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CASE REPORT

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Schistosomiasis of liver graft as a differential diagnosis of abnormal liver tests after transplantation: report of two cases

Lydia Teófilo de Moraes Falcão[1], Andrea Dória Batista[1], Erika Cavalcante Maranhão[1], Siglya Soares Ferreira dos Santos[1], Vitor Ribeiro Viana Madeiro[1], Fabio Mesquita Moura[1], Cesar Henrique Alves Lyra[1]

ABSTRACT

Schistosomiasis is a major health problem that affects over 200 million people worldwide. There are few reports of *Schistosoma mansoni* found in liver transplants as well as scarce information about the course of the disease and the long-term effects on the graft. Herein, we report two cases of schistosomiasis in liver transplant recipients who presented abnormal serum liver enzymes, with evidence of gradual improvement after antiparasitic treatment. Furthermore, we discuss the possible role of screening the parasite infection in potential liver transplant recipients from endemic areas.

KEYWORDS: Schistosomiasis. *Schistosoma mansoni.* Liver transplantation.

INTRODUCTION

Schistosomiasis is an endemic parasitic disease in emerging countries that leads to chronic morbidity, portal hypertension and decompensated liver disease. The World Health Organization estimated that over 200 million people from 76 countries were infected by the various species of *Schistosoma* in 2016, and, of those, several million all over the world suffer from severe morbidity as a consequence of the infection[1]. Of the six species of *Schistosoma* that parasitize humans, only *Schistosoma mansoni* (*S. mansoni*) exists in South America. In Brazil, schistosomiasis is mainly endemic on the coast of the Northeastern region[2].

The adult *S. mansoni* worms reside in the intestinal venous drainage where the females release eggs. Some of the eggs are passed out of the body in the feces to continue the parasite's lifecycle. However, numerous eggs per day drain to the liver via the portal circulation and become trapped in the stroma of the portal canals, where they induce inflammation, a granulomatous reaction consisting of T cells, macrophages, eosinophils, and collagen deposition[3]. Although much of the damage is immune-mediated, eggs can be directly hepatotoxic and potent inducers of the immune system[4]. The consequences of the parasite on the liver can range from hepatitis to portal fibrosis, more evident in the distribution of branches of the portal vein, causing non-cirrhotic portal hypertension. It must be stressed that, in mice, the development of hepatotoxicity by *Schistosoma* is unique to the *S. mansoni* species[5,6].

Praziquantel is the mainstay of treatment for schistosomiasis, combining high cure rates with mild side effects and very low toxicity. It is currently the only drug used by schistosomiasis control programs in the world and the drug of choice for the treatment of schistosomiasis in all its clinical forms.

[1]Real Hospital Português, Programa de Transplantes de Fígado, Recife, Pernambuco, Brazil

Correspondence to: Lydia Teófilo de Moraes Falcão
Real Hospital Português, Programa de Transplantes de Fígado, Av. Agamenon Magalhães, 4.760, Paissandu, CEP 52.010-075, Recife, PE, Brazil
Tel: +55 81 996486945

E-mail: lydiatmf@yahoo.com.br

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Despite stringent criteria for suitable organ donors, some undiagnosed and uncommon diseases are transmitted to recipients by liver transplants[7]. The occurrence of *Schistosoma* after solid organ transplantation is most studied in renal graft recipients, and the first cases of schistosomiasis in liver grafts were published in the 2000s. Since then, authors have discussed the pathogenesis and progression of the disease after liver transplantation[8-11]. In light of what has been published previously, there is no reason to believe that *S. mansoni* eggs in a liver graft will end up infecting the recipient. Individuals presenting with a perceptible infection are most probably infected before surgery or infected *de novo* in the common way[12].

We report the cases of two Brazilian patients who presented *S. mansoni* liver graft infection with significant alteration in serum liver biochemistry, mimicking acute graft rejection. This manuscript is compliant with the Helsinki Congress and the Istanbul Declaration and was approved by our institutional review board.

CASE 1

A 53-year-old male from Recife city, in Northeastern Brazil, was diagnosed with cirrhosis caused by hepatitis B and C coinfection and underwent an orthotopic liver transplant in November 2017. The biopsy of the donor's liver did not show significant alterations. The immunosuppression regimen consisted of tacrolimus (serum level 5–8 mg/mL) and mycophenolate mofetil 2 g/day. After 18 months of transplantation, there was a 3-fold increase in transaminases and total bilirubin, a 3-fold increase in alkaline phosphatase and a 10-fold increase in gamma-glutamyl transferase. The blood count showed total leukocytes at 4030/µL, being 24% eosinophils (967/µL). The infectious screening was negative, including for cytomegalovirus and viral hepatitis. The Doppler ultrasound and the nuclear magnetic resonance with a scan of biliary tracts were normal (Figure 1). Thus, the patient underwent a liver biopsy and the histological examination showed hepatitis with *Schistosoma* eggshell granuloma (Figure 1). A review of the explant biopsy also showed calcified granuloma with schistosomiasis eggs. Treatment with a single dose of praziquantel (50 mg/kg/dose) was performed, resulting in the progressive reduction of eosinophilia and liver serum enzymes (Figure 2).

CASE 2

A 23-year-old female student from Recife city, in Northeastern Brazil, was diagnosed with cirrhosis caused by autoimmune hepatitis and underwent a liver transplant in June 2019. A biopsy of the donor's liver did not show significant alterations. After two months of surgery, there was a 4-fold increase in transaminases and a 4-fold increase in gamma-glutamyl transferase. She was taking 10 mg/day of prednisone, tacrolimus (serum level 6–8 mg/mL) and 720 mg/day of sodium mycophenolate. Imaging tests and laboratory markers of recurrence of the underlying disease showed no alterations. A viral screening was also carried out, and cytomegalovirus infection was diagnosed and treated with ganciclovir. However, there was no biochemical improvement and a liver biopsy was performed. Histological findings were mild

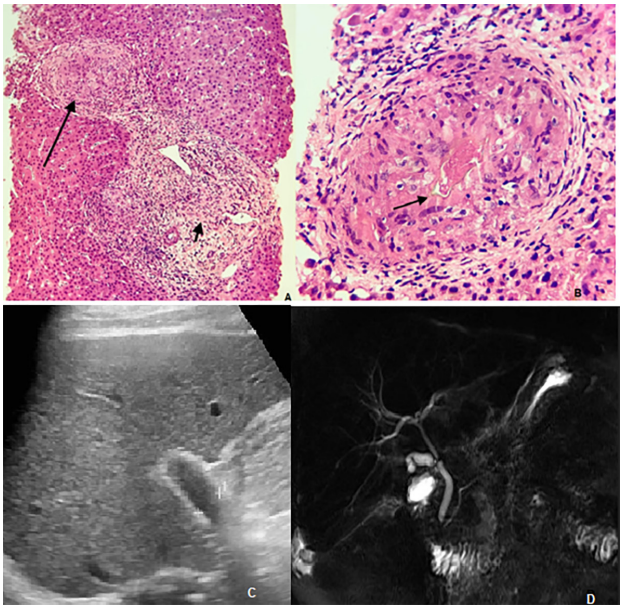

Figure 1 - Hepatic schistosomiasis post-liver transplantation: A) Liver biopsy sample showing a granulomatous reaction with eosinophils (left arrow) and periportal fibrosis (right arrow); B) Liver tissue demonstrating granuloma with birefringent elliptic central structure, exhibiting spicule (black arrow) compatible with *S. mansoni* egg (hematoxylin & eosin stain); C) Patient's liver ultrasound and D) Nuclear magnetic resonance of biliary tracts without significant changes.

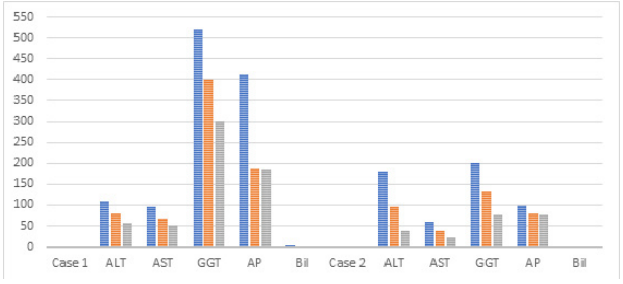

Figure 2 - Progressive decrease in liver tests after 30 and 60 days of treatment. ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; Bil = bilirubin (mg/dL); GGT = gamma-glutamyl transferase. Reference values: ALT (F: 7–30; M: 10–55 U/L), ALP (F: 30–100; M: 45–115 U/L), AST (F: 9–25; M: 10–40 U/L), GGT (F: 45; M: 65 U/L).

inflammatory infiltrate, predominantly lymphocytic, with histiocytes, rare plasma cells and eosinophils, which did not go beyond the limiting membrane. Furthermore, there was a granulomatous structure in the graft with multinucleated giant cells and frequent eosinophils around the *Schistosoma* eggshell, as described in the first case. There was no hepatocytic injury, aggression to bile ducts, endotheliitis or central perivenulitis. The review of the explant biopsy was suggestive of cirrhosis caused by autoimmune hepatitis. The patient received a 50 mg/kg dose of praziquantel, with subsequent regression of biochemical alterations (Figure 2).

DISCUSSION

In Latin America (LA), endemic diseases can impact the recipient's prophylaxis and infections. According to the most recent recommendations, schistosomiasis should be considered in any individuals who have resided in or traveled to endemic areas with significant freshwater contact[13]. However, the literature is scarce regarding *S. mansoni* infection after solid organ transplant despite its high prevalence in LA.

In endemic regions, hepatic schistosomiasis is commonly observed as an incidental finding in the explanted livers of patients who receive liver transplantation. In such cases, the presence of the parasite in the mesenteric veins of the recipient can be assumed, and therapy with praziquantel is indicated. However, if there are eggs in the periportal space of the donor's liver, the disease is unlikely to be transmitted after liver transplantation, and neither significant incidence of acute or chronic rejection nor reduced long-term patient/graft survival has been observed[7,14]. In a 10-year follow-up of patients with schistosomiasis after undergoing kidney transplantation, parasitic infection did not interfere with patient survival and graft loss[15]. Apparently, in the same way, in post-transplant liver infection, the treatment with praziquantel prevents graft failure when diagnosed early[12]. In our two cases, the treatment with praziquantel efficiently showed improvement of liver function tests.

In the immunocompromised host, there may be differences in the clinical presentation, in the pathological aspects and in the therapeutic approach for associated infectious diseases. Regarding schistosomiasis, there is the possibility of toxic hepatitis in the absence of granuloma, a reduction in the elimination of eggs in the feces and a decrease in the therapeutic efficacy of schistosomicidal agents[12,16]. The effects of immunosuppression on the *S. mansoni* infection are poorly understood. Although reports suggest that the calcineurin inhibitor cyclosporine has antischistosomal properties, it is not known whether using this drug instead of tacrolimus or sirolimus would reduce the risk of schistosomal reactivation or reinfection[17].

The diagnosis of schistosomiasis is confirmed by the microscopic demonstration of parasite eggs in feces or tissue, or by serology. Kato–Katz's quantitative technique is the gold standard for diagnosis, with a sensitivity of 70 to 80% of the cases of the hepatointestinal form and 30 to 40% of the cases of the hepatosplenic form[3,5,16]. Serology has a sensitivity of around 85% but circulating antibodies can remain for long periods even after treatment, and cannot distinguish previous exposure from active infection[3,16]. In most cases, schistosomiasis is underdiagnosed before transplantation because the donors and recipients are usually asymptomatic and the parasitological tests are false negatives or not performed[18]. Due to the lack of evidence that contraindicates the use of schistosome-infected grafts, donor screening is rarely performed. However, all transplant candidates originating from endemic areas should be screened by stool examination, since serological tests do not differentiate between current and past infections, and in immunosuppressed patients, seroconversion may be delayed or never occur[13]. Histological examination of the explanted organ can demonstrate a granulomatous reaction or the presence of *S. mansoni* eggs.

The increase in serum liver enzymes related to graft inflammation may be common after liver transplantation, arising from different etiologies – the most frequent being related to underlying diseases and viral infections, mainly by cytomegalovirus. Graft rejection and vascular and biliary complications are the main causes of morbidity and even mortality after liver transplantation[19]. Regarding schistosomiasis, the transplanted recipients can either present with a *de novo* infection or a reactivation of a previous infection. In addition to the inflammation and granulomatous reaction caused by the presence of the parasite egg in the liver, the antigens can stimulate the proliferation of cholangiocytes and osteopontin, which may be associated with schistosomal cholangiopathy and portal hypertension[20].

In the literature, reported cases of schistosomiasis after liver transplantation, in patients with different underlying diseases, showed graft recovery after the use of praziquantel[8-11]. In the cases reported herein, attention is drawn to the significant increase in serum liver tests, occurring over a period of two to eighteen months after transplantation, both requiring liver biopsy. The histology of the liver specimens in both cases showed no evidence of acute rejection or cholangiopathy, being compatible with *Schistosoma* infection. The treatment with praziquantel resulted in a remarkable improvement of liver serum enzymes, probably due to the reduced production of parasite

eggs. Therefore, considering that there are still important endemic areas for *S. mansoni* in LA, it is necessary to be aware of this possibility as a cause of elevated serum liver biochemistry after transplantation, as well as encouraging the screening of the parasite in patients who are candidates for liver transplantation.

CONCLUSION

Graft infection by *S. mansoni* after liver transplantation is underdiagnosed despite being endemic in several emerging countries. Corroborating the scarce literature, the reported cases showed recovery of the liver graft after antiparasitic treatment. Long-term follow-up is necessary to understand the impact of schistosomiasis on the graft after solid organ transplantation.

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