

Case report

## Cardiac toxoplasmosis after heart transplantation diagnosed by endomyocardial biopsy

L.A. Petty, S. Qamar, V. Ananthanarayanan, A.N. Husain, C. Murks, L. Potter, G. Kim, K. Pursell, S. Fedson. Cardiac toxoplasmosis after heart transplantation diagnosed by endomyocardial biopsy. *Transpl Infect Dis* 2015; **17**: 719–722. All rights reserved

**Abstract:** We describe a case of cardiac toxoplasmosis diagnosed by routine endomyocardial biopsy in a patient with trimethoprim-sulfamethoxazole (TMP-SMX) intolerance on atovaquone prophylaxis. Data are not available on the efficacy of atovaquone as *Toxoplasma gondii* prophylaxis after heart transplantation. In heart transplant patients in whom TMP-SMX is not an option, other strategies may be considered, including the addition of pyrimethamine to atovaquone.

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Key words: heart transplantation; *Toxoplasma gondii*; diagnosis; prophylaxis; endomyocardial biopsy; toxoplasmosis

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Received 23 December 2014, revised 14 May 2015,  
accepted for publication 11 June 2015

DOI: 10.1111/tid.12415  
*Transpl Infect Dis* 2015; **17**: 719–722

Acquisition of infectious diseases is a potential consequence of solid organ transplantation. Toxoplasmosis is of particular interest in the cardiac transplant population, as the donor heart could be a potential conduit for transmission, because cysts are commonly found in muscle tissue. The highest risk patients are seronegative recipients who receive seropositive donor hearts (D+R–). However, donor status is not routinely tested or available. In routine practice, trimethoprim-sulfamethoxazole (TMP-SMX) is used for prophylaxis against *Pneumocystis jirovecii* pneumonia; this also provides protection against toxoplasmosis after heart transplantation. Owing to allergies or intolerances, TMP-SMX is not always a possible agent. No clear guidance is available for the best choice for second-line prophylaxis. We describe a case of cardiac toxoplasmosis diagnosed by routine endomyocardial biopsy in a

patient with TMP-SMX intolerance on atovaquone prophylaxis.

### Case report

A 30-year-old African-American man with a history of familial cardiomyopathy underwent orthotopic heart transplantation after bridging with a Heartmate II for pulmonary hypertension. His induction immunosuppression included basiliximab, methylprednisolone, and mycophenolate mofetil (MMF). The patient's maintenance immunosuppressive regimen included tapering prednisone, tacrolimus, and MMF.

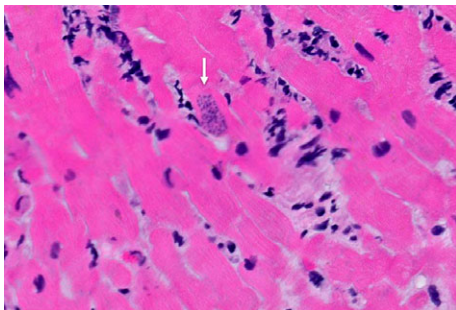
The donor's serologies available at transplantation were negative for cytomegalovirus (CMV), and the *Toxoplasma gondii* status was unknown; the recipient's

serologies were CMV and *T. gondii* negative. His prophylaxis regimen included valganciclovir, nystatin, and atovaquone (owing to TMP-SMX intolerance).

Four months after transplantation, the patient developed fevers, chills, diarrhea, and intermittent frontal headaches. Initial evaluation was significant for neutropenia (absolute neutrophil count 500) and fever. His valganciclovir and MMF were held, and he was started on broad-spectrum antibiotics and granulocyte colony-stimulating factor (G-CSF).

His fever remained unexplained, despite an extensive infectious work up including testing for hepatitis, human immunodeficiency virus (HIV), parvovirus B19, and CMV. Imaging was only significant for splenomegaly. Further studies showed negative *T. gondii* serologies and polymerase chain reaction (PCR) (Focus Diagnostics, reference range <100 copies/mL). Etiology for his neutropenia was attributed to his immunosuppressive regimen, and his fevers remained unexplained. His MMF was held during his hospital stay. He also received 5 doses of G-CSF and his neutropenia resolved. On day 4 through day 7, he developed a slight peripheral eosinophilia (9%) and, given the lack of infectious etiologies, consideration was given to drug fever from antibiotics or low-molecular weight heparin. On day 9, these treatments were discontinued, and his fever curve trended down and he became afebrile on day 12 of his hospital stay. At the time of discharge, he was feeling significantly better, and he had resumed his immunosuppressive and prophylactic regimen.

One month later, routine endomyocardial biopsy showed a single myocardial fiber with an encysted structure containing multiple microorganisms (Fig. 1). The biopsy also revealed focal lymphocytic inflammation and eosinophils near the infected myocyte. No myocyte damage was seen. The morphology was suggestive of *Toxoplasma* species. Because the inflammation was

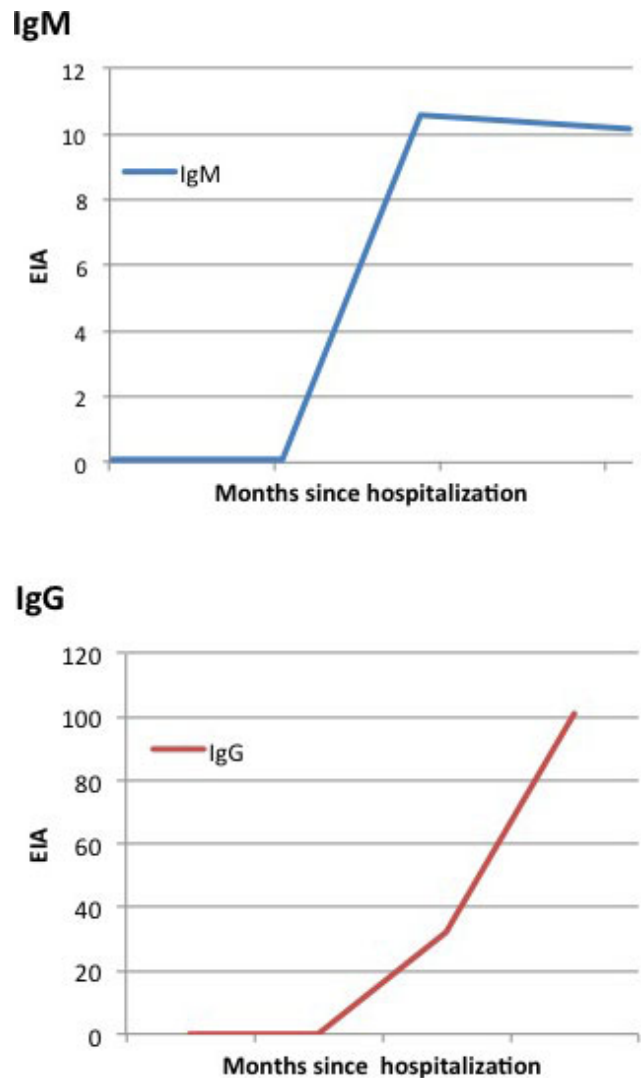


**Fig. 1.** Endomyocardial biopsy specimen with hematoxylin and eosin stain at high power showing cyst (white arrow).

associated with the organisms, the biopsy was not graded as acute cellular rejection. The organisms were seen in 2 of the multiple levels examined.

Based on the results of the cardiac biopsy, *T. gondii* serologies were retested and were positive (immunoglobulin [Ig]M and IgG) (Fig. 2). Clinically, he had improved and was asymptomatic. Despite his stable status at this point, in the setting of clearly documented seroconversion as well as positive cardiac pathology, it was decided to initiate therapy for *T. gondii* infection for 1 year. Because of his TMP-SMX intolerance, he was started on atovaquone 1500 mg oral twice daily.

His subsequent endomyocardial biopsies did not show any evidence of *T. gondii* infection, and



**Fig. 2.** *Toxoplasma gondii* immunoglobulin (Ig)M and IgG levels over 3 months following hospitalization. EIA, enzyme immunoassay.

serologies remained positive. He remains asymptomatic. On further discussion with the patient at a later date, he admitted to non-compliance with the increased dosing of atovaquone because of severe distaste. The potential severity of reactivation was discussed, and he now reports compliance with the medication.

This infection was considered most likely to be donor derived. The patient had negative *T. gondii* serologies before transplantation. He did have a cat at home, but reported that only his wife changed the litter box. He denied eating raw or undercooked meats.

## Review and discussion

We present a case of cardiac toxoplasmosis diagnosed by routine endomyocardial biopsy in a patient with TMP-SMX intolerance on atovaquone prophylaxis. His presentation consisted of fevers, diarrhea, and nonspecific constitutional symptoms. His symptoms resolved in the setting of short-term discontinuation of his immunosuppressive regimen and normalization of his white blood cell count. His diagnosis was made by the pathologic finding of intracytoplasmic organisms on routine surveillance biopsy, and subsequent re-testing of his *Toxoplasma* serologies that showed seroconversion with new IgM and IgG positivity. Upon further questioning, compliance with his atovaquone prophylaxis was also called into question owing to distaste.

Toxoplasmosis is a parasitic zoonosis transmitted to humans by ingestion of raw or undercooked meat containing *T. gondii* cysts or by ingestion of oocysts from fecally contaminated foods. Toxoplasmosis is of particular interest in the cardiac transplant population, as the donor heart could be a potential conduit for transmission, as cysts are commonly found in muscle tissue. The highest risk patients are seronegative recipients who receive seropositive donor hearts (D+/R-). Historically, the risk of D+/R- cardiac transplant patient developing acute toxoplasmosis was 50–75%, before prophylaxis. This risk has significantly decreased in the setting of widespread TMP-SMX prophylaxis. A matched case-control study tried to identify risk factors for toxoplasmosis in solid organ transplant recipients, and found only seronegative status prior to transplantation as increasing the risk (1). Toxoplasmosis did not occur in any patient while receiving TMP-SMX or pyrimethamine prophylaxis, but atovaquone prophylaxis was not assessed (1).

Prevention of toxoplasmosis in cardiac transplantation has not been extensively studied, in particular in the setting requiring alternative agents to TMP-SMX. One retrospective study showed an overall 0.2% risk of

acute toxoplasmosis, and 2% in the high-risk group, with the use of TMP-SMX prophylaxis (1 double-strength tablet 3 times weekly) (2). Per the International Society of Heart and Lung Transplantation Guidelines, the preferred agent is TMP-SMX (3). In the setting of allergy or G6PD-deficiency, options include dapsone with or without pyrimethamine, atovaquone, or clindamycin and pyrimethamine, without any preference given (3). The duration of prophylaxis is not definitive, ranging from 6 weeks to 1 year, with some centers continuing prophylaxis lifelong in the highest risk patients.

Atovaquone is a naphthoquinone with broad-spectrum antiprotozoal activity. It is a structural analog of protozoan ubiquinone, a mitochondrial protein involved in electron transport. The presumed mechanism of action is inhibition of ubiquinone binding to cytochrome *b* (4). In the past, it was formulated as a tablet, but this was discontinued owing to poor and unreliable bioavailability, and now exists as a liquid formulation only (4). Side effects of atovaquone are minimal, including rash, nausea, and diarrhea, and it does not cause bone marrow suppression (4). The taste of the liquid formulation is unpleasant, however, and this may result in the possibility of non-adherence.

Limited data are available to determine the best second-line agent for toxoplasmosis primary prophylaxis in the immunocompromised patient. The majority of available data are *in vitro*, or *in vivo* in HIV/AIDS patients. Atovaquone does show activity against tachyzoites in *in vitro* cell culture, with higher doses required to kill bradyzoites within cysts (5). Atovaquone was also shown to be effective in murine models (6). In a multicenter randomized trial comparing atovaquone and dapsone for *P. jirovecii* prophylaxis in patients with HIV, no significant difference was found between toxoplasmosis reactivation in a subgroup analysis (7). Of the patients who were seropositive at baseline, 7 of the 170 patients developed confirmed or probable toxoplasmosis (4 on atovaquone and 3 on dapsone) (7).

Diagnosis can be difficult, which can often delay treatment. A negative *T. gondii* PCR in the serum has a good negative predictive value, but it cannot rule out the diagnosis of toxoplasmosis, as cases of toxoplasmosis proven on organ tissue PCR and immunohistochemistry have also been reported with negative PCR results from serum (8, 9). In addition, serologies may initially be negative in the setting of immunosuppression. Both of these factors may have been present in our patient.

A few case reports of acute toxoplasmosis in immunocompromised hosts suggest that inability to take

TMP-SMX, for a variety of reasons, may increase risk as well. A 19-year-old man with congenital heart disease after his second orthotopic heart transplantation developed acute toxoplasmosis while not on prophylaxis because of a TMP-SMX allergy (10). Two patients demonstrated acute toxoplasmosis in the setting of atovaquone prophylaxis, both after stem cell transplantation (11, 12).

Data are not available on the efficacy of atovaquone as *T. gondii* prophylaxis after heart transplantation, specifically. We describe a case of cardiac toxoplasmosis uniquely diagnosed by routine endomyocardial biopsy in a patient on atovaquone prophylaxis. In our patient, delay in diagnosis may have been a result of initial immunosuppression. We hypothesize that the patient improved without therapy, in the setting of stopping his immunosuppression. Diagnosis was confirmed by endomyocardial biopsy and seroconversion. Afterward, non-adherence during treatment with twice-daily atovaquone hinted at potential non-adherence with earlier prophylaxis, but this was not confirmed. Therefore, it is not clear if this was a failure of atovaquone, or a failure to take the recommended prophylactic regimen. In heart transplant patients, in whom TMP-SMX is not an option because of allergy or intolerance, other strategies may be considered, including the addition of pyrimethamine to atovaquone, and suspicion should be heightened in the setting of unexplained fevers, given the minimal data to support its use.

### Acknowledgements:

*Author contributions:* L.A.P. and S.Q.: Drafting article, data collection, and approval of article. C.M., V.A., L.P.: Data collection and approval of article. A.N.H. and K.P.: Data analysis/interpretation, critical revision, and approval of article. G.K.: Critical revision and approval of article. S.F.: Drafting article, data collection, data analysis/interpretation; critical revision, and approval of article.

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