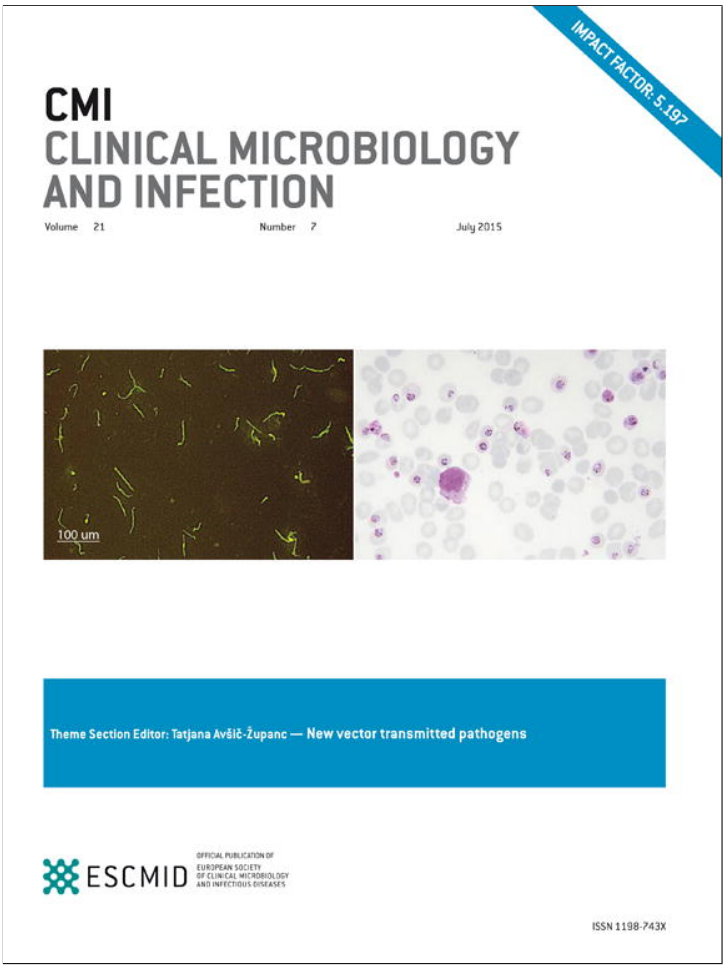

Trypanosoma cruzi infection in a Spanish liver transplant recipient

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Abstract

The shortage of suitable organ donors for transplantation has stimulated the use of organs from donors with transmissible infections such as Chagas disease in noninfected recipients. A case is described of liver transplantation from an anti–*Trypanosoma cruzi*–positive donor to a noninfected recipient who showed favorable evolution despite not having undergone preemptive therapy.

Keywords: Benznidazole, Chagas disease, evolution, liver transplant, therapy

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Introduction

Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi,* which is transmitted to humans through the feces of infected bloodsucking insects in endemic areas of Latin America, or occasionally by nonvectorial mechanisms including potential transmission linked to blood transfusion and organ transplants [1].

It is estimated that 8 to 10 million people are infected by *T. cruzi* worldwide [2]. Between 68 000 and 122 000 cases are expected in Europe, with Spain being the country most affected [3]. As a result of the shortage of organs for transplantation, reports on the use of organs from anti–*T. cruzi*–positive donors in noninfected recipients has increased in the literature, especially in kidney transplantation and, less frequently, liver transplantation. Here we describe a case of liver transplantation from an anti–*T. cruzi*–positive donor to a noninfected recipient who evolved favorably despite not having received preemptive therapy. This is defined as the treatment with benznidazole of any patient receiving an organ from an anti–*T. cruzi*–positive donor.

Case report

The patient was a Spanish woman, 52 years old, with no history of travelling abroad, transfusions or prior surgery. She received an orthotopic liver transplant in December 2008 due to a primary biliary cirrhosis in terminal stage. The patient remained asymptomatic except for acute rejection on the seventh day after transplantation, confirmed by biopsy. From transplantation to June 2009, she received prednisone and tacrolimus, then mycophenolate and tacrolimus. The donor was a woman from Bolivia who had lived in Spain since 2003 and who died of stroke. Carrier status of Chagas disease was communicated from the hospital of origin 10 months after transplantation, in October 2009. After receiving the epidemiological alert, the recipient was diagnosed with Chagas disease by positive serology using immunochromatography (Operon). A sample was sent to the National Microbiology Centre (Instituto de Salud Carlos III) to confirm the result by determination of anti–*T. cruzi* antibodies by indirect immunofluorescent antibody test and by PCR. *T. cruzi* DNA was detected by PCR with the use of oligonucleotides 121–122 and Tcz1–Tcz2, which amplified the variable region of the kinetoplast DNA minicircle (330 bp) and a repetitive sequence of satellite DNA (195 bp), respectively [4]. The presence of the parasite in blood was also detected by microhematocrit.

The patient remained asymptomatic, and ECG studies, chest x-ray, echocardiography, barium enema, oesophagogram and brain CT were normal. Treatment was initiated with benznidazole (Radanil; Roche, Argentina) (5 mg/kg/day) in ascending doses of 50 mg/2 days to reach a full dose with good tolerance. Before starting the treatment, the patient had a blood count with hemoglobin 10.1 g/dL, platelets 123 000/mm^3 and leukocytes

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4600/mm^3. During the first week of treatment, a daily follow-up, including a physical examination, hematologic and biochemic determinations, measurement of levels of immunosuppressants and determination of presence of the parasite in blood by microhematocrit method and PCR, was performed. Weekly follow-up was performed after that, until the end of the treatment. On the fourth day of treatment, negative results were found *via* both techniques, microhematocrit and PCR, but the patient developed severe neutropenia (160 neutrophils/mm^3), forcing the suspension of treatment and the introduction of granulocyte colony stimulating factor. In patients with Chagas disease, cases of neutropenia are usually mild and transitory [5], and treatment with granulocyte colony stimulating factor is not necessary. In this case, we followed local clinical guidelines aimed at immunocompromised patients with severe neutropenia. After neutrophil levels had recovered to above 1000 neutrophils/mm^3, treatment with benznidazole for 60 days was completed until the full intended dose was attained, adding colony-stimulating factor three times a week until the end of treatment. Follow-up was carried out every 6 months during the first 2 years after infection, then annually with a study protocol that included serology, PCR, ECG and echocardiography. During the monitoring period, the patient showed no clinical or laboratory abnormalities, and *T. cruzi* DNA was not detected in 21 sequential PCR tests. After 2 years of infection, serology became negative, until the last review in February 2015.

The shortage of suitable organ donors for transplantation has stimulated the use of organs from donors with transmissible infections such as Chagas disease in noninfected recipients. Although there is experience in kidney transplantation [6,7], the cases of successful liver transplantation are scarce, and in most of them, the patients received preemptive therapy immediately after surgery and during the following 14 days [8]. Following the same strategy, two cases of liver transplantation from anti–*T. cruzi*–positive donors to seronegative recipients have been published in Spain, with good results [9]. However, some authors proposed that anti–*T. cruzi*–positive donors may be accepted for liver transplant recipients only in emergency situations [10].

McCormack *et al.* [11] described the results of a protocol using livers from anti–*T. cruzi*–positive donors without preventive therapy. In that study, only 22% of patients became infected by *T. cruzi;* they had no clinical symptoms and experienced a good evolution after early benznidazole treatment. However, despite the good clinical evolution of our patient, there are certain differences between this case and others reported in the literature. Firstly, although Chagas disease in immunocompromised patients may present with severe clinical manifestations such as myocarditis and/or encephalitis accompanied with high morbidity and mortality, these symptoms are rarely seen. A possible explanation is the use of preventive treatments immediately after transplantation or the realization of close analytical controls during the subsequent monitoring period. However, it is remarkable that our patient remained asymptomatic for 9 months after transplantation without serious complications. Secondly, in these patients, there is a concomitant use of immunosuppressant drugs as mycophenolate and antiparasitic drugs (benznidazole, nifurtimox) used in Chagas disease. Our patient was treated with benznidazole, the adverse effects of which include development of neutropenia and altered liver function. Thus, the severe neutropenia developed by our patient may be aggravated by the concomitant use of immunosuppressants [12]. Little is known about the interactions between these drugs [12], but this could be a limiting factor in treating these patients, either due to potentiation of adverse effects or because potential interactions may decrease the levels of immunosuppressants and increase the possibility of transplant rejection.

In this patient, the period from transplantation to diagnosis of *T. cruzi* infection was 9 months. This was due to a late diagnosis of the infection in the donor. Although the patient remained asymptomatic and finally had a good therapeutic response, given the lack of experience and the unpredictability of the clinical course of these patients, clinical guidelines and clear policies are necessary to avoid these mismatches [13,14]. There are a range of transplantation policies in Europe, and not all European countries have the same guidelines, although current legislation allows organs to be trafficked between European countries. Moreover, at present, as a result of the economic crisis, immigrants from Latin America residing in Spain are moving to other European countries [13]. In general terms, a unification of European policies regarding the use of organs in these groups is necessary.

Other important points in these patients are the follow-up and the diagnostic tests used to confirm or exclude *T. cruzi* infection. In immunocompetent patients in the acute phase, the diagnosis can be made by direct parasitologic techniques, such as direct visualization of the parasite. In chronic phases, the presence of two positive serological tests performed by different techniques is required. Transplant recipients, as has occurred in other immunocompromised patients, may have no seroconversion and/or an early loss of antibodies due to immunosuppressive treatment. For this reason, performing sequential PCR in these patients is particularly useful, both in the early diagnosis and long-term monitoring [14]. Moreover, PCR may also detect the presence of the parasite before classical parasitologic tests and before clinical symptoms appear [15–17].

In conclusion, transplantation of livers from anti–*T. cruzi*–positive donors may be useful, given the shortage of available organs for patients who are in terminal stages of their illness,

but it is not a risk-free practice. Although many unknown points about treatment and their interactions with immunosuppressants, both in the diagnosis and follow-up, remain unclear, we have now useful tools that facilitate this type of practice.

Transparency declaration

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