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Kala-Azar as an AIDS-Related Opportunistic Infection

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ABSTRACT

Visceral leishmaniasis (kala-azar) is a worldwide disseminated protozoal infection primarily transmitted by sand flies. Because host defense against this intracellular infection is T-cell-dependent, kala-azar has predictably joined the list of AIDS-related opportunistic infections in endemic areas. The vast majority of patients with AIDS-associated kala-azar are currently found in southern Europe (the Mediterranean basin, especially Spain in injection drug users); future cases will inevitably arise in other endemic regions including India, East Africa and Sudan, and Brazil. In CD4 cell-deficient HIV-infected individuals, kala-azar likely represents recrudescence of previously controlled asymptomatic infection; in drug users, newly acquired infection may result from transmission via shared needles. Coinfected patients are frequently parasitemic and may show atypical clinical presentations, unusual multi-organ involvement, and absent antileishmanial antibodies. Diagnosis is made by microscopic examination or culture of aspirate or biopsy of any involved tissue (primarily bone marrow) or by blood smear or culture. Conventional treatment (pentavalent antimonials) induces initial remission in about 50% of patients; amphotericin B and its new lipid formulations appear more active. If suppressive maintenance therapy is not used, relapse within 1 year is typical. In AIDS patients with a first episode of visceral kala-azar, up to 25% die within 1 month if treatment is stopped. Optimal primary and secondary prophylaxis for AIDS-related kala-azar remain to be determined; life-long maintenance therapy is becoming an accepted approach.

INTRODUCTION

VISCERAL LEISHMANIASIS, also known as kala-azar ("black fever" in Hindi), is a disseminated protozoal infection spread by the bite of infected sand flies. While kala-azar has been reported from nearly 50 countries across the world, most of the estimated 500,000 new cases each year currently arise in rural areas of one of four endemic regions: India, East Africa and Sudan, Brazil, and southern Europe (Spain to Greece) along the Mediterranean coast. HIV, of course, is also well-established in these same regions.

Three strains of *Leishmania* cause most visceral infections: *L. donovani, L. chagasi,* and *L. infantum.* The name of the latter species, found almost exclusively in Mediterranean countries, reflected the high proportion of patients in these areas who, at least in the pre-HIV era, were children under the age of 15 years and often much younger. Young children are also most commonly infected in Brazil (*L. chagasi*), whereas in Asia and Africa (*L. donovani*) adults and children have been and currently remain at similar risk for developing kala-azar. However, as HIV and leishmaniasis continue to overlap in the future, more cases of kala-azar

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in adults are certainly expected in all regions. Cutaneous and mucosal disease, the two other principal forms of leishmaniasis, are quite distinct in all regards from visceral infection, and in contrast to kala-azar, have thus far seldom been associated with AIDS.

ACQUISITION AND PATHOGENESIS OF KALA-AZAR

After inoculation into the skin, visceralizing strains of *Leishmania* find their way into the liver, spleen, bone marrow, and lymph nodes, enter tissue macrophages, and replicate intracellularly. In the susceptible host who becomes symptomatic with fully established kala-azar, parasitization of visceral macrophages can be striking (Fig. 1). In the past, it was assumed that all infected individuals developed clinical evidence of kala-azar expressed as fever, weight loss, weakness, hepatosplenomegaly and pancytopenia. However, it is now clear that in many regions around the world, only a minority of those infected actually develop symptomatic disease. As many as three quarters of individuals appear to either spontaneously control infection and remain asymptomatic or develop oligosymptomatic disease, which resolves without treatment. The best correlate of such clinical responses is the development of an intact T-cell-dependent, cytokine-mediated mechanism that induces macrophage activation and antileishmanial activity (see below).

Nevertheless, it is also likely that all populations of infected children and adults, including those with subclinical infection as well as those who are treated and apparently cured, probably harbor quiescent intracellular parasites for life. Thus, while not necessarily common in otherwise healthy individuals, remote, or late, recrudescence is a well-recognized feature of kala-azar for which all previously infected patients remain at some risk. Relapse may occur spontaneously or be prompted by treatment with immunosuppressive agents (corticosteroids) or the development of a T-cell-deficient state. In countries where injection drug use is not common, AIDS-related kala-azar is thought to most likely represent recrudescence of previously controlled, latent visceral infection rather than newly acquired infection. Therefore, from this perspective, visceral leishmaniasis behaves like many other AIDS-associated intracellular opportunistic infections (OIs).

However, it is clear that patients may also first acquire leishmaniasis after becoming infected with HIV, often when they are already CD4 cell-deficient. This sequence may occur with some regularity in injection drug users (IDUs) in southern Europe, and has raised the possibility of man-to-man transmission of *L. infantum* via shared needles. Seroepidemiological studies, for example, have indicated not only a

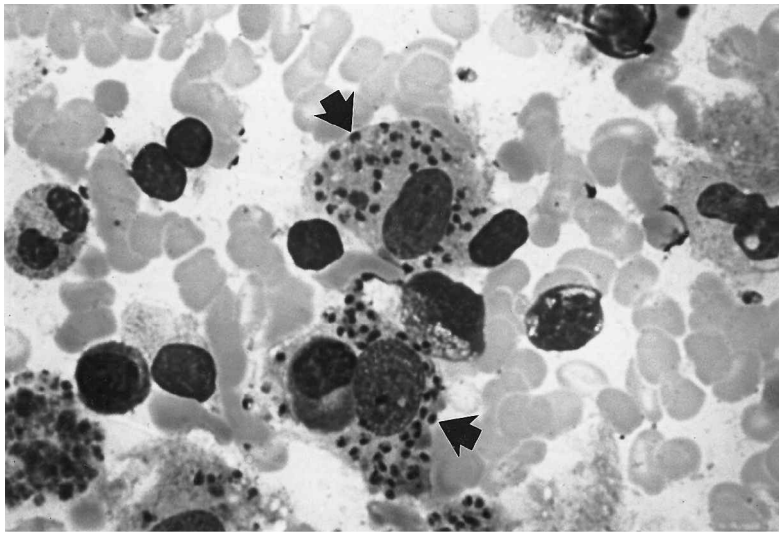

FIG. 1. Giemsa-stained smear of splenic aspirate from an Indian patient with kala-azar showing parasitized splenic macrophages containing numerous *L. donovani* amastigotes (arrows) (×600).

high seroprevalence rate for antileishmanial antibody in Spanish IDUs, but also documented seroconversion in urban areas where sandflies are not typically found. There also is no reason, of course, why CD4 cell-deficient individuals cannot be exposed to sandflies in rural or semiurban locales and acquire infection via the traditional route.

IMMUNE RESPONSE IN KALA-AZAR

A humoral response with high levels of antileishmanial IgG develops in virtually all otherwise healthy individuals, and antibody persists for life. However, specific antibody is not protective in initial infection; its presence does not distinguish between those who develop asymptomatic versus symptomatic infection nor distinguish between newly acquired versus reactivated infection, and antibody does not prevent relapse. In contrast, abundant experimental work and emerging clinical studies have demonstrated that the capacity to spontaneously control and resolve visceral infection is strictly T-cell-dependent and requires an intact CD4 cell-mediated response of the Th1-cell-associated phenotype. This complex response, which involves granuloma formation, is regulated by a variety of interdigitating inflammatory cytokines including interleukin 12 (IL-12), IL-2, and interferon-γ (IFN-γ) and probably others such as tumor necrosis factor-α. The net effect of this response is sufficient mononuclear phagocyte stimulation to induce potent intracellular leishmanicidal activity, control over infection, and satisfactory lifelong suppression of residual surviving parasites.

In some patients, however, presumably many of those who develop clinically overt symptomatic kala-azar, the Th1 cell response fails to fully develop and/or an aberrant anti-host defense (Th2-cell-associated) CD4 cell response is also triggered and becomes prominent. Probably via the suppressive/deactivating effects of cytokines such as IL-10 and IL-4 (and perhaps others), this Th2 cell mechanism inhibits T-cell and macrophage activation thereby permitting intracellular infection to flourish. The apparent capacity of HIV infection to induce a Th2 cell-like state and along with CD4 cell depletion to abolish the mechanisms of Th1 cell cytokine secretion clearly bear directly on the development of all intracellular OIs, including kala-azar.

HIV-ASSOCIATED KALA-AZAR

Epidemiology

The first case of AIDS-related kala-azar was reported in 1985. Although 30% of the world's HIV-infected population is estimated to reside in regions where leishmaniasis is endemic, it is surprising that fewer than 1000 cases of co-infection were reported to the World Health Organization during 1985–1995, and that the vast majority of cases occurred not in Africa or India but in southern Europe (Table 1). The absence of routine HIV testing in rural areas of the developing world, underreporting, and suboptimal diagnosis and data collection likely contribute to these latter observations. However, the pace of HIV intrusion into rural areas of endemic countries such as India and Sudan may not have been especially rapid during the first part of this particular 10-year period, and it is also well to recall that children and not adults are those typically at risk for kala-azar in regions such as Brazil.

The epidemiological picture of HIV-associated kala-azar, which has emerged from data collected in southern Europe (Table 1) may not be representative of coinfection in other parts of the world. For example, 25–75% of kala-azar in adults in Europe is now thought to be HIV-related, and in Spain, for example, visceral infection with *L. infantum* is a particularly common OI. In addition, amongst HIV-infected Europeans: (a) between 2–9% appear to be coinfected with *L. infantum,* (b) 7–17% of episodes of fever of unknown origin (FUO) are due to kala-azar, and (c) routine bone marrow aspirates in some regions may show *Leishmania* amatigotes in as many as 1 out of 10 patients, half of whom may be asymptomatic and not suspected of having *Leishmania* infection. Among co-infected patients in southern Europe, particularly Spain, there is also a striking preponderance of IDUs and likely additional transmission of *L. infantum* via needle use. Therefore, in ar-

Table 1. Selected Features in 858 Patients with HIV-Associated Kala-Azar Reported to the World Health Organization, 1985–1995[a]

	No. or % of patients
Continent and principal countries:	
Europe (Spain—450, Italy—130, France—127, Portugal—22)	729
Africa (Ethiopia—29, Tunisia—28, Kenya—25)	90
The Americas (Brazil—25, United States—5)	34
Asia (India—5)	5
Males	80–90%
Age, 20–40 years	80–90%
Injection drug users	65–70%
CD4 cell count at kala-azar diagnosis, cells/mm^3	
<200	80–90%
<100	50–60%
<50	30–40%

[a]Adapted from Alvar et al. (1997) and *World Health Organization Weekly Epidemiological Record* (21 February 1997).

eas of southern Europe, there may be considerably more urban man-to-man rather than rural sandfly-to-man spread and primarily newly acquired rather than reactivated infection. However, other important characteristics illustrated by co-infected patients in southern Europe related to clinical manifestations, diagnostic procedures, response to treatment, and outcome are likely to be generally relevant to AIDS-related kala-azar.

Clinical manifestations

In conventional kala-azar (unrelated to co-infection with HIV), most patients present with the triad of fever, splenomegaly (often striking), and varying degrees of pancytopenia; many also have hepatomegaly and a variety of associated constitutional symptoms as well. In immunocompetent individuals, infection is also thought to be largely restricted to the spleen, bone marrow, liver, and probably lymph nodes; seldom are parasites documented either outside macrophages or in locations other than within these reticuloendothelial system organs.

While as many as 75% of HIV-infected individuals with kala-azar also show that anticipated combination of fever, splenomegaly, and pancytopenia (Table 1), there are numerous reports in which up to 30–45% of such patients failed to show one or more of these three cardinal manifestations, sometimes making it quite difficult to initially suspect kala-azar. Ten to 15% of patients show clearly atypical clinical presentations including FUO alone, gastrointestinal involvement, pneumonitis, pleural effusion or solitary pulmonary nodule, and skin lesions. Of note, some patients, up to 10%, are entirely asymptomatic despite having characteristic amastigotes discovered within monocytes in peripheral blood smears or within macrophages on bone marrow or lymph node biopsy. However, in patients who die with unsuspected kala-azar (as well as in many who have received conventional treatment), postmortem examination typically confirms disseminated infection, parasitized cells other than macrophages, and multi-organ involvement, which was clinically inapparent. In the latter setting, parasites can be found in the lung, skin, gastrointestinal tract mucosa, pancreas, myocardium, larynx, and adrenal glands.

Not surprisingly, patients with HIV-associated kala-azar most often have advanced HIV infection with overt T-cell deficiency at the time kala-azar is first diagnosed: about 50% have already experienced other AIDS-related events including OIs and CD4 cell counts are usually <200 cells/mm^3 (Table 1). In 20–30% of patients in southern Europe in whom kala-azar develops, this infection is the first AIDS-defining event. In some instances, co-existing OIs (simultaneously present in 20–50% of patients) overshadow the manifestations of kala-azar and obscure the diagnosis. There is also preliminary evidence that visceral leishmaniasis, as an inflammatory disease, can promote or accelerate HIV infection as judged by increases in plasma viral load.

Suspecting the diagnosis

In an endemic region, kala-azar is not difficult to suspect in a febrile patient ill for several weeks or even months who also has splenomegaly and anemia, leukopenia, and/or thrombocytopenia. In these regions, other potential considerations in such patients would include malaria, typhoid fever, and tuberculosis as well as other less common infections. Because asymptomatic (subclinical) visceral infection may not reactivate and be expressed clinically until years or even decades after original acquisition, a careful history of where patients have lived or extensively traveled is particularly important in leading the clinician to suspect this diagnosis in nonendemic areas. Not surprisingly, the handful of patients with AIDS-related kala-azar thus far seen in the United States were all born or lived for years in endemic regions abroad. Presumably, these individuals were infected with *Leishmania* long before acquiring HIV; with time, they became sufficiently CD4 cell-deficient to develop recrudescent kala-azar years later while in the United States. However, it is worth pointing out that newly acquired leishmaniasis (a) can also develop in HIV-infected travelers who visit high-transmission endemic regions and (b) may also be common in drug users because of sharing blood-contaminated needles. The likelihood of needle-related transmission is supported, for example, by the remarkably high incidence of parasitemia documented by peripheral blood smear (50%) or buffy coat culture (67%) in such patients in Spain.

Diagnostic procedures

In any patient, HIV-infected or not, a firm diagnosis of kala-azar conventionally rests on microscopic demonstration of the amastigote form of the protozoan in clinical specimens, usually aspirate smears or biopsies of bone marrow, spleen, or lymph node (Fig. 1). These same materials (or any involved tissue or fluid, including buffy coat) can also be cultured, and after several days of *in vitro* transformation yield the motile, culture-derived promastigote form.

Serologic testing for circulating antileishmanial IgG, present in 95–100% of patients with conventional kala-azar, is often performed as an initial diagnostic assay in many regions of the world. It has been shown repeatedly, however, that as many as 45–65% of patients with AIDS-related kala-azar do not have detectable antileishmanial antibody, and even if seropositive, the presence of IgG alone does not necessarily indicate active infection. Why so many patients fail to produce (or maintain) detectable antileishmanial antibody is unclear and may in part reflect an AIDS-related failed humoral response to newly acquired infection.

A separate serologic assay, detecting anti-K39 IgG by enzyme-linked immunoadsorbent assay (ELISA) or by rapid immunochromatographic strip testing, is also available and shows nearly 100% specificity and sensitivity in active visceral infection in non-HIV-associated kala-azar. In a recent study in patients with AIDS-related kala-azar, 82% were seropositive for anti-K39 antibody, suggesting that this noninvasive diagnostic technique should also prove useful in this population. Similarly, parasite DNA can also be detected with reasonably high sensitivity and 100% specificity in peripheral blood mononuclear cells from otherwise healthy individuals with kala-azar. However, there is as yet little data for detection of parasite DNA by PCR in HIV-co-infected patients; and while other tissues may also yield a positive signal, seldom are such assays actually relevant (unavailable in the field) or necessary because examination of bone marrow and/or splenic aspirates or peripheral blood smear usually yields the diagnosis often within an hour.

In addition and in contrast to conventional kala-azar in immunocompetent patients (in whom infection is largely limited to bone marrow, spleen, liver, and perhaps lymph nodes), multiple other organs are parasitized in AIDS-related visceral infection. Thus, it is not surprising that aspirates, biopsies, smears, or cytocentrifuge preparations obtained from a wide variety of involved tissues or sites readily reveal amastigotes, often in great numbers in patients with advanced HIV infection (Table 2). Although parasitemia, for instance, is seldom observed in conventional kala-azar, peripheral blood smears show parasitized mononuclear phagocytes in nearly half of those examined. Because intracellular *Histoplasma capsulatum*, another AIDS-associated opportunistic pathogen, often infects the same sites involved in kala-azar and may, at first microscopic glance,

Table 2. Diagnostic Yield by Anatomical Site Confirming Kala-Azar in HIV-Infected Patients[a]

Site[b]	*No. samples tested*	*% Positive*
Bone marrow	647	98
Blood	159	75
Skin	50	88
Gastrointestinal tract	26	96
Liver	26	69
Spleen	24	100
Xenodiagnosis (blood)	22	59
Pleural fluid	11	100
Lymph node	7	100

[a]Adapted from *World Health Organization Weekly Epidemiological Record* (21 February 1997).
[b]Samples obtained by aspirate, biopsy, or smear and tested by microscopy and/or culture.

closely resemble *Leishmania* amastigotes, care must be taken to identify amastigotes by their characteristic rod-shaped kinetoplast.

Treatment and outcome

Traditional agents, the pentavalent antimonials (sodium stibogluconate, meglumine antimoniate) and amphotericin B (in conventional and new lipid formulations), have been used almost exclusively in AIDS-related kala-azar. While intravenous or intramuscular treatment with antimony (20 mg/kg/day for 28 days) induces long-term cure in >90% of non-HIV kala-azar (in all regions except India), results with the antimonials in patients with AIDS have not been satisfactory: (a) initial response rates have been quite variable (overall, about 50–60% show initial improvement), and (b) there have been predictably high rates of multiple relapses (60–90%) if patients who show a response are not subsequently maintained on antirelapse, suppressive therapy.

The poor response to antimony was predictable from experimental work that showed that host T cells were required for in vivo responsiveness to this agent. In contrast, amphotericin B's antileishmanial efficacy is not T-cell-dependent. Limited formal data in HIV-related kala-azar suggest that the initial response rate to amphotericin (or its potent lipid formulations) is higher than to antimony. Intravenous amphotericin B is given at 1 mg/kg daily for 15–20 days or on alternate days over a 30–40 day course; the use of its lipid formulations allow the same total dose to be delivered over about one half the time. Not surprisingly, however, and despite a good initial clinical response, once treatment with amphotericin B or its new formulations (or *any* antileishmanial agent) is discontinued, relapse also appears almost inevitably in CD4 cell-deficient patients. In addition to requiring prolonged duration of therapy, antimony and amphotericin B also induce well-recognized adverse reactions.

In a handful of HIV-infected kala-azar patients, macrophage-activating cytokine therapy (interferon-gamma) has been combined with antimony with some apparently enhanced response. A newly tested oral agent, miltefosine (hexadecylphophocholine), is remarkably active in kala-azar in India, but has not yet been tested in HIV-associated leishmaniasis.

As many as 10–20% of AIDS patients die during their first episode of visceral leishmaniasis, and up to 25% die within a month if treatment is discontinued. Approximately, 60% of patients are alive 12 months after their first episode of HIV-related kala-azar.

Somewhat belatedly, lifelong maintenance therapy, typical of that required to suppress most other AIDS-related OIs, is now being incorporated into the management of HIV-associated kala-azar. Although no specific maintenance regimen has been formally tested, 1 monthly injection of antimony is probably effective; twice-monthly injections of pentamidine (also reasonably active in the initial treatment of non-HIV-related kala-azar) may prove to be satisfactory. The lipid formulations of amphotericin B should also be useful as maintenance therapy and are now being tested; oral itraconazole may have some suppressive effect as well.

No information is as yet available on how to best and most accurately identify HIV-infected individuals who are at risk for reactivated or newly acquired kala-azar, how to manage those in whom seroconversion indicating new infection is documented, nor how or what to use as primary prophylaxis to prevent the clinical expression of kala-azar in patients who become CD4 cell-deficient.

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