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Candida endocarditis after heart surgery

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Four new cases of Candida endocarditis after heart surgery are described and predisposing factors are discussed. Details are given of the one patient diagnosed in life and treated successfully with amphotericin B.

CASE REPORTS

CASE 1 A 29-year-old man had suffered for five years from progressive angina and breathlessness on effort due to aortic stenosis. On 6 January 1966 his bicuspid, tightly stenosed, and heavily calcified aortic valve was replaced with a Starr–Edwards prosthesis.

His initial progress was good, but subsequently he developed the clinical signs of bacterial endocarditis although numerous blood cultures were sterile and others grew only micrococci after prolonged incubation. He was treated for seven weeks with large doses of intravenous penicillin and his fever subsided. During this time Candida was isolated from his sputum on two occasions.

In March 1966 slight aortic regurgitation appeared and by May had become gross. The heart had increased in size and he was in severe left ventricular failure with pulmonary oedema. The prosthetic valve had altered its position and was tilted in the aortic root. Splinter haemorrhages and early clubbing were present and, as the prosthesis was presumably still infected, his best chance of survival was thought to be by replacement with a homograft.

He was transferred to the National Heart Hospital. At operation on 23 May 1966 the Starr–Edwards valve was found to be completely detached over almost half its circumference. The whole valve ring appeared to be infected and had thrombotic masses attached to it. Two aneurysms were present—one posteriorly and below the ring, resulting in detachment of the mitral cusp from its aortic origin; the other anteriorly in the region of the right coronary orifice. Both aneurysms were obliterated, the mitral cusp was reattached to its aortic origin, and a reconstituted, freeze-dried aortic valve homograft was inserted.

In view of his past history he was given heavy antibiotic cover with penicillins and streptomycin before, during, and after operation, although cultures of the valve and excised tissue were subsequently sterile. Candida was present in the throat before operation and was isolated from the urine three days afterwards.

His immediate post-operative course was good, but on the tenth day he had rigors with a temperature of 104° F. *Candida albicans* was isolated from all of eight blood cultures taken over four days. Antibiotic treatment was changed to intravenous amphotericin B, increasing over three days to a dose of 1 mg./kg. body-weight. Blood cultures became sterile although he still had a moderate fever and occasional rigors which were thought possibly to be related to the amphotericin B infusions.

On the 32nd post-operative day rigors again became severe and his temperature rose to 104° F. A coagulase-positive staphylococcus (phage type 77 Ad/B5) was isolated from all of six blood cultures. Intravenous cloxacillin in divided doses was given. A total of 18 g. daily was needed before the temperature was controlled. Blood cultures became and remained sterile.

In all, he had eight weeks' treatment with amphotericin B (2,580 mg.) and 10 weeks' treatment with cloxacillin (1,040 g.). The blood urea level remained normal but he became depleted in potassium, the serum values dropping as low as 2·8 mEq/l., with a total body level of 1,460 mEq (normal range for his build 1,810–3,120 mEq). The daily urine potassium loss was high (average 130 mEq), partly due to the large urine volume consequent on the amount of intravenous fluid needed to carry his drugs. With oral and intravenous potassium supplements the serum levels became normal. Shortly before discharge a soft early diastolic murmur was heard.

He was last seen in May 1967, one year after insertion of the homograft and eight months after cessation of all antifungal and antibiotic treatment. He was well with no complaints, and back at work. His Hb was 15 g./100 ml., E.S.R. 2 mm./hr., and W.C.C. 6,000/c.mm., with a normal differential. Tests for renal and hepatic function were normal. Clinically the slight aortic regurgitation had not progressed. He remains on daily digoxin and a twice-weekly diuretic.

CASE 2 A 55-year-old man with mitral valve disease had been treated for subacute bacterial endocarditis in July 1965. In the following year mitral regurgitation increased, but no clinical or bacteriological evidence of bacterial endocarditis was found. At operation in August 1966 the valve appeared to be the seat of active bacterial endocarditis. It had a ragged, irregular edge and the posterior atrial wall was excavated and ulcerated in the line of the regurgitant jet. Several

chordae tendineae were ruptured. The valve was excised and replaced by a mitral homograft.

He was treated for five weeks with intravenous antibiotics (penicillin and cloxacillin throughout; streptomycin for the first 10 days and then ampicillin). A low-grade fever persisted. Culture of the excised tissue and numerous blood cultures were all sterile, but when the antibiotics were stopped his temperature went up to 100°–101° F. and remained there. Intravenous antibiotics (penicillin, streptomycin, and cephaloridine) were therefore restarted with some remission of the fever. It was then found that complement fixation tests for *Coxiella burnetii* were positive at 1/160 phase 1 and 1/2,560 phase 2. He died shortly afterwards; at necropsy the mitral valve orifice was found to be virtually occluded on its atrial aspect by massive vegetations. These were proved histologically and on culture to be due to *C. albicans*.

CASE 3 A man aged 42 with severe calcific aortic stenosis had a closed valvotomy in 1958. He was initially improved, but symptoms returned and on 16 November 1966 a freeze-dried aortic valve homograft was inserted. Prophylactic cloxacillin and ampicillin were given for three weeks after operation. He was well during the first two weeks but then developed chest pain. This was thought to be part of a post-cardiotomy syndrome and he was treated for two weeks with steroids. The pain became more severe and radiated to the back and right chest. Six weeks after operation he became pyrexial and developed splinter haemorrhages, but there was no sign of aortic regurgitation. Multiple blood cultures were sterile. Chest radiography showed a bulge in the region of the ascending aorta and at reoperation on 1 January 1967 a large false aneurysm eroding the sternum was found. It communicated with the lower part of the aortic suture line. Large vegetations covered the cusps of the aortic homograft. An attempt to close the aneurysm was unsuccessful, the aortic wall tissue being too friable to hold stitches. Culture of the vegetations grew coagulase-negative staphylococci and *C. albicans*. Histological examination showed Candida spreading from the valve through the aortic wall.

CASE 4 An 18-year-old girl had an aortic coarctation resected, with direct anastomosis of the two ends, and also a patent ductus arteriosus divided on 19 November 1958. Prophylactic antibiotics, started on the day before operation, were continued until her discharge four weeks later. She was then well and apyrexial. She was next seen 11 weeks after operation and found to be pyrexial but with none of the stigmata of bacterial endocarditis. Repeated blood cultures were sterile. Chest radiographs showed a bulge in the region of the aortic knuckle. She was given penicillin and streptomycin but remained pyrexial and three weeks later developed splinter haemorrhages and Osler nodes. A few days later she coughed up blood. This was thought to be due to an aneurysm of the aorta leaking into the lung. At operation on 1 March 1959 a large false aneurysm was found with an opening in the aortic suture line. The tissues were friable and a successful direct repair was thought to be impossible. The affected segment of the aorta was therefore excised and a homograft was inserted. The patient died three days later, anuric and deeply jaundiced. Histological examination of the excised segment of the aorta showed infiltration of the wall around the original suture line by Candida.

DISCUSSION

Joachim and Polayes (1940) described the first undoubted case of Candida endocarditis in 1940. When Soler-Bechara and his associates reviewed the literature in 1964 (Soler-Bechara, Soscia, Kennedy, and Grace, 1964), 36 cases had been recorded: 32 of the patients had previously had rheumatic fever or bacterial endocarditis, 6 were 'main-line' drug addicts, and 13 had had heart operations. The case they reported underlined the importance of antibiotic and steroid therapy and of indwelling venous catheters as predisposing factors in the disease.

The first case of Candida endocarditis after heart surgery was reported by Koelle and Pastor in 1956. With the present series the total number recorded is 23. One of these patients had had a ventricular septal defect closed (Sanger, Taylor, Robicsek, Germuth, Senterfit, and McKinnon, 1962), another had an aortic coarctation resected (case 4 above). The other 21 patients all had valve operations. Those described by Koelle and Pastor (1956), Louria and Dineen (1960), Hyun and Collier (1960), Persellin, Haring, and Lewis (1961), Sanger *et al.* (1962), Andriole, Kravetz, Roberts, and Utz (1962), Simmons and Turner (1963), Jamshidi, Pope, and Friedman (1963), and Newsom, Lee, and Rees (1967) had undergone aortic or mitral valvotomy and in one case mitral annuloplasty. Climie and Rachmaninoff (1965) and cases 1 and 3 above describe the lesion after aortic homograft replacement, and Carey and Hughes (1967) found the infection on a Starr-Edwards aortic prosthesis. In case 2 above it occurred on a mitral homograft.

Clinically, Candida endocarditis is indistinguishable from the bacterial variety, although emboli, when they occur, tend to be larger. The fungus grows readily on ordinary media and was isolated from the blood stream in 16 of the 23 post-operative patients. In one patient (Climie and Rachmaninoff, 1965) the diagnosis was made from a culture of a femoral artery embolus although blood cultures were sterile. Newsom and his co-workers (1967) suggested that a raised agglutinin titre to Candida may be diagnostically helpful when blood cultures are sterile. Because of the

ubiquity of the fungus and its ease of growth, there is a real danger that it may at first be regarded as a contaminant when isolated from blood cultures, as in the patients reported by Koelle and Pastor (1956), Persellin *et al.* (1961), Kroetz, Leonard, and Everett (1962), and Simmons and Turner (1963).

There are many potential exogenous sources of infection in patients subjected to surgery. Andriole *et al.* (1962) isolated the same species of Candida from the heart–lung machine after operation as from two of their patients. If the valve is replaced, the homograft or prosthesis could be infected when inserted. We do not think that this was so in our patients, since extensive cultures of the ethylene oxide sterilized homografts, both before freeze-drying and after reconstitution in the operating theatre, remained sterile. Infected suture material could also be a source of infection, and the lesion has been reported in suture lines several times. Again there is always the chance of contaminated solutions being given intravenously after operation.

All our patients were given antibiotic therapy, and in cases 1 and 2, particularly, this was massive, prolonged, and intravenous. We suspect that the source of the Candida infection was endogenous. Kroetz *et al.* (1962) and Soler-Bechara *et al.* (1964) are among those who have described patients in whom previous proven bacterial endocarditis treated by prolonged intravenous antibiotics was followed by the Candida variety. The latter authors, as well as Louria and Dineen in 1960, reported patients in whom Candida was isolated from pus around the site of the polyethylene catheter used for antibiotic therapy.

As regards treatment, we feel that early and adequate amphotericin B therapy is essential since Candida endocarditis, particularly after heart surgery, has a high mortality. When Andriole and his colleagues published their review article in 1962, apparent cure had followed amphotericin B therapy in three patients with Candida septicaemia. Five patients with proven Candida endocarditis received reasonably prolonged and good intravenous dosage but all died. It seems that energetic treatment before the infection has had time to become established on the valve offers the best hope of success.

Sanger *et al.* in 1962 successfully treated a patient with Candida septicaemia after closure of a ventricular septal defect; he received 485 mg. of amphotericin B over 11 days. Kay, Bernstein, Feinstein, and Biddle in 1961 cured a patient with a ventricular septal defect by closing it and excising the infected portion of the tricuspid valve. They had given amphotericin B without success before surgery, although the effectiveness of giving it on alternate days might now be open to doubt. No amphotericin B was given postoperatively, blood cultures remained sterile, and six months later he was fit and well.

Our case 1 is the only one who has survived the complication after valve surgery, and abundant evidence that the fungus will attack homograft valves is given by the post-mortem findings in our second and third cases and in the two reported by Climie and Rachmaninoff (1965). Our patient was fortunate in being able to tolerate a long course of treatment but the nephrotoxic properties of the drug should be borne in mind. Carey and Hughes (1967) considered that the fatal ventricular fibrillation in their patient was due to this nephrotoxicity resulting in hypokalaemia (serum potassium 2·0 mEq/l.) and digitalis toxicity. Adequate potassium supplements should be given where possible and the serum level should be constantly watched.

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