CHAPTER 39

Leishmaniasis

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The leishmaniases are a group of chronic cutaneous, mucocutaneous, and visceral diseases caused by infection with one of several species of the protozoan parasite *Leishmania*. Members of the genus *Leishmania* are obligate intracellular parasitic protozoa in the family Trypanosomatidae. They exist as elongate, 10-15 μm, flagellated forms called promastigotes in their sand fly vectors. When an infected sand fly bites a mammalian host, it injects the promastigotes into the wound with its saliva. Tissue macrophages phagocytize the organisms, which then transform into round or oval, 2-3 μm nonflagellated forms called amastigotes. The amastigotes undergo successive asexual division until the macrophage ruptures, releasing the amastigotes, which enter other macrophages. When a sand fly bites an infected mammalian host, it ingests amastigote-laden macrophages along with its blood meal. The amastigotes transform into promastigotes and reproduce in the gut of the fly before migrating to the proboscis of the fly to complete the cycle with the next fly bite.

Hematophagous female sand flies in the genus *Phlebotomus* in the Old World and *Lutzomyia* and *Psychodopygus* in the New World transmit the *Leishmania* organisms (**Fig. 39.1**). Several nonhuman mammals serve as reservoirs for leishmaniasis, including domestic and wild canines and various rodents, depending on the geographic distribution and the species of *Leishmania* involved.

Currently, experts recognize over a dozen species, some of which they group into complexes of closely related species (i.e., the New World *L. mexicana* and the *L. viannia* complexes).

CLINICAL MANIFESTATIONS

There are three major clinical manifestations:

- Cutaneous leishmaniasis
- Mucocutaneous leishmaniasis
- Visceral leishmaniasis.

CUTANEOUS LEISHMANIASIS

Based on its geographic distribution, cutaneous leishmaniasis can be divided into Old World (including Southern Europe, the Middle East, parts of Southwest Asia, and Africa) and New World leishmaniasis (from the southern United States through Latin America to the highlands of Argentina). This distribution has clinical relevance, since Old World species cause mostly benign and often self-limiting cutaneous disease, while New World species cause a broad spectrum of manifestations, from benign to severe, including mucosal involvement.

Cutaneous leishmaniasis is a chronic ulcerative, frequently self-healing, skin infection. The worldwide distribution is shown in **Figure 39.2**. Local peoples apply many common names to this disease (see below). Depending on the species involved, the infecting organisms may spread by direct extension or metastasis to involve the mucosa of the upper

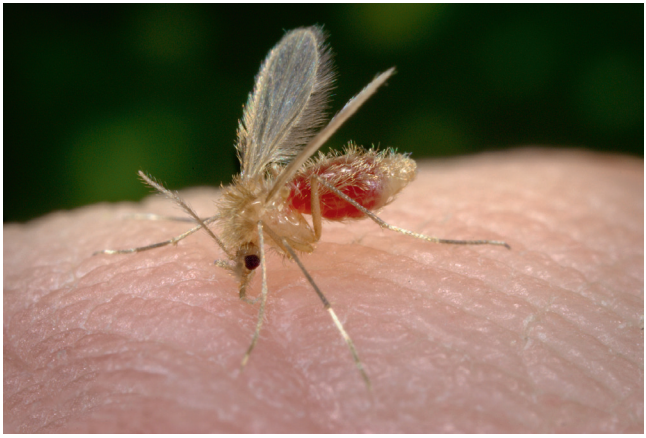

Fig. 39.1 The sand fly vectors of leishmaniasis are very small, only 2-3 mm (1/8 inch) in length. The photograph shows a *Phlebotomus papatasi* sand fly. (From http://phil.cdc.gov/phil/details.asp?pid=10275. Photo by J. Gathany, courtesy of CDC/Frank Collins.)

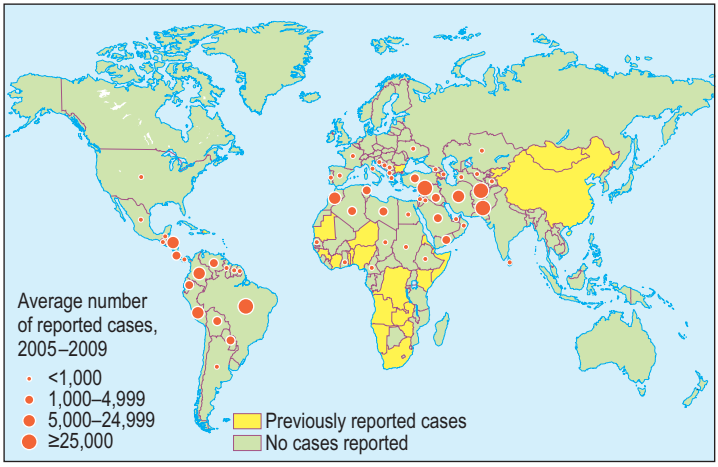

Fig. 39.2 Distribution of cutaneous leishmaniasis (WHO data). (From: World Health Organization, 2010. First WHO Report on Neglected Tropical Diseases: Working to Overcome the Global Impact of Neglected Tropical Diseases. Available at <http://whqlibdoc.who.int/publications/2010/9789241564090_eng.pdf>.)

respiratory tract (mucocutaneous leishmaniasis), resulting in painful disfigurement or even death.

Old World Cutaneous Leishmaniasis (OWCL)

Common names include Oriental sore, Rose of Jericho, Delhi boil, and Aleppo boil.

Etiology and Epidemiology

OWCL is caused by four species: *L. major*, *L. tropica*, *L. aethiopica*, and *L. infantum*.

L. major causes rural, wet, and zoonotic cutaneous leishmaniasis. The animal reservoirs are desert rodents. It is endemic in desert areas of northern Africa, Central Asia, the Sudan, and the Middle East. In certain communities, local prevalence may approach 100% and travelers may be affected.

L. tropica usually causes urban, dry, and more often anthroponotic cutaneous leishmaniasis. Experts now think that in some places (e.g., Afghanistan) humans are the primary host and may serve as a reservoir. In a recent outbreak in Israel, rock hyraxes were found to be the reservoir. Endemic areas include urban areas of the Mediterranean basin, Central Asia, and the Middle East.

L. aethiopica occurs mainly in Ethiopia and Kenya in rural mountain areas. Hyraxes, distant relatives of elephants, serve as the animal reservoir.

L. infantum occurs in the Mediterranean basin, China, Central Asia, and the Middle East. Adults infected with this species tend to develop a mild self-limited cutaneous disease, whereas infants tend to develop visceral disease. Infection can occur person-to-person among intravenous drug users sharing syringes. Animal reservoirs include domesticated and wild canines.

Clinical Features

Following inoculation by the sand fly, characteristic skin lesions generally appear within 6 weeks but may be delayed for prolonged periods depending on the size of the inoculum. The lesion begins as a small, pruritic, erythematous papule that slowly enlarges and breaks down to form a small ulcer or is sometimes a nodular lesion. Lesions may be single or multiple and occur on exposed skin surfaces. Ulcers persist for a variable time (measured in months) and heal slowly with scarring.

L. major often causes multiple lesions with an exudative base (**Fig. 39.3**). The infection runs a more rapid course, and the lesions may heal in 6 months. Spread to regional lymph nodes is rare.

L. tropica usually causes a single, more indolent ulcer that may require over 1 year for spontaneous healing. Internal organ involvement ("viscerotropic" infection) with *L. tropica* has been demonstrated in six US soldiers returning from prolonged deployment in the Middle East during the Gulf War.

L. aethiopica produces an even more indolent ulcer that may persist for several years. Diffuse cutaneous leishmaniasis, an anergic state with extensive skin infiltration by organisms resembling lepromatous leprosy, occurs in approximately 20% of endemic *L. aethiopica* infections.

New World Cutaneous Leishmaniasis (NWCL)

Common names include American cutaneous leishmaniasis, chiclero ulcer, espundia, bush yaws, uta, and picadura de pito.

Etiology and Epidemiology

NWCL is a disease of rural forest and jungle areas of most of Central and South America. Forest workers, agricultural workers, and others in rural, forested areas are primarily at risk. Several species belonging to the *L. viannia* and *L. mexicana* complexes cause NWCL (**Table 39.1**). Species from either complex may be principal causes of leishmaniasis in a given area. Both complexes are pathogenic throughout the range of disease in the New World, with the exceptions of southern Texas and the Dominican Republic, where *L. mexicana* is the

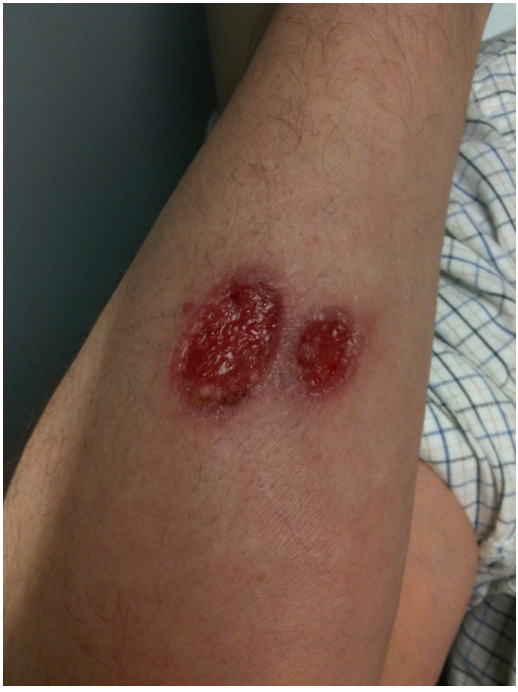

Fig. 39.3 Forearm lesions due to *L. major* in a defense contractor based in Iraq. (Photo by author, Fred Buckner.)

TABLE 39.1 New World Cutaneous Leishmaniasis

Subgenus	Common Species
Viannia	*L. (V.) brasiliensis*
	L. (V.) guyanensis
	L. (V.) panamensis
	L. (V.) peruviana
Mexicana	*L. mexicana*
	L. amazonensis
	L. venezuelensis

sole identified species. Animal reservoirs include foxes, sloths, and forest rodents, depending on the species.

Clinical Features

Cutaneous lesions may resemble those of OWCL with a few distinctive differences. Lesions tend to be larger, up to 7 cm in diameter, with an elevated, indurated border that is mostly ulcerative (**Fig. 39.4**). In addition, subcutaneous nodules with sporotrichoid distribution may be present, as well as regional lymphadenopathy. The cutaneous lesions heal very

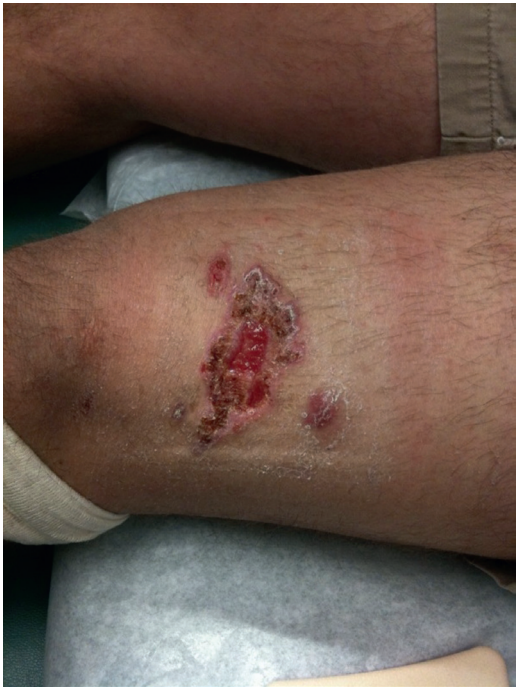

Fig. 39.4 Lesions above the knee in a traveler to Costa Rica with *L. panamensis* infection. Note the satellite lesions. (Photo by author, Fred Buckner.)

slowly, and they may spread to the oropharyngeal mucosa, causing mucocutaneous leishmaniasis.

Chiclero ulcer refers to cutaneous disease found in the Yucatan, Belize, and Guatemala caused primarily by *L. mexicana*. Lesions tend to be solitary and occur most frequently on the ear. Ear ulcers may persist for many years before healing and may result in destruction of the ear. Lesions in other skin areas often heal within 6 months. Mucosal spread is rare with *L. mexicana*.

Mucocutaneous leishmaniasis results primarily from infections caused by *L.* (*Viannia*) *braziliensis*. The cutaneous lesions spread along lymphatics, resembling sporotrichosis, and mucosal disease occurs in 5-10% of cases. Mucosal involvement occurs by metastatic spread of infection from the skin and presents months to years after the initial cutaneous lesions. It typically begins as erythema, edema, and ulceration of the nasal septum, with gradual extension to the palate, pharynx, and larynx. Occasionally, the anus and other mucosal sites may be involved. This destructive, granulomatous process of the soft tissue can involve cartilage but not bone. Perforation of the nasal septum and collapse of the nasal bridge is typical, giving the so-called tapir nose. Mucosal disease is progressive and mutilating and may be fatal. The severe form of mucosal disease is called *espundia*.

Diffuse cutaneous leishmaniasis occasionally occurs and is similar to this form of OWCL.

Diagnosis of Cutaneous Leishmaniasis

Cutaneous leishmaniasis should be considered in patients with characteristic nonhealing skin lesion(s) with the appropriate exposure history. Frequently, patients have been treated with

antibiotics without benefit. The differential diagnosis includes cutaneous fungal infection (sporotrichosis, histoplasmosis, coccidioidomycosis, etc.), mycobacterial infection (including nontuberculous mycobacterial infections such as *M. fortuitum*, *M. abscessus*, and *M. marinum*), leprosy, and skin cancer, particularly squamous cell carcinoma.

A definitive diagnosis requires tissue obtained by scrapings or punch biopsy. When the face or other sensitive sites are involved, needle aspirates can be obtained using small amounts of nonbacteriostatic normal saline. Tissue should be submitted for histology, culture, and, most importantly, molecular diagnostic analysis. Histology from touch preparations, aspirates, or tissue sections can reveal the amastigotes within macrophages. On Giemsa stain, these 2-3 μM oval structures contain a bar-shaped organelle, the kinetoplast, adjacent to the cell nucleus. Observing these structures establishes the diagnosis of leishmaniasis; however, species identification that is critical for clinical management decisions requires culture or molecular diagnostics.

A variety of specialized culture systems are available for biopsies, skin scraping, or needle aspirates. Promastigotes that grow can be subjected to species identification by biochemical or molecular techniques. The cultures are usually held for 4 weeks before they are considered negative. However, polymerase chain reaction (PCR) has become the test of choice for establishing the diagnosis of cutaneous leishmaniasis. DNA is extracted from punch biopsy specimens or needle aspirates and subjected to PCR and sequencing. Importantly, the results can be available in 2-3 days. Sensitivity ranges from 89 to 100%. It is uncommon for the direct PCR to be negative and cultures to be positive. DNA sequence methods have largely replaced biochemical methods (isoenzyme analysis) for species identification, since it is faster.

Drug susceptibility testing for *Leishmania* clinical isolates is not available.

The leishmanin skin test (Montenegro test) gives evidence of present or past infection and is usually positive 3 months after onset of lesions except in the diffuse form. It involves a subcutaneous injection of a given inoculum of killed promastigotes and is read at 48 hours after application. A response of ≥5 mm is positive.

Serologic tests are available in some centers, but their role in the diagnosis of cutaneous leishmaniasis is very limited.

Treatment

Few infectious diseases are as complex as cutaneous leishmaniasis when it comes to clinical management. Treatments can be lengthy, expensive, and toxic, so it is important to establish a parasitological diagnosis before initiating therapy. Furthermore, appropriate management depends on the species of *Leishmania* involved, therefore the diagnostic test should be one that provides species identification (discussed above). Even with species information available, there are inadequate clinical studies to always guide the best management. Individual circumstances will influence management decisions, such as the number, location, and age of the lesions. Three levels of management may be considered for cutaneous leishmaniasis.

1. For mild disease caused by less aggressive species, observation alone may be appropriate, particularly when considering the potential toxicity of drugs.
2. The next level involves local treatment such as topical ointments or intralesional injections with antileishmanial drugs. For practitioners in the United States, this approach is not commonly used due to the unavailability of approved drugs/formulations for this application. Other local treatment options include cryotherapy or thermotherapy, which have advocates under certain circumstances but require a certain level of skill and experience for optimal use.
3. Finally, systemic treatment (oral or intravenous [IV]) is recommended when local therapy is not an option or inappropriate. The indications for systemic treatment are summarized in **Table 39.2**.

Treatments for specific forms of cutaneous leishmaniasis are discussed below. Many of these treatments are dictated by local experiences, where options may be limited by

TABLE 39.2 Indications for Systemic Treatment for Cutaneous Leishmaniasis

- Lesion caused by *Viannia* subspecies (especially *L.* (*Viannia*) *brasiliensis*)
- Metastatic spread to lymph nodes
- Localization in the face
- Multiple lesions
- Chronic ear infection (chiclero, *L. mexicana*)

availability and cost of certain drugs. **Table 39.3** summarizes the doses and other details of the various treatment options.

Treatment of OWCL

For *L. major* local treatment is preferred. Where available, 15% paromomycin/12% methylbenzethonium chloride ointment is proven to be effective. Local infiltration with sodium stibogluconate is used in Europe and in Israel but has not been approved in the United States. Cryotherapy with liquid nitrogen can be used with relatively new and small lesions (<3 mm). Close observation is reasonable for mild cases of *L. major* infection, since it very rarely metastasizes and usually self-heals within a few months. When systemic therapy is indicated due to extensive disease or the location of lesions on face, hands, or feet, then IV antimony is most often used, although small studies suggest a role for liposomal amphotericin B. Fluconazole has been used successfully in Saudi Arabia but seems to be less effective in cases from North Africa or Iraq. There are not enough data available to support the use of miltefosine for *L. major*.

Whereas *L. major* infection can resolve without treatment in months, *L. tropica* infection tends to be slower healing and usually warrants antiparasitic treatment. *L. tropica* is thought to be less responsive to paromomycin ointment, therefore it is common practice to treat with intralesional sodium stibogluconate. Local thermotherapy (discussed further below) has been used with some success. When parenteral therapy is indicated, either sodium stibogluconate or liposomal amphotericin B are the best options. A role for miltefosine is uncertain.

Treatment of NWCL

Cutaneous leishmaniasis that is acquired in the Americas should be diagnosed as being caused by species in the *Viannia* complex (i.e., *L. braziliensis*, *L. guyanensis*, *L. panamensis*, or *L. peruviana*) versus the Mexicana complex (i.e., *L. mexicana*, *L. venezuelensis*, or *L. amazonensis*). The former tends to be more destructive and has higher potential for causing mucosal leishmaniasis, thus systemic therapy is usually indicated. Traditionally, parenteral antimony has been used for infections caused by *Viannia* species. However, recent studies show that oral miltefosine has high success rates (75-88%). An exception may be cases acquired in Guatemala where miltefosine success rates were only 45%. There is also growing experience with the successful use of liposomal amphotericin B for cutaneous leishmaniasis due to *Viannia* complex species. Better availability and shorter courses make liposomal amphotericin B preferable to sodium stibogluconate (at least in the United States), although high cost is a factor.

When a diagnosis of NWCL is made due to *L. mexicana*, either a "wait and see" approach or local therapy are considerations. Local therapy usually consists of injections of antimony combined with cryotherapy. Systemic antimony provides high cure rates when required. Infections due to *L. amazonensis* are usually treated either locally or systemically. There are limited data on the use of miltefosine, so parenteral antimony or liposomal amphotericin B is preferable.

Patients with cutaneous leishmaniasis should be reevaluated 6 weeks after the treatment course is completed, and if lesions are not improved by at least 75%, retreatment or

TABLE 39.3 Treatment Options for Leishmaniasis[a]

	Therapy	Route of Administration	Dose	Directions	Pros	Cons
Local therapy	Paromomycin ointment	Topical	15% paromomycin/12% methylbenzethonium chloride	Twice per day for 10-20 days	Topical	Not available in USA except through compounding
	Sodium stibogluconate	Intralesional injection	0.5-2.0 mL of 100 mg/mL pentavalent antimony	Intralesional every 3-7 days until healed	Local	Special skills required; drug not available in USA
	Cryotherapy (liquid nitrogen)	Cotton tipped applicator	Freeze-thaw-freeze	Repeat on 3-week cycles up to 3 times	Local	Special skills required; appropriate only with small lesions
	Thermotherapy	Thermal prongs	30-sec intervals in grid pattern over lesion	1-3 treatments	ThermoMed instrument is FDA approved	Special skills required; painful (local anesthesia required)
Oral therapy	Miltefosine	Oral	50 mg	BID (30-44 kg) or TID (>45 kg) × 28 days	FDA approved for cutaneous leishmaniasis; oral route	Gastrointestinal side effects; teratogenic
	Fluconazole	Oral	400-600 mg	Daily × 6 weeks	Oral; well-tolerated	Limited track record of success
	Ketoconazole	Oral	600 mg	Daily × 4 weeks	Oral	Limited track record of success
Parenteral therapy	Sodium stibogluconate	IV or IM	20 mg/kg/day	Daily × 10-20 days	Available through CDC; standard of care	High toxicity; provided via IND in USA
	Meglumine antimoniate	IV or IM	20 mg/kg/day	Daily × 10-20 days	Long track record	Not available in USA
	Amphotericin B deoxycholate	IV	0.5-1.0 mg/kg	Every other day × 20-30 days	Less expensive than AmBisome	Toxic; long duration of treatment
	Liposomal amphotericin B (AmBisome)	IV	3 mg/kg	5-7 daily doses	Shorter course, better tolerated than antimony	Expensive
	Pentamidine	IV	2-4 mg/kg	Every other day × 4-7 doses		Toxic; limited indications

[a]See text for indications.
CDC, Centers for Disease Control and Prevention; *IM*, intramuscular; *IND*, investigational new drug; *IV*, intravenous.

alternative treatment should be considered. After completion of treatment, lesions should be monitored for relapse for 1 year.

Mucosal leishmaniasis tends to be difficult to treat. Parenteral antimony (20 mg/kg per day of sodium stibogluconate for 28 days) gives cure rates approximating 60%. A study in travelers has shown that liposomal amphotericin B 3 mg/kg IV given daily for 5 days with another dose at day 10 is very effective. This treatment was given first only to cases of stibogluconate failure but was later used as primary treatment with high cure rates. However, because of the strong potential for relapse, it is recommended that mucosal lesions be followed for several years after completion of drug therapy.

VISCERAL LEISHMANIASIS

Visceral leishmaniasis, or kala-azar, results from infection with *L. donovani* in Africa and India, *L. infantum* in the Mediterranean basin, and *L. chagasi* in the New World. It, like the cutaneous leishmaniases, is transmitted by the bite of phlebotomine sand flies. Reservoir animals include various rodents and domesticated or wild canines, except in India where man is the only known reservoir.

Clinicians practicing in North America or Europe are less likely to see cases of visceral leishmaniasis than cutaneous leishmaniasis. Nonetheless, visceral leishmaniasis should be suspected in residents of or recent travelers to endemic areas (**Fig. 39.5**) who present with *intermittent fever*, *anemia*, and *marked hepatosplenomegaly*—a syndrome evocative of lymphoma. Occasionally, military groups have experienced epidemics; for example, kala-azar occurred in British soldiers in India. Visceral leishmaniasis has been reported in US veterans of the Gulf War, although most of the latter cases appear to have been due to *L. tropica*. Infection can result from brief exposure in an endemic area.

Clinical Features

Kala-azar arising in different regions may show many variations in its clinical and epidemiologic appearance. A cutaneous nodule often develops at the site of the parasite inoculation

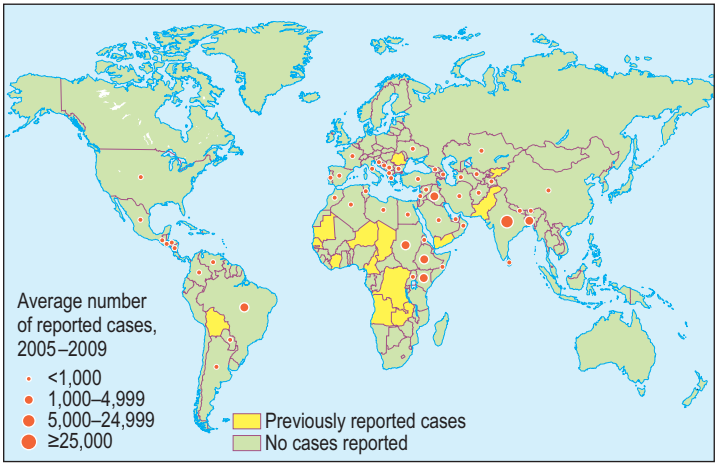

Fig. 39.5 Distribution of visceral leishmaniasis (WHO data). (From: World Health Organization, 2010. First WHO Report on Neglected Tropical Diseases: Working to Overcome the Global Impact of Neglected Tropical Diseases. Available at <http://whqlibdoc.who.int/publications/2010/9789241564090_eng.pdf>.)

in the African and Central Asian forms of the infection. Often this will have resolved before clinical illness develops. After an incubation period of 2-6 months, systemic manifestations develop insidiously, although the presentation may occasionally be abrupt. The earliest symptom is fever. On physical examination, the liver and spleen are large, firm, and nontender. Lymphadenopathy is more frequently reported in the Mediterranean countries, East Africa, and China. Brazilian and Mediterranean kala-azar occur more frequently in children. Oral and nasopharyngeal lesions may occasionally be seen in the Sudan, East Africa, and India.

The clinical manifestations of kala-azar are due to the invasion of the reticuloendothelial cells of the spleen, liver, bone marrow, and skin and the subsequent multiplication of amastigotes within the cells. Untreated infections become chronic; in addition to the above physical findings, patients typically become markedly wasted. Patients with light-colored skin may develop a grayish cast—"kala-azar" is a Hindi name meaning "black fever."

Untreated visceral leishmaniasis may be complicated by intercurrent infections such as pneumonia, pulmonary tuberculosis, and dysentery; these often prove fatal. Some patients die from gastrointestinal hemorrhage.

The clinical presentation of visceral leishmaniasis in patients with acquired immunodeficiency syndrome (AIDS) is felt to be similar to the presentation in hosts without human immunodeficiency virus (HIV). Fever, splenomegaly, and pancytopenia are common. Involvement of the gastrointestinal tract is more common in AIDS patients. Abundant parasite-laden macrophages are found in the submucosa from the esophagus to the rectum. However, these patients typically respond poorly to treatment and have a high mortality rate.

Long after apparently successful treatment, some patients in India and East Africa develop post-kala-azar dermal leishmaniasis, a condition that resembles leprosy and features depigmented or nodular cutaneous lesions.

Diagnosis

The diagnosis of visceral leishmaniasis should be suspected in individuals presenting with characteristic signs and symptoms who have emigrated from or visited an area where leishmaniasis is endemic.

Laboratory studies reveal anemia, leukopenia, neutropenia, and occasionally thrombocytopenia. The eosinophil count is also low. A marked hyperglobulinemia due to increased IgG is usually present.

Microscopic examination and culture of bone marrow aspirates provide the best methods for reaching a definitive diagnosis of visceral leishmaniasis. Splenic aspiration is described in the literature but is discouraged due to risk of hemorrhage. In visceral leishmaniasis cases, serologic testing might be useful for diagnosis, followed by monitoring the response to treatment.

The introduction of PCR improves diagnostic sensitivity in bone-marrow aspirates. Recently it was also shown that the sensitivity of PCR of peripheral blood samples was similar to PCR of bone marrow aspirate (98%).

Treatment

In the absence of treatment, mortality from visceral leishmaniasis is >90%, thus systemic treatment is essential. The treatment options will depend on the availability and cost of drugs, likelihood of resistance, and host factors (particularly HIV status).

Liposomal amphotericin B (AmBisome), where it is affordable, has become the treatment of choice. Studies in India demonstrate cure rates of 96-100% with total doses of 14-20 mg/kg. The dose approved by the US Food and Drug Administration (FDA) is 3 mg/kg on days 1-5, 14, and 21, for a total of 21 mg/kg. In attempts to find the minimal dose, studies in India have shown a single dose of 7.5 mg/kg gave a 90% cure rate at 6 months. Higher cumulative doses (up to 60 mg/kg) are needed when treating HIV-infected patients. Liposomal amphotericin B is preferable to amphotericin B deoxycholate due to shorter course

and less nephrotoxicity. Even so, liposomal amphotericin B is associated with infusion-related toxicity and nephrotoxicity and must be used with close supervision.

Parenteral antimony (sodium stibogluconate or meglumine antimoniate) has been a standard treatment for decades, but spreading resistance (mainly in India) is limiting its use. The side effects are significant, including myalgia, arthralgia, nausea, vomiting, rash, pancreatitis, and potentially fatal cardiotoxicity. Electrocardiograph monitoring is mandatory. Unless cost constraints are overriding, liposomal amphotericin B is preferred to antimony. Antimony is not FDA approved but can be appropriated through the Centers for Disease Control and Prevention (CDC) under an investigational new drug protocol. US providers will typically need to obtain institutional review board approval from their local institution. The current regimen recommended by the CDC is 20 mg/kg per day for 28 days; it is better tolerated intravenously, although it can be given intramuscularly. Patients typically feel better within 1 week of beginning treatment, but it may take weeks for laboratory values to normalize and months before splenomegaly resolves. Accurate assessment for complete cure mandates follow-up at frequent intervals over a 1-year period.

Miltefosine is an oral option for treating visceral leishmaniasis that has become available in the past decade. It was approved by the FDA in 2014. Cure rates in Indian studies are 94-97%. The standard regimen is 2.5 mg/kg/day for 28 days (available in 50-mg capsules). The oral route of administration is an obvious advantage, although 65% of patients experience vomiting. Importantly, miltefosine is teratogenic and needs to be used with extreme caution in woman of reproductive age. Resistance is an emerging problem in parts of India.

Parenterally administered paromomycin is a new and less expensive alternative for treating visceral leishmaniasis, although it is not approved in the United States. It is administered by the IV or IM route for 21 days. Indian studies show cure rates in the range of 88-95%. Adverse effects are relatively uncommon, although signs of hepatotoxicity, ototoxicity, and nephrotoxicity need to be monitored.

Due to increasing drug resistance, combination chemotherapy is emphasized, particularly in endemic regions. Reported combinations include liposomal amphotericin B plus miltefosine or paromomycin plus sodium stibogluconate.

Prevention of Leishmaniasis

Avoidance of sand flies (**Fig. 39.1**) is the essence of prevention. These insects are especially active at dusk and dawn. In areas of transmission, persons should wear protective clothing and apply insect repellent to exposed skin. Sleep in well-screened areas, although the sand flies can pass through screens or bed nets that are not closely woven. Apply pyrethroid-containing insecticide to clothing, bed nets, screens, and so on. No preventative vaccine or prophylactic drugs are available.

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