Case reports

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Candida endocarditis treated with a combination of antifungal chemotherapy and aortic valve replacement

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A case of Candida albicans endocarditis is described in which treatment with 5-fluorocytosine was started after aortic valve replacement, but relapse followed discontinuance of treatment. At a second operation the aortic valve was replaced under 5-fluorocytosine cover and treatment was continued with both 5-fluorocytosine and amphotericin-B. No resistance to 5-fluorocytosine developed, and the candida infection was eradicated. The patient is well 22 months after his operation.

This report describes the use of two antifungal agents, amphotericin-B and 5-fluorocytosine in combination with aortic valve replacement for the treatment of endocarditis caused by *Candida albicans*.

Case history

A man aged 63, a lavatory attendant, was first admitted to hospital on 12 August 1972, with a 6-week history of shortness of breath on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, and recent onset of ankle oedema. On examination he was pyrexial (37.5°C) and had clubbing of the fingers and multiple splinter haemorrhages. He was in sinus rhythm. There was gross ankle and sacral oedema, with raised jugular venous pressure and hepatomegaly to 8 cm beneath the costal margin.

There was clinical evidence of left ventricular hypertrophy, an ejection systolic murmur, and a quiet early diastolic murmur at the left sternal edge. There were fine crepitations at both lung bases. A clinical diagnosis of aortic valve disease with subacute bacterial endocarditis was made. Chest x-ray showed a large heart with a calcified aortic valve. Electrocardiogram confirmed left ventricular hypertrophy. Multiple blood cultures were taken, all of which were negative. Rickettsial antibodies were negative.

There was an initial improvement in signs of heart failure, but on 19 August the shortness of breath increased, and three days later fresh splinter haemorrhages were noted. In view of this, treatment was started with benzyl penicillin 8 mega units intravenously per day, though as yet no organism had been isolated from the cultures of blood or urine. The pyrexia settled, but after 5 days the patient began to suffer sweating attacks, and

again his temperature rose. The antibiotic used was changed to cephaloridine 6 g daily, and within one week the patient became afebrile.

On 11 September, at 10.15 p.m., he suddenly developed gross left ventricular failure with a respiratory rate of 50 per minute, and a full length diastolic murmur. A diagnosis of ruptured aortic cusp was made, and emergency valve replacement was performed by Mr. J. E. C. Wright using a Series 1200 Starr-Edwards prosthesis (No. 11). At operation the aortic valve was heavily calcified and there were large vegetations involving all three cusps, the non-coronary cusp being destroyed and incompetent. Antibiotic therapy during and shortly after the operation was with the current standard post-operative antibiotic regimen: intravenous gentamycin 40 mg t.d.s. and cloxacillin 500 mg q.d.s.

The immediate postoperative course was uneventful, but on 18 September *Candida albicans* was isolated from blood cultures taken before operation on the 11 and 14 September. This was sensitive to 5-fluorocytosine at a minimum inhibitory concentration of 0.35 µg/ml. Culture of the valve itself grew the same organism, as did three midstream urine specimens taken during this period. One culture from the excised valve also grew actinobacter. Histology of the valve revealed subacute inflammation with lymphocytes and plasma cells, and Gram-positive budding yeasts were demonstrated. Serum contained no precipitins for *Candida albicans* on 14 September, and the agglutinin titre was less than 1:4. No murmurs were heard at this time.

On 19 September treatment was started with 5-fluorocytosine 12 g daily and intravenous carbenicillin 30 g daily. On 25 September a grade 2/4 early diastolic murmur was noticed, and by 27 September it was thought that this was slightly longer and louder. The patient was anaemic (haemoglobin 9.2 g/dl), and the

dose of 5-fluorocytosine was reduced to 8 g per day. On 29 September, serum precipitins for *Candida albicans* were present, and the agglutinin titre was 1:128. On 3 October the serum precipitins were still positive, and agglutinin titre was again 1:128. Improvement continued and on 16 October carbenicillin was discontinued after 4 weeks. On 8 November the diastolic murmur was still present, but had not increased in length. On 16 November the 5-fluorocytosine therapy was stopped.

Two days later he had a sudden rigor, with a temperature of 40°C and the 5-fluorocytosine therapy was restarted. Blood cultures were negative, and on 27 November the drug was discontinued and the patient discharged to careful outpatient follow-up.

On 2 January 1973, he was readmitted complaining of progressive shortness of breath and sweating attacks. On examination, he was breathless and in heart failure, and had developed fresh splinter haemorrhages; blood cultures grew *Candida albicans* which was sensitive to amphotericin-B at a minimum inhibitory concentration of 0.5 µg/ml and remained sensitive to 5-fluorocytosine at a minimum inhibitory concentration of 0.35 µg/ml. Treatment was again started with 12 g of 5-fluorocytosine per day, but this was reduced to 8 g daily, as the patient had developed severe diarrhoea. Serum precipitins to *Candida albicans* were present, and the agglutinin titre was 1:8. The diastolic murmur was still present, and the recurrence of candida endocarditis on or around the prosthetic valve was suspected. After a pre-operative transfusion of packed cells for anaemia (haemoglobin 9.4 g/dl) on 17 January the prosthetic valve was removed, a paraprosthetic leak was noted at the operation, and another series 1200 silastic ball Starr-Edwards prosthesis (No. 11) was inserted. No vegetations were seen, but culture from the prosthesis grew *Candida albicans* (minimum inhibitory concentration 0.35 µg/ml for 5-fluorocytosine, and 0.20 µg/ml for amphotericin-B). The operative area and new prosthesis were soaked in a solution of 100 mg amphotericin-B in 500 ml 5 per cent dextrose.

5-fluorocytosine (8 g daily) was restarted immediately after operation, and on 26 January amphotericin-B therapy was started (11 days postoperatively).

The initial dose was 1 mg daily in 500 ml 5 per cent dextrose over 6 hours, and this was increased to 50 mg within 2 weeks and continued on alternate days. He developed thrombophlebitis and shivering attacks during the infusion, which were alleviated by intravenous chlorpheniramine maleate and oral aspirin. He became anaemic (haemoglobin 8.4 g/dl) and required blood transfusion. There was little deterioration in renal function, the highest blood urea level being 10.3 mmol/l (62 mg/100 ml), though there was some hypokalaemia (plasma potassium 2.8 mmol/l) which was treated with oral potassium supplements. The serum levels on this relatively low dose of amphotericin-B varied from 0.6 to 1.2 µg/ml, i.e. between 3 and 6 times the minimum inhibitory concentration. The 5-fluorocytosine was continued at 8 g daily throughout, and serum levels varied from 84 to 138 µg/ml.

The patient improved on this therapy, and remained well. No murmurs were heard, and on 17 March, after a

total of 1.067 mg, the amphotericin-B therapy was stopped. No further positive blood or urine cultures were obtained after the start of treatment, and the agglutinin titre had dropped to 1:2 on 19 March, though precipitins were still present. Treatment with 5-fluorocytosine was stopped on 26 March, and the patient was discharged. Since then he has remained free of symptoms and has started light work. He was last seen 22 months after his second operation. On 2 April 1974 serum precipitins were absent.

Discussion

Candida endocarditis is a serious disease. The mortality in all untreated cases is 100 per cent, and those treated with amphotericin-B alone 83 per cent (Kay *et al.*, 1968), though Seelig *et al.* (1973) report a 4 out of 7 success rate with early diagnosis.

Treatment with amphotericin-B is limited by toxicity, and Drutz, Spickard, and Koenig (1966) and Drutz *et al.* (1968) have reported a modified dose schedule in which a lower dose of amphotericin-B was used, sufficient to produce a serum level of twice the minimum inhibitory concentration. The daily dose required is less than the usually recommended 0.5 to 1.5 mg/kg and the total dose is 1 to 2 g. Kay *et al.* (1968) report a few cases in which a combination of surgical excision and amphotericin-B therapy was used in treatment with a 75 per cent success rate.

5-fluorocytosine has been introduced more recently for the treatment of the systemic mycoses. It is essentially fungistatic in action *in vivo* (Record *et al.*, 1971; Steer *et al.*, 1972) and is thought to act on the nucleic acid metabolic pathways of the fungus cell (Vandeveld, Mauceri, and Johnson, 1972). It achieves satisfactory blood levels when given orally, and is relatively non-toxic, though rises in liver enzymes have been reported (Steer *et al.*, 1972), as have nausea and vomiting, skin rashes, and haematological changes (Tassel and Madoff, 1968; Grunberg, Prince, and Utz, 1967; Vandeveld *et al.*, 1972). A significant problem has been the development of resistant strains of various fungi both *in vitro* and in cases of endocarditis (Logan and Goldberg, 1972; Shadomy, 1969; Block and Bennett, 1972). Record *et al.* (1971) report 3 cases of candida endocarditis treated with 5-fluorocytosine, 2 of which had endocarditis superimposed on a prosthetic valve. These 2 cases did not survive. Naveh *et al.* (1975) report a case of endocarditis caused by *Rhodotorula pilimanae*, which was treated successfully with 5-fluorocytosine.

Medoff, Comfort, and Kobayashi (1971) and Block and Bennett (1973) have demonstrated that 5-fluorocytosine and amphotericin-B are syner-

gistic when acting against candida and other fungi *in vitro*. Medoff *et al.* (1972) showed an increased penetration of 5-fluorocytosine through the cytoplasmic membrane of a single isolate of *Candida albicans* in the presence of amphotericin-B, and Block and Bennett (1973) found that amphotericin-B inhibited the *in vivo* development of resistance to 5-fluorocytosine in murine cryptococcosis.

In the case described a modification of the combined chemotherapeutic and surgical approach as described by Kay *et al.* (1968) was used. The first admission reveals the difficulty in diagnosis of candida endocarditis, the fungus not being isolated until after the emergency valve replacement for ruptured aortic valve cusp. It is possible that the candida infection was secondary to an initial bacterial infection which was suppressed with antibiotics. The sequence of events in this case also demonstrates that anti-fungal therapy is necessary during the valve replacement to prevent the re-infection of the valve; in this instance therapy was started one week after the first operation. On his second admission therapy with 5-fluorocytosine was started almost immediately, and controlled the systemic symptoms. This was continued over the operative period, and after operation, as soon as the patient had recovered from the effects of the bypass, amphotericin-B therapy was used as well as 5-fluorocytosine. The 'low dose' regimen (Drutz *et al.*, 1966, 1968) was used, as the amphotericin therapy produced severe toxic reactions and was being used in combination with 5-fluorocytosine. Side effects of treatment were anaemia and hypokalaemia, both corrected easily, and both probably caused by amphotericin-B. Though higher doses of 5-fluorocytosine produce gastrointestinal side effects there was no rise in aspartate or alanine transferase levels, as has been reported previously (Steer *et al.*, 1972).

Few cases of combined chemotherapy of candida endocarditis with 5-fluorocytosine and amphotericin-B have been described (Seelig *et al.*, 1974). Harris *et al.* (1972) described 2 patients both well 6 months after initial treatment, and who have been continued on 5-fluorocytosine. The present case report confirms that the two drugs may be used together and suggests that by combination with 5-fluorocytosine a lower dose regimen for amphotericin-B may be used, and a cure effected. Since resistance to 5-fluorocytosine of *Candida albicans* has been described, this drug was discontinued on discharge to careful outpatient follow-up, and the patient has remained well in the 22 months since then. The fall in serum precipitins and agglutinin levels suggests that eradication of the infection was achieved (Seelig *et al.*, 1973, 1974).

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