**Case Report**

**Visceral Leishmaniasis in a Child Infected with the Human Immunodeficiency Virus in a Non-endemic Region**

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**Summary**

We reported the case of a boy who fled from Chechnya to Belgium. He was diagnosed with a human immune deficiency virus (HIV)/Visceral leishmaniasis (VL) coinfection. In both countries, the prevalence of HIV-infected children is low and VL is not endemic. Migration of people results in confrontation with diseases that are not frequent in the countries of destination and becomes a challenge for pediatricians.

**Key words:** HIV, visceral leishmaniasis, amphotericin B, septic shock.

**Introduction**

Leishmaniasis is a parasitic infection transmitted by female sand flies with a mainly canine reservoir and may present as cutaneous, mucocutaneous or visceral forms. An estimated 12 million cases are reported worldwide, with 90% of visceral leishmaniasis (VL) occurring in the Indian subcontinent, Brazil and Sub-Saharan Africa [1, 2]. In endemic areas, VL is an important opportunistic coinfection in patients with the human immune deficiency virus (HIV). VL accelerates the onset of AIDS by cumulative immunosuppression and by stimulation of the virus replication. Both infections switch the predominant cellular immune response from Th0 or Th1 to Th2, leading to a mainly humoral response. This may inhibit the production of interferon-γ and results in a defective lytic capacity of the macrophages [1, 2].

We report on a pediatric case of HIV/VL coinfection in a child originating from Chechnya and diagnosed in Belgium. In both countries, no data are available about the coinfection of VL and HIV [3–5].

**Case Report**

A 6-year-old boy originating from Grozny, Republic of Chechnya, fled with his family to Belgium. During the 7 days journey by car, our patient became progressively irritable, pale and short of breath. He presented at the Emergency Department with severe dyspnea and irresponsiveness. After intubation for respiratory failure, blood samples and cultures were taken. Broad spectrum antibiotics and IV immunoglobulins were started. Blood gases showed an acidosis with a pH of 7.11.

Further laboratory investigation showed 0.6 × 10E9/l white blood cells and a C-reactive protein of 24 g dl−1 (normal value <0.1 mg dl−1). Blood gases showed an acidosis with a pH of 7.11. *Streptococcus*
*Pneumocystis jirovecii* pneumonia (PJP) was confirmed in the bronchial alveolar lavage fluid.

Because of the hepatosplenomegaly with severe anemia and leucopenia a bone marrow examination was performed. It showed signs of overwhelming infection, almost no CD4+ cells, ruptured macrophages and scattered amastigotes, confirming the diagnosis of VL (Fig. 1). Polymerase chain reaction (PCR) for *Leishmania* species in the blood remained negative.

The ELISA and western blot tests for HIV were positive. After repeated and insistent questioning of the mother, she declared that she knew she was HIV positive, as was the boy's father. The PJP treatment involved a combination of clindamycine, primaquine and corticosteroids. On Day 8, liposomal amphotericin B was initiated to treat VL at a regimen of 60 mg day\(^{-1}\) for 5 days and consequently a similar dose on Days 10, 17, 24, 31 and 38 after the first dose. Highly active anti-retroviral therapy (HAART) therapy, i.e. the combination of didanosine, lamivudine and nevirapine, was started on Day 18 of the hospitalization, after stabilization of the initially extremely shocked and septic child. The boy was diagnosed with multiple infections during the hospitalization, i.e. blood stream infection with *S. pneumoniae* and *Staphylococcus aureus*, treacheo-bronchial infections with *Candida* species, Para-influenza virus and *Sphingomonas* species, a Herpes simplex stomatitis and a *Cytomegalovirus* (CMV) infection.

Despite initial improvement and extubation after 8 days, the condition of the boy deteriorated after Day 21 with progressive and irreversible respiratory insufficiency. He died on Day 44 of the hospitalization.

**Discussion**

There are diagnostic difficulties in the diagnosis of HIV/VL coinfections, especially in children, because of the frequent atypical clinical presentation and the lack of experience with the disease in non-endemic regions [6].

The presentation of VL varies from an acute febrile illness to a slowly progressive disease over different years. Chronic VL leads to progressive wasting and pancytopenia leads to secondary infections. Diarrhea is common due to secondary infection or submucosal infiltration with *Leishmania*-loaded macrophages.

In HIV/VL coinfected patients, there are five major clinical characteristics: parasitic dissemination, atypical localizations, chronic and relapsing course, poor response to standard therapy and lack of anti-*Leishmania* antibodies. Cytopenia is more frequent in coinfected patients and gastrointestinal symptoms like diarrhea, malabsorption, hypoalbuminemia and weight loss occur very often. Unfortunately, these symptoms are non-specific in HIV-infected patients. Cutaneous symptoms are seen in 2–12% of patients with HIV/VL coinfections [6]. Clinical manifestations of HIV/VL coinfected patients may be influenced by the CD4+ count. In patients with a low CD4+ count, the parasitic amastigotes are often found in atypical locations and involvement of the gastrointestinal and respiratory tract is common [1].

The parasite can be found on microscopic examination or culture of blood smears, buffy coats, bone marrow and splenic aspirates. The sensitivity of bone marrow aspiration is lower as amastigotes are only seen in 50% of the bone marrow aspirates. Culture can be done from blood, buffy coat or tissue aspirates but is time consuming; the positivity rate is 50–100% [4–7]. *Leishmania* PCR assays of bone marrow and peripheral blood smears were proven to be a very reliable technique for the diagnosis of VL in HIV-seropositive patients, with sensitivities of 82–100% and 72–100%, respectively. PCR is useful for monitoring the efficacy of treatment and the prediction of relapses. Real-time quantitative PCR was recently applied and has the advantages of time reduction and determination of the parasitic load [4, 7].

Anti-*Leishmania* antibodies can be detected in patients with VL; this technique is highly sensitive and specific [3, 9]. In HIV/VL coinfected patients, antibodies are positive in only 40–50%, which is inversely correlated with the CD4+ depletion, due to a lack of appropriate B-cell stimulation [4, 6, 8].
A urinary antigen detection test is available, has a high specificity, moderate sensitivity and is useful for monitoring the efficacy of treatment [4].

Treatment options for VL include pentavalent antimonial compounds, amphotericin B (conventional or liposomal), paromomycin and miltefosine. Amphotericin B is the preferred drug in Europe and the USA, but is less used in other parts of the world because of its high cost [6]. Lipid formulations are better tolerated and have the advantage of being taken up by macrophages. The regimen duration varies between 10 and 40 days. Reported efficacy is over 95% in the Mediterranean area [7, 8]. Patients should feel better within the first week of treatment. Laboratory findings usually recover within 2–4 weeks [9]. Children are more sensitive to symptoms of toxicity at infusion, i.e. fever, tremors and respiratory problems [7]. Pentavalent antimonials are efficacious and a safe alternative for amphotericin B. [7].

HIV/VL coinfected patients show lower cure rates, higher drug toxicity, higher relapse rates and higher mortality rates. Factors that predict survival are HAART, a high CD4þ cell count and the use of secondary prophylaxis for VL [4]. Successful implementation and maintenance of HAART is the most important factor in the control of opportunistic infections in HIV-infected children [10]. The combination of liposomal amphotericin B and potent antiretroviral treatment showed a long-term remission of HIV-associated VL [8]. There is no evidence that certain combinations of HAART are more effective than others [4].

The pronounced immunodeficiency in HIV/VL coinfected patients led to experiments that combine immuno- and chemotherapy. The hematopoietic growth factor granulocyte-macrophage colony-stimulating factor granulocyte-macrophage colony-stimulating factor (GM-CSF) inhibits intracellular replication of the leishmania parasite. Several experiments suggest that GM-CSF can be used as antileishmanial treatment, and the combination with liposomal amphotericin B may improve clinical response and give a faster reduction of the parasitic load [1, 7].

Currently, no recommendations for primary prophylaxis against VL in seropositive patients are formulated. Nevertheless, secondary prophylaxis can be useful to prevent relapses after a first episode of VL. In 27% of patients, relapse occurs within 6 months after treatment, and in up to 60% of patients within 1 year [7]. Different regimens with pentavalent antimonials and amphotericine B have been used. Fifty per cent of patients receiving secondary prophylaxis did not show any relapse. Further research is needed to formulate indications and regimens. There is no consensus among authors whether secondary prophylaxis can be withdrawn when CD4þ cells reach the threshold of 200 cells mm−3 for >6 months [4, 6].

**Conclusion**

HIV and VL are rarely seen in north-western Europe, but may be occasionally imported by migrant families from endemic areas. VL is associated with several diagnostic and therapeutic difficulties, especially in seropositive patients. HIV/VL coinfected patients show lower cure rates, higher drug toxicity, higher relapse rates and higher mortality rates than other patients infected with the leishmania parasite. Diagnostic and therapeutic difficulties are surmounted by collaboration between physicians of different specialties and the help of literature. Caring for refugee children carrying diseases with which we have no experience in our sheltered life is a real challenge.

**References**