Review Article

Chronology of cutaneous leishmaniasis: An overview of the history of the disease

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Abstract

Leishmaniasis is a zoonotic infection caused by the protozoa belonging to the genus *Leishmania*. It is named after Leishman, who first described it in London. The discovery of parasites in lesions of cutaneous or visceral leishmaniasis was reported in the late 1800s and early 1900s. By the mid 1900s, the transmission and life cycle of the *Leishmania* organism had been confirmed scientifically. Since that time, many clinical syndromes and numerous (at least 20) morphologically similar species and subspecies of the protozoan have been discovered. This article is an attempt to describe chronicals of the disease; broadly dividing into three periods, i.e., ancient times, discoveries of nineteenth and twentieth centuries and current research.

Key words
Cutaneous leishmaniasis, visceral leishmaniasis, *Leishmania donovani*, *L. tropica*.

Disease in ancient times

Old World cutaneous leishmaniasis, known as oriental sore, is an ancient disease and can be traced back many hundreds of years. There exist records of what seems to be cutaneous leishmaniasis at least as far back as 650 BC, and possibly much earlier in the Tigris/Euphrates basin. There are detailed descriptions of oriental sore by Arab physicians including Avicenna in the 10th century, who described what was (and is) called Balkh sore from northern Afghanistan, and there are later records from various places in the Middle East including Baghdad and Jericho; many of the conditions were given local names by which they are still known. Texts from the 15th and 16th centuries, and then during the Spanish colonization, mention the risk run by seasonal agricultural workers who returned from the Andes with skin ulcers which, in those times were attributed to "valley sickness" or "Andean sickness". Later, the cases of disfigurements of the nose and mouth were known as "white leprosy" because of their strong resemblance to the lesions caused by leprosy. In the Old World, Indian physicians applied the Sanskrit term kala azar (meaning "black fever") to an ancient disease later defined as visceral leishmaniasis. One of the first and most important clinical descriptions of cutaneous disease was made in 1756 by Alexander Russell following an examination of a Turkish patient. The disease, then commonly known as "Aleppo boil", was described in terms which are quite relevant: "After it is cicatrized, it leaves an ugly scar, which remains through life, and for many months has a livid colour. When they are not irritated, they seldom give much pain." So the disease was well-known by the people in Aleppo and Baghdad by the 18th century AD but they didn’t have any idea about the cause.1-4

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Discoveries of 19th & 20th centuries (parasite)

In Old World
The leishmanial parasite owes its discovery to military men. It was first described in 1885 by sergeant major Cunningham of the Indian medical service in Calcutta from a tissue taken from a sore called the Delhi boil. He found nucleoid bodies of equal size clustered in mass. He thought they were spores and thus postulated that the Delhi boil had a fungal origin. In 1898, a Russian military sergeant D.F. Borovsky reported from the Tashkent military hospital that bacterial agents described in Start sores were artifactual and the actual causative organism was a protozoan and described the anatomy of the organism and pointed out the kinetoplast. He described in detail these parasites in cases of cutaneous leishmaniasis, but he did not name them. The cause remained unknown, and several eminent clinicians, including Ronald Ross, were convinced that kala azar was a virulent form of malaria. It was not until 1900, when a Scottish army doctor, William Leishman and the Professor of Physiology at Madras University, Charles Donovan (Figure 1) independently discovered the parasite in the spleens of patients with kala azar and attributed to them the etiology of this life-threatening Indian disease, now called visceral leishmaniasis. The link between these organisms and kala azar was further explored by Major Ross, who named them Leishmania donovani. The credit for discovery of the parasites responsible for the Old World cutaneous disease is usually given to an American, James Homer Wright (1903), although there is no doubt that they were actually seen in 1885 by David Cunningham, who did not realize what they were, and in 1898 by a Russian military surgeon, P.F. Borovsky. It is fair to point out that Cunningham’s and Borovsky's discoveries were unknown to Wright and to Leishman and Donovan. Since then, this organism has been found to be a complex grouping of species, at least 20 of which cause infections in humans. Some species cause visceral leishmaniasis, some cause cutaneous disease, and some cause both.

In New World
Cutaneous leishmaniasis is believed to be an autochthonous disease (natural to an area or country, i.e. not imported). In Peru, the pre-Columbian indians sculptered these destructive lesions, especially on the nostrils and upper lips on ceramics with human shapes called huacos, that when analysed with our current knowledge leave no doubt as to its leishmanial nature. In 1908, Escomel indicated the great similarity existing between the physiognomy presented by the huaco and people afflicted with cutaneous leishmaniasis. In Brazil in 1895, Moreira observed the existence of this illness, clinically identifying it with Biskra’s nodule. In Italy in 1895, Breda described the disease in Italians who had returned from Sào Paulo to their homeland. In 1908, in the Santa Casa de Sào Paulo a great number of sick people with leishmaniasis appeared and the disease received various denominations (Bauru ulcer, sharp wound, Northeast wound) without the etiological cause being known. Then, on 30 March 1909, Adolfo Lindenberg announced the discovery of the leishmaniasis parasite. In 1911, Pedroso and Dias da Silva, using the Neal, Nory and Nicolle medium, obtained Leishmania cultures from material from Bauru ulcers. In 1922 successful animal inoculation was done in Brazil. Leishmania brasiliensis was experimentally inoculated in man by Montenegro in 1923 and later by Herrer and Batistini in 1951.
Parasite, vector and host relationship

The idea that cutaneous leishmaniasis was transmitted by man-biting insects of the genus Phlebotomus was suggested for the first time in 1905 by Sergent et al. In 1904, Leishman and Rogers demonstrated the oval amastigotes turn into promastigotes in cultures and its relationship to trypanosomes was seen. In 1908, Nicolle and Sicre related the flagellated forms of the parasites from the cutaneous lesions and those from visceral disease. Nicolle and Compte discovered the role of wild and domestic animals as reservoirs of infection in 1908 when they found visceral leishmaniasis in a Tunisian dog. In 1922 in Brazil, Aragão succeeded in reproducing ulceration in a dog by injecting squashed infected insects. L. brasiliensis was experimentally inoculated in man by Montenegro in 1923 and based upon these studies, he introduced in 1926 the intradermal test, currently still in use for the diagnosis of leishmaniasis. It was in 1942 that Col. Shortt and his colleagues discovered the experimental transmission of leishmaniasis by sandflies in India. Leishmaniasis was classically described by Rey in 1973 as a wild animal zoonosis, especially affecting rodents, transmission of which depends on Phlebotomus spp. living in primitive tropical forests. Now the inter relationship of parasites (L. donovani, L. infantum, L. major and L. tropica in Old World and L. brasiliensis complex and L. mexicana complex in the New World), vectors (different species of sandfly Phlebotomus) and hosts (rodents/animals as definitive and man as incidental host) is well established.

Recent advancements

The diagnosis of cutaneous leishmaniasis is conventionally made by the demonstration of amastigotes of the parasite in slit skin smears, culture preparations or skin biopsy specimens. The parasite demonstration and isolation rates are rather poor from cutaneous and mucocutaneous lesions due to low parasite load and high rate of culture contamination. Genetic heterogeneity and clonal diversity is common among Leishmania strains. Gene knockout, over expression, and re-introduction studies have identified a number of genes that play a role in parasite virulence. Recently several recombinant proteins (rK 39) have been developed to accomplish accurate diagnosis. Studies in experimental animal models have further defined the roles of CD4 and CD8 T cells, IL-4, IL-10, and IL-12 in the control, maintenance, or progression of disease. The effect of Leishmania on dendritic cells and macrophage effector function has also been an important area of investigation. Molecular techniques targeting various genes of the parasite have also been reported, and PCR has been found to be the most common molecular technique successfully used for diagnosis and for differentiation of species. Surprisingly, the importance of the surface lipophosphoglycan in parasite virulence appears to differ among Leishmania spp. A number of new vaccine candidates have been identified through experimental animal studies. Clinical studies of leishmaniasis have focused on the host determinants of disease (most notably HIV co-
infection), serological and DNA-based diagnostic assays, and treatment. Antimony-resistant cases of cutaneous and visceral leishmaniasis have become more common; liposomal amphotericin and oral miltefosine are promising alternative therapies.1-2,21

Conclusion

Almost a century after the discovery of causative agent, many features of leishmaniasis and its major syndromes (i.e. visceral, cutaneous, and mucosal) have remained the same; but significant advances have been made in the areas of pathogenesis, host defense, and treatment of leishmaniasis. A number of new vaccine candidates and potential targets of drug therapy have been identified, but progress from preclinical studies to clinical trials has been slow. The need of hour is to speed up the translational research, built upon the solid foundation of existing and ongoing basic investigation in this field.

References