Atypical manifestations of visceral leishmaniasis in patients with HIV in north Ethiopia: a gap in guidelines for the management of opportunistic infections in resource poor settings

Ermias Diro, Johan van Griensven, Rezika Mohammed, Robert Colebunders, Mesfin Asefa, Asrat Hailu, Lutgarde Lynen

In regions where it is endemic, visceral leishmaniasis is an important opportunistic infectious disease in people living with HIV. Typically, clinical presentation of visceral leishmaniasis includes chronic fever, hepatosplenomegaly, and weight loss. In *Leishmania infantum* endemic regions in Europe, atypical visceral leishmaniasis presentations have been well documented, with almost every possible organ involved. However, such reports are rare in *Leishmania donovani* endemic regions such as east Africa. In this Personal View, we describe the various atypical disease presentations in patients screened as part of an HIV and visceral leishmaniasis clinical trial in north Ethiopia, where up to 40% of patients with visceral leishmaniasis are co-infected with HIV. Atypical presentations such as these are not covered in clinical guidelines used in these settings. Apart from the lack of diagnostic facilities, this gap contributes to the underdiagnosis of atypical visceral leishmaniasis, with associated morbidity and mortality. Involvement of clinicians experienced with the management of HIV and visceral leishmaniasis co-infection in the development of HIV clinical guidelines in affected regions is warranted.

Introduction

In areas where it is endemic, visceral leishmaniasis has become an important opportunistic infectious disease in the era of HIV. Co-infection has been reported in 35 countries. The north part of Ethiopia is one of the regions with a high incidence of co-infection, with the prevalence of HIV infection ranging from 15% to 30% in patients with visceral leishmaniasis. In east Africa in Sudan, Ethiopia, Somalia, Kenya, and Uganda the cause of visceral leishmaniasis is *Leishmania donovani* and the transmission is anthroponotic; the cutaneous form is mainly caused by *Leishmania aethiopica* with hyrax as the animal reservoir.

Clinical manifestations of visceral leishmaniasis are chronic fever, weight loss, organomegaly, and pancytopenia. These major clinical manifestations are similar in HIV-positive and HIV-negative patients. However, one of the challenges in patients with co-infection is the variety of atypical clinical presentations, with leishmania parasites isolated from unusual sites such as gastrointestinal and oral mucosa, skin, pleura, pericardium, lymph nodes, Kaposi’s sarcoma lesions, and respiratory tract. These case reports were mainly from *Leishmania infantum* transmission regions in Europe, and were invariably associated with very low CD4 cell counts at diagnosis. Combined with the many opportunistic infections that can occur in patients with HIV, these atypical presentations add to the challenge of making a timely diagnosis.

By contrast with numerous accounts from Europe, reports on atypical clinical manifestations of HIV infection and visceral leishmaniasis in *L donovani* endemic regions (east Africa and the Indian subcontinent) are extremely scarce (table 1). Although the occurrence of atypical presentations might be associated with the different species of leishmania, we believe that underdiagnosis is the most likely explanation, and mainly related to a low index of clinical suspicion and a lack of diagnostic facilities.

In this Personal View, we describe various atypical disease presentations noted in the screening of patients for enrolment into a clinical trial of therapy for HIV and visceral leishmaniasis in north Ethiopia. We discuss the reports on cases of *L donovani* and *L infantum* infection in endemic regions and to what extent atypical presentations are covered in clinical treatment guidelines in east African countries where both HIV and visceral leishmaniasis are endemic.

The atypical cases discussed here are taken from patients screened for inclusion in an ongoing clinical trial (NCT01360762) on the use of secondary prophylaxis with pentamidine for visceral leishmaniasis relapses in patients with HIV at the leishmaniasis research and treatment centre of the University of Gondar (Gondar, Ethiopia). The clinical trial has been approved by the relevant ethical committees involved (University of Gondar and National Research Ethics Committee, Ethiopia; and Institute of Tropical Medicine and University Hospital Antwerp, Belgium) and written consent was given by patients. Eight (15%) of 54 patients with visceral leishmaniasis co-infected with HIV screened during 14 months had atypical clinical presentations of leishmaniasis: three had skin lesions (one patient with scattered nodular lesions and two with post-kala-azar dermal leishmaniasis-like lesions [PKDL]); two had oral lesions, two had lymph node involvement (one with intra-abdominal lymph node involvement), and one patient had rectal lesions.

Although liposomal amphotericin B is the recommended treatment for these patients according to WHO and national guidelines, the scarcity of this medicine leads to the use of alternative drugs. Three of the four
This man presented with 4 months of high-grade persistent fever, weight loss, and symptoms of anaemia. He had hepatosplenomegaly and bilateral cervical lymphadenopathy. An abdominal mass, later proven to be lymph nodes, was palpable in the periumbilical and left lower quadrant of the abdomen. His haematology profile showed pancytopenia. He was already diagnosed with HIV and had been on combination antiretroviral therapy (cART) and co-trimoxazole for 5 months. His CD4 count had declined from 84 cells per μL at the start of cART to 30 cells per μL at presentation. Differential diagnoses of HIV treatment failure, lymphoma, and disseminated tuberculosis were considered, of which the last was also supported by a fibrotic lesion seen on chest radiography. A Giemsa-stained abdominal lymph node aspirate (ultrasound-guided fine-needle aspiration) showed many histiocytes filled with Leishman-Donovan bodies with a parasite load of grade 3. The patient was successfully treated with sodium stibogluconate and the enlargement of the lymph nodes was absent on control ultrasound, whereas the splenomegaly persisted, but spleenic aspirates tested negative for leishmania parasites. The patient was successfully treated with sodium stibogluconate, and one of whom needed prolonged treatment. The most critically ill of these patients, with extensive oral lesions, died of sepsis while on liposomal amphotericin B.

Table 1: Atypical cases reported from leishmania endemic regions

<table>
<thead>
<tr>
<th>Skin (other than PKDL)</th>
<th>Leishmania donovani</th>
<th>Leishmania infantum</th>
</tr>
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<tbody>
<tr>
<td>East Africa</td>
<td>This report and 10</td>
<td>15 reports</td>
</tr>
<tr>
<td>Indian subcontinent</td>
<td>One report 14</td>
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</tr>
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Associated with other lesions: Kaposi’s sarcoma, herpes zoster, dermatofibroma, squamous-cell cancer, and rheumatoid nodules

Upper aerodigestive and oral tract

Intestinal mucosa (stomach and duodenum, and colon) and malabsorption syndrome

Intra-abdominal lymphadenopathy

Renal involvement (nephritic syndrome and amyloidosis)

Lung, heart, pleura, pericardium, and peritoneum

Liver

Adrenal gland

PKDL—post kala-azar dermal leishmaniasis. This summary table is not an exhaustive list of all atypical case reports from the L. infantum endemic region.

Panel 2: Oral mucosal involvement in a 29-year-old woman from a Leishmania donovani transmission region

A woman who was HIV positive stayed without combination antiretroviral therapy for 7 years after diagnosis of HIV, and presented with watery diarrhoea, fever, vomiting, and oral lesions of 3 month duration. The oral lesions had increased in size causing dysphagia and bleeding. On examination, the patient looked chronically ill, emaciated, and was unable to support herself. She was febrile and anaemic. Inspection of the mouth revealed a ragged, fungating, and disfiguring mass on the palate. The mass was dark purple, and easily bled with movement of the teeth. She was severely pancytopenic (white blood cell count 1300 cells per μL, haemoglobin 75 g/L, platelet count 10 000 per μL) and with a very low CD4 count (71 cells per μL). Aspirates from the bone marrow had Leishman-Donovan bodies with a parasite load of grade 4; aspirates from the palatal lesions had Leishman-Donovan bodies with a parasite load of grade 3.

Treatment was started with liposomal amphotericin B for the leishmania infection and broad spectrum antibiotics (ceftriaxone and metronidazole) for possible sepsis secondary to a superinfected oral lesion. At the start of treatment, the oral mass was sloughing off and the bleeding worsened, hindering the ingestion of food and necessitating feeding of the patient through a nasogastric tube. Eventually, the patient died of septic shock.

Visceral leishmaniasis caused by dissemination of L. donovani to the oral mucosa or visceralisation of mucocutaneous leishmaniasis caused by Leishmania aethiopica (a common cause of the cutaneous form of leishmaniasis in Ethiopia) is a possibility in this patient. Parastasis species identification was not done.

Panel 1: Intra-abdominal lymphadenopathy in a 35-year-old man from a Leishmania donovani transmission region

This man presented with 4 months of high-grade persistent fever, weight loss, and symptoms of anaemia. He had hepatosplenomegaly and bilateral cervical lymphadenopathy. An abdominal mass, later proven to be lymph nodes, was palpable in the periumbilical and left lower quadrant of the abdomen. His haematology profile showed pancytopenia. He was already diagnosed with HIV and had been on combination antiretroviral therapy (cART) and co-trimoxazole for 5 months. His CD4 count had declined from 84 cells per μL at the start of cART to 30 cells per μL at presentation. Differential diagnoses of HIV treatment failure, lymphoma, and disseminated tuberculosis were considered, of which the last was also supported by a fibrotic lesion seen on chest radiography. A Giemsa-stained abdominal lymph node aspirate (ultrasound-guided fine-needle aspiration) showed many histiocytes filled with Leishman-Donovan bodies with a parasite load of grade 4; aspirates from the palatal lesions had Leishman-Donovan bodies with a parasite load of grade 3. The patient was successfully treated with sodium stibogluconate and the enlargement of the lymph nodes was absent on control ultrasound, whereas the splenomegaly persisted, but spleenic aspirates tested negative for leishmania parasites. The patient was successfully treated with sodium stibogluconate, and one of whom needed prolonged treatment. The most critically ill of these patients, with extensive oral lesions, died of sepsis while on liposomal amphotericin B.

Intra-abdominal lymphadenopathy

Patients with leishmaniasis presenting with isolated and persistent peripheral lymphadenopathy, or complicating other diseases that cause lymphadenopathy, were
repeatedly reported from both *L. donovani* and *L. infantum* endemic regions.\(^{14,80–84}\) Peripheral lymphadenopathy is one of the frequent manifestations of visceral leishmaniasis seen in Sudan.\(^{85}\) However, lymph node involvement is less frequent in patients with visceral leishmaniasis in north-west Ethiopia, occurring in 15% of patients.\(^{6}\) A 35-year-old male patient with leishmaniasis involving-intra-abdominal lymph nodes and HIV co-infection is described in panel 1.

### Oral mucosal disease

A mucocutaneous form of leishmaniasis that involves the margins of the lips and nostrils can be caused by a number of the *Leishmania* spp. Deep mucosal involvement of oral and upper aero-oesophageal areas in leishmaniasis in *L. infantum* transmission regions in patients with HIV co-infection has also been reported\(^{17,45,86}\) and can further complicate the diagnosis.\(^{17,45,86}\) A patient with oral mucosal disease from an *L. donovani* transmission region is described in panel 2.

### Lower gastrointestinal involvement

Although several reports\(^{18,19,21,22,62,87,88}\) from *L. infantum* endemic regions have discussed patients with visceral leishmaniasis and gastrointestinal system involvement this finding has not been reported from the *L. donovani* endemic regions in east Africa to date (table 1; panel 3).

### Skin and visceral lesions

Papular, nodular, papulonodular, macular and other types of skin lesions might occur in patients with visceral leishmaniasis before, during, or after treatment of an episode (panel 4). Skin lesions in patients with leishmaniasis and HIV co-infection can occur as a reactivation of a latent infection or as dissemination of a recent infection,\(^{39}\) and might produce PKDL-like lesions. As a result, in patients with HIV infection, whether the
Panel 4: Atypical cutaneous manifestations in a 41-year-old man from the Leishmania donovani transmission region

This man presented with one variety of atypical cutaneous manifestation concomitant with visceral leishmaniasis. He was HIV-positive and had been on combined antiretroviral therapy (cART) and co-trimoxazole preventive therapy for the previous 4 years and presented with numerous nodular skin lesions of 1 year duration. The lesions were painless and involved the face and upper extremities predominantly at the tip of the nose and on the elbows (figure 2A). He had been treated for visceral leishmaniasis twice, 7 years previously. During his recent presentation the common symptoms of patients with visceral leishmaniasis such as fever, anorexia, weight loss, and bleeding were absent. He had splenomegaly, 6 cm below the costal margin and was pancytopenic (white blood cell count 1300 cells per μL, haemoglobin 110 g/L and platelet count 60 000 per μL). His CD4 count after 4 years on cART was 72 cells per μL coming from a nadir of 19 cells per μL. Leishman-Donovan bodies were detected in Giemsa-stained smears from the spleen and the skin lesions on the face and the arms with a parasite load of grade 6. He was treated with sodium stibogluconate for 45 days with a brief interruption to treatment because of transient renal dysfunction. The spleen became non-palpable and the skin lesions subsided (figure 2B). Because of failed parasite clearance, treatment was prolonged from day 30 to day 45 when bone-marrow aspirates showed no parasites. His CD4 count increased to 116 cells per μL after treatment. The very low CD4 count and high parasite load shown both in the skin lesions and the spleen indicate profound immunosuppression and overwhelming disseminated disease.

Overview of published reports on atypical visceral leishmaniasis

We did a literature review to compare reports of atypical disease presentation in visceral leishmaniasis endemic regions. Most of the published reports relate to the L infantum transmission regions in southern Europe at the peak of the HIV epidemic in the late 1990s and early 2000s (table 1). Skin and gastrointestinal mucosa were the most common sites involved. However, the case reports show that potentially all organs and systems can be affected by visceral leishmaniasis. Some of these case reports have shown leishmania infection complicating other diseases involving lesions of the kidney, liver, adrenal glands, lung, and serous membranes. Only recently, was visceral leishmaniasis with disseminated cutaneous lesions, as an atypical presentation caused by L. donovani in patients with HIV co-infection, reported from Ethiopia.25 Reports from the Indian subcontinent are equally few in number.

Guidelines on use of a syndromic approach for the management of opportunistic infections

Many guidelines propose a syndromic approach to the diagnosis and treatment of opportunistic infections in people who are HIV-positive in low-resource settings. We looked at the guidelines’ coverage of visceral leishmaniasis in the syndromes of skin lesions, gastrointestinal and mucosal problems, and lymphadenopathy in patients with HIV infection. We used a Google Scholar search for guidelines on the treatment of opportunistic infections, with the search terms “opportunistic infections” and “HIV” and “syndromic approach” and “leish*” and “Africa”.

Although classic visceral leishmaniasis is dealt with in most of the guidelines on opportunistic infections with respect to chronic fever, the atypical lesions of visceral leishmaniasis are often excluded from guidelines on the differential diagnosis of patients with oral lesions, lymphadenopathy, skin lesions, and gastrointestinal ulcers (table 2).90–93

We accessed the national guidelines on management of opportunistic infections in Ethiopia published in 2008, Sudan (2008), and Kenya (2008).79–83 None of them used a syndromic approach. Only the guidelines from Ethiopia mention that presentation of visceral leishmaniasis...
might be atypical in patients who are HIV-positive, without going into further details. No national guidelines on opportunistic infections were electronically available for Uganda and Somalia. Since 2006, WHO has judged atypical disseminated leishmaniasis as a stage 4 (AIDS) defining condition. The 2010 WHO technical report on the control of leishmaniasis also provides guidance for diagnosis and treatment of co-infection with HIV.

Conclusions and recommendations

Only a few cases of atypical visceral leishmaniasis had been reported from east Africa. Factors contributing to this scarcity of published reports on atypical disease presentation probably relate to a lack of clinical suspicion and limitations of the diagnostic facilities available in endemic regions. Importantly, these atypical presentations are not included in the opportunistic infection guidelines that use a syndromic approach to diagnosis and treatment, especially the national guidelines in leishmania endemic regions. The starting point for screening patients and investigations for visceral leishmaniasis is WHO case definition of a patient with suspected visceral leishmaniasis (prolonged fever, weight loss, and splenomegaly), which addresses the typical presentation. This approach carries the risk that atypical visceral leishmaniasis remains undiagnosed in clinical settings, or is diagnosed with substantial delay. Visceral leishmaniasis is a fatal disease that needs early recognition and treatment. Most of the unusual clinical manifestations occur in patients with HIV with very low CD4 counts, who might also be affected with other opportunistic infections. To increase survival for these susceptible patients, clinicians should consider fatal but treatable conditions in their differential diagnosis. For patients in Leishmania spp endemic regions, this should include visceral leishmaniasis.

In addition to diagnostic delays, the prognostic importance of atypical presentation of visceral leishmaniasis needs to be addressed. In these reports, the CD4 counts of patients were very low even in those who were already on combination antiretroviral therapy. Dissemination of visceral leishmaniasis to organs that are not normally involved suggests advanced immunosuppression. This finding was also described in reports from L infantum endemic regions. Damage to the involved organs by leishmania infection can lead to further complications. The oral lesions causing dysphagia in one patient were complicated by secondary bacterial sepsis, which led to the death of the patient. Rectal involvement led to anal sphincter insufficiency in another patient. Overall, atypical visceral leishmaniasis causes substantial morbidity and mortality.

We recommend that guidelines for the management of opportunistic infections in the Leishmania spp endemic regions in east Africa include these atypical visceral leishmaniasis lesions in the differential diagnosis of oral lesions, lymphadenopathy, gastrointestinal ulcers, and skin lesions. To achieve this aim, the involvement of physicians who frequently treat HIV-leishmania co-infected patients in the development of treatment guidelines is essential.

Table 2: Coverage of visceral leishmaniasis presentations in guidelines for opportunistic infection diagnosis using a syndromic approach in resource-poor settings

<table>
<thead>
<tr>
<th>Typical symptoms</th>
<th>Atypical symptoms</th>
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</thead>
<tbody>
<tr>
<td>Gastrointestinal mucosal lesions</td>
<td>Addressed</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Skin</td>
<td>Addressed</td>
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MSF=Médecins Sans Frontières. IMAI=integrated management of adolescent and adult illness. IMCI=integrated management of childhood illness.

References

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