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Leishmaniasis: current challenges and prospects for elimination with special focus on the South Asian region

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SUMMARY

Leishmania donovani, arguably the most virulent species of *Leishmania*, is found in the South Asian region that harbor the majority of visceral leishmaniasis (VL) cases in the world. The traditionally accepted relationships between the causative species of *Leishmania* and the resultant disease phenotype have been challenged during recent years and has underscored the importance of revisiting the previously established taxonomy with revisions to its classification. The weak voice of the afflicted with decades of neglect by scientists and policy makers have led to the miserably inadequate and slow advancements in product development in the fields of diagnostics, chemotherapeutics and vector control that continue to hinder the effective management and control of this infection. Limitations notwithstanding, the regional drive for elimination of VL initiated over a decade ago that focused on India, Nepal and Bangladesh, the three main afflicted countries in the Indian subcontinent is therefore, commendable, with the subsequent status reviews and restructuring of strategies possibly even more so. However, the renewed efforts would need to be combined with plans to combat new challenges in the south-Asian region that includes the emergence of atypical parasite variants, in order to realistically achieve the set goal of regional elimination of VL.

Keywords

neglected tropical disease; kala azar; Indian subcontinent; skin lesions; *Leishmania*

INTRODUCTION

Leishmaniases are a group of parasitic diseases endemic in 98 countries worldwide, with over 350 million people living at risk and the annual case incidence ranging from 0.7 – 1.3 million (Alvar *et al.*, 2012). The disease is prevalent both in the ‘New’ (South and the Central America) and the ‘Old’ World (Southern Europe, Africa, Middle East, Central Asia and Indian subcontinent). Of the 16 categories of neglected tropical diseases (NTDs) assessed for the period from 2005 to 2013, leishmaniasis ranks next only to malaria as the

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CONFLICT OF INTEREST

None

second worst in the age-standardized DALYs (disability-adjusted life years) and second only to dengue fever in the rate of DALY increase, from 5.7 to 5.9 million (Murray *et al.*, 2015). The disease often reaches epidemic proportions in areas of low endemicity due to natural or man-made disasters, including famine, drought, flood, earthquakes and civil wars (Reithinger and Dujardin, 2007; Bern *et al.*, 2008). The poor socio-political background of the afflicted has largely contributed to the minimal interest shown towards leishmaniases by the policy makers, and even scientists, with resultant lack of good diagnostics and chemotherapeutic agents to enable effective management and control of this infection. Its apparent overlap with the spread of AIDS has highlighted the increasing threat of HIV-*Leishmania* co-infections, particularly in India and East Africa (Cruz *et al.*, 2006; Bern *et al.*, 2008).

PHENOTYPES AND CAUSATIVE AGENTS

Leishmaniases are considered as a disease complex rather than a single disease. Clinical manifestations occur under three main categories i.e. cutaneous, mucocutaneous and visceral leishmaniasis (WHO, 2017). Cutaneous leishmaniasis (CL) is caused by Old World *Leishmania* species such as, *Leishmania major/L. tropica* and is marked by the appearance of varying types of skin lesions, which are often innocuous and self-healing. Mucocutaneous leishmaniasis (MCL) is caused by New World *Leishmania* spp. such as *L. braziliensis* and is a protracted disease, resulting sometimes in extensive facial disfigurement and tissue destructions in the mouth and nose. Most cases of MCL are not life-threatening *per se.* However, death could occur due to complications associated with secondary infections. Visceral leishmaniasis (VL) caused by *L. donovani/L. infantum* is far more serious. It is often fatal, if untreated and results from systemic and progressive infection of macrophages in the reticulo-endothelial systems or lymphoid organs, mainly in the spleen, liver and bone marrow. Clinical manifestations of VL include hepatosplenomegaly, fever, anemia, leucopenia, hypergammaglobulinemia and cachexia (Dedet and Pratlong, 2003). The development of leishmaniasis follows a chronic course lasting for months and sometimes years. Interestingly, the traditionally established relationships between the causative species of *Leishmania* and disease phenotype have become obscure in certain instances and the leishmaniasis situation in Sri Lanka is a case in point (Karunaweera *et al.*, 2003), with the known visceralizing species *L.donovani* resulting in essentially dermotropic disease (Fig. 1) (Kariyawasam *et al.*, 2018). In this context, it is noteworthy that with the accumulation of information over the years has led to the taxonomy of trypanosomatids in general, and *Leishmania* in particular to be revised and therefore, classical classifications may soon become outdated (Esponosa *et al.*, 2018).

There are over 20 species of *Leishmania* that cause disease in humans (Maroli *et al.*, 2013; Akhoundi *et al.*, 2016). Transmission occurs through the bite of an infected female sandfly (*Phlebotomus* or *Lutzomyia* spp), which introduces the infective stages of *Leishmania* to a mammalian host. Sand flies are inconspicuous, fragile and hairy winged dipterans, similar to, but smaller in size than an average sized mosquito. Most *Leishmania* species are considered as zoonotic parasites with humans acting as accidental hosts (Dedet and Pratlong, 2003). The causative agent of visceral leishmaniasis in the Indian subcontinent, *L. donovani*

is however, widely considered as strictly anthroponotic, although this view remains debateable (Bhattarai *et al.*, 2010; Ready, 2014; Akter *et al.*, 2016).

CLINICAL MANAGEMENT OF LEISHMANIASIS

Confirmation of diagnosis of leishmaniasis is made through laboratory means. Visualization of parasites in the clinical samples from symptomatic patients constitutes the time-honored gold standard for definitive diagnosis of leishmaniasis (de Vries *et al.*, 2015). The routine procedures for this include microscopic examinations of Giemsa-stained smears of lesion aspirates (in the case of CL and MCL; Fig. 2) or splenic or bone marrow aspirates (in the case of VL) for the presence of amastigotes and/or cultivation of the samples in suitable media for their differentiation into and/or replication as promastigotes. These century-old practices have been gradually replaced by less cumbersome, and more sensitive and specific methods, i.e. serodiagnosis for the presence of *Leishmania*-specific antibodies or circulating antigens and by PCR-amplification of *Leishmania*-specific DNAs (Singh and Sundar, 2015; Akhoundi *et al.*, 2017).

The mainstay of treatment for leishmaniasis is chemotherapy, but none of the drugs in use had been specifically designed and developed for treating this disease, i.e. antimonials (meglumine antimoniate or glucantime®, sodium stibogluconate or Pentostam®), miltefosine, pentamidine, amphotericin B, ketoconazole and paromomycin (Singh *et al.*, 2016a). The antimonials remain as the first line of treatment for VL in most endemic settings for the past so many decades although the mode of action of these compounds remains largely unknown. As reviewed by Hendrickx et al., (2018) and also Uliana et al. (2018), the chemotherapeutic agents widely available for treatment of leishmaniasis are toxic with prolonged use resulting in significant side effects and even death due to renal and/or cardiac complications. Better alternatives are urgently needed and drug repurposing is a promising strategy for finding new agents for oral or topical administration with anti-*Leishmania* activity (Trinconi et al., 2018). Amphotericin B-liposome (AmBisome®), a superior but expensive drug, is limited in use in endemic areas of poverty. Appearance and spread of drug resistance is also a major cause of concern hence, as extensively reviewed in this special issue (Sundar and Singh, 2018). Strategies for boosting hosts' immune responses to potentiate chemotherapy are considered as important future tools to meet such challenges and are reviewed by Taslimi et al. (2018) in this special issue.

Chemotherapy of CL faces the dilemma of its necessity, due to the dogma based on its tendency for self-resolution. However, treatment hastens healing, thereby minimizes the scar formation, prevents spread, progression in to more complicated disease forms, such as MCL and helps to avoid poor responsiveness of protracted disease (Marsden, 1986; Cannella *et al.*, 2011).

Prevention of spread, though believed as a hindrance for the potential development of herd immunity, would be important from a public health standpoint at least in countries with CL due to potentially visceralizing *L.donovani* infections (Kariyawasam *et al.*, 2017). Alternative approaches for treating CL are now available by using physical means e.g. thermotherapy that uses radio-frequency generated heat (RFHT) that is cost-effective and

safe (Refai *et al.*, 2017). The outcome of numerous clinical trials using RFHT for treatment of CL caused by varying *Leishmania* spp. have been carefully reviewed in this special issue (David, 2018).

LEISHMANIASIS IN THE INDIAN SUBCONTINENT

The Indian subcontinent accounts for nearly 70% of the world's anthroponotic VL cases, amounting to several hundred thousand annual cases (Alvar *et al.*, 2012). VL is however, substantially under-reported, with reported coverage varying not only between countries but even between districts within a given country (Bern *et al.*, 2008; Alvar *et al.*, 2012). India has the world's highest national VL incidence, Nepal and Bangladesh being the next. Taken together, the population at risk of acquiring VL is ~200 million in these three countries. VL data with regard to other south Asian countries such as Bhutan and Sri Lanka however, are sparse with the general belief of it being sporadic and scattered upheld in most part (Alvar *et al.*, 2012).

Clinical features of VL is marked by splenomegaly as the most noticeable symptom and is commonly accompanied by other non-specific signs such as anaemia, weight loss and helpatomegaly. Post-kala azar dermal leishmaniasis (PKDL) is also an intriguing clinical scenario described in India and occurs in 5-10% of VL cases following apparent cure of VL (and sometimes with no history of preceding VL). PKDL patients presents with macular papular skin lesions and are speculated to act as reservoirs for VL transmission (due to the parasite-rich nature of the skin lesions) (Ready, 2014), although such significance of PKDL remains debatable (Le Rutte et al., 2016; Hirve et al., 2017).

Leishmaniasis is a relatively newly established disease in Sri Lanka with the first autochthonous case of CL reported in 1992 (Athukorale *et al.*, 1992). There has been a steady increase in the numbers and distribution of CL across the country during the past two decades (http://www.epid.gov.lk/web/images/pdf/wer/2015/vol_42_no_24-english.pdf). The causative agent of CL in Sri Lanka is *L. donovani*, of type MON-37 (Karunaweera *et al.*, 2003), which is indeed a cause for concern, and is transmitted by *Phlebotomus argentipes*, the same vector found elsewhere in the south Asian region (Gajapathy *et al.*, 2013). *L. donovani* is an established agent of human VL in other south Asian countries, though dermotropism, as abundantly seen in Sri Lanka, has only been occasionally observed elsewhere (Elamin *et al.*, 2008; Kumar *et al.*, 2015). This has led to investigations on the role for both the parasite (Siriwardana *et al.*, 2007; Zhang *et al.*, 2014) and host genetics in determining the disease phenotype (Samaranayake *et al.*, 2010). However, the debate continues and the theories on CL-inducing *L.donovani* being 'essentially' dermotropic still remain inconclusive.

ELIMINATION OF LEISHMANIASIS FROM THE INDIAN SUBCONTINENT

A memorandum of understanding was signed in May 2005 during the World Health Assembly between the World Health Organization and the government representatives of India, Nepal and Bangladesh that committed themselves to work in mutual cooperation to achieve elimination of visceral leishmaniasis from these countries by 2015 (World Health

Organization., 2005). The objective of the VL elimination initiative as laid down at the outset was to reduce the annual incidence of VL below 1 per 10,000 population at district, subdistrict or *upazilla* level in India, Nepal and Bangladesh respectively (Picado *et al.*, 2012). The strategies adopted were based on case detection and management together with vector control. Though there was substantial progress in selected areas with conspicuous reduction of the VL burden in the region, certain gaps acted as road blocks and prevented the expected progress towards achievement of targeted outcome. Such deficiencies included the low coverage of health services at community level, parasite resistance to antimonial compounds, limited availability and high cost of alternative therapeutic agents and the lack of effectiveness of vector control measures (Bhandari *et al.*, 2011; Chowdhury *et al.*, 2014; Muniaraj, 2014). The VL elimination framework was subsequently updated (World Health Organization., 2012a). In the new framework there were 5 key strategies described viz. early diagnosis and complete case management, effective disease and vector surveillance, social mobilization and building partnerships, and clinical and operational research, to achieve the elimination goal. A more recent initiative led the WHO to define a road map for prevention, control, elimination, and eradication of 17 NTDs, including VL, as a step toward achieving the Sustainable Development Goals (World Health Organization., 2012b). These efforts included the extension of support to enable better access to drugs and related interventions, and monitor progress towards VL elimination by 2020 with all stake holder involvement (Hirve *et al.*, 2017).

There are obvious advantages of moving towards elimination of leishmaniasis from the South Asian region. However, the deficiencies would need to be carefully addressed in order to ensure a more successful outcome at least by year 2020. In addition to the obvious factors that may have contributed to the sustained parasite transmission (Hirve *et al.*, 2017), the presence of phenotypic/genotypic variants of *L.donovani* in the region with the potential to act as reservoirs of infection has obvious implications on the ongoing plans for elimination of VL from the South-Asian region; a factor that has been largely overlooked thus far.

Though vector control is an essential component in the overall strategy towards disease elimination there have been obvious lack of innovations in that field going back to many decades (Picado *et al.*, 2012). On the other hand there have been some notable progress in the fields of diagnostic, therapeutic, and vaccine development (Singh and Sundar, 2015; Srivastava *et al.*, 2016; Sundar and Singh, 2016), but many hurdles persist (Singh *et al.*, 2016b). For regional elimination of *L. donovani*-induced leishmaniasis to become a reality, effective deployment of existing and new tools will be essential. A strong political as well as active community participation would be imperative and so would inter country cooperation and partnerships. Furthermore, appropriate diagnostic and treatment services as well as effective epidemiological surveillance also would need to be ensured in order to achieve a more successful outcome of the renewed efforts in the regional drive towards elimination of *L. donovani(*induced leishmaniasis.

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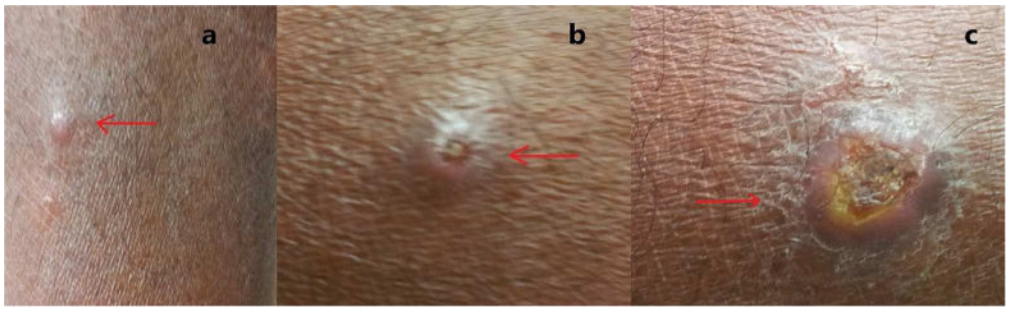

Fig. 1.
Skin lesions observed in cutaneous leishmaniasis patients. **a**, papule; **b**, Scaling nodule; **c**, Ulcer.

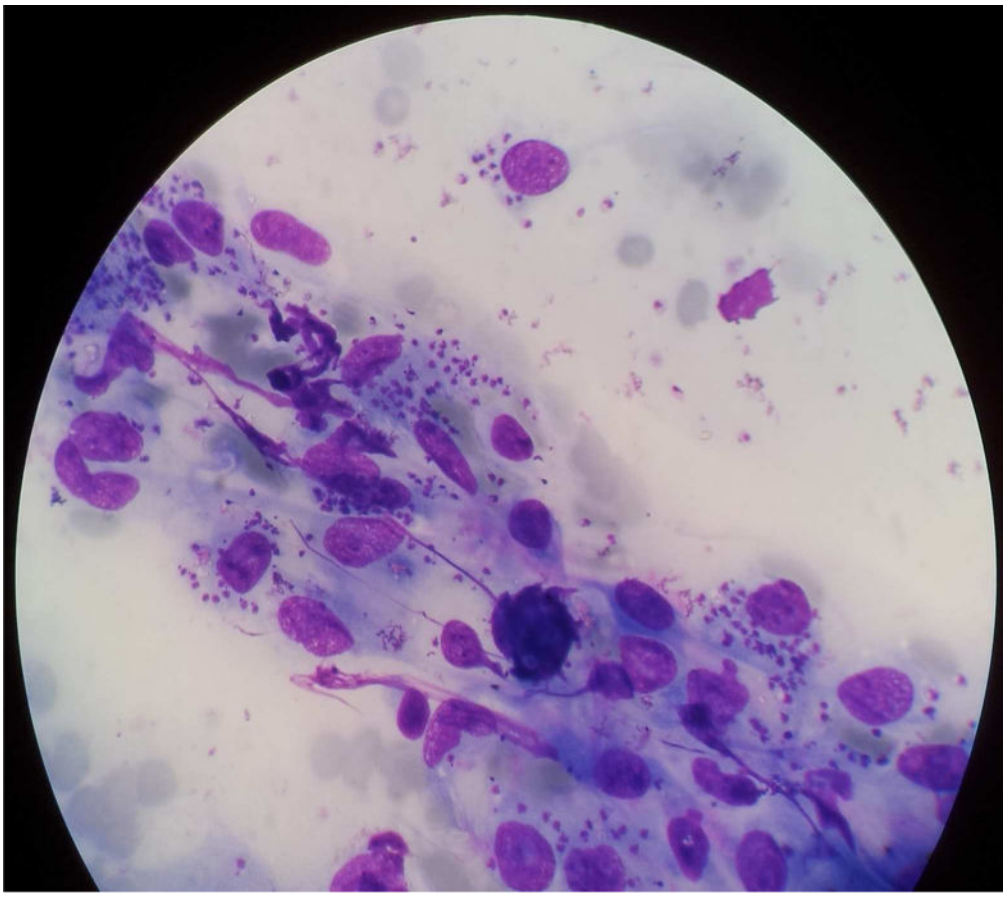

Fig 2.
Microscopic appearance of a Giemsa-stained smear made from tissue aspirates from a skin lesion of a cutaneous leishmaniasis patient (under oil immersion (×1000 magnification).