CASE REPORT

Multiple parasitic infections in a cardiac transplant recipient

Bruno Fernandes Sanches,¹ Joana Morgado,² Nuno Carvalho,³ Rui Anjos³¹Department of Pediatrics, Hospital Garcia de Orta, Almada, Portugal²Department of Pediatrics, Hospital Espírito Santo, Évora, Portugal³Department of Pediatric Cardiology, Hospital Santa Cruz, Lisbon, Portugal

Correspondence to

Dr Bruno Fernandes Sanches, brsan82@gmail.com

Accepted 30 May 2015

SUMMARY

Infectious complications represent an important cause of morbidity and death in patients with transplant. Parasitic infections are less frequent than viral and bacterial agents, and are often overlooked. We describe the case of a 13-year-old adolescent, born in São Tomé Island, who was under immunosuppressive therapy after a cardiac transplant. The patient had an intermittent course of diarrhoea, abdominal pain and vomiting. She was admitted dehydrated, and *Strongyloides stercoralis*, *Schistosoma intercalatum* and *Cystoisospora belli* were isolated in her stools. The patient was treated with ivermectin, albendazole, praziquantel and ciprofloxacin with clinical and microbiological resolution. Her immunosuppressive therapy was reduced during hospitalisation. We believe that the parasitic infection was a result of a recrudescence of dormant infections acquired in her homeland. To the best of our knowledge, there are no reports of cystoisosporiasis or schistosomiasis in heart transplant recipients.

BACKGROUND

Heart transplantation is considered a life-saving therapy for selected patients with an untreatable heart disease. Nevertheless, it exposes the patient to chronic diseases with infectious susceptibility. Infectious complications are in fact an important cause of post-transplantation morbidity and death.¹ The relationship between epidemiological exposures of the individual and the net state of immunosuppression are the determinants of the risk of infection in patients with transplant.² It is important to assess epidemiological exposures taking a detailed history of possible contacts with a variety of pathogens, even if the exposure was relatively remote, since latent pathogens can be reactivated. The relevance of these epidemiological exposures will vary according to the net state of immunosuppression, which is the sum of all factors that contribute to individual susceptibility to infection (congenital, acquired, therapeutic, metabolic, surgical and transplant related). Usually, more than one factor is present, and identification and correction of any modifiable risk factor is essential for prevention and treatment of infection.

In the first month after transplantation, bacterial and surgical related infections predominate.^{1–3} In the following months, viral and opportunistic agents become more frequent.^{1–3} Inflammatory responses associated with microbial invasion are impaired by immunosuppressive therapy. This can lead to mild symptoms or to late diagnosis of infections.

CASE PRESENTATION/INVESTIGATION/TREATMENT

We report a case of a 13-year-old girl, born in São Tomé Island, living in Portugal for the past 4 years. The patient received a cardiac transplant at 11 years of age for a dilated cardiomyopathy. The donor was Portuguese and had negative IgM and positive IgG for *Toxoplasma gondii* (the recipient had negative IgM and IgG). Post-transplant, the patient was on prophylactic trimethoprim and sulfamethoxazole for 17 months, which was suspended after the development of neutropaenia. Severe cellular rejection was diagnosed 1 year after transplantation and she was started on everolimus (2.5 mg/day), tacrolimus (20 mg/day) and prednisolone (5 mg/day). The patient developed diabetes at 12 years of age.

Six months before admission, the patient had diarrhoea (4–5 watery stools per day) and mild diffuse abdominal pain accompanied sporadically with vomiting. The intermittent clinical course was interpreted as viral gastroenteritis (several stool samples performed were negative). Along this period, there was a quantified weight lost of 16.5 kg (approximately 25% of total body weight). At admission, the patient was dehydrated and weighed 46.5 kg, with decreased turgor and dry mucosa, blood pressure of 106/44 mm Hg and heart rate of 128 bpm. Abdominal palpation was diffusely tender in all quadrants, with no signs of peritoneal irritation, no hepatosplenomegaly and no perineal lesions. Laboratory results revealed: haemoglobin 10.8 g/dL (laboratory reference (LR) 12.0–16.0); leucocytes $4.0 \times 10^9/L$; neutrophils $1.73 \times 10^9/L$ (LR 2.0–8.0); lymphocytes $0.93 \times 10^9/L$ (LR 1.0–5.0); monocytes $0.58 \times 10^9/L$ (reference 0.2–1.0); eosinophils $0.74 \times 10^9/L$ (LR 0.1–1.0); basophils $0.02 \times 10^9/L$ (reference 0–0.1); platelets $215 \times 10^9/L$ (LR 180–400); C reactive protein 1.28 mg/dL (LR <0.5); and urea 58 mg/dL (LR 15–36). Hepatic function was preserved. Epstein-Barr virus, cytomegalovirus (CMV) and HIV serologies were negative. Abdominal ultrasound was inconclusive, with normal liver and spleen structure and dimensions. Intravenous fluids were started; and blood, stool and urine samples were collected. *Strongyloides stercoralis* rhabditiform and filariform larvae were detected in stool samples (agar plate method) and antiparasitic therapy was started with ivermectin (200 µg/kg/day) and albendazole (800 mg/day). On the sixth day of hospitalisation (3rd day of antiparasitic therapy), *Schistosoma intercalatum* eggs (with large terminal spines) were identified in stool samples and praziquantel (40 mg/kg/day, for 2 days) was started. After a short period of clinical recovery, on the 11th day of

CrossMark

To cite: Sanches BF, Morgado J, Carvalho N, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-207033

hospitalisation the patient again had watery diarrhoea and was vomiting. *Cystoisospora belli* infection was then diagnosed by the detection of thin-walled and ellipsoidal oocysts in stool samples (acid-fast staining technique). She was started on trimethoprim and sulfamethoxazole (160+800 mg two times a day), which were replaced with ciprofloxacin (500 mg two times a day, for 10 days) on the third day of therapy, as the patient developed pancytopenia. During hospitalisation, prednisolone was suspended, and everolimus and tacrolimus dosages were reduced. Blood cultures were repeatedly negative.

The patient was asymptomatic on the 15th day of hospitalisation. Ivermectin was maintained until stool tests were negative for 2 weeks (23rd day of medication). During the hospitalisation, cardiac function was stable, without clinical, echocardiographic or histopathological signs of transplant rejection. The patient was discharged weighing 55 kg, with negative stool, urine and blood cultures. After haematological recovery, she received prophylactic trimethoprim and sulfamethoxazole (160+180 mg three times a week) for 2 months.

OUTCOME AND FOLLOW-UP

Twelve months after admission, the patient was asymptomatic, without diarrhoea, vomiting or abdominal pain, and with full weight recovery. There were no signs of transplant rejection or cardiac function deterioration. Immunosuppressive therapy was maintained with tacrolimus and everolimus, and adjusted according to therapeutic values.

DISCUSSION

Parasitic infections are an important threat in transplant recipients, causing significant post-transplant morbidity and mortality. Often overlooked and with a late diagnosis, they are less prevalent than bacterial or viral infections,^{1–3} demanding a high index of suspicion. Only 5% of human pathogenic parasitic infections have been reported in transplant receivers.⁴ However, these infections can cause serious complications and can be life-threatening. Transmission of parasitic infections in transplant receivers can occur in three ways: with a graft or blood transfusion, via *de novo* infection, or recrudescence of a dormant infection.

Strongyloidiasis has been well documented in patients with transplant. Cases have been reported in recipients of heart,^{5 6} liver,⁷ lung⁸ and combined heart and kidney transplants.⁹ All recipients in those cases had epidemiological exposure, before transplantation, where *Strongyloides* spp are endemic. Cases of strongyloidiasis in intestinal¹⁰ and pancreas¹¹ transplant have also been reported, most likely related to graft transmission.

St. stercoralis is a nematode that can complete its entire life cycle within the human host through an autoinfection cycle. Although limited by an intact immune system, a low level of autoinfection grants the survival of the parasite for decades in the human host. In patients with depressed cell-mediated immunity or under immunosuppressive therapy, massive increases in reproduction of the larvae have been reported,¹² related to an augmentation of the normal life cycle of the parasite. A potentially fatal hyperinfection with disseminated disease (lungs, liver, heart, central nervous system, endocrine glands) may result from this augmentation, with a reported mortality rate higher than 50%.¹² Steroids play an important role and even short courses have led to hyperinfection and death.^{13 14} For patients in whom the corticoid therapy is tapered, the prognosis improves.¹⁵ In this matter, it is also relevant to mention that our patient was not screened for *Strongyloides* prior to transplant. This is an important learning point, and we now

consider that transplant candidates from endemic countries should be screened for *Strongyloides* by antibody testing and stool ova and parasites (O & P) testing.

To the best of our knowledge, there are no reports of cystoisosporiasis or schistosomiasis in heart transplant recipients. However, there are several reports of cystoisosporiasis in liver and renal transplant disease,^{16 17} and infection with *Schistosoma* spp in liver and renal transplant.^{18–21} In our literature review, we found that *Schistosoma* infections in patients with transplant are mainly related to species of *Sc. mansoni* and *Sc. haematobium*, as was reported in specific endemic areas. It seems that schistosomiasis infection is not more severe in patients with transplant as compared with patients without transplant, and treatment with praziquantel is sufficient. The reports also show that schistosomiasis does not compromise long-term outcome after liver transplantation.¹⁷ The outcome after cystoisosporiasis in transplant recipients also seems good, however, the data are scarce. Protozoan reactivation is usually related to an immunocompromised state, alerting for the risks of being on high immunosuppression and not on trimethoprim and sulfamethoxazole therapy.

Taking into account our patient's epidemiological context (of western African origin), we hypothesise that the infection with three parasites was a result of recrudescence of dormant infections. Since there were no signs of other usual opportunistic infections (such as CMV infection), the hypothesis of overimmunosuppression is debatable. In our literature review, the majority of cases reported concerning strongyloidiasis, schistosomiasis or cystoisosporiasis infections in patients with transplant did not have other opportunistic infections. We believe that the immunosuppression was not the sole cause of these infections. It was the relationship between the epidemiological exposure of the patients to these agents combined with the net state of immunosuppression that were determinant. This is relevant even if the exposure was relatively remote, since latent pathogens can be reactivated. The relevance of these epidemiological exposures will vary according to the net state of immunosuppression, which we consider as the sum of all factors that contribute to individual susceptibility to infection (congenital, acquired, therapeutic, metabolic, surgical and transplant related). It is probable that more than one factor were present.

The parasitic infection diagnosis was suspected due to the intermittent and prolonged clinical course. The patient had an absolute eosinophil value within normal range but its relative value (18%) was high (under an immunosuppressive background), supporting the hypothesis of parasitic infection. The diagnosis of strongyloidiasis was readily made by detection of the rhabditiform and filariform larvae in stool samples. *Cystoisospora* infection can also be diagnosed by the detection of the parasite oocysts in stool samples. However, in the present case, the diagnosis was not made immediately, which can be explained by an intermittent shedding of the parasite. Therefore, multiple sample analysis may be required for the diagnosis.²² Similarly, the diagnosis of schistosomiasis was made by demonstration of the parasite eggs in stools. Screening stool samples has high specificity but low sensitivity, especially in light infections.²³ Egg detection sensitivity can be improved by concentration techniques, but an excretion of about 3000–6000 eggs per day is needed to be readily visualised.²³ As with strongyloidiasis, schistosomal antigens and antibody responses can also be detected by serology assays (ELISA), which have an approximate sensitivity of 85%.^{24 25} However, despite adequate treatment, antibody titres can remain high for long periods, which make the diagnosis of reactivation or reinfection

difficult.^{24 25} If the stool examination is not diagnostic, besides serological tests, duodenal aspirates or even intestinal biopsy are the next steps in the investigation of a parasitic infection. Despite the severe dehydration seen in our patient, we did not confirm a hyperinfection syndrome, since there was no dysfunction of other organs and the parasite was only isolated in stools.

Presently, the treatment of choice for strongyloidiasis is ivermectin. Given the severe presentation of the infection and the state of immunosuppression of our patient, the option for first treatment was the association of ivermectin with albendazole. No randomised trials have been carried out, but there are case reports of the improved efficacy of this combination treatment and it is often considered a reasoned approach.^{13 26} In immunocompromised patients, the optimal treatment and its duration is debatable, as data are limited. The duration can be determined by the patient's response and ivermectin should be maintained until stool tests are negative for at least 2 weeks (1 autoinfection cycle).²⁷ For all *Schistosoma* spp, the treatment of choice is praziquantel. For cystoisosporiasis, the option of treatment was ciprofloxacin (after the development of pancytopenia related with a possible myelotoxic effect) followed by secondary prophylaxis with trimethoprim plus sulfamethoxazole. The optimal duration of secondary prophylaxis is yet unknown but considered necessary to prevent relapse in patients with severe immunosuppression.²⁸

Reduction of immunosuppressive therapy is an important adjunct to any antiparasitic therapy. Since it carries the risk of graft rejection, prolongation of antiparasitic therapy should be considered.

In summary, we described the case of a cardiac transplant recipient who developed simultaneous strongyloidiasis, cystoisosporiasis and schistosomiasis. We hypothesised that it was a recrudescence of dormant infections in relation to the patient's epidemiological exposure combined with the net state of immunosuppression.

Learning points

- Epidemiological exposures of the individual combined with the net state of immunosuppression are determinants of the risk of infection in patients with transplant.
- Latent pathogens can be reactivated by the onset of immunosuppression.
- Although less prevalent than viral or bacterial infections, parasitic agents can cause significant morbidity and mortality in post-transplant patients.
- Strongyloidiasis, schistosomiasis and cystoisosporiasis should be considered in the differential of post-transplant patients with prolonged diarrhoea and epidemiological exposure.

Acknowledgements The authors acknowledge Dr José Pedro Neves, cardiothoracic surgeon, Hospital Santa Cruz; Dr Miguel Abecasis, cardiothoracic surgeon, Hospital Santa Cruz; and Dr Maria José Rebocho, cardiologist, Hospital Santa Cruz.

Contributors BFS and JM were responsible for drafting of the manuscript. NC and RA revised the manuscript critically for important intellectual content.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Schowengerdt KO, Naftel DC, Seib PM, *et al.* Infection after pediatric heart transplantation: results of a multi-institutional study. The Pediatric Heart Transplant Study Group. *J Heart Lung Transplant* 1997;16:1207–16.
- 2 Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med* 2007;357:2601–14.
- 3 Gurgui M, Muñoz P. Infection in heart transplantation. *Enferm Infecc Microbiol Clin* 2007;25:587–97.
- 4 Barsoum RS. Parasitic infections in transplant recipients. *Nat Clin Pract Nephrol* 2006;2:490–503.
- 5 El Masry HZ, O'Donnell J. Fatal strongyloides hyperinfection in heart transplantation. *J Heart Lung Transplant* 2005;24:1980–3.
- 6 Schaeffer MW, Buell JF, Gupta M, *et al.* Strongyloides hyperinfection syndrome after heart transplantation: case report and review of the literature. *J Heart Lung Transplant* 2004;23:905–11.
- 7 Vilela EG, Clemente WT, Mira RR, *et al.* Strongyloides stercoralis hyperinfection syndrome after liver transplantation: case report and literature review. *Transpl Infect Dis* 2009;11:132–6.
- 8 Balagopal A, Mills L, Shah A, *et al.* Detection and treatment of Strongyloides hyperinfection syndrome following lung transplantation. *Transpl Infect Dis* 2009;11:149–54.
- 9 Mizuno S, Iida T, Zendejas I, *et al.* Strongyloides hyperinfection syndrome following simultaneous heart and kidney transplantation. *Transpl Int* 2009;22:251–3.
- 10 Patel G, Arvelakis A, Sauter BV, *et al.* Strongyloides hyperinfection syndrome after intestinal transplantation. *Transpl Infect Dis* 2008;10:137–41.
- 11 Ben-Youssef R, Baron P, Edson F, *et al.* Strongyloides stercoralis infection from pancreas allograft: case report. *Transplantation* 2005;80:997–8.
- 12 Roxby AC, Gottlieb GS, Limaye AP. Strongyloidiasis in transplant patients. *Clin Infect Dis* 2009;49:1411–23.
- 13 Mejia R, Nutman TB. Screening, prevention, and treatment for hyperinfection syndrome and disseminated infections caused by *Strongyloides stercoralis*. *Curr Opin Infect Dis* 2012;25:458–63.
- 14 Ghosh K, Ghosh K. Strongyloides stercoralis septicaemia following steroid therapy for eosinophilia: report of three cases. *Trans R Soc Trop Med Hyg* 2007;101:1163–5.
- 15 Keiser PB, Nutman TB. Strongyloides stercoralis in the immunocompromised population. *Clin Microbiol Rev* 2004;17:208–17.
- 16 Atambay M, Bayraktar MR, Kayabas U, *et al.* A rare diarrheic parasite in a liver transplant patient: *Isospora belli*. *Transplant Proc* 2007;39:1693–5.
- 17 Koru O, Araz RE, Yilmaz YA, *et al.* Case report: *Isospora belli* infection in a renal transplant recipient. *Turkiye Parazit Derg* 2007;31:98–100.
- 18 Ariza-Heredia E, Razonable RR. Incidental hepatic schistosomiasis in a liver transplant recipient. *Transpl Infect Dis* 2012;14:75–8.
- 19 Vincenzi R, Neto JS, Fonseca EA, *et al.* *Schistosoma mansoni* infection in the liver graft: the impact on donor and recipient outcomes after transplantation. *Liver Transpl* 2011;17:1299–303.
- 20 Hoare M, Gelson WT, Davies SE, *et al.* Hepatic and intestinal schistosomiasis after orthotopic liver transplant. *Liver Transpl* 2005;11:1603–7.
- 21 Ahmed K, Safdar K, Kemmer N, *et al.* Intestinal schistosomiasis following orthotopic liver transplantation: a case report. *Transplant Proc* 2007;39:3502–4.
- 22 Leder K. Epidemiology, clinical manifestations, and diagnosis of Cystoisospora infections. In: Basow DS, ed. *UpToDate*. Waltham, MA: UpToDate, 2014.
- 23 Elliot DE. Schistosomiasis. Pathophysiology, diagnosis, and treatment. *Gastroenterol Clin North Am* 1996;25:599–625.
- 24 Doenhoff MJ, Chiodini PL, Hamilton JV. Specific and sensitive diagnosis of schistosome infection: can it be done with antibodies? *Trends Parasitol* 2004;20:35–9.
- 25 Rodrigues RM, Oliveira MC, Sopelete MC, *et al.* IgG1, IgG4, and IgE antibody responses in human strongyloidiasis by ELISA using *Strongyloides ratti* saline extract as heterologous antigen. *Parasitol Res* 2007;101:1209–14.
- 26 Pornsuriyasak P, Niticharoenpong K, Sakapibunnann A. Disseminated strongyloidiasis successfully treated with extended duration ivermectin combined with albendazole: a case report of intractable strongyloidiasis. *Southeast Asian J Trop Med Public Health* 2004;35:531–4.
- 27 Segarra-Newnham M. Manifestations, diagnosis, and treatment of Strongyloides stercoralis infection. *Ann Pharmacother* 2007;41:1992–2001.
- 28 Kaplan JE, Benson C, Holmes KK, *et al.* Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009;58 (RR-4):1–207.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow