

## Editorial

# AIDS and leishmaniasis

### Transmission of *Leishmania*

*Leishmania* are protozoal parasites carried from one infected host to another by sandflies. *Leishmania* cause a range of cutaneous, mucocutaneous, and systemic (visceral) diseases in humans and animals. In Europe *L infantum* is enzootic among domestic dogs in the Mediterranean littoral, where approximately 10–30% of pet dogs have clinical or serological evidence of leishmaniasis.<sup>1,2</sup> Dogs are generally unable to mount an effective cellular immune response against *L infantum*, so parasites remain in skin lesions, in circulation, or in tissue macrophages permanently. Canine leishmaniasis responds poorly to treatment, typically running a chronic, relapsing course until the parasites become unresponsive and the animal dies. Clinical leishmaniasis among immunocompetent humans is more than 1000-fold rarer than canine leishmaniasis, with only about 500 infections occurring annually in the Mediterranean area; children are mainly affected. Transmission of *L infantum* occurs during the summer and is focal, with small zones of transmission in suburban and semirural areas.

### Infection, latency, and disease

Subclinical infection with *Leishmania* confers lifelong immunity. In contrast with clinical leishmaniasis, this is common in southern Europe: 5–15% of adults in parts of Italy, for example, have a positive leishmanin skin test.<sup>1,2</sup> Animal models suggest that, in previously infected individuals, antigen specific T cells and NK cells interact with parasitised phagocytes in an equilibrium such that only a very low level of replication of *Leishmania* occurs: this in turn boosts cellular immunity.<sup>3</sup> In immunocompromised hosts this equilibrium is lost. There are numerous cases and case series which show that, in humans, suppression of cell mediated immunity by HIV (or less commonly, by steroids, cytotoxics, or malignancies) encourages the reactivation of latent *Leishmania* infection.

### Visceral leishmaniasis as an opportunistic infection

Currently, 20–70% of patients with visceral leishmaniasis (VL) in the Mediterranean countries are infected with the human immunodeficiency virus (HIV+).<sup>4</sup> In cohort studies from France, Italy, Spain, and Portugal, 1.5–9% of HIV+ patients developed VL.<sup>4</sup> Leishmaniasis is even more common among HIV+ patients who are febrile—the clinicopathological conference in this issue of *Genitourinary Medicine* (p 308) is a good illustration of this. A study in Madrid of pyrexia of unknown origin (PUO) among HIV+ patients (who were predominantly injecting drug users (IDUs)), found VL to be the cause in 14% of cases.<sup>5</sup> In Alicante, Spain, 46% of 24 episodes of PUO among 231 HIV+ patients were caused by *Leishmania*.<sup>6</sup> In Paris, 8% of 49 episodes of PUO among 270 HIV+ patients were caused by *Leishmania*.<sup>7</sup> In the endemic area, these

episodes could either represent new infections or reactivation of subclinical infections. Some authors suggest that serological responses in HIV+ patients can differentiate reactivation of leishmaniasis (resulting in low anti-*Leishmania* antibody titres) from newly acquired infection (with high titres).<sup>1</sup> The predominance of IDUs who are coinfecting with HIV and *Leishmania*, and the occurrence of small clusters of coinfections, have led to the suggestion that transmission of leishmaniasis occurs in shared injecting equipment.<sup>1,2</sup> However, molecular typing of strains of *Leishmania* among IDUs, which could confirm this hypothesis, has not been done. Over 700 HIV+ patients have now been reported with all clinical forms of leishmaniasis.<sup>4</sup> The absence of cell mediated immunity means parasites are not localised to a single site, and the most commonly reported form of *Leishmania* infection in HIV+ patients is VL. Less commonly reported forms in HIV+ patients have been cutaneous or diffuse cutaneous leishmaniasis (species: *Leishmania major*, *L mexicana* complex, *L braziliensis* complex, *L infantum*; reported from Kenya, Ethiopia, Malawi, Israel, Europe); mucocutaneous leishmaniasis (species: *L braziliensis* in Brazil or *L infantum* in Europe); or post kala-azar dermal leishmaniasis (due to *L infantum* in Spain). In the United Kingdom and northern Europe, VL is regularly diagnosed in HIV+ patients, such as the patient reported in this issue of *Genitourinary Medicine*; around 5–10 such cases occur annually in the United Kingdom. There is always a history of the patient having visited the endemic area months or years previously, but no previous illness suggestive of leishmaniasis. Presumably, all of these patients are suffering from a reactivation of subclinical leishmaniasis. Cases of VL in HIV+ patients have been reported mainly from southern Europe, but also from North Africa (*L infantum*), Brazil (*L chagasi*), Kenya, Ethiopia, Sudan, and India (*L donovani*).

### Clinical features of *Leishmania*/HIV coinfection

The clinical presentation may be entirely typical of kala-azar, with massive splenomegaly, pancytopenia, fever, and wasting. Other patients have “atypical” VL with slight or no splenomegaly and non-specific symptoms of fever, wasting, and malaise. They may be diagnosed unexpectedly when a bone marrow aspirate is taken for suspected *M avium* infection or lymphoma. HIV/*Leishmania* coinfecting patients may have predominantly gastrointestinal involvement, with symptoms of diarrhoea and wasting, and *Leishmania* detected in biopsies of oesophagus, duodenum, or rectum. The larynx may also be involved, either alone or with gastrointestinal involvement. *Leishmania* amastigotes may be an incidental finding in biopsies of skin lesions such as Kaposi’s sarcoma or herpes zoster. No characteristic skin lesions have been described in HIV+ patients, and it is possible that normal skin is also parasitised. *Leishmania* serology is negative in 20–40% of HIV+ VL patients. Parasites are abundant in bone mar-

row, and microscopy of bone marrow aspirates yields the diagnosis in 91–97% of cases. The single most important factor in the diagnosis is the experience of the laboratory, and specifically the skill of the microscopist. In 50–75% of HIV+ VL patients, microscopy or *Leishmania* culture of the buffy coat of peripheral blood will be positive.<sup>4</sup> *Leishmania* can be cultured in special media from bone marrow aspirates in more than 95% of HIV+ VL cases. Cultures are necessary for parasite identification. The *L. infantum* strains (zymodemes) in European HIV+ patients are a mixture of three types. Commonest are strains found in canines and in immunocompetent patients with VL—for example, MON-1. Some strains are found which cause canine leishmaniasis and occasionally cause cutaneous leishmaniasis in humans, such as MON-24. Most intriguing are the eight or more zymodemes which have never previously been isolated from humans or animals, suggesting that they are of low virulence. Because they belong to the species *L. infantum*, an animal reservoir will probably be found eventually.

*Leishmania* infections in HIV+ patients are clinically important, and are very different clinically and epidemiologically from classic leishmaniasis, so it seems logical to consider them as being AIDS defining; many authors have suggested this, and the WHO endorses this view.<sup>4</sup> While this would not lead to large numbers of HIV+ patients being redesignated as having AIDS, it would allow more complete data collection of HIV/*Leishmania* coinfections, which are likely to become more common in countries beyond Europe. About 80% of HIV/*Leishmania* coinfecting patients have had another AIDS defining opportunistic infection, and more than 87% have a CD4 + count < 200 × 10<sup>6</sup>/l at the time leishmaniasis is diagnosed.<sup>8</sup>

### Treatment

The median survival among HIV+ VL patients is around 13–19 months.<sup>4,9</sup> How should coinfecting patients be treated? At present, treatment of leishmaniasis HIV+ patients is unsatisfactory, just as it is in canine leishmaniasis. Central to both situations is the lack of cell mediated immunity to assist in parasite clearance, and the fact that a “sterile cure” is never obtained. Interferon gamma (IFN- $\gamma$ ) combined with anti-leishmania drug regimens can improve parasite clearance rates in immunocompetent patients with VL. This approach has been tried in HIV+ patients, but the effect on relapses is either unknown<sup>10</sup> or unsatisfactory.<sup>11</sup> The response to the pentavalent antimonials (Sb<sup>v</sup>)—that is, sodium stibogluconate and meglumine antimoniate, or other anti-*Leishmania* drugs seems both slower and less satisfactory in HIV+ patients.<sup>4,8,9</sup> Amphotericin B, whether as the parent drug (Fungizone) or in liposomal form (AmBisome) is effective against VL.<sup>12,13</sup> AmBisome is more effective than amphotericin B in murine models, probably because it produces very high levels in liver and spleen.<sup>14</sup> It is also less toxic in animals and in humans. However, the targeting of liposomes to liver and spleen could be less important in HIV+ VL patients, in whom very large parasite loads, unusual sites of infection, and infection of cells other than macrophages—for example, circulating neutrophils, occur. There are no randomised trials comparing any agents for treatment or prophylaxis of visceral leishmaniasis in HIV+ patients. Clinical remission should usually be achievable in the first presentation of VL by using any of the following: Sb<sup>v</sup> 20 mg/kg/day for 30 days; or amphotericin B 0.5 mg/kg/day (or 1 mg/kg on alternate days) to a total dose of about 20 mg/kg; or AmBisome 3–4 mg/kg/day or on alternate days to a total dose of about 30 mg/kg.<sup>4,12</sup> The major side effects of Sb<sup>v</sup> are hyperamylasaemia

or pancreatitis, ECG changes, arthralgia, malaise, and cytopenias. Exaggerated toxicity of Sb<sup>v</sup>, including severe pancreatitis, is sometimes seen.<sup>15</sup>

### Can maintenance therapy prevent relapses?

Several drugs have been tried as maintenance therapy: Sb<sup>v</sup> 850 mg monthly,<sup>16</sup> pentamidine 4 mg/kg 2–4 weekly, allopurinol, or itraconazole. The true value of maintenance is unknown, as there are no controlled trials. In a series of 78 HIV+ VL patients from Italy who were treated with Sb<sup>v</sup>, amphotericin B, AmBisome, pentamidine, allopurinol, and itraconazole, alone or in combination, none achieved definitive parasitological cure. Most of them had a relapse of VL within 2–7 months of receiving treatment.<sup>1</sup> The definition of “relapse” is also problematic: parasites may fall below the level of detection, only to become detectable again in the majority of cases. Moreover, patients who have relapsed after Sb<sup>v</sup> or AmBisome treatment may become unresponsive to the same drug when used again, and isolates of *Leishmania* may become less sensitive in vitro. As the CD4+ count falls, so the clinical picture of VL may become less typical, but the symptoms may also become milder. This may seem paradoxical, but it suggests that it is the host response to *Leishmania*, and not toxicity of the parasites, which causes the clinical illness. In some cases, the patient may have a huge burden of parasites in bone marrow, gut mucosa, or skin, but few symptoms, and remain stable for months without treatment.<sup>11</sup> For these reasons, the decision to treat each relapse of leishmaniasis should be based on a careful weighing up of the benefits, risks, and costs of treatment, and the likely outcomes.

### Global prospects

Most of the overlap between the HIV pandemic and the endemic areas for *Leishmania* infection has been in Europe. What does the future hold for other endemic areas, in the light of the European experience? There is still little geographical overlap in Kenya, Sudan, and India—but this situation is changing. In Brazil, for example, HIV is most prevalent in urban areas in the south and *Leishmania* infections are endemic in rural areas in the north east: but *Leishmania* is urbanising just as HIV is becoming more prevalent in smaller settlements. Of the “tropical” parasites, *Leishmania* and *Trypanosoma cruzi* are most akin to *Toxoplasma gondii*. It is likely that physicians in *Leishmania* endemic countries will become increasingly familiar with HIV/*Leishmania* coinfections in the years ahead.

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