Leishmaniasis

By Brentye McAtee

Etiologic Agent

Leishmaniasis is a disease caused by single-celled protozoa from the family Trypanosomatidae, and the genus *Leishmania*. At least twenty-one species are known to cause the disease in humans. Some species are more commonly found in Central and South America, for example *L. peruviana*, *L. mexicana*, and *L. braziliensis*. Others are more often associated with the Middle-east and Asia, including *L. aethiopica* and *L. tropica*. *L. donovani* is found in both regions.

This obligatory parasite exists in two prominent developmental stages:

- **Amastigote**: This form is present within vesicles in phagocytic cells of vertebrates, including humans. They are identified as being spherical and non-flagellated. They are very small in size, about 2-4 micrometers in diameter.
- **Promastigote**: This stage survives extracellularly, and generally attaches to the midgut of the sand fly, its most common vector. These elongated cells are flagellated, and larger, approximately 5-15 micrometers in length.

The Life Cycle of *Leishmania*:

1. The sand fly consumes blood, along with cells that contain amastigotes, from an infected host.
2. Amastigotes transform into promastigotes within the midgut of the sand fly. Here the parasite multiplies.
3. When the sand fly takes its next blood meal from a human or other vertebrate, promastigotes are released into the bloodstream of its host.
4. Macrophages phagocytose the promastigotes.
5. The promastigotes change into amastigotes, and then multiply within cells.
6. The cycle continues when a sand fly bites the infected individual, taking up some of the amastigotes during the process (1).

Transmission

The biological vector is an insect from the family Phlebotominae, and is more commonly referred to as a sand fly. Two notable genera exist: *Lutzomyia*, which exists in Central and South America, and *Phlebotomus* which dominates the Middle-east and Asia (5). There are at least thirty species known to spread the disease (1).

The sand fly uses its serrated mouth part to saw into the superficial layers of the skin of its mammalian host. This creates a pool of blood from which the fly feeds. If the sand fly feeds on an infected host, it may uptake *Leishmania*-infected cells that exist within the superficial layers. The parasitic protozoa then travel to the gut of the sand fly. They are transferred to another vertebrate when the sand fly takes its next blood meal (3).

Although less common, infection with *Leishmania* can also occur via blood transfusion, through sharing of needles, and congenitally during childbirth (1).

Reservoirs
*Leishmania* exists in a variety of vertebrate reservoirs which vary depending on the species of parasite and geographical location. The most common reservoirs are humans, dogs, and rodents (5). In Asia and Africa, humans are the primary reservoir for visceral Leishmania, and in the Middle East and Brazil, dogs are more commonly seen as a reservoir (8).

**History of the Disease**

There is evidence of leishmaniasis in early Middle-eastern texts dating back many hundreds of years. Beginning in the 10th century physicians referred to it as Balkh sore. Cutaneous forms of the disease, which cause skin lesions, provoked the term “white leprosy”. The term kala-azar, Sanskrit for “black fever”, was used to describe visceral forms of the disease.

By the 19th century, the protozoan was isolated and studied microscopically. Around the same time, both Dr. William Leishman, a Scottish army physician working in India, and researcher Charles Donovan, linked these protozoa to visceral leishmaniasis. The amastigotes present in vertebrates became known as Leishman-Donovan bodies, and *L. dovanii* was named as the disease causing agent for visceral leishmaniasis.

Further experimental research occurred during the 20th century. For example, *Leishmania*-infected insects were introduced into dogs, giving evidence that it is a zoonotic pathogen in which sand flies serve as a vector. (6)

**Signs and Symptoms**

The signs and symptoms of the disease vary depending on the species of *Leishmania* that causes the infection, and consequently the geographical location. There are three main types Leishmaniasis.

Cutaneous leishmaniasis: This is the most common form of leishmaniasis. Within weeks of a sand fly bite, a small papule on the skin may progress to a larger ulcerated skin lesion.

Mucocutaneous leishmaniasis: This form of the disease generally occurs when the original cutaneous infection is not completely treated. The parasite may spread to mucous membranes, including the nose, mouth and throat. Lesions can cause severe deformity and destruction to the mucosal regions.

Visceral leishmaniasis: This is the most serious form of the disease, as it is lethal without treatment. Within months of a sand fly bite, and transmission of *L. dovanii*, the illness will progressively set in. In this case the internal organs are affected. Signs and symptoms include: low red and white blood cell counts, fever, enlargement of the spleen and liver, and weight loss. (2)

**Diagnosis**

If cutaneous leishmaniasis is suspected, the physician might take a biopsy from an ulcer. The amastigotes can then be viewed microscopically (1). A second method, the Montenegro test, involves injecting killed *Leishmania* into the skin. The antigens result in an immune response, and a visible nodule appears if the person was or is currently infected (7).

If visceral leishmaniasis is suspected, a bone marrow sample might be taken and viewed under a microscope. The Leishman stain is often used in order to identify the parasites within macrophages. In some cases, a physician may utilize serological tests. An agglutination test might be used, in which a blood sample would be taken in order to identify if antibodies to the parasite are present. Tests for antibodies would need to be used in conjunction with other diagnostic procedures since they would not be able to distinguish the species of
parasite, nor can they distinguish between current or past infection. Another option is to use biochemical technology, like the polymerase chain reaction. The DNA of the parasite will be amplified if present within human tissues (5).

Virulence Mechanisms

*Leishmania* has developed numerous mechanisms for circumventing and delaying the immune response of its host. Upon initial infection of *Leishmania* in its human host, it is phagocytozed by macrophages. There the parasite utilizes mechanisms for inhibiting lysosomal enzymes, therefore possessing the ability to evade degradation. Furthermore, the parasite has a variety of methods for modulating the host’s cells. For example, it can alter the normally protective role of IgG, causing it to produce cytokines that suppress the immune response. Some species also have the ability to interfere with antigen presentation of macrophages, or inhibit the production of specific interleukins involved in the cell-mediated destruction of the parasite (7).

Treatment

Some forms of the disease may require little intervention or treatment. For example, the lesions present in cutaneous leishmaniasis will often heal on their own over a long period of time, though they often leave severe scars. Antimonial or miltefosine chemical compounds may be used to combat the parasite.

Visceral leishmaniasis is fatal if left untreated, and chemotherapy is the most commonly used form of control. Antimonial compounds induce changes in parasite cell membranes, though it is a toxin known to have adverse side effects. Additional potential barriers exist, for example *L. doyani* is becoming increasingly resistant to drugs in parts of the world where humans serve as the primary reservoirs. Also, the comorbidity of HIV and visceral leishmaniasis is increasingly common, and complicates the diagnosis and treatment process. In general, there are many different species of *Leishmania*, each with varying pathogenic mechanisms, clinical manifestations, and possible comorbidities. A combination of drugs must be used to cater to each individual (1).

While a number of anti-parasitic drugs exist, access to adequate treatment still remains a problem in some parts of the world. Countries in which leishmaniasis is endemic tend to be less developed, and therefore serves as a less profitable market. Suitable drugs may prove to be unaffordable for those that require medical care (9).

Prevention

Currently, a highly effective vaccine does not exist, though recovery from the disease renders an individual resistant to future infection so the creation of a vaccine is promising. Using attenuated parasites, protein subunits, or genetically engineered DNA segments to vaccinate individuals against cutaneous leishmaniasis are viable options that are currently being tested (10).

Control of sand flies is one approach to prevention. Sand flies are very small, about 1/3 the size of mosquitoes, so unfortunately they can slip through most mosquito nets, and an individual may be bitten without notice. It is recommended to apply insect repellent and keep skin covered while outdoors, especially during dusk and dawn when sand flies most actively feed (1). In addition, reducing sand fly bites, and therefore infection, of reservoir animals is a plausible preventative method in some locations. (10).

Current Outbreaks
A lack of surveillance mechanisms in rural and developing areas makes it difficult to know the exact incidence of leishmaniasis worldwide. It is estimated that approximately 1 million new cases of cutaneous leishmaniasis and as many as 400,000 cases of visceral leishmaniasis occur each year. The disease is considered to be endemic in 88 countries throughout the world, all located in tropical or temperate regions where the sand fly lives. In the Western Hemisphere both visceral and cutaneous leishmaniasis is endemic throughout Central and South America, and in the Eastern Hemisphere most cases occur in the Middle East, Africa and India. Overall, 20,000 to 40,000 deaths are attributed to leishmaniasis per year (1).

The occurrence of leishmaniasis is rare within the United States, and when it does occur in humans, it is generally a result of travel to an area in which the parasite is more common. There is evidence to suggest that leishmaniasis is an endemic disease within the southern regions of the United States, including Texas. Here the most common reservoirs are rodents, dogs, and cats. In 2008, 9 cases of cutaneous leishmaniasis were reported in North Texas. It is suspected that wood rats were the initial reservoir, and sand flies served as the vector (11).

There are many reasons that leishmaniasis outbreaks might occur, one being large migratory shifts of a population. In some cases, civil unrest or overpopulation forces people to flee to refugee camps or outlying settlements, where they are more likely to expose themselves to infected sand flies. To complicate matters, these individuals risk malnutrition or unsanitary conditions that affect the immune system, therefore making them more susceptible to parasitic infection. These were contributing factors in leishmaniasis outbreaks that have occurred in many areas, for example Sudan in 1984, Brazil in 1999, Afghanistan in 2002, and Chad in 2007 (2).

References


