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Review Article: Impact of *Leishmania* spp. on Public Health

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Abstract
The genus of *Leishmania*, intracellular protozoan parasite, *Leishmania* that belongs to the Trypanosomatida Order under Kinetoplastea Class of Euglenozoa Phylum, includes a large number of species that infect a wide variety of vertebrates and invertebrates, such as rodents and humans resulting in variable clinical manifestations. Taxonomy of the parasite is not fully elucidated, and debate continues not only over the number of species in the subgenus, but also over the definition of species. Leishmaniasis, caused by several different strains of *Leishmania*, remains a major public health problem globally. The disease is transmitted by mosquitoes and is endemic in mainly arthropod-carrying tropical areas. Due to fast changes in global climate, mosquitoes are expected to expand widely to become more susceptible to disease. There are four main types of disease including cutaneous leishmaniasis (CL), diffuse cutaneous (DCL), mucocutaneous leishmaniasis (MCL) and visceral leishmaniasis (VL) which varies in their characteristics. However, sequalae of the disease based upon the species of parasite and an immune response. With few treatments available, antimonials compounds remain very important in the therapeutic strategies which used most commonly in different areas. However, drug resistance has recently emerged including resistance to the oral therapy for the most recent drug used against VL. This alarming has led to use of non-toxic drugs to treatment of disease and to prescription-related complications. The prospect of widespread drug resistance therefore indicates an urgent need to develop effective new treatments for leishmaniasis. In conclusion, there is a necessary for limiting the complications and preventing death. Additionally, vector control can be implemented wherever possible.
Keywords: Cutaneous leishmaniasis, Diffuse-cutaneous leishmaniasis, Mucocutaneous leishmaniasis, Visceral leishmaniasis, Immunotherapy, Iraq

1.1. Introduction

Leishmaniasis is a disease that caused by several different strains of the intracellular protozoan parasite, *Leishmania* that belongs to the Trypanosomatida Order under Kinetoplastea Class of Euglenozoa Phylum. This parasite remains a major public health problem globally in four ecoepidemiological regions (Ruiz-Postigo et al., 2021). The disease is transmitted by mosquitoes and is endemic in mainly arthropod-carrying tropical areas. As global climate change continues, mosquitoes are expected to expand in range to become more susceptible to disease (Amro et al., 2022). The parasite is spread by sand-flies that carry flagellated promastigotes, and during feeding, the mosquito injects promastigotes into the skin to be engulfed rapidly by the phagocytic cells. Although, infected cells include neutrophils, macrophages and monocytes, but these organisms reside primarily in macrophages and manifest as infectious amastigotes (Teixeira et al., 2013). Surprisingly, unlike other intracellular parasites such as *Toxoplasma gondii* and *Trypanosoma cruzi*, *Leishmania* has evolved the ability to survive, multiply in phagolysosomes, and survive in an environment capable of killing many bacteria (Kolářová and Valigurová, 2021). After several rounds of replication, amastigotes infect infected cells and invade other nearby macrophages. When taken up by the sand-flies, the protozoan divides into promastigotes and the infectious cycle (Van Assche et al., 2011). Due to the geographical distribution of different species, *Leishmania* protozoa causes mainly three types of disease are cutaneous (KL) and mucocutaneous (MCL) and visceral (VL) leishmaniasis which occurs as a result of infection of macrophages throughout the skin, nasopharyngeal mucosa, or endothelial reticular system, respectively, and the sequalae of disease is based upon the species of parasite and the immune response (Van Griensven et al., 2014).

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Although, there are many types of *Leishmania* such as *L. amazonensis*, *L. brazil*, *L. ethiopica*, *L. guayanensis*, *L. major*, *L. mexicana*, *L. panamensis*, *L. peruviana*, and *L. tropica*; few treatments available, antimonials compounds remain very important in the therapeutic strategies used in the most commonly used areas (Mohammadiha et al., 2018). Despite resistance in some *Leishmania* species, initial treatment of leishmaniasis lasted approximately 70 years (Mohabali et al., 2019). Unfortunately, there has been no vaccine for leishmaniasis for many years and disease control relies primarily on chemotherapy (Olías-Molero et al., 2021). The first line of treatment is a pentavalent meglumine antimonate (glucanthyme) indicated for the treatment of leishmaniasis. The current second line of treatment is sodium stibogluconate. Pentostam is a short course of amphotericin B containing pentamidine isothionate and miltefosine and is used when first-line drugs do not respond adequately (Seifert et al., 2011). Use of these substances is injectable and can be very dangerous. Furthermore, drug resistance has recently emerged in *Leishmania*, including resistance to the oral alkylphospholipid miltefosine, the most recent drug used against VL (Olivier and Zamboni, 2020). This alarming trend has led to the use of non-toxic drugs to treat the disease and/or subject to prescription-related complications. The prospect of widespread drug resistance therefore indicates an urgent need to develop effective new treatments for leishmaniasis (Carvalho et al., 2019). Hence, the current study was aimed to focus on the worldwide distribution of leishmaniasis.

1.2. Taxonomic classification

The genus of *Leishmania* includes a large number of species demonstrating that this parasite can utilize a wide variety of vertebrates and invertebrates, such as rodents and humans, as an intermediate host and to cause a wide range of clinical manifestations (Akhoundi et al., 2016). Taxonomy is not fully elucidated, and debate continues not only over the number of species in the subgenus, but also over the definition of species (Cecílio et al., 2022). Recent molecular data and phylogenetic analyzes support the simplification of Leishmania taxonomy to multiple species (Maurício, 2018).

1.3. Life Cycle

Leishmania lives as an intracellular parasite (amastigote) in macrophages of mammals and other vertebrates, and as an extracellular parasite (promastigote) in the gut of insect vectors (De Muylder et al., 2011; Kelly et al., 2017). The insect absorbs the blood of its vertebrate host and regurgitates the promastigotes upon skin infection. Parasites are recognized and phagocytosed by surface receptors on macrophages and dendritic cells. Interestingly, the parasite has a hard time infecting (and surviving) neutrophil-deficient animal. This result strongly suggests the relevance of a macrophage invasion mechanism that uses polymorphonuclear leukocytes as the first phagocytic cells encountered within the host. The parasite induces programmed cell death in infected neutrophils and is recruited by macrophages (Liu and Uzonna, 2012; von Stebut and Tenzer, 2018; Kupani et al., 2021). Within host cell, the parasite moves into phagolysosomes, divides into amastigotes, and multiplies by binary fission (Shirbazou and Jafari, 2012). Ablation of macrophages releases infected amastigotes, and released parasites are engulfed by simple macrophages, dramatically increasing the number of infected cells and spreading the disease throughout the host (Dar et al., 2018). Feeding on blood-sucking insects of infected individuals, the amastigotes develop into promastigotes in the digestive tract of the vector insect, where they survive for 4-7 days, differentiate into infected parasites, migrate to heart valves, and promastigote. When the mosquito re-pierces the host's skin, the bacteria enter the bloodstream and complete the cycle (Telleria et al., 2012; Teixeira et al., 2013; Inbar et al., 2017).

1.4. Vector

Mosquitoes are part of the family *Psychodidae*, a subfamily of *Phlebotomina* (Akhoundi et al., 2016). The four stages are the adult aerial stage and the stage of development from the egg, the larvae and pupae found in moist soils rich in organic matter (Solano-Gallego et al., 2017). Adults are small flying insects, about 2 to 4 mm long, with yellow hairs on their bodies (Claborn, 2010). They hide in the dark during the day and act in the dark and at night. Both sexes eat plants, but females also need blood before ovulation of reptiles, amphibians, birds, and mammals that act as the main hosts (Klein and Flanagan, 2016). Feeding habits depend on the mosquito species and host conditions, and the main factor in the transmission of leishmaniasis is the blood meal that mosquitoes ingest (Pruzinova et al., 2015). About 800 species have been described and classified into five widely accepted genera. Of these, approximately 70 species in the genera Phlebotomy and *Lutzomyia* are known or suspected hosts of *Leishmania*, with some specificity between *Leishmania* species and mosquitoes. Severe infections are mainly caused by his *Phlebotomus papatasi*. The

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housefly *Phlebotomus sergenti* is the primary vector for *L. tropica* in Middle East (Dostálová and Volf, 2012; Lahouiti et al., 2013; Khan and Awan, 2021).

1.5. Origin

Most species of *Leishmania* are animals, with various mammalian reservoirs involved in the long-term maintenance of *Leishmania* in nature (Alemayehu and Alemayehu, 2017). Depending on host, reservoirs can be wild or domesticated mammals, possibly humans. Most leishmaniasis reservoirs are well-adapted and develop mild disease that can last for years, with the exception of dogs, which often develop chronic fatal disease. These instruments are available in 7 different styles for mammals (Alemayehu and Alemayehu, 2017; Abbate et al., 2019). Mice, hyraxes, marsupials, and carnivores are common enemies of cutaneous leishmaniasis in humans and wild animals. Humans have reservoirs of *L. donovani* and *L. tropics*. The locality of *Rhombomys opimus* is a major reservoir of important in the arid regions (Medkour et al., 2019; Pareyn et al., 2020).

1.6. Types of disease

Leishmaniasis causes significant morbidity and mortality (Al-Kamel, 2017). A common term for several diseases with different clinical manifestations, leishmaniasis is divided into four main types by him based on clinical manifestations. The fatal form that may leave without treatment is visceral leishmaniasis (VL). There are many other forms of CL and MCL which cause significant morbidity in endemic settings (Banerjee et al., 2016; Sunter and Gull, 2017).

1.6.1. CL

This is the most common form of disease, which manifested by a simple skin lesion appears at site of mosquito biting and heals within a few months, leaving a scar (Remadi et al., 2016). Incubation could be lasted to several weeks, and gradually enlarges and becomes red. Wound healing involves migration of leukocytes that divide the affected area, resulting in necrosis of the affected tissue and healing of granulomas. Bark lesions are the most common clinical manifestation of *L. majoris* infection, occurring mainly on the extremities (Iqbal, 2012; Aoun et al., 2014). Wounds become dangerously infected, multiple ulcers and moist mucus are common, and healing is slow. Self-healing occurs within 2 to 8 months in more than half of patients (Keogan, 2018). It can also appear as large dry, scaly, or ulcerated form often appears on the face and other exposed areas of *L. tropica* patients (Abdellatif et al., 2013; Rostamian and Niknam, 2019).

1.6.2. DCL

It is chronic, persistent and polyparasitic species occurs with certain forms of leishmaniasis and leprosy-like non-ulcerative skin lesions. The main pathogens are *L. aethiopca* and *L. mexicanana* species complex (Tabah, 2018; Guma, 2018; Malli et al., 2019).

1.6.3. MCL

This type causes horrific ulcers, facial cuts, and severe destruction of the nasal, oropharyngeal, and pharyngeal cavities with chronic pain. MCL has been reported occasionally in Sudan (Babiker et al., 2014; Carvalho et al., 2019). MCL usually exists as an unmanned disease whose life cycle transitions from rodent to rodent and mammalian and is spread by the forest floor mosquito, *Lutzumia* spp. (Silva-Almeida et al., 2012; Borghi et al., 2017).

1.6 4. VL

It is highly dangerous and destructive, which also named as kalaazar, black disease, black fever, buldwan fever, dum dum fever, and sarkari disease (Pradhan et al., 2022). The organism is responsible for many clinical manifestations that can progress from asymptomatic infections to the fatal form of VL in severe cases (Chakravarty et al., 2019; Lewis et al., 2020; Mann et al., 2021).

1.7. Diagnosis

Diagnosis of CL is based on clinical features, epidemiological data, and laboratory tests. Traditionally, diagnostic tests for CL are classified as direct tests, including microscopic parasitological examination, histology and parasite culture (visual observation of *Leishmania* parasites), or indirect tests, including serology and molecular diagnostics. It's been done. The choice of which diagnostic test is used depends on diagnostic center infrastructure and capacity rather than diagnostic accuracy (de Vries et al., 2015; Handler et al., 2015; Reimão et al., 2020). Accurate identification of Giemsa-stained lesion scrape astigmatism by sampling, scraping, or imaging is frequently used to confirm the diagnosis in routine cases and in human

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participants of clinical trials (Pourmohammadi et al., 2010). Parasite culture is a laborious and time-consuming procedure typically performed in reference centers and laboratories (Rasti et al., 2016). Several serological tests have been tested, but only a few are commercially available and used, possibly due to low sensitivity, poor testicular response to infection, or difficulty in obtaining a positive test. Serological testing is primarily based on enzyme-linked immunosorbent assay (ELISA), Western blot, lateral flow assay, or direct correlation (Lévêque et al., 2020; Piyasiri et al., 2022). Molecular diagnostic assays appear to have better sensitivity and specificity than traditional diagnostic methods, requiring less sampling for diagnosis. Molecular assays also allow identification of *Leishmania* species that infect patients. This is important change that contains useful data for evaluating clinical trials and selecting the best treatment for infected patients. PCR has been extensively evaluated as a single assay, in a nested format, or as a quantitative assay, using basic principles and sources of clinical material (Saldarriaga et al., 2016; Sundar and Singh, 2018; Schallig et al., 2019). Clinical manifestations, especially regeneration of ulcerative lesions or flattening of un-respectable wounds, are used as parameters to determine the clinical treatment of CL (Kassiri et al., 2014). Because the presence of parasites in healing wounds, association with clinical recurrence is unclear, most clinical trials measure treatment outcomes based solely on clinical observations (Simon et al., 2011).

1.8. Treatment

1.8.1. Pentavalent antimony (Sbv)

In India, sodium stibogluconate (Pentostam®, GlaxoSmithKline and generics) and meglumine antimonate (AM) (Glucanthyme™, Sanofi), commonly known as SSG, have been used in LC since their discovery by Albert David in the 1940s has been used as a first-line treatment for came out (Moore and Lockwood, 2010; Patino et al., 2019). The mechanism the drug by which act is not fully understood; however when used, Sbv (SbIII) is an active secondary metabolite, which inhibits DNA topoisomerases and causes depletion of intracellular ATP, possibly by inhibiting glycolysis and β-fatty acid oxidation in amastigotes (Keshav et al., 2021). This inhibits amastigote macromolecular biosynthesis (Fatima et al., 2016). Pentavalent antihistamines are prescribed for local or systemic treatments. In patients with more complicated CL, anticonvulsants can be administered systemically (Cuestas et al., 2018).

1.8.2. Amphotericin B

The polyene antibiotic amphothecin B (AmB) is commonly prescribed for VL and CL treatment (Solomon et al., 2011; Brotherton et al., 2014). Common formulations of drug cause severe nephrotoxicity that lowers lipid levels (Sundar et al., 2015). It acts through modulating of parasite membrane permeability by activating trans-membrane channels, causing a decrease in parasite ionic levels and leading to parasite death (Shirzadi, 2019).

1.8.3. Miltefosine

Miltefosine is a systemic drug for VL and CL cure, which exhibits highly time-dependent effects in pharmacokinetic and pharmacodynamic studies significant activity against various *Leishmania* species (Dorlo et al., 2012). This activity against *Leishmania* is associated with impaired alkylphospholipid metabolism and glycolipid and glycoprotein biosynthesis in the parasite's outer membrane (Rios-Marco et al., 2017). Another postulated mechanism is cell-mediated activation of macrophages to undergo apoptosis *via* the phosphoinositide-3-kinase pathway (Crauwels et al., 2015; Palić et al., 2019). The drug might be a teratogenic and should be avoided in women of childbearing (Vakil et al., 2015).

1.8.4. Paromomycin Sulphate

It is aminoglycoside antibiotic acting through binding to small subunit of ribosome, causing misfolding and inhibition of bacterial protein synthesis. It was found to have antipsychotic properties in the 1960s (de Morais-Teixeira et al., 2014; Santos et al., 2020). Another study suggested that it may cause mistranslations, thereby compromising the accuracy of *Leishmania* protein synthesis (Kattoof, 2018). Elevated levels of RNA misread result in a host growth arrest properties of parasites (Oliveira et al., 2021).

1.8.5. Topical treatment

Evaluation of local therapy is also very difficult because the dose is difficult to measure during administration. Topical therapy is of high activity but the skin barrier can be a problem. Local injection of drugs is most reliable treatment for CL and several studies have compared treatment with injection in experimentally treatments (Solomon et al., 2014; Azim et al., 2021). A meta-analysis conducted and the placebo-control trials of topical treatment were therapeutically effective in new and old CL and increased

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local reactions (Cota et al., 2016). Many topical agents are compound preparations used for systemic therapy and are prescribed as cream or ointment with high antiparasitic activity and lack of systemic toxicity when applied to CL lesions (Carneiro et al., 2012; Escrivani et al., 2020; Jamshaid et al., 2021).

1.8.6. Physiotherapy

Cryotherapy and heat therapy have commonly methods of physical therapy which applied based on extreme temperatures to kill a parasite without causing significant damage to the host and the body can repair damage to healthy skin. Cryotherapy consists of applying liquid nitrogen-filled potatoes for 10-25 seconds (Jowkar et al., 2012; Shaddel et al., 2018). There are different uses of this method including the application of Cryotherapy alone, cryotherapy plus intralesional meglumine antimonate (MA), and intralesional MA alone (Ullah et al., 2022). Complete cure in these methods as reported by different studies was ranged 52-67% for cryotherapy alone, 80-89% for cryotherapy and intralesional MA, and 52-75% for intralesional MA alone (Brito et al., 2017; Ullah et al., 2022).

1.8.7. Immunotherapy

Unlike chemotherapy, this type of treatment can stimulate immune response for destroying of parasite through production of nitric oxide (NO) in macrophages, improving infection-fighting (Ikeogu et al., 2020; Akbari et al., 2021). Host protective effects were also associated with reduced ear parasite burden and lymph node recruitment. Topical administration of immune-therapy can reduce disease severity, and protected against both resistant and susceptible hosts (Adhikari et al., 2012; Montakhab-Yeganeh et al., 2017).

1.9. Control strategy

Effective treatment depends on earlier detection and treatment. This necessary is for limiting the complications and preventing death (Mahmoud, 2014). Patient care is an effective means of managing the storage and transportation of human sites. Additionally, vector control can be implemented wherever possible. Household pesticide residue application was significant step with restriction used today (Romero and Boelaert, 2010; Werneck, 2014; Dantas-Torres et al., 2019).

Conclusion

Although, *Leishmania* is one of the most prevalent parasitic pathogen in the world, many aspects are still unknown and need to be clarified. However, the development the methods of control and prevention are of great importance to avoid the diseases and its complications.

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