Managing two decades of HIV-Visceral Leishmaniasis co-infection; a case report that illustrates the urgent research needs in the field

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Running Head

HIV-visceral leishmaniasis co-infection

Key words

HIV, visceral leishmaniasis, Kala-azar, opportunistic infection, co-infection

Abstract

Visceral leishmaniasis and HIV co-infection presents diagnostic, monitoring and treatment challenges. We report a co-infected patient who developed multiple complications and treatment side-effects, including renal and liver failure, pancytopenia

with recurrent sepsis along with anal cancer, depression and poor quality-of-life spanning over two decades. Urgent research specific to this cohort is needed.

Introduction

Leishmaniasis is a vector-borne disease transmitted by sandflies with three well-recognised clinical syndromes: visceral, mucosal and cutaneous. Visceral Leishmaniasis (VL), or kala-azar, is transmitted by parasites of the *Leishmania donovani* complex and leads to approximately 500,000 new diagnoses each year, 90% of these in India, Bangladesh, Ethiopia, Sudan, Kenya & Brazil[1]. Untreated, VL is almost universally fatal[1].

Early in the HIV epidemic, VL was recognised as an opportunistic infection in patients in Southern Europe[1-3]. Most patients develop clinical features of visceral leishmaniasis when CD4+T-cell counts are <200cells/μL. As visceral leishmaniasis is not classified as a Category C disease[4] it is likely to have been underreported. Data on incidence and prevalence of co-infection is lacking but indicates HIV infection increases the risk of developing visceral leishmaniasis by >100 fold in endemic countries[4]. Incidence appears to have declined in Southern Europe since widespread use of combination antiretroviral therapy (cART)[1-5].

Both HIV and visceral leishmaniasis target key effector immune cells;[1-3] death ensues from secondary bacterial infections, malnutrition, anaemia or haemorrhage[1]. Host immunocompetence determines clinical manifestations and in most HIV-infected patients represents reactivation of latent leishmania[1,3,4]. cART-induced immune restoration, a key

component of treatment, may allow withdrawal of anti-leishmania therapy. However, even with 'adequate' immune restoration, relapse is common[2-3]. Overall, treatment-response in the HIV setting is suboptimal compared with the mono-infection setting[2] and suppression of clinically active disease rather than cure is the therapeutic goal[4].

Case Report

A Caucasian male was diagnosed with HIV-1 infection in 1985, aged 27 years. During the 1990's his HIV-infection was treated with dual therapy, zidovudine plus didanosine. In 1996, after presenting with hepatosplenomegaly and deranged liver function, visceral leishmaniasis was confirmed on bone marrow biopsy, later speciated as *Leishmania infantum*[6]. The diagnosis coincided with a drop in CD4+T-cells to 90cells/μL and was presumed reactivation from childhood exposure in Greece. In 1996, he commenced protease inhibitor-based (PI) cART and maintained HIV virologic suppression thereafter. His absolute CD4+T-cell count remained suboptimal and low at between 100-250 cells/μL(15%), presumably secondary to splenic consumption. Antiretroviral switches were undertaken as new agents became available to reduce the pill burden and risk of overlapping toxicities and drug-drug interactions.

The patient was treated for visceral leishmaniasis, in the context of HIV co-infection, with cyclical induction-maintenance with Intravenous (IV)) antimonial agents, the standard of care at that time, first, sodium stibogluconate (standard weight based dosing of 20mg/Kg/day), then meglumine antimoniate (20mg/Kg/day) which was sourced from Brazil. A trial of miltefosine monotherapy in the early 2000s, in an endeavour to relieve the patient of the burden of long-term parenteral therapy, led to rapid clinical

failure. Miltefosine was sourced, pre licensure, from Germany under a special compassionate access program. Subsequently he received monthly cycles of IV liposomal amphotericin B, however due to quality-of-life concerns he resumed maintenance therapy with IV meglumine antimoniate.

The nodular lesions he developed on his head and ear in 2003 correlated with an improvement in clinical and haematological parameters and were thought to represent an Immune reconstitution inflammatory syndrome (IRIS) and in this setting, a form of post Kala-azar dermal leishmaniasis[6]. They resolved with topical paromomycin and continued leishmania maintenance therapy with meglumine.

In 2004, he was diagnosed with non-cirrhotic portal hypertension, splenomegaly and varices manifesting with gastrointestinal bleeds. Aetiology of the former was unclear, but exposure to didanosine probably played a role. Later that year, he developed *Listeria monocytogenes* bacteraemia. In 2008, after bone marrow biopsy indicated relapse, he underwent re-induction with several weeks of daily IV liposomal amphotericin plus oral posaconazole and was subsequently maintained on monthly IV pentamidine with daily posaconazole. The latter was sought through compassionate access for off license use. Anal squamous cell carcinoma was diagnosed and successfully treated in 2009 however ongoing per-rectal bleeding, post-radiation anal stenosis and chronic severe pain prompted colostomy formation.

From 2011 until his demise in 2013, he developed repeated sepsis episodes and progressive pancytopenia. Exacerbations of renal failure precluded adequate

leishmaniasis treatment. His pre-morbid condition included catastrophic leg cellulitis (Figure 1a) with *Escherichia coli, Enterococcus* spp and biopsy confirmed *L. infantum* (Figure 1b) which failed to respond to aggressive antibiotic therapy, wound debridement and skin grafting.

Case Discussion

Clinical diagnosis in HIV co-infected patients is complex. Symptoms can be atypical, in particular increased gastrointestinal symptoms including diarrhoea and less frequent splenomegaly, though most patients do present with pancytopenia and fever and lethargy[1,2,4]. Concurrent opportunistic infections may confound clinical appearances[4]; clinicians need to have a high index of suspicion, particularly in patients from an endemic region. Parasitological diagnosis remains the gold standard. Speciation is important, but the PCR molecular test we used to speciate was an 'in-house' assay and thus not validated. Splenic aspiration is used for monitoring disease burden/activity[2,4], however safety concerns precluded this in our patient with monitoring restricted to clinical assessment, blood parameters and repeated bone marrow aspiration. Using a combination of serologic and molecular tests improves sensitivity, however further research is required to determine the value in both screening and diagnosis[2,7].

An ongoing challenge remains the paucity of randomised control trial data with results derived from the mono-infected extrapolated with mixed findings[4]. Whilst pentavalent antimonials for HIV-visceral leishmaniasis have fallen from favour due to toxicities and clinical failure, they remain the mainstay of treatment due to cost and access constraints, especially in low income countries with the highest burden of disease.

Liposomal amphotericin B has found increasing utility, however it has been shown to be comparatively less efficacious in the HIV-infected population[1,2,4,8].

Importantly, and a lesson already learned in the HIV setting, is the inherent danger of sequential monotherapy. Focus is shifting towards combination therapy with promising data on single dose liposomal amphotericin with miltefosine in the HIV-negative cohort[9]. A phase 3 clinical trial is recruiting in Ethiopia to study AmBisome© monotherapy vs. AmBisome© & miltefosine in HIV-positive patients *(ClinicalTrials.gov:NCT02011958)*[10]. This combination approach has been replicated in a recently published retrospective Indian study, where co-infected patients were followed up at 18 months after treatment with 6 infusions of AmBisome© (each dose 5mg/Kg; cumulative dose 30mg/Kg) and 14 days of miltefosine[11]. While results were promising, the overall relapse rates and all-cause mortality (16.6% at 18 months) were far higher than in mono-infected patients given lower doses of liposomal amphotericin (cumulative dose of 20mg/Kg).

Recently published data from Ethiopia studying secondary prophylaxis in co-infected patients on cART with monthly pentamidine also shows improved relapse rates[12]. With regards to the triazoles, oral posaconazole has been used to treat cutaneous *L. infantum*; there is also promising *in-vitro* data against *L.amazonensis*[13-14]. Further research is needed.

The current suggested regimen for HIV co-infected patients relies on Liposomal amphotericin B. Doses and schedules differ depending on the organisation, with doses

between 2-5mg/kg recommended and daily verses intermittent schedules considered. Miltefosine is promoted as an alternate or combination agent, though sodium stibogluconate is still recommended by the World Health Organisation (WHO) as second line therapy[2,15].

cART underpins treatment of HIV-visceral leishmaniasis[1,2] but uncertainty remains regarding timing in relationship to antiprotozoal agents, to avoid IRIS and overlapping toxicities. Moreover, the exact CD4+T-cell threshold at which anti-leishmania therapy can safely be withdrawn is unclear. Splenomegaly, leading to low peripheral CD4+T-cell counts, makes defining CD4+ thresholds harder still. Importantly, immune restoration may be blunted and relapses still occur despite 'adequate' immune restoration[3,4].

Ultimately, our patient's immune failure, recurrent sepsis and renal failure reduced therapeutic options available for leishmaniasis. Malignancy forced compromised management. We had no restriction on cART choice so were able to switch away from ritonavir-boosted PI to minimise drug-drug interactions and avoid drugs that might compound haematological manifestations and renal toxicities of active visceral leishmaniasis and or its treatment.

Despite excellent resources, our patient succumbed to complications from chronic HIV-visceral leishmaniasis co-infection. The case illustrates challenges faced in the real-life management in a resource rich setting, and emphasises gaps in knowledge. Visceral Leishmaniasis is a WHO neglected tropical disease[3] and as such new drugs need to be developed. Data specific to co-infected patients is urgently needed. These therapeutic

advances must be coupled with improved methods to diagnose and monitor disease activity without requiring invasive tests. As the burden of disease is predominantly in resource-poor countries, these modalities must be available at affordable prices.

Authors' contributions

Melissa L Kelly and Sarah L Pett contributed equally to writing this manuscript. All other authors read and approved the final manuscript. Melissa Kelly, Sarah Pett, Angie Pinto, Dan Suan, David Cooper and Debbie Marriott were directly involved in the clinical care of this patient over many years.

Figure 1a: Left leg cellulitis with *Escherichia coli and Enterococcus spp.* growth.

Figure 1b: Left leg biopsy site, confirming *L .infantum.*

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