

# Fungal endocarditis after homograft valve replacement: difficulties in diagnosis and treatment

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**ABSTRACT** Fungal endocarditis is an uncommon but important problem after cardiac surgery. Two cases of fungal endocarditis after homograft valve replacement are reported. In both patients prolonged periods of antifungal chemotherapy with apparently satisfactory clinical responses ultimately failed to eradicate the infection. Both patients remain free of infection two years after excision of the infected valves and further chemotherapy. The value of serial estimations of fungal antibody titres in diagnosis and treatment is demonstrated and the necessity for early operation is emphasised.

Fungal endocarditis is an uncommon complication of open-heart surgery but it is important because of its grave prognosis. Since classical features of endocarditis may not be present and blood cultures may be persistently negative, the diagnosis is often not made until late in the course of the disease, sometimes after serious embolism has occurred. The following reports of two cases of fungal endocarditis after homograft aortic valve replacement illustrate these difficulties, and the use of fungal antibody titres and echocardiography as aids to diagnosis is discussed. In both patients antifungal chemotherapy alone failed to eradicate the infection and the need for treatment with a combination of early operation and antifungal agents is emphasised.

## Case reports

### CASE 1

A 53-year-old woman presented in 1967 with exertional dyspnoea. She had the signs of severe mitral stenosis and mild mixed aortic valve disease. A successful mitral valvotomy was performed and she remained well for eight years. In 1975 dyspnoea recurred and she was found to have developed severe aortic stenosis. In February 1976 her aortic valve was replaced with a fresh homograft,<sup>1</sup> and a second open mitral valvotomy was performed. The immediate post-operative course was uneventful but during the

next three months the patient was admitted on two occasions for investigation of pyrexia. No cause was discovered: the blood count and erythrocyte sedimentation rate remained normal and repeated blood cultures were sterile.

In July 1976 she was readmitted to hospital with a high fever and blood cultures at this time grew *Candida parapsilosis*. Candida antibodies were positive—the *C parapsilosis* precipitin titre was 1:16. An echocardiogram suggested multiple vegetations on the aortic homograft valve (figure). Amphotericin B, to which the organism was fully sensitive, was administered by intravenous infusion for 13 weeks. Adequate serum levels were recorded throughout this period and the total dose of amphotericin B was 4 g. The pyrexia settled, the homograft remained competent without evidence of obstruction, and an echocardiogram showed clearance of the vegetations. Blood cultures were repeatedly sterile, but the *C parapsilosis* precipitin titre remained positive at 1:16. The patient was asymptomatic and was discharged.

An embolus to the right leg resulted in re-admission in February 1977. Thrombus removed at femoral embolectomy showed well-preserved and viable fungal hyphae. The *C parapsilosis* precipitin titre had risen to 1:64 but blood cultures were repeatedly sterile. The valve remained competent clinically and the echocardiogram was unchanged, showing no evidence of vegetations. At operation the aortic homograft was found to be functioning normally and the cusps were soft and pliable. However, on

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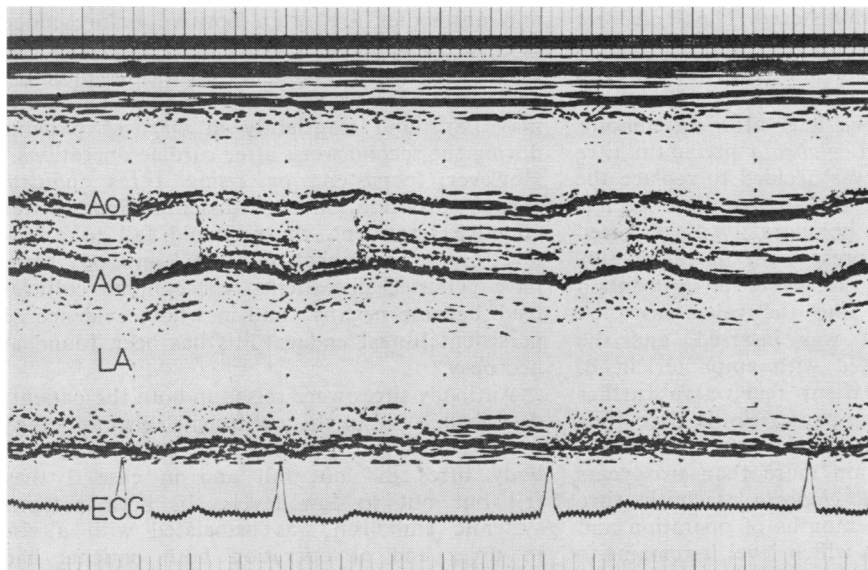


Figure Multiple echoes in the aortic root in diastole, suggestive of the presence of vegetations. Ao=aorta. LA=left atrium, ECG=electrocardiogram.

the undersurface of the right and non-coronary cusps some minute vegetations were found. Microscopy showed these to contain fungal hyphae which were eroding the ventricular surface of the cusps and extending deeply into the valve tissue. A further homograft replacement of the aortic valve was performed and the mitral valve was also replaced using a porcine heterograft (Hancock). The aortic root was irrigated with amphotericin B in the course of the operation.

Recovery was satisfactory and the patient was discharged after receiving a further 2 g of amphotericin B over a period of seven weeks. She remains well over two years later. The *C parapsilosis* precipitin titre fell to 1:2 within four weeks of the operation and subsequently to 1:1 at which level it remains more than two years after cessation of therapy.

#### CASE 2

A 26-year-old man was admitted to another hospital in April 1975 with a history of malaise and fever for one week. He had the signs of aortic regurgitation which had not been noted at previous medical examinations. A clinical diagnosis of infective endocarditis was made. Numerous blood cultures were sterile and despite treatment with intravenous benzyl penicillin and gentamicin the aortic regurgitation worsened. The development of left ventricular failure un-

responsive to medical treatment necessitated early operation. A bicuspid aortic valve with a perforated right cusp was replaced with a fresh homograft. Histology of the valve showed inflammatory changes but no organisms were identified.

In June 1976 the patient was readmitted with a history of fever for two weeks. On examination Osler's nodes were noted. Blood cultures were negative and he was treated with benzyl penicillin. His temperature settled rapidly but after one week of treatment he suffered a cerebral embolus resulting in a right hemiparesis and dysphasia. Candida agglutinin antibodies were found to be positive at this stage but in view of the apparent response to penicillin this was not considered significant. Six weeks of treatment with benzyl penicillin were completed and an echocardiogram before discharge showed an apparently normal aortic valve.

In March 1977 there was a recurrence of the pyrexia and blood cultures grew *Torulopsis glabrata*, a fungus cross-reacting serologically with *Candida* species. Moderate aortic incompetence had developed and the echocardiogram suggested multiple vegetations on the homograft valve. The patient was treated with amphotericin B by intravenous infusion, and oral flucytosine. Serum levels of each drug were kept at more than 10 times the minimum inhibitory concentration for the organism and a total of 1.5 g of

amphotericin B was administered. The *T glabrata* precipitin titre was initially 1:64, but after six weeks of treatment had fallen to 1:16. The patient was discharged on flucytosine alone, but was readmitted one week later after an embolus to his right leg. The *T glabrata* precipitin titre had risen to 1:32. It was decided to replace the diseased aortic homograft. At operation the left coronary cusp of the homograft was distorted and vegetations were present on its under surface. Histology showed the vegetations to contain fungi which extended into the valve cusps. A new aortic homograft was inserted, and the aortic root was irrigated with amphotericin B. After operation the patient received a further 0.8 g of intravenous amphotericin B over four weeks and oral flucytosine for 10 months. He remains free of infection more than two years after operation. The *T glabrata* precipitin titre fell to 1:8 within two months of operation and subsequently to 1:1 at which level it remains.

### Discussion

Fungaemia can occur after open-heart surgery or during the course of prolonged intravenous therapy.<sup>2</sup> The route of entry of the organism is uncertain. *Candida* species and *Torulopsis glabrata* are found as commensals in the human gastrointestinal tract. Invasiveness is enhanced when the bacterial flora is disturbed by broad spectrum antibiotics, and these are given prophylactically at the time of the operation and for five days afterwards. It is thought unlikely that the homograft valves were infected by fungi before insertion, as the method of preparation involves storage in a solution containing a high concentration of nystatin as well as antibacterial agents. In addition, pieces of valve tissue are cultured for bacteria and fungi before the valve is accepted for surgical use.<sup>1</sup>

It is unwise to ignore the isolation of fungi from the blood as fungal endocarditis has been recorded up to 18 months after apparently transient fungaemia.<sup>3</sup> Classical signs of endocarditis often do not occur until late in the course of the disease, and in a significant proportion of cases may be absent. Arterial emboli may be the first manifestation and they occur more commonly and tend to be larger than in bacterial endocarditis.<sup>4 5</sup>

The prognosis of fungal endocarditis is poor and a means of earlier diagnosis is needed. Echocardiography can reliably identify vegetations but it is an insensitive test.<sup>6 7</sup> Serological tests may give an early indication of fungal infection,

and antibodies are often positive before blood cultures. The detection of antibodies does not necessarily imply clinically significant infection and it has been reported that *Candida* antibodies may be found transiently in 40% of patients during the second week after cardiac operations.<sup>8</sup> However, persistent or rising titres indicate fungal proliferation or dissemination. After effective treatment, titres should fall to a low level or become negative. Raised antibody titres have persisted in patients whose blood cultures have become negative and in whom evidence of persistent fungal endocarditis has been found at necropsy.<sup>9</sup>

Antibody titres were raised in both the patients described. Although antifungal chemotherapy produced clinical remissions, in case 1 the antibody titres did not fall and in case 2 they fell but not to low levels. In both patients systemic embolism was associated with a rise in titres and at operation both patients had viable fungi in their homografts. After operation the titres fell to and remained at low levels. Precipitin titres were assayed by counter-immunoelectrophoresis using a preparation containing cytoplasmic antigens. Agglutinin titres were obtained using whole cells. Precipitin and agglutinin titres moved in the same direction but the precipitin titre was more stable, and changes were consistently associated with changes in the clinical condition.

In reported medical cures of *Candida* endocarditis the diagnosis has usually been based on the finding of fungaemia alone, without definite evidence of fungal invasion of heart valves.<sup>10</sup> Several reported cures have been followed by relapse up to one year after treatment was discontinued.<sup>11</sup> Failure of chemotherapy may be the result of poor penetration of amphotericin B into the vegetations of fungal endocarditis. Cultures positive for *Candida* have been obtained after incubation of homogenised vegetation in a medium containing 12.8 µg/ml of amphotericin B for 168 hours.<sup>12</sup>

The best chance of cure and of preventing potentially dangerous arterial embolism is provided by excision of the infected valve and removal of any other lesions. The infected area should be irrigated with amphotericin B at the time of operation, and this should be followed by systemic antifungal therapy.<sup>13</sup> Antibody titres should be estimated regularly until at least a year after cessation of chemotherapy: if treatment has been successful titres should fall to a low level. A significant rise in titres or persistence of high titres should be regarded as indicating

the need for further treatment.

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