, Ihalamulla RL, Karunaweera ND. First report of mucosal tissue localisation of leishmaniasis in Sri Lanka. *Ceylon Med J* 2005; **50**(2): 90-1.
14. Abeygunesekara PH, Costa YJ, Seneviratne N, Ranatunga N, Wijesundera M de S. Locally acquired visceral leishmaniasis in Sri Lanka. *Ceylon Med J* 2007; **52**(1): 30-1.
15. Rathnayake D, Ranawake RR, Sirimanna G, Siriwardhane Y, Karunaweera N, De Silva R. Co-infection of mucosal leishmaniasis and extra pulmonary tuberculosis in a patient with inherent immune deficiency. *Int J Dermatol* 2010; **49**(5): 549-51.

16. Siriwardana HVYD, Thalagala N, Karunaweera ND. Clinical and epidemiological studies on the cutaneous leishmaniasis caused by *Leishmania donovani* in Sri Lanka. *Ann Trop Med Parasitol* 2010; **104**(3): 213-23 .

17. Herwaldt H. Leishmaniasis. *Lancet* 1999; **354**: 1191-9.

18. Chappuis F, Sundar S, Hailu A, Ghalib H, Rijal S, Peeling RW, *et al.* Visceral leishmaniasis: what are the needs for diagnosis, treatment and control? *Nat Rev Microbiol* 2007; **5**: 873-82.

19. Ihalamulla RL, Siriwardana HVYD, Gamage S, Perera AJ, Karunaweera ND. First successful in-vitro cultivation of autochthonous Leishmania species in Sri Lanka. *Ceylon Med J* 2002; **47**(2): 58.

20. Report of World Health Organization on the workshop on control of visceral leishmaniasis, WHO/Leish/96:40. 1996. World Health Organization, Geneva, Switzerland.

21. Sadeghian G, Iraji F, Anilfroushzadeh I. Disseminated cutaneous leishmaniasis on lymphedema following radiotherapy. *Int J Dermatol* 2005; **44**: 610-11.

22. Sundar S, Singh VP, Sharma S, Makharia MK, Murray HW. Response to interferon-gamma plus pentavalent antimony in Indian visceral leishmaniasis. *J Infect Dis* 1997; **176**(4): 1117-9.

23. Pearson RD, De Queiroz Sousa A. Leishmania species: visceral (kala-azar), cutaneous and mucosal leishmaniasis. In: Mandell GL, Bennett JE and Dolin R (eds). Principles and Practice of Infectious Diseases (4th ed). New York: Churchill Livingstone, 1995: 2434.

24. Ranawaka RR, Weerakoon HS, Opathella N. Liquid nitrogen cryotherapy on *L. donovani* cutaneous leishmaniasis. *J Dermatolog Treat* 2010.

25. Siriwardana HVYD, Udagedara C, Karunaweera ND. Study on clinical patterns, risk factors and efficacy of cryo therapy in cutaneous leishmaniasis in Sri Lanka. *Cey Med J* 2003; **48**(1): 10-12.

26. Nawaratna SS, Weligama DJ, Wijekoon CJ, Dissanayake M, Rajapaksha K. Cutaneous leishmaniasis, Sri Lanka. *Emerg Infect Dis* 2007; **13**(7): 1068-70.

27. Rajapaksa US, Ihalamulla RL, Udagedera C, Karunaweera ND. Cutaneous leishmaniasis in Southern Sri Lanka. *Emerg Infect Dis* 2007; **101**(8): 799-803.

28. Samaranayake TN, Dissanayake VH, Fernando SD. Clinical manifestations of cutaneous leishmaniasis in Sri Lanka – possible evidence for genetic susceptibility among the Sinhalese. *Ann Trop Med Parasitol* 2008; **102**(5): 383-90.

29. Siriwardana HVYD, Senanayake S, Weerasena KHW, Jayasinghe S, Karunaweera ND. Epidemiological study of leishmaniasis in a selected area in Sri Lanka. Proceedings of the 4th World Congress on Leishmanioses, India 2009; 96.

30. Carter, Anthonypulle. Observations on sand flies in Delft island in North. *Ceylon Med J* 1949; **43**: 62-73.

31. Gajapathy K, Jude PJ, Surendran SN. Morphometric and meristic characterization of *Phlebotomus argentipes* species complex in northern Sri Lanka: evidence for the presence of potential leishmaniasis vectors in the country. *Trop Biomed* 2011; **28**(2): 259-68.

32. Thakur CP. National level policy issues. In: Thakur H (ed). Kala Azar – Emerging Perspectives and Prospects in South Asia. Centre for Health Policy, Planning and Management, School of Health Systems Studies, Tata Institute of Social Sciences (TISS) (2011); 311-69.

33. Nawaratna SS, Weilgama DJ, Rajapaksha K. Cutaneous leishmaniasis in Sri Lanka: a study of possible animal reservoirs. *Int J Infect Dis* 2009; **13**(4): 513-7.

34. Rosypal AC, Tripp S, Kinlaw C, Hailemariam S, Tidwell RR, Lindsay DS, *et al.* Surveillance for antibodies to *Leishmania spp.* in dogs from Sri Lanka. *J Parasitol* 2010; **96**(1): 230-1.

35. Accelerated work to overcome the impact of neglected tropical diseases. A roadmap for implementation. WHO (2012). Geneva, Switzerland. Accessed on line http://whqlibdoc.who.int/hq/2012/WHO_HTM_NTD_2012.1_eng.pdf