8.8.13 Leishmaniasis 1467

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8.8.13 Leishmaniasis 1467 to divide in the blood, possibly in sequestered sites. Trypomastigotes are rarely seen in human blood: they are much larger than T. cruzi, with a small subterminal kinetoplast (Fig. 8.8.12.10). Antibodies to T. cruzi certainly crossreact strongly with T. rangeli. Based on ex- perimental work in mice, T. rangeli infections are thought to induce very low crossreactive antibody titres to T. cruzi. As with T. cruzi, there is subspecies genetic heterogeneity, with up to four distinct T. rangeli lineages, thought to be linked to two species groups within the triatomine genus Rhodnius. FURTHER READING Bern C (2015). Chagas disease N Eng J Med, 373, 456–66. Bhattacharyya T, et al. (2018). Severity of chagasic cardiomyopathy is associated with response to a novel rapid diagnostic test for Trypanosoma cruzi TcII/V/VI. Clin Infect Dis, 67, 519–24. Carter YL (2012). Acute Chagas disease in a returning traveller. Am J Trop Med Hyg, 87, 1038–40. Dutra WO, et al. (2014). Immunoregulatory networks in human Chagas disease. Parasit Immunol, 36, 377–87. Garcia MN, et al. (2015). Historical perspectives on the epidemiology of human Chagas disease in Texas and recommendations for en- hanced understanding of clinical Chagas disease in the southern United States. PLoS Negl Trop Dis, 9, e00003981. Lewis MD, et al. (2011). Recent, independent and anthropogenic ori- gins of Trypanosoma cruzi hybrids. PLoS Negl Trop Dis, 5, e1363. Lewis MD, et al. (2014). Bioluminescence imaging of chronic Trypanosoma cruzi infections reveals tissue-specific parasite dy- namics and heart disease in the absence of locally persistent infec- tion. Cell Microbiol, 16, 1285–300. Maudlin I, Holmes P, Miles MA (eds) (2004). The trypanosomiases. CABI Publishing, Wallingford. Messenger LA, Bern C. (2018). Congenital Chagas disease: current diagnostics, limitations and future perspectives. Curr Opin Infect Dis, 31, 415–21. Messenger LA, Miles MA, Bern C (2015). Between a bug and a hard place: Trypanosoma cruzi genetic diversity and the clinical outcomes of Chagas disease. Expert Rev Anti Infect Ther, 13, 995–1029. Miles MA (2004). The discovery of Chagas disease: progress and prejudice. Infect Dis Clin North Am, 18, 247–60. Molina I, et al. (2014). Randomized trial of posaconazole and ben znidazole for chronic Chagas disease. N Eng J Med, 370, 1899–908. Morillo CA, et al. (2015). Randomized trial of benznidazole for chronic Chagas cardiomyopathy. N Eng J Med, 373, 1295–306. Pinazo MJ, et al. (2017). A strategy for scaling up access to compre- hensive care in adults with Chagas disease in endemic countries: The Bolivian Chagas Platform. PLoS Negl Trop Dis, 11, e0005770. Raia AA (1983). Manifestações digestivas da moléstia de Chagas. Sarvier, São Paulo, Brazil. Riera C, et al. (2006). Congenital transmission of Trypanosoma cruzi in Europe (Spain): a case report. Am J Trop Med Hyg, 75, 1078–81. Sanchez-Camargo CL, et al. (2014). Comparative analysis of 11 com- mercialized rapid diagnostic tests for detecting Trypanosoma cruzi antibodies in serum banks in areas of endemicity and nonendemicity. J Clin Microbiol, 52, 2506–12. World Health Organization (WHO) (2002). Control of Chagas disease, Technical Report

Series 905. WHO, Geneva. Bhattacharyya T, et al. (2018) Severity of chagasic cardiomyopathy is as- sociated with response to a novel rapid diagnostic test for Trypanosoma cruzi TcII/V/VI. Clin Infect Dis, 67, 519–524. 8.8.13 Leishmaniasis Antony D.M. Bryceson and Diana N.J. Lockwood ESSENTIALS Leishmaniasis is caused by parasites of the genus Leishmania, which are transmitted to humans from human or animal reservoirs by the bites of phlebotomine sandflies. In places the disease is common and important, with perhaps 500 000 cases of visceral leishmaniasis and 1.5–2 million cases of cutaneous leishmaniasis worldwide each year. As an imported disease, cutaneous leishmaniasis is common in travellers, military per- sonnel, and immigrants coming from endemic areas, while the diagnosis of the less common visceral leishmaniasis is frequently overlooked. Cutaneous leishmaniasis Clinical features—at the site of the infected sandfly bite, an erythema- tous nodule typically develops into a sore which fails to heal spon- taneously and might progress to mucosal leishmaniasis (espundia)—a condition in which mucosal lesions develop in 4 to 40% of patients with untreated cutaneous ulcers due to L. brasiliensis. Diagnosis and treatment—diagnosis is by demonstration of leish- mania organisms in tissue smears or biopsy material by microscopy, cul- ture, or detecting leishmaniai DNA by polymerase chain reaction. Many leishmanial sores will heal naturally, but treatment is indicated for those that are severe, or failing to heal spontaneously, or due to particular spe- cies (e.g. L. brasiliensis). Treatment may be (1) local (e.g. surgery/curettage); infiltration with a pentavalent antimonial; or (2) systemic—most cutaneous species of leishmania are sensitive to pentavalent antimonials. Visceral leishmaniasis Zoonotic disease is common around the Mediterranean littoral, across the Middle East and central Asia, in northern and eastern China, and in South and Central America. Anthroponotic disease causes large outbreaks in Northeast India and the Sudan. Clinical features—most infections are subclinical, but clinical pres- entation is with gradual onset of fever, discomfort from an enlarged spleen, abdominal swelling, weight loss, cough, or diarrhoea. The illness can be associated with HIV infection. Diagnosis and treatment—diagnosis is by isolation of leishmania from spleen, bone marrow, liver, lymph node, or buffy coat. Serology is useful for diagnosis, and might replace direct demonstration of parasites in remote areas. The best treatment is intravenous liposomal amphotericin B, but (much cheaper) pentavalent antimonials are most often used in countries where visceral leishmaniasis is endemic. An oral agent, miltefosine is now being used in the Indian subcon- tinent and this has simplified treatment Prevention Prevention is by controlling reservoir hosts and sandfly vectors, or by avoiding bites by vectors. There is no vaccine. Introduction Leishmaniasis is caused by parasites of the genus Leishmania, which are transmitted by sandflies of the genus Phlebotomus in the Old

section 8 Infectious diseases 1468 World and Lutzomyia in the New World. The infection may be anthroponotic or zoonotic, having human or animal reservoirs, respectively. In humans, the disease is usually either cutaneous or visceral. The most important variant is mucosal leishmaniasis of South and Central America. In places the disease is common and important, but there are few accurate statistics. The World Health Organization (WHO) estimates 500 000 cases of visceral leishman- iasis and 1.5 to 2 million cases of cutaneous leishmaniasis occur annually, with 200 million people at risk of each disease, but these figures may underestimate the problem. As an imported disease, cu- taneous leishmaniasis is common in travellers, military personnel, and immigrants coming from endemic areas, while the diagnosis of the less common visceral leishmaniasis is frequently overlooked. Aetiological agent and lifecycle In its vertebrate host, the oval amastigote form of the parasite (2–3 μm in diameter) is found in cells of the reticuloendothelial system (Fig. 8.8.13.1). In the sandfly or in culture medium, it is in the

elongated, motile, promastigote form with an anterior flagellum. The most important species of Leishmania that cause disease in humans and their own reservoir hosts are shown in Table 8.8.13.1. Isoenzyme patterns and DNA hybridization are used to distinguish species. Sandflies require a precise microclimate that is provided in cer- tain places in each endemic focus at particular seasons of the year. Transmission is often seasonal. Amastigotes are ingested from blood or tissues of the mammalian host by the female fly and transform into promastigotes in the gut, rendering the fly infective after about 10 days. Cutaneous leishmaniasis Epidemiology The vectors of Leishmania major live in rodent burrows. Visiting hunters, travellers, soldiers, and tourists, and dwellers at oases or in new settlements, are affected. The disease may be sporadic or epidemic, as seen recently among Afghan refugees in camps in Fig. 8.8.13.1 Amastigotes of L. donovani in a reticuloendothelial cell. From the splenic aspirate of a child with visceral leishmaniasis in Kenya. Copyright A. D. M. Bryceson. Table 8.8.13.1 Epidemiology of leishmaniasis Organism Geographical location Reservoir Major vectors Old World L. donovani North-east India, Bangladesh, Nepal Humans Phlebotomus argentipes L. infantum Mediterranean basin, Sudan, West Africa, Middle East, China, central Asia Dogs, foxes, jackals P. perniciosus, P. perfiliewi, P. chinensis, etc. L. donovani (Africa) Sudan, Kenya, Horn of Africa Humans P. orientalis, P. martini L. major Semideserts in North Africa and Middle East, north India, Pakistan, central Asia Gerbils (especially Rhombomys, Meriones) P. papatasi L. major Sub-Saharan savannah, Sudan Rodents (especially Arvicanthis, Tatera) P. duboscqi L. tropica Towns in Middle East, Mediterranean basin, central Asia Humans,?dogs P. sergenti L. aethiopica Highlands of Kenya, Ethiopia, Uganda Hyraxes (Procavia, Heterohyrax) P. longipes, P. pedifer New World L. chagasi (= L. infantum) Most of Central and South America, especially Brazil Dogs, foxes, opossums (Didelphis) Lutzomyia longipalpis, Lu. evansi L. mexicana Central and northern South America Forest rodents (especially Ototylomys) Lu. olmeca L. amazonensis Tropical forests of South America Forest rodents (especially Proechimys, Oryzomys) Lu. flaviscutellata L. brasiliensis Tropical forests and cultivated land throughout South and Central America Rodents, opossums, dogs, and equines Lu. wellcomei, Lu. whitmani, etc. L. guyanensis Northern South America Sloths (Choleopus), arboreal anteaters (Tamandua) Lu. umbratilis L. panamensis Central America, Ecuador, Colombia Sloths (Choleopus) Lu. trapidoi, etc. L. peruviana West Andes of Peru Dogs, rodents, opossums Lu. verrucarum, Lu. peruensis

8.8.13 Leishmaniasis 1469 Pakistan. The vectors of L. tropica live in crevices in buildings and walls. The disease may be endemic or epidemic. The vector of L. aethiopica bites people sleeping in their huts. The disease is en- demic, and most people are affected by early adulthood. L. infantum causes simple, self-healing skin lesions in some parts of southern Europe and North Africa. L. donovani causes post-kala-azar dermal leishmaniasis (PKDL) in India. In the New World, transmission is usually in the forest. L. brasil iensis, the major cause of American cutaneous and mucosal leish- maniasis, is the most widely distributed of the New World species. Its vectors are highly anthropophilic and human infection is common. Periurban and urban foci of infection are increasing. Malnutrition is a risk factors for mucosal leishmaniasis. Infection with L. peruviana occurs in high Andean valleys, where it may be locally common. Pathogenesis and pathology Leishmania, when inoculated by the sandfly, invade and multiply in macrophages in the skin. The parasitized macrophage granuloma is in- filtrated by lymphocytes and plasma cells. Piecemeal or focal necrosis destroys parasitized cells. The overlying epidermis shows hyperkera- tosis and ulcerates. In chronic lesions, epithelioid cells and Langhans giant cells produce a picture similar to that of noncaseous tubercu- losis. Rarely, the cellular immune response is suppressed, and histology shows heavily parasitized macrophages with little or no lymphocytic infiltrate,

characteristic of diffuse cutaneous leishmaniasis. L. aethiopica, L. mexicana, and L. brasiliensis may invade cartilage. Cartilaginous lesions are extremely chronic. L. brasiliensis, and oc- casionally L. panamensis or L. guyanensis, may metastasize through the bloodstream to sites deep in the mucosa of the upper respiratory tract, where they can lie dormant. After months or years, a lesion de- velops, characterized by necrosis, vasculitis, and tissue destruction. Immunity to a given species of leishmania is usually lifelong. Second infections occur occasionally, especially in older people or immunosuppressed. Clinical features After an incubation period of a few days to several months, an ery- thematous nodule develops at the site of the infected sandfly bite. A golden crust forms (Fig. 8.8.13.2). The sore reaches its final size, usually 1 to 5 cm in diameter, over weeks or months. The crust may fall away, leaving an ulcer with a raised edge (Fig. 8.8.13.3). Satellite papules are common. After months or years, the lesion starts to heal leaving a depressed, mottled scar. Any secondary bacterial infection is superficial and unimportant. The lesion is not normally painful, but can disfigure or disable if scarring is severe or over a joint. Draining lymphatic vessels might be thick- ened or nodular. There are many variations on this classical pattern. Sores due to L. major form and heal rapidly (mean 3–5 months) and might be inflamed and exudative: the so-called wet or rural sore. Sores due to L. tropica tend to be less inflamed and to heal more slowly (mean 10–14 months): the so-called dry or urban sore (Fig. 8.8.13.4). Fig. 8.8.13.2 Nodular lesion of cutaneous leishmaniasis. Showing crusting and small satellite papules, typical of early lesions of all species; in this case L. brasiliensis. Copyright A. D. M. Bryceson. Fig. 8.8.13.3 Cutaneous leishmaniasis due to L. brasiliensis. Shallow ulcer with raised edge. Copyright A. D. M. Bryceson. Fig. 8.8.13.4 Cutaneous leishmaniasis due to L. tropica in a young man in Kabul. Crusty nodular lesions are spreading on the face. There is a typical depressed scar of a previous lesion on the right cheek. Copyright Dr Mark Bailey.

section 8 Infectious diseases 1470 Lesions due to L. infantum have an incubation period of many months and can persist over several years. In L. aethiopica infec- tions, lesions are usually central on the face. Satellite papules accu- mulate to produce a slowly growing, shiny tumour or plaque that might not crust or ulcerate, taking between 2 and 5 years to heal (Fig. 8.8.13.5); mucocutaneous leishmaniasis may develop, produ- cing swelling of the lips and expansion and elongation of the nose. Leishmanial lymphangitis might accompany sores of any species but is more common in the New World than the Old World (Fig. 8.8.13.6). On occasion, hard thickened lymphatics might accom- pany an insignificant cutaneous lesion. L. brasiliensis often causes deep, spreading ulcers, which heal over 6 to 24 months. Up to 15% of patients will relapse after spontaneous or therapeutic cure. L. mexicana lesions are commonly on the limbs or side of the face and heal in 6 to 8 months. Sores on the pinna of the ear can invade the cartilage, persist for many years, and destroy the pinna. Three forms of cutaneous leishmaniasis do not heal spontan- eously: diffuse cutaneous leishmaniasis, leishmaniasis recidivans, and American mucosal leishmaniasis. Diffuse cutaneous leishmaniasis This occurs with L. aethiopica and L. amazonensis infections but is rare. The primary nodule spreads locally without ulceration and secondary blood-borne lesions appear at other sites in the skin, af- fecting especially the face and the cooler extensor surfaces of the limbs (Fig. 8.8.13.7). The eye, mucosae, viscera, and peripheral nerves are spared, which differentiates it clinically from lepromatous leprosy. The infection proceeds gradually over many years. Leishmaniasis recidivans (lupoid leishmaniasis) This is a rare complication of L. tropica infection. The initial sore heals, but papules recrudesce in the edge of the scar and the lesion spreads slowly over many years (Fig. 8.8.13.8). American mucosal leishmaniasis (espundia) Depending on the geographical location, between 4 and 40% of patients with untreated cutaneous

ulcers due to L. brasiliensis Fig. 8.8.13.5 Spreading nodular lesion typical of L. aethiopica, Kenya. Fig. 8.8.13.6 Leishmanial lymphangitis in a man with cutaneous leishmaniasis from Belize. On occasion, hard thickened lymphatics may accompany an insignificant cutaneous lesion. Copyright A. D. M. Bryceson. Fig. 8.8.13.7 Diffuse cutaneous leishmaniasis caused by L. aethiopica, Ethiopia. Fig. 8.8.13.8 Lupoid or recidivans leishmaniasis in a citizen of Baghdad. Courtesy of Dr Ahmed.

8.8.13 Leishmaniasis 1471 develop mucosal lesions, half of them within 2 years of the appear- ance of the original lesion and 90% within 10 years. About one in six patients gives no history of a previous skin lesion. In most cases the nasal mucosa is affected, and in one-third another site is also involved: in order of frequency, the pharynx, palate, larynx, or upper lip. The initial lesion is a nodule and the initial symptom is of nasal obstruction. It commonly presents as protuberant new growth of the nose or lips (Figs. 8.8.13.9 and 8.8.13.10), or cicatrization, which causes an elongated ‘tapir’ nose. Mucosal leishmaniasis is slowly destructive, the septum perforates, and eventually the whole nose and mouth might be destroyed. Death can result from secondary sepsis, starvation, or laryngeal obstruc- tion. Mucosal leishmaniasis is occasionally seen in travellers re- turning from South America. Mucosal lesions are occasionally caused by Old World species, usually in the mouth or larynx, and these patients might have risk factors such as old age, corticosteroid medication, or other immuno- suppression (Fig. 8.8.13.11). Laboratory findings Parasitological diagnosis Leishmania organisms can be isolated from 80% of sores during the first half of their natural course. An incision a few millimetres long is made into the dermis with the point of a scalpel, which is used to scrape dermal tissue and juice. Material obtained can be used to prepare smears for staining with Giemsa, Wright’s, or Leishman’s stains (Fig. 8.8.13.1). Biopsy material can be used to make impres- sion smears, for culture and for histology for differential diagnosis. Leishmanai DNA can be detected by polymerase chain reaction (PCR) using kinetoplast DNA primers and is nearly 99% sensitive and 93% specific. Diagnosis of mucosal leishmaniasis requires a deep punch biopsy specimen. Species identification by PCR is de- sirable in patients with American leishmaniasis to assess the risk of mucosal leishmaniasis. Treatment Old World sores, or those due to L. mexicana, L. amazonensis, and L. peruviana that are not troublesome, can be left to heal naturally. But those that are disfiguring, potentially disabling, inconvenient, or around the ankle where they heal slowly, should be treated ei- ther locally or systemically. Systemic treatment is required when there is risk that the sore might be due to L. brasiliensis, L. pana mensis, or L. guyanensis, when the sore is too large or badly sited for local treatment, when there is lymphatic spread, and for mucosal leishmaniasis, diffuse cutaneous leishmaniasis, and recidivans leishmaniasis. Fig. 8.8.13.9 Espundia. Swollen upper lip and ‘tapir’ nose due to mucosal leishmaniasis, at Instituto de Medicina Tropical ‘Alexander von Humboldt’ Universidad Peruana Cayetano Heredia, Lima, Peru. Copyright D. A. Warrell. Fig. 8.8.13.10 Infiltration of lip and palate due to mucosal leishmaniasis in Peru. Fig. 8.8.13.11 Mucosal leishmaniasis due to L. infantum. Showing erythematous infiltration of the hard palate in an elderly British expatriate living in southern Spain and taking steroids for asthma. Copyright A. D. M. Bryceson.

section 8 Infectious diseases 1472 Local treatment Surgery, curettage, CO_2 laser, cryotherapy, and thermotherapy are effective methods of removing small sores. Infiltration into the le- sion with a pentavalent antimonial, weekly for 2 or 3 weeks or longer, can be successful. The technique needs practice and the infiltration is transiently painful (Fig. 8.8.13.12). An ointment containing 12% paromomycin and 15% methylbenzethonium chloride cures 70% lesions due to L. major in 20 days and might be suitable for lesions caused by other species, except L. brasiliensis, but is not always

well tolerated. Systemic treatment All cutaneous species of leishmania are sensitive to pentavalent antimonials in conventional dosage except L. aethiopica, where paromomycin can be used. Pentamidine is effective but seldom warranted because of toxicity. Miltefosine is effective for L. major, L. mexicana, L. guyanensis and L. panamensis infections. Patients with diffuse cutaneous leishmaniasis should be treated with two drugs for at least 2 months longer than it takes to clear parasites from the skin, Miltefosine is also effective for mucoal leishmaniasis. In addition, they might require antibiotics for secondary sepsis, atten- tion to nutrition, and, later, plastic surgery. Visceral leishmaniasis Epidemiology Visceral leishmaniasis is found in four main zoogeographical zones: the Ganges Brahmaputra plains, the Mediterranean basin extending into West and Central Asia, Sudan and East Africa, and Brazil (see Table 8.8.13.1). Around the Mediterranean littoral, across the Middle East and central Asia, and in northern and eastern China, zoonotic visceral leishmaniasis is endemic in many places, where as many as 50% of domestic and stray dogs are infected. Children under 5 years of age are especially affected. It is the second most common infectious cause of fever of unknown origin in children in the Balkan countries. HIV infection is a risk factor for adults. In other places, the disease is sporadic. Nonimmune adults such as tourists, hunters, and soldiers are susceptible. The Ganges and Brahamputra river valleys of India and Bangladesh are the home of epidemic anthroponotic visceral leishmaniasis, or kala-azar, which returns approximately every 15–20 years. Most cases are in young people under 15 years of age and are found in clusters. The annual incidence is about 250 per 100 000. About 50% of household contacts of cases in Bihar India are seropositive, one in four of whom will develop disease. Malnutrition predisposes to clinical disease. In the interepidemic period, the parasite survives in patients with post-kala-azar dermal leishmaniasis. Visceral leishmaniasis is endemic in parts of Sudan, where it can be both anthroponotic and zoonotic, and in adjacent parts of Ethiopia and Kenya. Older children and teenagers are most com- monly affected. Sporadic cases also occur in nomads and visitors. In remote areas, half the cases do not reach a medical facility and 90% of deaths go unreported. In South America, the disease is most common in north-eastern Brazil, where older children are affected. Previously a rural disease, it is becoming increasingly important in towns. Visceral leishmaniasis might appear unexpectedly in immuno- suppressed patients (e.g. after renal transplantation), with haem- atological malignancies, while receiving immunosuppressive drugs, and in pregnant women. In endemic areas, it is an opportunistic in- fection in patients with HIV infection. Visceral leishmaniasis can be transmitted by blood transfusion from subclinical cases; parasites were cultured from 2 to 4% of donor blood samples in endemic areas of France and Spain. Pathogenesis and pathology For every case of classical visceral leishmaniasis, there are about 30 subclinical infections that cause leishmanin positivity and lifelong immunity to the infecting species. Established visceral infections are Fig. 8.8.13.12 Infiltrating a lesion of cutaneous leishmaniasis with sodium stibogluconate. The edge of the lesion is demarcated using a ballpoint pen and infiltrated radially from several points on its perimeter using an intradermal syringe and needle. Copyright A. D. M. Bryceson. Table 8.8.13.2 Dosage regimens for the treatment of leishmaniasis Drug Dose Sodium stibogluconate or meglumine antimoniate By body surface area, so that: 10–20 mg Sb/kg body weight is given once daily for 21 days (visceral or cutaneous disease) or 28 days (visceral or mucosal disease)—PKDL may need treatment for 2–4 months. By body weight: 20 mg/kg per dose as described, but less well tolerated by adults Amphotericin B desoxycholate 1 mg/kg body weight on alternate days for 2 weeks (visceral disease) or 4–6 weeks (mucosal disease) Liposomal amphotericin B Ampoules of 50 mg, 3–5 mg/kg body weight per daily dose over a 3–6 day period, to a total of 21 mg/kg. In India, a total dose of 15 mg/ kg is sufficient. A single dose of 10 mg/kg has a comparable cure rate. A 20-day regimen of

2.5 mg/ kg cures PKDL in Sudan Miltefosine Adult dose 100–150 mg daily for 28 days; paediatric dose 2.5 mg/kg body weight daily for 28 days Paromomycin 15 mg (11 mg base)/kg body weight daily for 21 days Ketoconazole 60 mg/day (adult) for 4–6 weeks Coadministered combinations Two of the three drugs liposomal amphotericin B, miltefosine, and paromomycin, given in the doses described for 7–10 days See text for choice of drug regimen.

8.8.13 Leishmaniasis 1473 characterized by the failure of specific cell-mediated immunity. The leishmanin test is negative. The parasite multiplies freely in macro- phages in the spleen, bone marrow, lymphoid tissues, jejunal sub- mucosa, and Kupffer cells of the liver. Histology shows a variable degree of granuloma formation and interstitial inflammation in the liver that might lead to fibrosis. In the spleen especially, there is mas- sive reticuloendothelial hyperplasia and infiltration with plasma cells. Small splenic infarcts might develop. Antibodies, polyclonal IgG, and immune complexes circulate at high concentration but rarely cause complications. About half of the patients have mild malabsorption but seldom diarrhoea. When present, jaundice usually has another cause such as viral hepatitis. Spontaneous bleeding is unusual and is associated with hypoprothrombinaemia. Visceral leishmaniasis is characterized by anaemia, leukopenia, thrombocytopenia, and hypoalbuminaemia. The anaemia results mainly from shortened red-cell survival with destruction of cells in the spleen, together with splenic pooling and sequestration (hypersplenism). In young children, profound an- aemia might develop rapidly as a result of severe haemolysis. Death is usually due to secondary infection. Clinical features The male/female ratio is between 3:1 and 4:1. The incubation period is usually 2 to 8 months. In endemic areas, the onset is usually ill defined. The patient develops fever, discomfort from an enlarged spleen, abdominal swelling, weight loss, cough, or diarrhoea. Classically, the fever spikes twice daily, usually without rigors, but daily, irregular, or undulant fevers are common. During an epidemic or in visitors to an epidemic area, symptoms can start abruptly with high fever and rapid progression of illness with toxaemia, weakness, dyspnoea, and acute anaemia. Physical examination of early cases might show only symptom- less splenomegaly. Patients with advanced disease are wasted, with hair changes and pedal oedema typical of hypoalbuminaemia. Hyperpigmentation is characteristic of visceral leishmaniasis in India (kala-azar means ‘black disease’). The spleen is huge, smooth, and nontender unless there has been a recent infarct. The liver is moderately enlarged in one-third of cases. In African patients, a generalized lymphadenopathy is common. Over months or years, the patient becomes emaciated, with a distended abdomen (Fig. 8.8.13.13). Intercurrent infections are common, especially pneumococcal otitis media, pneumonia, septicaemia, tuberculosis, measles, dysentery, other locally im- portant infections, and rarely, cancrum oris. Untreated, between 80 and 90% of patients die. Post-kala-azar dermal leishmaniasis (PKDL) Up to 10% of Indian patients and up to 50% of Sudanese and East African patients develop a rash on the face, extensor surfaces of the arms and legs, and trunk after recovery from visceral leishman- iasis. In India, the rash begins after an interval of 1 or 2 years and progresses over many years: pale macules become erythematous plaques, papules, or nodules resembling lepromatous leprosy, and almost the entire body surface may be involved, including buccal and genital mucosa, and conjunctiva (Fig. 8.8.13.14). In Kenya, the rash usually appears while the patient is still recovering, as dis- crete nodules which show a granulomatous histology with scanty parasites. It heals spontaneously within 6 months (Fig. 8.8.13.15). Sudanese patients show a mixture of these two forms. PKDL is rarely seen after L. infantum infections. Visceral leishmaniasis immunosuppression and HIV infection Visceral leishmaniasis can be associated with HIV infection. The presentation might be atypical and with unusual skin lesions. Antiretroviral treatment has greatly reduced the

clinical impact of coinfection, but in some patients leishmaniasis now presents as an immune reconstitution inflammatory syndrome. The parasite might be found by chance, for example, in a rectal or skin biopsy taken for other purposes, or in bronchoscopic lavage. The bone marrow has abundant parasites, but two-thirds of cases have no detectable antileishmanial antibodies. In 90% of cases, the CD4 count is less than 200 cells/μl. Response to treatment is poor and relapse usual (see 'Treatment', next). Patients are now regularly seen who have Fig. 8.8.13.13 Visceral leishmaniasis in a Kenyan child. Note the wasting, massive enlargement of liver and spleen, and increased pigmentation. Fig. 8.8.13.14 Post-kala-azar dermal leishmaniasis in an Indian child. Showing the typical hypopigmented macular rash. Note also the nodules on the lower lip.

section 8 Infectious diseases 1474 acquired their leishmaniasis in the Mediterranean and have a risk factor such as autoimmune disease, treatment with biological agents of diabetes. Laboratory diagnosis Parasitological diagnosis Leishmania organisms can be isolated from reticuloendothelial tissue. Yields are of the order of: spleen, over 95% cases; bone marrow or liver, 85%; lymph node in Sudan, 65%; and buffy coat, 70%. Bone marrow aspiration is most commonly used, but splenic aspiration is simple, painless, and safe if the prothrombin time is normal and the platelet count above 40 × 109/litre. PCR for leishmanial DNA in bone marrow is even more sensitive. PCR for leishmanial DNA in blood is useful for follow up HIV coinfected patients. Serological diagnosis Except in HIV coinfections, antibodies are present in high titre, useful for diagnosis, and may replace parasite diagnosis in remote areas. Indirect immunofluorescence is the gold standard but, for fieldwork, it has been replaced by enzyme-linked immunosorbent assay, direct agglutination, and the rK39 antigen dipstick. All give comparable results with sensitivities of about 90% and specificities above 95% (positive predictive value c.99% and negative predictive value c.70%). The leishmanin skin test is negative. Other findings There is a normochromic, normocytic anaemia without reticulocytosis, and neutropenia, eosinopenia, and thrombocytopenia. Serum albumin is low (c.20 g/litre) and globulin high (c.70 g/litre), IgG and IgM are ap- proximately thrice and twice the normal population values. Hepatic en- zymes and prothrombin and partial thromboplastin times are usually normal. Treatment Chemotherapy Liposomal amphotericin B by intravenous infusion is the best drug for visceral leishmaniasis in adults and children. It is concentrated and retained in reticuloendothelial cells and is not toxic. Over 99% patients respond promptly, but HIV coinfected patients might re- lapse. The drug is also effective against PKDL in India and Sudan and it is the drug of choice in pregnancy. The drug is becoming afford- able in endemic countries where the World Health Organization has negotiated a 90% reduction in price. Otherwise, a pentavalent an- timonial remains the drug of choice in most situations, except in Bihar, India. See Table 8.8.13.2 for dosage regimens. Conventional amphotericin B deoxycholate is cheaper than liposomal amphotericin B and just as effective, though more toxic, and is useful for patients unresponsive to antimonials. Sodium stibogluconate containing 100 mg Sb/ml and meglumine antimoniate containing 85 mg Sb/ml are of equal efficacy and tox- icity. The drug is administered by intramuscular injection, which can be painful, or by intravenous injection through a fine-gauge needle, slowly or by infusion in 50–100 ml of 5% dextrose over 20 min to reduce the risk of venous thrombosis. Treatment is given daily for 28 days. Usually the drug is well tolerated but towards the end of treatment there may be malaise, anorexia, nausea, vomiting, and muscle pains. Should toxic effects develop, rest for 1 day and re- duce each dose by 2 mg Sb/kg. Hepatic and pancreatic enzyme levels might rise, and haemoglobin levels fall, but they return to normal when treatment is stopped. The electrocardiogram develops unim- portant T-wave changes. At higher doses, the corrected QT interval might be prolonged, heralding the development of a serious ar- rhythmia. Cure rates exceed 95%, except in Bihar, north of the river Ganges, where primary antimony

resistance is spreading and up to 60% patients do not respond to antimonials. The aminoglycoside antibiotic paromomycin, is equally effective and well tolerated, but cure rates vary between countries and en- demic foci. It is given by intramuscular injection or intravenous infusion over 90 min. Renal function and hearing should be moni- tored. Paromomycin is not readily available outside countries with control programmes. The sole oral drug, miltefosine, cures from 90 to 94% of HIV- negative adults and children with visceral leishmaniasis in Sudan and India, even in areas of parasite resistance to antimonials. Trials in Bihar have shown that 7–10 days courses of combined treatment with any two of liposomal amphotericin B, paromomycin and miltefosine are highly effective. It has now been recommended for use in treating patients with visceral leishmaniasis in the Indian subcontinent. Miltefosine is associated with significant nausea and vomiting. It is also potentially teratogenic, so patients should avoid pregnancy. Patients who are immunosuppressed as a result of HIV coinfec tion or immunosuppressive drugs respond slowly, require longer treatment, and are more liable to relapse than immunocompe- tent patients. Ideally, treatment of such patients should be moni- tored by splenic aspirate counts of parasites and continued for 2 or 3 weeks beyond parasitological cure. Antimonials cause adverse ef- fects in two-thirds of HIV coinfected patients and can precipitate clinical pancreatitis. Liposomal amphotericin B and paromomycin are effective and well tolerated. Relapse might be prevented by secondary prophylaxis with pentamidine given every 2 weeks. Antiretroviral therapy (ART) reduces the number of relapses and delays their onset. PKDL can be treated in India with miltefosine for 12 weeks or amphotericin B deoxycholate for 3–4 months; and in Sudan and East Fig. 8.8.13.15 Post-kala-azar dermal leishmaniasis in a Kenyan child. Showing the typical collection of small discrete nodules on the face. Copyright A. D. M. Bryceson.

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