Disseminated toxoplasmosis in cardiac transplantation

CGA McGregor,* DG Fleck,† J Nagington,‡ PGI Stovin,§ R Cory-Pearce,*
TAH English*

From *Papworth Hospital, Cambridge, the §§Sims Woodhead Memorial Laboratory, Papworth Hospital,
Cambridge, the †PhL, Cambridge and the ‡PhL, St George’s Hospital, London

SUMMARY The first case of disseminated toxoplasmosis following cardiac transplantation in the
UK is described, with details of Toxoplasma antibody tests made on other cardiac transplant
patients. Sixteen of 40 (39%) of recipients had Toxoplasma antibody before operation. Eleven of
30 (37%) of donors had Toxoplasma antibody. The were four occasions when a negative recipi-
ent received a heart from a positive donor. Three survived the immediate postoperative period
and two became infected with toxoplasmosis. The implications of this are discussed.

Disseminated toxoplasmosis appears much more often when heart muscle from a dye test
positive donor is given to a dye test negative recipient. Antibiotic therapy is limited by the fact
that the antitoxoplasma drugs available are static in their effect, and need to be given for
prolonged periods postoperatively.

Disseminated toxoplasmosis has been described in immunocompromised hosts after transplantation of
the heart,1 liver,2 and kidney.3 The infection seems rare after renal and hepatic transplantation probably
due to the paucity of Toxoplasma cysts in these donor tissues in man. No extensive quantitative
estimate of the prevalence of toxoplasma cysts has been made in various human tissues in chronic infec-
tive toxoplasmosis.

Case history

When aged 12, this 31-year-old man first noticed that his exercise tolerance was less than his peers.
He first saw a cardiologist when aged 18 yr and a diagnosis of constrictive cardiomyopathy was made.
Digoxin and diuretic therapy was commenced and he remained well until 1977 when he developed
atrial fibrillation and he had a presumed cerebral embolus. The next year he had a grand mal fit and
he was put on phenytoin. In 1980 at the age of 30 yr he was reinvestigated because of increasing heart
failure, left ventriculography showed the appearances of hypertrophic non-obstructive cardiomyopathy with an end diastolic pressure of 30
mmHg. Deterioration continued despite full medical treatment and on 10.9.81 orthotopic cardiac trans-
plantation was carried out. The postoperative period was unremarkable and immunosuppression with
azathioprine, prednisolone and equine antithymo-
cyte globulin (ATG) (Upjohn Ltd) was established
using the regimen described by English.9 The patient
was reverse barrier nursed in an isolation cubicle
throughout the rest of his life. The first myocardial
biopsy was performed on the 9th postoperative day
and this was normal. He had right heart failure at
this time and following the right ventricular biopsy
he complained of abdominal pain, diarrhoea and
fever which settled in a few days. The patient's
peripheral oedema increased and he developed
intermittent pyrexias up to 39–7°C with anorexia,
nausea, hypotoniaemia, hypoalbuminaemia, a falling
creatinine clearance, and a persistently raised
ESR. On the 20th postoperative day the second
right ventricular biopsy showed the presence of
Toxoplasma cysts in two muscle cells. In the absence
of any other source of infection a presumptive diag-
nosis of toxoplasmosis was treated with
pyramethamine 25 mg/day, sulphadiazine 1 g three
times/day and folinic acid. The antithymocyte globu-
lin stopped to allow some recovery of
immunocompetence. Sulphadiazine treatment had to
be stopped in the following week because of crystals
and deterioration of renal function. The next
routine right ventricular biopsy was performed on
the 28th day. This showed evidence of moderate
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rejection and a short course of methylprednisolone and antithymocyte globulin was given. The effectiveness of this therapy was confirmed by a further myocardial biopsy on the 31st day. In the hope of relieving the signs of right heart failure and improving renal function a tricuspid annuloplasty was performed. However, the patient’s condition deteriorated and he died 12 days later.

Material and methods

HISTOPATHOLOGY

Histopathological material consisted of the patient’s own heart, biopsies taken at five different times from the donor heart, and the postmortem performed 43 days after the transplant operation. At each myocardial biopsy session three separate biopsies were taken. The first was put into OCT medium and after frozen sections had been cut and examined the specimen was unfrozen and fixed in formol saline. The other two specimens were fixed straight away in formol saline. All three specimens were paraffin processed and the short serial sets of sections stained with haematoxylin, phloxin and saffron (HPS) methyl green and pyronin and Masson’s trichrome.
The recipient's original heart weighed 454 g and contained a band of organised thrombus on the lateral wall of the right atrium close to the surface of resection. The tricuspid valve annulus and right ventricle were dilated with a mild degree of hypertrophy of the right ventricular wall which was 6 mm thick at the anterior wall of the conus. The mitral valve was normal. The left ventricle showed asymmetrical hypertrophy being 1-4 cm thick laterally and 2-3 cm thick in the interventricular septum and inferior wall. Microscopical examination showed interstitial fibrosis, multidirectional fibres and hypertrophy confirming the diagnosis of asymmetrical cardiomyopathy, as described by other workers.78 In addition multiple endocardial small papillomata were seen in both ventricles, more frequently in the right than in the left.

The second right ventricular endomyocardial biopsy taken on the 20th post-transplant day showed the presence of Toxoplasma parasites within two heart muscle cells (Fig. 1). The first post-transplant biopsy and the biopsy from the donor ventricle at the time of replacement of the heart had both been normal. Subsequent biopsies also showed the toxoplasma parasites on the 28th but not on the 31st postoperative days. An interesting feature of the biopsies was the apparent replacement of individual muscle cells by fibrous tissue (Fig. 2) suggestive of past damage by the parasite.

At necropsy on the 43rd post-transplant day toxoplasma was seen in the donor heart but not in the residual recipient atria, in the rectus abdominis, intercostal, pectoral, sternamastoid, diaphragmatic, lingual and oesophagopharyngeal muscles, in the liver and a few in the brain. Toxoplasma organisms were isolated from the cardiac muscle at post-mortem by inoculation into mice.

SEROLOGY
Toxoplasma antibodies were measured using the dye test4 and found to be negative postoperatively in the patient. The donor however had a dye test titre of 1/32 with Toxoplasma IgM of 1/16. On the 12th postoperative day the patient’s dye test titre was 1/64 Toxoplasma IgM 1/32. Sera from the six blood donors involved was also tested for Toxoplasma antibody. Only two of these were positive and those only to a titre of 1/16. No Toxoplasma IgM was present.

Pretransplant sera from 41 cardiac recipients were tested for Toxoplasma antibodies using the Latex test; of these 16 were positive (39%). Sera from 30 heart donors were tested likewise and 11 were positive (37%). Of 24 matched donor-recipient pairs only four instances of a positive donor heart put into a negative recipient occurred. Two of these developed toxoplasmosis, although Toxoplasma was not isolated from the second case, the third died eight days postoperatively from acute rejection and the fourth is alive and well.

Discussion
Immunosuppressed transplant patients are at increased risk of infection. The organisms encountered during the course of the Stanford heart transplant programme have been listed in Jamieson et al.1 Among these patients were eight who developed Toxoplasma infection seven of whom died. In two of these cases4 evidence was produced that the organisms were conveyed in the donated heart. This evidence consisted of the signs of infection in the perioperative period in recipients without serological evidence of previous Toxoplasma exposure. These authors thought that it was very unlikely that the toxoplasma infection was acquired from the hospital environment or from transfused blood.

In our case the serological evidence indicates that the donor but not the recipient had experienced previous Toxoplasma infection and that the blood donors had no evidence of active or developing Toxoplasma infection at the time of the blood collections.

Besides assessing the presence and degree of rejection myocardial biopsy may also show the presence of infecting organisms4 andBillingham mentions that cytomegalovirus, coxidiomycosis, fungi and Toxoplasma have all been diagnosed on routine endomyocardial biopsy. In our case routine endomyocardial biopsy showed the presence of the Toxoplasma parasites and helped to explain the patient’s fever.

It is difficult to diagnose the infection without frequent antibody tests and the available drugs are of limited value in controlling the infection. In our patient anti-Toxoplasma chemotherapy had to be abandoned because of the marked deterioration in renal function.

Possibly a vaccine would be effective but it would need to be shown to be protective in heart transplant patients where a Toxoplasma infected donor heart was supplied to the recipient. The overall prevalence of Toxoplasma organisms in donor hearts remains unknown.

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References
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Requests for reprints to: Dr DG Fleck, Public Health Laboratory, St George’s Hospital, Blackshaw Rd, London SW17 0QT, England.

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