

# Recurrent cytomegalovirus disease, visceral leishmaniasis, and Legionella pneumonia after liver transplantation: a case report

*[Infection récurrente à cytomégalo­virus, leishmaniose viscérale et légionellose à la suite d'une transplantation hépatique : une étude de cas]*

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**Purpose:** Recurrent cytomegalovirus (CMV) disease is a frequent complication of liver transplantation. Visceral leishmaniasis in a transplant recipient is, on the other hand, extremely rare and only two cases of kala-azar have been described after liver transplantation. Immunosuppressed patients are known to be at risk of Legionella infection and the relationship between infection with this organism and hospital water supplies has been well described. These three diseases carry a high mortality rate. Our report examines the potential relationship between these complications.

**Clinical features:** We describe the case of a liver transplant recipient who presented the three complications successively and survived. After reviewing the literature, we explore hypotheses linking these infections and discuss treatment strategies.

**Conclusions:** In the patient described, infection with leishmania probably occurred months prior to the clinical presentation, a delay that matches the incubation period of kala-azar. The simultaneous onset of leishmaniasis and of a high CMV viremia may have been a coincidence. However, CMV infection has been shown to be an independent predictor of invasive fungal infection in liver transplant recipients. CMV does indeed have a suppressive effect on the humoral and cellular immune response *in vitro* as well as *in vivo*. The clinical manifestations of leishmaniasis may, therefore, have been precipitated in this patient by the additive immunosuppressive effect of antirejection drugs and CMV.

**Objectif :** L'infection récurrente au cytomégalo­virus (CMV) est une complication fréquente de la transplantation hépatique. La leishmaniose viscérale chez un receveur d'organe est, par contre, extrêmement rare et on ne rapporte que deux cas de kala-azar à la suite d'une greffe de foie. Les patients immunodéprimés sont à risque d'infections

à Légionella et la relation entre cet organisme et l'alimentation en eau des hôpitaux a été bien décrite. Ces trois maladies présentent un taux de mortalité élevée. Nous étudions ici la relation possible entre ces complications.

**Éléments cliniques :** Nous décrivons le cas d'un patient greffé du foie qui a présenté successivement les trois complications et a survécu. Après avoir passé en revue les publications, nous explorons des hypothèses pouvant relier ces infections et discutons des traitements possibles.

**Conclusion :** Chez ce patient, l'infection à Leishmania est probablement survenue plusieurs mois avant les manifestations cliniques, ce qui correspond à la période d'incubation du kala-azar. La survenue simultanée d'une leishmaniose et d'une importante virémie au CMV pourrait n'être qu'une coïncidence. Cependant, l'infection au CMV s'est révélée un prédicteur indépendant d'infection fongique invasive chez les receveurs d'un foie. Le CMV a certainement un effet inhibiteur sur la réponse immunitaire humorale et cellulaire, *in vitro* aussi bien qu'*in vivo*. Les manifestations cliniques de la leishmaniose peuvent donc avoir été précipitées par l'effet immunodépresseur supplémentaire des médicaments anti-rejet et du CMV.

**R**ECURRENT cytomegalovirus (CMV) disease is an uncommon complication of liver transplantation. Visceral leishmaniasis is even more rare as only two cases have been described. Immunosuppressed patients are also at risk of Legionella infection as this micro-organism may contaminate hospital water supplies. We

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report on a liver transplant recipient who presented successively all these three potentially lethal complications and survived.

### Case report

The medical history of the 59-yr-old Caucasian male patient included three myocardial infarcts and coronary bypass surgery. One year before admission, he presented with fatigue, coagulopathy and refractory ascites. The diagnosis of auto-immune cirrhosis was reached, including autoimmune hepatitis and primary biliary cirrhosis, by the detection of high titers of anti-smooth muscle antibodies and a liver biopsy. Steroids were prescribed for six months. This did not prevent deterioration of the liver function so that the patient had eventually to be listed for liver transplantation. The operation and the early postoperative course were uneventful. The patient was discharged home after three weeks on tacrolimus ( $2 \times 3 \text{ mg}\cdot\text{day}^{-1}$ ) and prednisone ( $20 \text{ mg}\cdot\text{day}^{-1}$ ) immunosuppression. Although the donor's CMV serology was positive and the recipient's negative, no antiviral prophylaxis was administered.

On postoperative day 41 (Figure 1), the patient presented with fever, chills and alteration of the liver function tests. CMV detection on buffy coat leucocytes was positive by shell vial assay, amounting to 540 infectious units (IU) per  $10^6$  peripheral blood lymphocytes (PBL). Intravenous ganciclovir ( $5 \text{ mg}\cdot\text{kg}^{-1}$  every 12 hr) was prescribed for 14 days. The symptoms subsided and the patient could be discharged with a negative buffy coat test. Only four days later, he was re-admitted with the same clinical picture and a positive buffy coat test ( $54 \text{ IU}/10^6 \text{ PBL}$ ). Intravenous ganciclovir was restarted for another two weeks. This was apparently successful but on postoperative day 93, the CMV disease relapsed ( $33 \text{ IU}/10^6 \text{ PBL}$ ). Ganciclovir was again administered for two weeks.

On postoperative day 130, the patient was re-admitted with fever, diarrhea and extreme fatigue. The buffy coat test was positive ( $350 \text{ IU}/10^6 \text{ PBL}$ ). This time, the symptoms failed to improve under ganciclovir treatment: fever spikes and chills occurred every evening. Pancytopenia developed: a bone marrow biopsy demonstrated leishmania parasites within monocytes and neutrophils (Figure 2). Culture and serology confirmed the diagnosis of visceral leishmaniasis (*L. infantum*). The patient was treated with *iv* antimonate salts (stibogluconate antimonate,  $20 \text{ mg}\cdot\text{kg}^{-1}$  every day) for 28 days. Due to the pancytopenia, ganciclovir was discontinued; *iv* foscarnet was given instead ( $4.2 \text{ g}$  every eight hours). The fever and symptoms regressed gradually; the white blood cells and platelet counts rose back to normal. However,

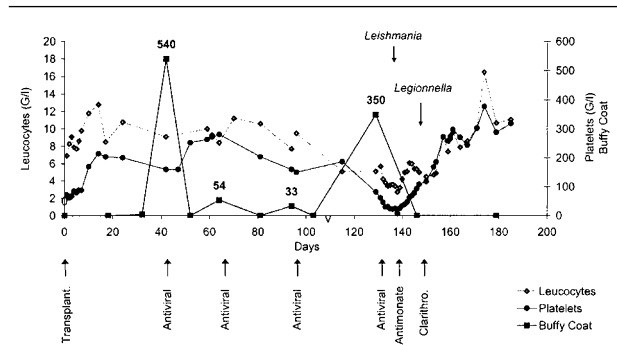


FIGURE 1 Laboratory parameters, viral DNA load and treatments.

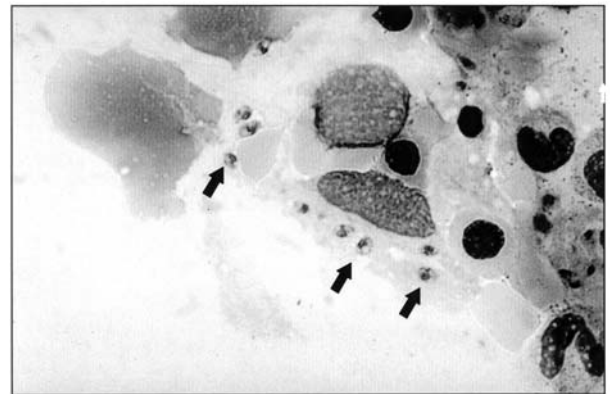


FIGURE 2 Bone marrow smear showing intracellular leishmania parasites.

three days after completion of the antimonate treatment, the fever spikes recurred and the patient complained of dyspnea. A chest *x-ray* showed a patchy, nodular infiltrate and *Legionella* rods were demonstrated on the bronchio-alveolar lavage fluid by immunofluorescence and culture. Intravenous clarithromycin ( $500 \text{ mg}$  every 12 hr for 21 days) was started and the radiological infiltrate disappeared within five days. For the next six months, the patient received oral ganciclovir prophylaxis ( $1 \text{ g}$  every eight hours). Two years later, he remains free of infections.

### Discussion

Infections are very common after liver transplantation, occurring in up to 70% of patients.<sup>1</sup> Although the

majority are bacterial, CMV infection or disease represent the most frequent identified organism.<sup>2</sup> Recurrent CMV disease after therapy is however unusual. It can be anticipated when a positive organ is allocated to a seronegative recipient (D+/R-) or after anti-rejection therapy.<sup>3</sup> In these settings, mortality is significantly higher than in a case of primary disease (55% *vs* 13%),<sup>4</sup> which may explain the scarcity of reports describing three or more recurrences. This patient suffered three relapses in a D+/R- constellation and was treated three times by *iv* ganciclovir and once by foscarnet. In retrospect, primary prophylaxis may have been more efficacious than pre-emptive therapy but it was assumed at the time that mild or moderate CMV disease could induce and promote subsequent long-term protection anti-CMV antibodies.<sup>5</sup> Similarly, secondary prophylaxis after the initial episode may have eased the clinical course. This view is supported by a retrospective analysis of the leukocyte CMV DNA load by real time polymerase chain reaction testing that showed a minimal decrease only during the first ganciclovir treatment. Subsequent courses resulted in a 1.5 to 2 log decrease of CMV DNA load but, at the end of every ganciclovir treatment, substantial amounts of CMV DNA were still detectable, thus suggesting a persistent infection (data not shown). The efficacy of the secondary oral ganciclovir prophylaxis given after the third relapse strengthens further the hypothesis that prophylaxis would have been beneficial after the primary infection already. In addition, CMV having an immunosuppressive effect of its own,<sup>6,7</sup> chemoprophylaxis might also have impacted positively on the course of the leishmaniasis and of the Legionella pneumonia.

Visceral leishmaniasis after organ transplantation has been described on some 26 occasions, mostly in renal patients<sup>8,9</sup> and, to the best of our knowledge, ours is only the third case following liver grafting.<sup>10,11</sup> The mortality is high, as Berenguer *et al.* reported five deaths out of 18 patients.<sup>6</sup> In the patient described, as the signs and symptoms were non-specific, and since serologic testing of the donor's blood was negative, the diagnosis was reached by bone marrow biopsy only. The simultaneous occurrence of leishmaniasis and of a high CMV viremia may have been a coincidence but a retrospective interview of the patient revealed a trip to Turkey the year before the transplantation. It is therefore possible that the clinical presentation of the parasitic infection was triggered by the CMV disease. A similar mechanism has been described by George *et al.* who showed that CMV infection is an independent predictor of invasive fungal infection in liver transplant recipients.<sup>9</sup> The same

phenomenon might explain the Legionella pneumonia of our patient, by the additive effects of CMV and of the tacrolimus-based immunosuppression regimen.<sup>12</sup> Singh *et al.* have indeed suggested that tacrolimus induces more fungal and Legionella pulmonary infections in liver transplant recipients than cyclosporine does.<sup>13,14</sup>

In conclusion, this case report suggests that primary CMV prophylaxis may be indicated in the D+/R- constellation. It indicates also that persistent or recurrent CMV disease in spite of treatment requires an aggressive search for other and possibly rare infectious agents.

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