Leishmaniasis

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Objectives

1. Identify the two types of leishmaniasis.

2. Explain the differences in the reasons leishmaniasis is spreading in Afghanistan and India.

3. Discuss how the leishmaniasis protozoon infects the human body and how it spreads.

4. Describe the two classes of drugs approved by the Food and Drug Administration (FDA) for the treatment of leishmaniasis.

5. Explain why soldiers deployed to areas endemic for leishmaniasis tend to have a lower morbidity rate than do tourists.

Introduction

United States military activity in the Middle East carries with it not only war wounds, but infections and other diseases which are brought back to the U.S. when troops return. One of the diseases many soldiers may contract while deployed in the Middle East is leishmaniasis. Of 20,000 soldiers that returned to Fort Campbell, Kentucky in late 2003 and early 2004, five percent had skin complaints; of those five percent, twenty-five percent were diagnosed with cutaneous leishmaniasis.[1] It may not be unexpected to see patients with leishmaniasis in the civilian clinical or nursing setting once these soldiers are released from active military service and return to the civilian sector. Civilian travelers to other countries where leishmaniasis is endemic may also return to the U.S. with the disease. The differential diagnosis of any non-healing ulcer on a patient who has traveled to such an area should include leishmaniasis.

Leishmaniasis is an infection cause by protozoa belonging to the genus Leishmania, transmitted to humans by the bite of the female sand fly. The species that mainly affect humans are Leishmania donovani, which causes visceral leishmaniasis (also known as kala-azar, which is Hindi for black sickness or fever), while cutaneous leishmaniasis is caused by Leishmania tropica. Cutaneous leishmaniasis (CL) can reach epidemic proportions in a nonimmune population such as soldiers and tourists, and is maintained endemically in local mammals such as rodents and dogs. In visceral leishmaniasis (VL), parasites replicate in the endothelial system, such as the liver, spleen and bone marrow. The infection can remain asymptomatic or subclinical and can become clinically manifest with an acute, subacute or chronic course. In the classic kala-azar syndrome of VL, patients have potentially life-threatening disease, typically after an incubation period of weeks or months. The syndrome includes fever, marked malnutrition, hepatosplenomegaly and pancytopenia.[2]

An estimated 12 million cases of visceral and cutaneous leishmaniasis occur worldwide each year[2] , with approximately 100,000 deaths a year.[3,4] The cutaneous form of leishmaniasis is the most common, causing 50% to 75% of all new cases, while the visceral form is the most fatal, especially in persons infected with the HIV virus.[5] The number of leishmaniasis cases is increasing, mainly due to man-made environmental changes such as road building, lumbering and dam-building such as is seen in the Amazon rain forest. Continuing migration from rural to urban areas and continuing urbanization worldwide are among the primary causes for the increased exposure to the sand fly. Another risk factor is the movement of large populations into endemic areas. In the city of Kabul, Afghanistan, an estimated 270,000 cases of leishmaniasis occurred in 1996; this with a population of less than 2 million. In India, the resurgence of visceral leishmaniasis has occurred because of deficiencies in the control program. This has seen the emergence of resistant strains of the organism.[3] American troops returning from the Middle East war may unsuspectingly bring quiescent leishmaniasis with them, so it may be seen by clinicians in America whom have never seen a case of leishmaniasis.

Life Cycle

The life cycle involves a human host and the female sand fly (the vector) which transmits the parasite between vertebrate hosts (see Figure 1 at End of Course). In the vector the parasite develops into a form called the promastigote which reproduces asexually in the vector's gut, then migrates to the pharynx of the insect. Promastigotes are injected into the human host when the sand flea bites. The promastigotes then enter the cells of the human host and change into a form termed the amastigote. The amastigotes then reproduce in the human cell. When the cell is packed with amastigotes, it ruptures, where the amastigotes are then released to infect other cells. The symptoms and pathology of leishmaniasis are a result of the amastigotes killing the human cells.[6] Most infections are transmitted via a sand fly bite, but other potential methods of transmission are congenital, sexual contact, blood transfusion, needle-sharing and organ transplantation.[7]

Leishmania tropica and L. major are the two primary causes of cutaneous leishmaniasis, L. tropica resides primarily in the urban areas, while L. major is generally found in the dry desert areas.[9] After two to eight weeks of incubation, an erythematous papule develops at the site of the bite, which eventually evolves into a nodule and then ulcerates and crusts over. Ulcers are typically large and painless. Secondary infection is not uncommon.[8,9,10] Most cutaneous lesions will eventually heal, leaving a depressed, disfiguring scar. Infected persons tend to form immunity to future infection.[11]

Mucocutaneous leishmaniasis destroys the tissues of the upper respiratory tract. Lesions in this area usually develop by organisms which travel from other cutaneous sites. The progress of the disease is slow, methodical and destructive. Mucosal disease occurs in 1% to 5% of untreated patients, with lesions developing years or decades after the initial infection; therefore, children are rarely affected. Mucocutaneous leishmaniasis usually presents with respiratory symptoms

such as nasopharyngeal congestion which may cause epistaxis. The lesions then infiltrate the nasal mucosa and ulcerate, which will result in scarring and subsequent respiratory difficulty.[13]

Visceral leishmaniasis can follow an acute or relatively asymptomatic course but is generally fatal if untreated.[13] The incubation period from time of exposure to the first indications of symptoms is ten days to greater than two years, but is usually three to eight months. Patients present with fever, hepatosplenomegaly and weight loss.[9] Other symptoms may appear, such as weakness, night sweats, anorexia, epistaxis and thinning hair. Since visceral leishmaniasis is becoming an important opportunistic infection in patients with HIV infection, all patients with visceral leishmaniasis should be tested for HIV.[14] Similarly, HIV-positive patients in endemic areas should be evaluated and followed for the development of the visceral form leishmaniasis.[9]

Another form of leishmaniasis called viscerotropic is a subset of the visceral form. Viscerotropic leishmaniasis is caused by L. tropica, which is generally considered to be exclusive to the cutaneous form. Viscerotropic leishmaniasis was described by U.S. soldiers in Saudi Arabia during the Desert Storm and Desert Shield operations. Patients developed signs and symptoms of visceral leishmaniasis eight weeks to one year after arrival. Parasites found in bone marrow illustrate the ability of the Leishmania species to express itself in unexpected clinical forms.[15]

Case Histories

Patient A: A 23-year-old male graduate student in Ohio noted an ulceration on his left middle finger. He had visited the jungles of Panama one month earlier and was bitten by many insects. The ulcer became larger despite the administration of oral erythromycin and dicloxacillin. A month later the student was admitted to a regional hospital with a 2x2 cm indurated ulcer overlying the proximal interphalangeal joint. There was no evidence of lymphatic spread. A biopsy from the edge of the lesion showed an intense lymphohistiocytic infiltrate involving the entire dermis. Cultures for bacteria, fungi and mycobacteria were negative. He was treated with intravenous nafcillin and discharged on oral tetracycline.

The lesion persisted, and three weeks later another biopsy was performed. The same histologic picture was seen and again, all cultures were negative. A serum specimen submitted to the Centers for Disease Control for Leishmania antibody testing had a titer of 1:16 by complement fixation (CF) and of 1:16 by indirect immunofluorescent antibody (IFA). The lesion continued to expand with subcutaneous nodules on the back of the hand extending up the arm. Epitrochlear and axillary adenopathy were present. A third biopsy was performed and submitted to Walter Reed Army Hospital for Leishmania culture. Growth of Leishmania braziliensis was reported several weeks later.

The patient was treated with 10mg/kg/day sodium stibogluconate intravenously for 21 days. At the beginning of the treatment, the ulceration measured 4.8 cm x 3.5 cm; by the end of therapy the lesion had decreased in size by 75% and was granulating well, while the subcutaneous nodules on the hand and arm had resolved. Three months after the completion of therapy, the ulcer had completely healed with only minimal adenopathy remaining.[16]

Patient B: A soldier having left Afghanistan approximately three months previously noted fevers of up to 1040 F in December of 2003, along with rigors, sweats, flushing and mild orthostasis in early January of 2004. During the course of his illness, the patient experienced fluctuating temperatures and lost 13 pounds of body weight. No leishmanial parasites were noted in light-microscopic examinations of cultures of bone marrow and liver-biopsy specimens. No leishmanial DNA was detected by genus-specific polymerase chain reaction (PCR) analysis[17] of the bone-marrow specimen. The findings in the splenic region of a whole-body Positron Emission Tomography (PET) scan were suggestive of lymphoma, and surgical splenectomy was briefly considered. In February, 2004, because of the continuing concern that the patient may have VL, the liver-biopsy specimen was reexamined by light microscopy; one definite and one probable leishmanial parasites were noted. The patient became afebrile after one week of antileishmanial therapy with a lipid formulation of amphotericin B.[18]

Patient C: A soldier having left Afghanistan several months previously noted abrupt onset of fevers (maximum 1040 F), myalgias and abdominal pain in December of 2003. Unintentional loss of up to 25 pounds of body weight and anorexia accompanied the symptoms. The patient's symptoms worsened during the next six weeks. Leishmanial parasites were not found in light-microscopic examinations of the bone marrow and buffy-coat specimens, but were present in liver-biopsy specimens. During February 3 to 17, 2004, the patient was administered six courses of a lipid formulation of amphotericin B. Although his symptoms improved during and after the course of therapy, they worsened in late February. He was rehospitalized on March 5, 2004 with a temperature of 1020 F. Leishmanial parasites and DNA were detected by light-microscopic examination and genus-specific polymerases chain reaction (PCR) of a liver-biopsy specimen, while the test results for a bone-marrow specimen was negative. In addition, the PCR analysis of the liver specimen was positive for Leishmania donovani-L. infantum species complex, whereas the PCR results for the L. major were negative. On March 19th, a 28-day course of antileishmanial therapy was begun with the pentavalent antimonial compound sodium stibogluconate with an intravenous dose of 20mg/kg/day.[18]

Treatment

Sodium stibugluconate (available in English-speaking countries), and meglumine antimoniate (available in Latin American countries) are both of the pentavalent antimony class, and have been used for the treatment of leishmaniasis for over 50 years. These medications work by inhibiting adenosine triphosphate synthesis. These drugs are not ideal; difficult administration, toxicity and numerous side effects including arthralgias, pancreatitis and drug resistance can present a problem.[6,19] Side-effects usually resolve within a week of cessation of treatment and may not return upon resuming treatment. The lesions start resolving in about 20 days.[8]

Dosage is 20 mg/kg/day, either intravenously or by intramuscular injection. Relapse of up to 30% has been reported in Kenya, while increasing resistance is being reported in India. Baseline ECG and blood tests should be done prior to the initiation of therapy. Liver function tests and renal function tests should be done weekly during treatment.[20]

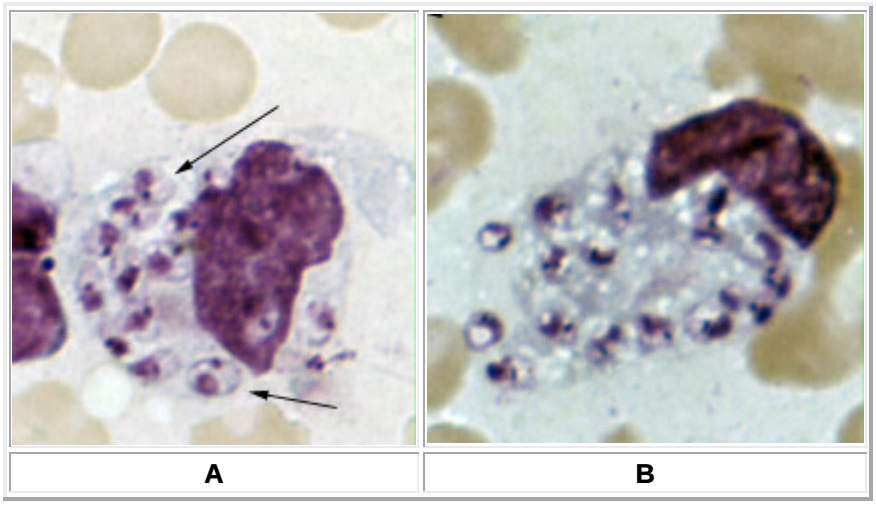
Systemic antifungal agents such as amphotericin B, ketoconazole and itraconazole are antifungal drugs with antileishmanial activity; however, close monitoring of blood tests is required to preclude severe hepatic, renal and hematological problems.

Cure rates of greater than 90% has been shown with the use of amphotericin B; however, its high cost has prevented its use in areas where visceral leishmaniasis is prevalent. The dose is 3-4 mg/kg IV for 5 days. Ketoconazole is given 600 mg/d in three divided doses for 28 days. Itraconazole is given 200mg/d in a single dose for 28 days.[6]

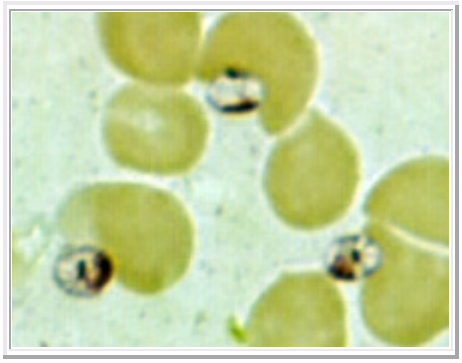
Ankylphosphocholine miltefosine is a drug currently undergoing clinical trials. It has produced a 94% cure rate at dosages of about 2.5 mg/kg/d (100 mg daily for 4 weeks) even among patients with antimony-resistant disease.[21,22] Miltefosine was registered for the treatment of visceral leishmaniasis in India in March, 2002.5, [21]

The most effective way to control the disease is to avoid being bitten by the sand fly through the use of insecticides and using bed nets when sleeping. Soldiers deployed to endemic areas tend to show a lower incidence of leishmaniasis infection than do tourists traveling to endemic areas. This may be due to the training soldiers received either before deployment or just after arrival to the war zone. This training includes disease prevention, use of insect repellants and netting and prompt evaluation and treatment by trained military medical personnel. Civilians may not have the training to prevent becoming infected and may not recognize the symptoms once infected.[23]

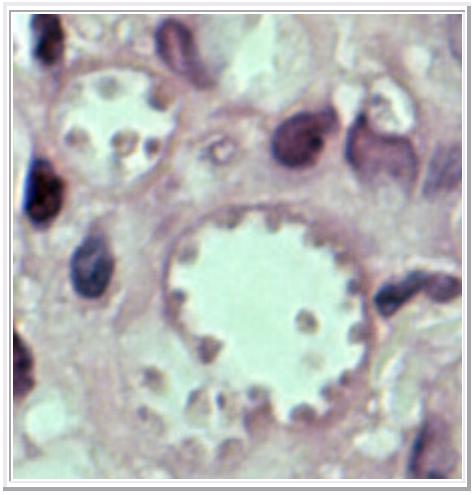
Figure 1



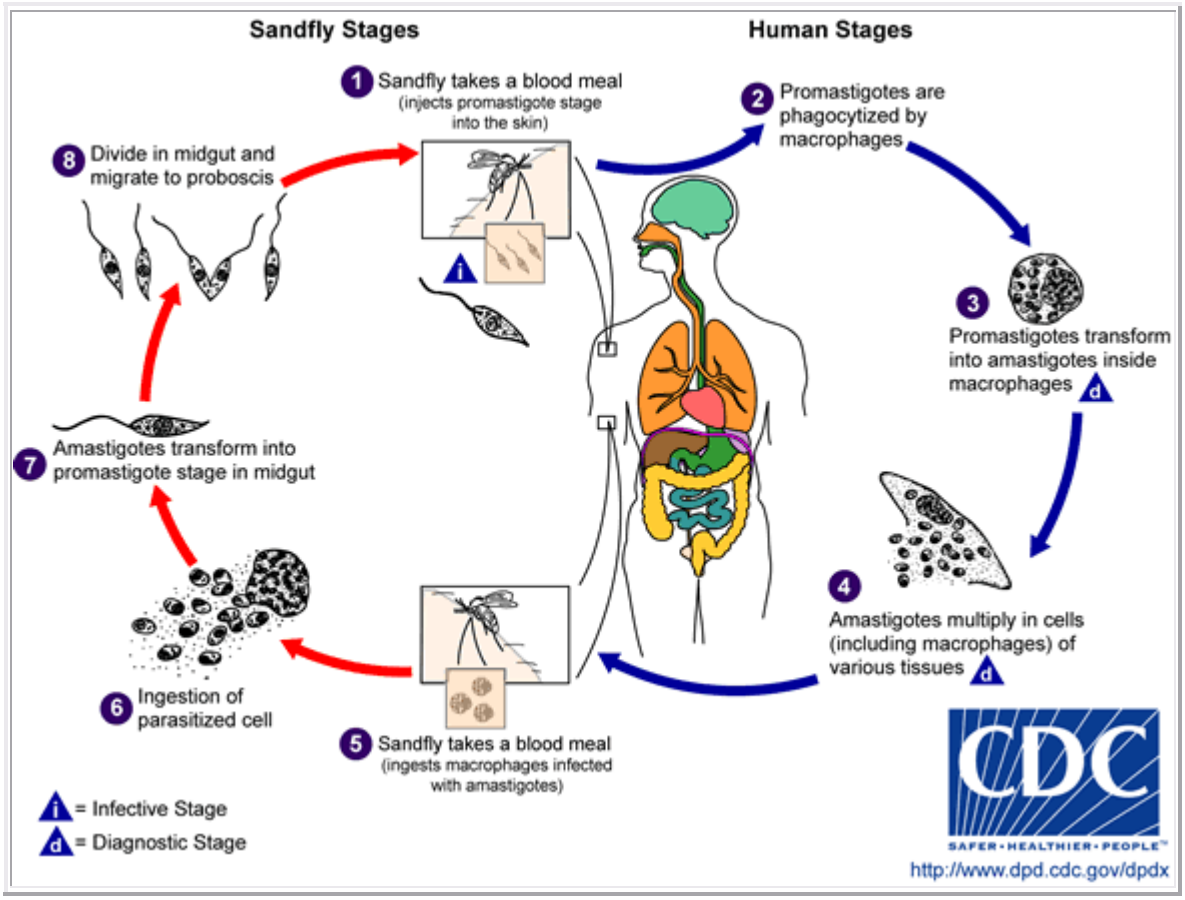
A, **B:** *Leishmania tropica* amastigotes from an impression smear of a biopsy specimen from a skin lesion. In **A**, an intact macrophage is practically filled with amastigotes (arrows), several of which have a clearly visible nucleus and kinetoplast; in **B**, amastigotes are being freed from a rupturing macrophage. Patient had traveled to Egypt, Africa, and the Middle East. Based on culture in NNN medium, followed by isoenzyme analysis, the species was *L. tropica*.



Three *Leishmania* amastigotes, each with a clearly visible nucleus and kinetoplast, from the same impression smear as in **A** and **B** on the previous page.



Leishmania mexicana in a biopsy specimen from a skin lesion stained with hematoxylin and eosin. The amastigotes are lining the walls of two vacuoles, a typical arrangement. The species identification was derived from culture followed by isoenzyme analysis. Infection was acquired in Texas.



Leishmaniasis is transmitted by the bite of female phlebotomine sandflies. The sandflies inject the infective stage, promastigotes, during blood meals 1. Promastigotes that reach the puncture wound are phagocytized by macrophages 2and transform into amastigotes 3. Amastigotes multiply in infected cells and affect different tissues, depending in part on the *Leishmania* species 4. This originates the clinical manifestations of leishmaniasis. Sandflies become infected during blood meals on an infected host when they ingest macrophages infected with amastigotes (5, 6). In the sandfly's midgut, the parasites differentiate into promastigotes 7, which multiply and migrate to the proboscis 8.

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