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ORIGINAL ARTICLE

Safety of Liver Transplantation With Chagas Disease–Seropositive Donors for Seronegative Recipients

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The shortage of organs for transplantation has prompted the investigation of extended criteria donors, such as donors with transmissible infectious diseases. Here we report our recent experience with liver transplantation using organs from donors who were serologically positive for Chagas disease. We also provide a review of the literature and emphasize donor screening and preventive measures. ***Liver Transpl 17:1304-1308, 2011.*** © **2011 AASLD.**

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Chagas disease is a zoonotic infection endemic to South America that is caused by the protozoan parasite *Trypanosoma cruzi*. Most cases result from transmission by triatomine insects, but the parasite can be acquired in other ways, such as blood transfusions,[1] organ transplantation,[2] and congenital transmission (from mother to child).[3]

The increasing shortage of organs for transplantation has prompted transplant centers to investigate the use of extended criteria donors, such as donors with transmissible infectious diseases.[4] Serological positivity for Chagas disease is not an exclusion criterion for kidney transplantation for seronegative recipients when the procedure is followed by careful postoperative monitoring and treatment with benznidazole.[5] Successful cases of heart transplantation for patients with chagasic cardiomyopathy have been reported, and after treatment with benznidazole, there has been no reactivation in the first 60 postoperative days.[6] In Brazil, the same experience has been described for liver transplantation using grafts from seropositive donors in seronegative recipients.[7]

In this study, we report our experience with liver transplantation using organs from donors who were serologically positive for Chagas disease, and we provide a review of the literature and emphasize donor screening and preventive measures.

CASE REPORTS

Patient 1

Orthotopic liver transplantation with preservation of the vena cava was performed for a 62-year-old woman in October 2007. The patient had liver cirrhosis due to alcohol abuse, a hepatitis C virus (HCV) infection, and hepatocellular carcinoma (HCC).

The deceased donor immigrated to Spain from Bolivia and was serologically positive for Chagas disease according to enzyme immunoassay (EIA) and serum hemagglutination testing. The recipient's serological findings for Chagas disease were negative at the time of transplantation. The recipient was aware of the

Abbreviations: EIA, enzyme immunoassay; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RT-PCR, real-time polymerase chain reaction; TESA, trypomastigote excreteo secreteo antigen.

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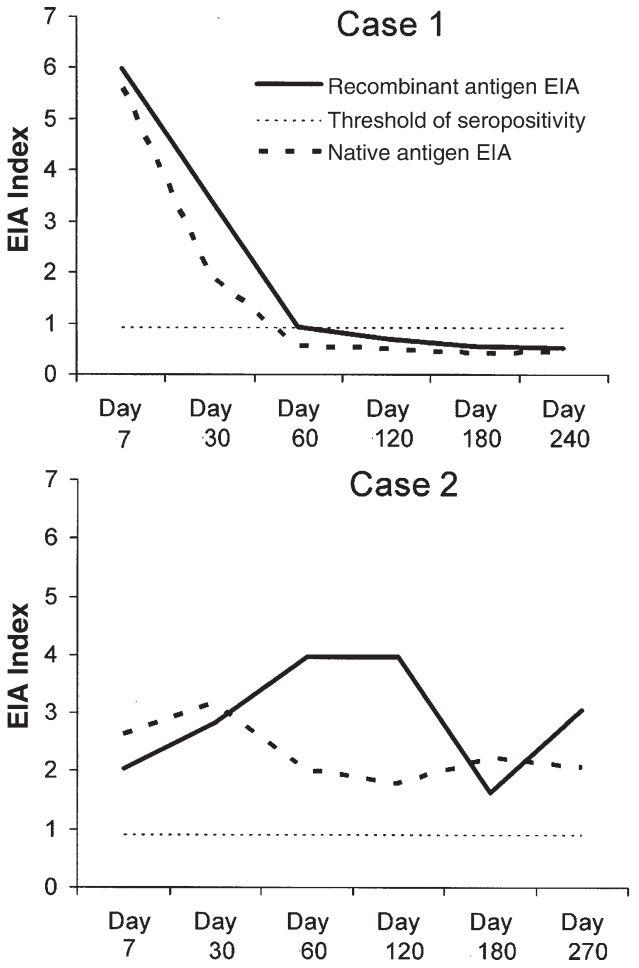

Figure 1. EIA follow-up.

required prophylactic treatment and the risk of transmission of Chagas disease, she provided written informed consent, and the procedure was approved by the liver transplantation board of our centre.

Benznidazole (100 mg) was orally administered every 8 hours (5 mg/kg/day) for 60 days after the operation as a prophylactic measure against Chagas disease. There were no adverse events requiring the interruption of benznidazole.

The patient's immunosuppressive treatment included tacrolimus (which was adjusted to a blood level of 7-10 ng/mL) and mycophenolate mofetil (conventional doses). The tacrolimus treatment was suspended because of neurological toxicity 1 month after transplantation, and everolimus was added. No acute cellular rejection occurred during follow-up. The postoperative follow-up included serological and molecular testing on days 7, 30, 60, 120, and 180 after transplantation. All serum samples were simultaneously tested with a recombinant antigen EIA (Bioelisa Chagas, Biokit, Lliçà d'Amunt, Spain) and a lysate antigen EIA (Ortho *T. cruzi* enzyme-linked immunosorbent assay test system, Johnson and Johnson, United Kingdom). In addition, peripheral blood samples were collected and processed for real-time polymerase chain reaction (RT-PCR), as described elsewhere.[8] All analyses for Chagas disease yielded negative results, except for the first 2 serological tests (Fig. 1).

The patient was readmitted 8 months after transplantation with dyspnea due to heart failure, and she ultimately died of cardiogenic shock. At that time, her serological tests and RT-PCR findings were still negative. The autopsy revealed paraneoplastic mitral valve vegetations with renal and splenic embolisms and bilateral HCC metastases to the lungs. There were no signs of a *T. cruzi* infection.

Patient 2

A 63-year-old man with liver cirrhosis due to alcohol abuse and HCC underwent orthotopic liver transplantation in November 2009. The deceased donor immigrated to Spain from Paraguay and was serologically positive for Chagas disease. The recipient was negative for Chagas disease at the time of transplantation. He provided written informed consent, and the procedure was approved by the liver transplantation board of our centre. Benznidazole (100 mg) was orally administered every 8 hours for 60 days after the operation as a prophylactic measure against Chagas disease, and the patient experienced no adverse events. The immunosuppressive therapy included tacrolimus (which was adjusted to a blood level of 7-10 ng/mL) and mycophenolate mofetil (conventional doses).

The postoperative follow-up was the same as that for patient 1. For patient 2, all the serological tests yielded positive results (Fig. 1), whereas DNA determinations by RT-PCR were always negative. Moreover, microhematocrit testing was performed 7, 30, and 60 days after transplantation; all results were negative. One year after the procedure, the patient and his organ were doing well.

LITERATURE REVIEW

We carried out a MEDLINE search for 1984-2009 with the terms *Trypanosoma*, *Chagas*, and *liver transplantation*, and we retrieved 9 additional cases in which the liver donor was seropositive for *T. cruzi* and the recipient was seronegative (Table 1). Two of these cases were reported by the Centers for Disease Control and Prevention in 2002[9] and 2006.[10] The donor's positive serological status for Chagas disease was not known before transplantation in either case. One patient experienced seroconversion and Chagas myocarditis. That patient was treated with nifurtimox but ultimately died of sepsis unrelated to Chagas disease.[9] The other patient did not experience seroconversion.[10]

A single Argentinean case was described by Barcán et al.[2] in 2005. The recipient's follow-up included serial serological studies and direct diagnosis techniques (Strout testing). Seroconversion and parasitemia were demonstrated 84 days after transplantation, and the patient was treated with benznidazole for 60 days. Eighteen months after transplantation, the patient died of sepsis unrelated to Chagas disease.[2]

TABLE 1. Characteristics of Liver Transplant Recipients With Chagas Disease–Seropositive Donors

Study	Age (Years)	Sex	Liver Disease	Benznidazole as Prophylaxis	Test	Chagas Detection	Chagas Disease	Treatment	Follow-Up (Months)	Evolution
Centers for Disease Control and Prevention[9]	32	Female	—	No	Hemoculture	Yes	Myocarditis	Nifurtimox	4	Died of sepsis
Barcán et al.[2]	33	Female	Autoimmune disease	No	Indirect fluorescent antibody, EIA, and Strout testing	Yes	No	Benznidazole	18	Died of sepsis
Centers for Disease Control and Prevention[10]	—	—	—	No	Indirect fluorescent antibody and polymerase chain reaction	No	No	No	18	Alive
D'Albuquerque et al.[7]	46	Male	HCV	Yes	Hemagglutination and EIA	No	No	No	17	Alive
D'Albuquerque et al.[7]	54	Male	HCV	Yes	TESA blot assay	No	No	No	59	Alive
D'Albuquerque et al.[7]	39	Male	Primary sclerosing cholangitis	Yes	TESA blot assay	No	No	No	23	Alive
D'Albuquerque et al.[7]	47	Female	Primary biliary cirrhosis	Yes	TESA blot assay	No	No	No	79	Alive
D'Albuquerque et al.[7]	42	Female	Alcohol	Yes	Parasitemia	No	No	No	3	Died of sepsis
D'Albuquerque et al.[7]	47	Female	Alpha-1-anti-trypsin deficiency	Yes	Parasitemia	No	No	No	4	Died of pulmonary tuberculosis
This study	62	Female	HCV, alcohol, and HCC	Yes	EIA and polymerase chain reaction	No	No	No	8	Died of HCC metastasis
This study	63	Male	Alcohol and HCC	Yes	EIA and polymerase chain reaction	Yes (EIA)	No	No	14	Alive

In 2007, D'Albuquerque et al.[7] reported 6 cases from Brazil. On the basis of previous experience with kidney transplantation, all patients were given prophylaxis in the form of benznidazole (200 mg/12 hours) for 60 days after transplantation. There was no evidence of seroconversion in any of the patients.

DISCUSSION

The shortage of suitable organ donors for transplantation is a recognized problem worldwide. The disparity between the supply and the demand has led the transplant community to look at more marginal candidates, such as donors who could potentially transmit diseases to their recipients. Another related factor is the increase in immigration from South America to Western countries (particularly the Mediterranean area); this has led to the possibility of imported illnesses among our potential donors and recipients.

The development of acute Chagas disease after solid organ transplantation has been described in kidney recipients.[11] The first 2 reports of the disease in liver transplant patients (published in 2002[9] and 2005[2]) involved recipients who experienced seroconversion during follow-up. Although they were treated with nifurtimox[9] or benznidazole,[2] both died of sepsis unrelated to Chagas disease.

To the best of our knowledge, the cases reported here are the first in Europe in which liver transplantation was performed for a seronegative recipient with an organ from a donor seropositive for Chagas disease. Our patients were prophylactically treated with benznidazole according to the recommendations of Brazilian health authorities[12] and on the basis of previously published data[7]; nonetheless, the use of benznidazole for this purpose remains controversial. Transplant recipients can experience severe infections, myocarditis, or meningoencephalitis because their immunosuppressive therapy limits their ability to control these diseases. When prophylactic therapy was not administered, Chagas disease was transmitted during the first 6 months after transplantation,[2,13] the recipients required treatment, and some of them died.[14] However, 2 studies of kidney and liver transplant patients who received organs from Chagas disease–seropositive donors reported no signs of transmission when benznidazole was used for prophylaxis.[5,7] Benznidazole is reasonably well tolerated. The side effects include rashes, itching, and, less frequently, nausea and vomiting. Uncommon severe side effects include granulocytopenia, liver toxicity, and peripheral neuropathy. In the reviewed cases, the drug was well accepted.

A patient seronegative for *T. cruzi* who receives an organ from a donor with a Chagas infection can develop acute Chagas disease.[9] This condition can be diagnosed in the acute phase by direct techniques (Strout testing, microhematocrit testing, Giemsa-stained thin and thick films or buffy coat films, hemocultures, and DNA determination by RT-PCR). In the chronic stage, however, the organism persists at low levels in blood and tissue, and it is rarely detected by direct methods. Several highly sensitive immunoglobulin G serological tests (eg, EIA, immunofluorescence, and western blotting) are routinely used in this phase. Two of these 3 techniques are required to establish a diagnosis of Chagas disease because of the high rates of both false-negative and false-positive results. Like direct methods, RT-PCR is not useful for diagnosing Chagas disease in the chronic phase because of the low level of parasitemia, but it may be a promising diagnostic tool for patients in the acute phase. Maldonado et al.[15] showed that in comparison with other direct techniques (eg, microhematocrit testing and the Strout technique), serial RT-PCR is more sensitive and yields positive results faster. However, RT-PCR has problems of validation because of the variable levels of sensitivity and specificity, and it still cannot replace other direct techniques.

Our proposal for the duration of follow-up (180 days) is based on reported experiences with kidney transplantation. In kidney recipients, the average time to the presentation of acute Chagas disease has been reported to be 80.5 days (range = 36-165 days).[13] Our 2 patients received prophylaxis, and despite their immunosuppressive therapy, neither had positive RT-PCR test results for Chagas disease during follow-up. These negative RT-PCR findings and the absence of clinical symptoms indicate the ability of prophylaxis to protect patients against acute Chagas disease. Nevertheless, the second patient was seroconverted, and this indicates that contact with the parasite was likely. Notably, seroconversion can be delayed or absent in transplant recipients. In fact, the serological tests for case 1 may have become negative because of immunosuppression. So far, there are no data elucidating the evolution to chronic Chagas disease in this particular situation. However, in our first case, a postmortem study disclosed no signs of a *T. cruzi* infection 8 months after transplantation.

Recommendations from the US Chagas in Transplant Working Group have been published recently.[16] This group has also considered the use of livers from *T. cruzi*–infected donors. Posttransplant follow-up must include polymerase chain reaction and microscopic studies of blood specimens. If an infection is confirmed in a recipient, antitrypanosomal treatment is indicated.

In summary, we stress the importance of Chagas disease screening for all donors from endemic areas. The results for our patients and those reported in the literature suggest that livers from infected donors without acute disease can be successfully used as allografts. Benznidazole (100 mg every 8 hours) for 60 days after transplantation seems to be safe and effective for the prevention of transmission. In addition, we suggest periodic serological, microhematocrit, and DNA analyses after transplantation to ensure the effectiveness of the prophylaxis. However, because of the low level of experience with these patients, further studies with larger numbers of patients and longer follow-up periods are needed to confirm the effectiveness of our proposed prophylaxis protocol.

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