Disseminated toxoplasmosis in cardiac transplantation

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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. There were four occasions when a negative recipient 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 infective 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 antithymocyte 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, hyponatraemia, 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 diagnosis of toxoplasmosis was treated with pyramethamine 25 mg/day, sulphadiazine 1 g three times/day and folinic acid. The antithymocyte globulin stopped to allow some recovery of immunocompetence. Sulphadiazine treatment had to be stopped in the following week because of crystalluria and deterioration of renal function. The next routine right ventricular biopsy was performed on the 28th day. This showed evidence of moderate

Fig. 1 *Toxoplasma gondii* in cardiac biopsy. HPS $\times 1110$

Fig. 2 Pale grey myocyte-sized fibrotic loci (F) in cardiac biopsy. Massou $\times 570$

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.^{7,8} 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, sternomastoid, 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 test⁶ 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 organisms^{4,5} and Billingham mentions that cytomegalovirus, coccidiomycosis, 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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