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Case Report: Successful Lung Transplantation from a Donor Seropositive for *Trypanosoma cruzi* Infection (Chagas Disease) to a Seronegative Recipient

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Abstract. The increasing shortage of organs for transplantation has prompted transplant programs to investigate the use of extended criteria donors, such as those with transmissible infectious diseases. Successful cases of organ transplantation (mostly kidney and liver) from *Trypanosoma cruzi* seropositive donors to seronegative recipients have been reported. We present a case of lung transplantation from a donor serologically positive for Chagas disease to a seronegative recipient, and provide a review of the literature. Left single lung transplantation was performed in a 44-year-old Spanish woman presenting with interstitial lung disease in February 2016. The deceased donor was a Colombian immigrant living in Spain who was serologically positive for Chagas disease. Oral administration of 5 mg/kg/day benznidazole divided in three doses for 60 days was given for specific Chagas disease prophylaxis after transplantation. Periodic follow-up with serological reverse transcription polymerase chain reaction to detect *T. cruzi* DNA were performed until 6 months after the end of treatment. All results were negative, indicating that transmission of *T. cruzi* had not occurred. In a review of the literature, two similar cases were identified in Argentina and the United States. In both cases *T. cruzi* infection was detected posttransplant in the recipients, after which they were treated with benznidazole. The course of the patient described herein confirms that lungs from donors with chronic *T. cruzi* infection can be used successfully as allografts, and that posttransplant prophylaxis with benznidazole may reduce the probability of transmission of *T. cruzi* to the recipient.

INTRODUCTION

Chagas disease is a parasitic infection endemic in all the countries of Central and South America as well as in Mexico, which is caused by the hemoflagellated protozoan *Trypanosoma cruzi*. Is estimated that 6–7 million people are infected worldwide, and 10,000 people die annually mostly due to chagasic cardiomyopathy.[1] The main transmission routes are through hematophagous triatomine vectors and congenitally from mother to child, but the parasite also can be acquired through other routes, such as blood transfusion and organ transplantation from infected donors, laboratory accidents, and by consumption of contaminated food and drink.[2]

In recent years, the increasing shortage of organs for transplantation has prompted transplant programs to investigate the use of extended criteria donors, such as those with transmissible infectious diseases.[3] Acute Chagas disease in an organ donor is an exclusion criterion, and in addition transplantation of the heart or intestines from a donor with any stage of *T. cruzi* infection is not recommended.[4] However, successful cases of transplantation of other organs (mostly kidney and liver) from *T. cruzi* seropositive donors to seronegative recipients have been reported with close postoperative monitoring and benznidazole treatment.[5–10]

In this report, we describe our experience with lung transplantation from a donor serologically positive for Chagas disease to a seronegative recipient, and provide review of the literature.

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CASE REPORT

Left single lung transplantation was performed in a 44-year-old Spanish woman in February 2016. The patient presented with interstitial lung disease (desquamative interstitial pneumonitis) diagnosed on June 2013, and was receiving treatment with corticosteroids, mycophenolate, and home oxygen therapy during the months before transplantation. The deceased donor was an immigrant from Colombia living in Spain who was serologically positive for Chagas disease, as assessed by an enzyme-linked immunosorbent assay (ELISA) based on recombinant antigen (Bioelisa Chagas, Biokit, Lliçà d'Amunt, Spain), and an ELISA based on a whole cell lysate (Ortho *T.cruzi* ELISA, Johnson and Johnson, High Wycombe, UK) at the moment of donation; hence treatment with benznidazole was not performed before transplantation. The recipient was aware of the risk of transmission of Chagas disease and provided written informed consent for the procedure.

The patient's immunosuppressive treatment included tacrolimus adjusted to a target blood level of 7–10 ng/mL, mycophenolate mofetil in conventional doses, and corticosteroids. The patient had several postoperative complications: grade 3 primary graft dysfunction, multiorganic failure, left radial artery thrombosis, critical illness myopathy and polyneuropathy, gastroparesis, *Candida albicans* catheter-related bloodstream infection, and urinary tract infection by *Enterococcus faecium*.

On day 16 posttransplantation, after resolution of the multiorganic failure, oral administration of 5 mg/kg/day benznidazole divided in three doses for 60 days was begun for specific Chagas disease prophylaxis. There were no relevant adverse events, and modification of the doses of immunosuppressive drugs was not required. The recipient was

monitored for evidence of *T. cruzi* infection after the transplant by serological testing with the assays mentioned earlier and by reverse transcription polymerase chain reaction (RT-PCR) as described by Piron and others.[11] This monitoring protocol was started on the day of the transplant and continuing on a weekly basis through the end of the 60-day course of benznidazole, and on a monthly basis thereafter. All serological tests and RT-PCR during follow-up were negative (see Table 1); thus there was no evidence that transmission of *T. cruzi* from donor to recipient had occurred.

The patient had a hospital stay of 113 days (73 days in intensive care and 40 days on a thoracic surgery ward) and at 11 months posttransplantation the patient was doing well, although intermittent home oxygen therapy was still required because of desaturation with moderate exercise.

LITERATURE REVIEW

We identified previous cases of lung transplantation from seropositive Chagas disease donor to seronegative recipient using a MEDLINE search, with the terms "*Trypanosoma cruzi* infection AND lung transplantation," "Chagas disease AND lung transplantation," with no restriction regarding language or date of publication.

Two additional cases were identified. The first case was described by Cura and others in Argentina in 2013.[12] Lung transplantation was performed from a 58-year-old Argentinean donor with positive Chagas disease serology to a 57-year-old man. The recipient was monitored with serial serological studies and direct parasitological techniques (PCR, and Strout technique). On day 72 following transplantation, parasitemia was demonstrated by PCR, the Strout technique was positive on day 119, and the serological tests on day 210, and the patient was given 5 mg/kg/day benznidazole for 60 days, starting on day 126 after transplantation. The patient did not presented any clinical manifestations associated to the acute infection, and direct diagnosis techniques turned negative during treatment and remained so for at least 239 days after transplantation.

The second case was described by Huprikar and others in the United States in 2013.[13] Bilateral lung transplantation was performed from a 48-year-old female donor from El Salvador with positive Chagas disease serology to a 36-year-old man who had cystic fibrosis. Immunosuppression included prednisone, mycophenolate, and tacrolimus. The recipient was monitored for *T. cruzi* infection with PCR, hemoculture, and trypomastigote excreted-secreted antigens immunoblot. Unfortunately all three assays turned positive in weeks 29 and 30. The patient was asymptomatic and received treatment with benznidazole for 60 days. By week 43, the results of serologic and PCR testing were negative. However, at 61 and 63 weeks after transplantation, PCR was positive again, and second course of treatment was given.

TABLE 1
Serological and *Trypanosoma cruzi* RT-PCR follow-up after lung transplantation

Posttransplantation days	Ortho *T. cruzi* ELISA (native), absorbance (cut-off 1.1)	Bioelisa Chagas Biokit (recombinant), absorbance (cut-off 1.1)	*T. cruzi* RT-PCR (in-house assay)
+5	0.09	0.16	Negative
+15	0.06	0.11	Negative
+16	Onset of benznidazole treatment		
+24	0.02	0.11	Negative
+29	0.08	0.17	Negative
+36	0.12	0.42	Negative
+44	0.19	0.33	Negative
+53	0.28	0.26	Negative
+59	0.30	0.30	Negative
+66	0.61	0.35	Negative
+75	0.44	0.44	Negative
+78	End of benznidazole treatment		
+80	0.5	0.39	Negative
+109	0.5	0.22	Negative
+148	0.68	0.37	Negative
+173	0.61	0.17	Negative
+208	0.61	0.33	Negative
+235	0.58	0.42	Negative

ELISA = enzyme-linked immunosorbent assay; RT-PCR = reverse transcription polymerase chain reaction.

DISCUSSION

In this study, we present the successful lung transplantation from a *T. cruzi* seropositive donor to a seronegative recipient, to whom prophylactic treatment with benznidazole was given, and who was followed with repeated testing for evidence of *T. cruzi* transmission, which was constantly negative. To the best of our knowledge, this is the third reported case of lung transplantation with Chagas disease seropositive donor, and the first one in a European country.

Transmission of Chagas disease and development of the acute form of the disease has been previously described following solid organ transplantation, mostly in kidney recipients.[14,15] Acute form or reactivation of Chagas disease in immunosuppressed patients (human immunodeficiency virus-infected patients, transplant recipients) may result in high parasitemia and severe clinical manifestations, such as meningoencephalitis, acute myocarditis, and skin lesions.[16] The risk of developing these clinical complications post-transplant underscore the importance of the screening for Chagas disease both in solid organ donors and recipients coming from endemic areas; hence, different expert groups have elaborated consensus documents to address this issue.[3,4,17] Notwithstanding, no national legislation regarding solid organ transplantation in European countries includes Chagas disease as a specific topic; only three national transplant organizations (from Italy, Spain, and the United Kingdom) have included a specific section regarding how to control transmission of Chagas disease through donor screening.[18]

The economic stagnation in some Latin American countries endemic for Chagas disease have stimulated the flow of migration to developed countries during recent decades, making Chagas disease a global health problem.[19] After the United States, Spain is the second most affected country, and Chagas disease is increasingly being diagnosed in immigrant populations coming from endemic areas; however, it is estimated that 95% of *T. cruzi*-infected persons living in European countries remain undiagnosed.[20,21] These migration flows from Chagas disease endemic countries to the United States and European countries has contributed that Chagas disease patients are increasingly receiving different immunosuppressive therapies and participating in transplant programs (both as a donors and recipients), so that Chagas disease and immunosuppression coexistence is being reported increasingly in nonendemic countries.[22,23]

As mentioned previously, the shortage of organs for transplantation has stimulated transplantation programs the use of "extended criteria donors," such as those with Chagas disease. In this situation, two different strategies have been proposed: the prophylactic treatment (treatment with benznidazole or nifurtimox is administered to the recipient as soon as possible after transplantation) and the preemptive treatment (treatment is only administered if transmission of the infection is detected sometime during the posttransplant period). Even though the use of benznidazole as a prophylactic treatment remains controversial due to its safety profile, we opted for this strategy based on the higher Chagas disease transmission rate described with the preemptive strategy, and based in our own experience in liver transplantation.[5–10] It is remarkable that our patient did not have any of the side effects typically associated with benznidazole, and apparently that there were no untoward interactions with the immunosuppressive drugs she was concurrently receiving.

The risk of Chagas disease transmission through organ transplantation may also depend on the transplanted organ. Taking into account the main studies about organ transplantation with *T. cruzi* seropositive donors to seronegative recipients, transmission of Chagas disease was 66.6% in lung transplantation (two out of three; our case and the two previously reported), 27.3% in liver transplantation (nine out of 33), and 14.9% in kidney transplantation (seven out of 47).[5–10,12,13] These differences could be due to the amount of blood contained in the transplanted organ or to infected cells in the organ itself.

Regardless of the strategy used (prophylactic versus preemptive), a close follow-up is essential to detect disease transmission as early as possible. Acute infection by organ transplantation transmission must be diagnosed through classical parasitological techniques, such as the Strout technique, microhematocrit, or hemoculture.[24] However, these techniques are tedious and require considerable skill. Fortunately, however, PCR is often used in these situations, and it offers the advantages of quick turnaround and relatively high sensitivity.[5,25,26] Moreover, real-time techniques (such as RT-PCR) may add quantitative results, which could improve monitoring these patients.

In summary, we present a case of lung transplantation from a *T. cruzi* seropositive patient to a seronegative recipient, with no evidence of disease transmission after prophylactic treatment with benznidazole and close posttransplant monitoring. We stress the importance of screening for Chagas disease in all donors and recipients coming from endemic areas. The course of the patient described herein confirms that lungs from donors with chronic *T. cruzi* infection can be used successfully as allografts, and that posttransplant prophylaxis with benznidazole may reduce the probability of transmission of *T. cruzi* to the recipient, which should be sought through close monitoring with serologic assays and PCR.

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