

Aspergillus Endocarditis After Aortic Valve Replacement

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Postoperative endocarditis produces significant morbidity and mortality and is difficult to treat in the presence of an intracardiac prosthesis.^{1,6,7,13,25} One of the common causative organisms is coagulase negative *Staphylococcus*,^{1,13} previously considered nonpathogenic. In order to eradicate this difficult problem, detailed preventive measures⁸ and prophylactic antibiotic coverage^{1,2,8,18,25} are used. Though these measures have decreased the incidence of endocarditis due to staphylococci,^{2,8,18,25} the

number of superinfections²⁷ or opportunistic infections²² due to *Candida*^{9-11,21,26} and *Aspergillus*^{12,15,17,19} has increased considerably. In the reports of *Aspergillus* infection of prosthetic valves, all proven instances involved the mitral region. A case of *Aspergillus* infection of a Starr-Edwards prosthesis in the aortic area is here reported.

Case Report

A 51-year-old Negro male was admitted with shortness of breath of five months' duration. The patient had had no symptoms of rheumatic fever in childhood. Army induction and discharge physical examinations were normal. His presenting symptoms included left upper quadrant pain followed by decreased tolerance to exer-

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cise. He was treated with digitalis and diuretics and when he failed to improve was referred to the hospital.

The patient weighed 145 pounds; he was five feet, eleven and one-fourth inches tall, myopic and had a highly arched palate. His span measurements and metacarpal index were within normal limits.²³ Blood pressure was 160/60 mm of Hg, pulse 64/minute, regular but collapsing in character. A marked left ventricular heave was seen and the apical impulse was in the sixth left intercostal space in the anterior axillary line. A diastolic thrill was felt in the aortic area and to the left of the sternal border. In the aortic area, the first sound was of normal intensity, but the second sound was decreased with a grade II/VI systolic murmur. Immediately after the second sound, a medium pitched diastolic murmur, grade IV/VI, was heard and was loudest to the left of the sternal border in the fourth left intercostal space. There was evidence of heart failure. Electrocardiogram showed left ventricular hypertrophy. Roentgenogram of the chest and fluoroscopy showed marked left ventricular enlargement. Blood cultures taken on admission were sterile. An aortogram showed widening of the ascending aorta and marked aortic insufficiency.

At operation, the aortic leaflets were found to be extremely thin and were incompetent. There was a three millimeter fenestration in the left coronary cusp. Microscopically, the valve showed myxomatous degeneration.³ A Starr-Edwards valve prosthesis was inserted. The patient received erythromycin, 250 mg q.i.d., and streptomycin, 0.5 gm intramuscularly b.i.d., one day preoperatively and for eight days postoperatively. He developed a temperature of 103° F immediately after surgery, which continued for the next two days. Cephalothin was added for the first three postoperative days and the temperature dropped to 100° F. At this time cephaloth-

in was discontinued. One blood culture obtained from this period showed coagulase negative *Staphylococcus*. The patient was placed on Coumadin* on the fifth postoperative day and maintained on therapeutic levels of anticoagulation for most of his subsequent course.

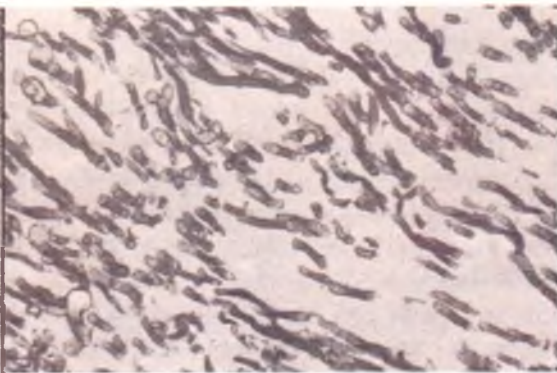
He continued to have a low grade fever. On the 17th postoperative day all antibiotics were discontinued. A diagnostic grade II/VI murmur was heard in the aortic area, though valve sounds were normal. Blood pressure remained 110/70 mm of Hg. Two days later the diastolic murmur disappeared and the patient became confused and developed abdominal distention. The abdominal distention disappeared after nasogastric suction and Foley catheter drainage, but on the 23rd postoperative day a right hemiplegia occurred. Repeated lumbar punctures and blood cultures for bacteria were nondiagnostic. He continued to have a temperature of 100-101° F and because of this was placed on cephalothin on the 26th day after operation. The aortic diastolic murmur reappeared. Two days later, the previously palpable left dorsalis pedis arterial pulsation disappeared and the left foot became pale and cold. From this period onwards, the patient deteriorated rapidly with increasing aortic insufficiency and neurologic impairment. He died 36 days after operation.

At autopsy, the heart showed marked hypertrophy and dilatation and weighed 1140 grams. There were prominent vegetations about the ring of the Starr-Edwards valve, involving both the aortic and ventricular sides. On the aortic side these extended to the wall of the aorta for a short distance. On the ventricular side, the mass almost covered the orifice of the valve and prevented the ball from seating properly

*Coumadin®, Endo Laboratories Inc., Garden City, N.Y.



Fig. 1.—Left. Aortic side of Starr-Edwards valve showing prominent vegetations over the sewing ring. A large vegetation in the left ventricle is also seen. Fig. 2.—Lower left. Photomicrograph of vegetation removed from the valve. Note extensive growth of mycelia (x100). Fig. 3.—Below. Photomicrograph showing lateral dichotomous branching of septate mycelia of *Aspergillus* (x900).



(Fig. 1). There were multiple areas of infarction in both kidneys and in the spleen. No emboli were seen in the vessels of the gastrointestinal tract. Permission for examination of the brain was not given.

Microscopically, the vegetations were found to be composed of a tangled mass of mycelia (Fig. 2). These were septate, showed the dichotomous branching characteristics of aspergilli (Fig. 3) and superficially infiltrated the adjacent myocardium. Sections of the adjacent aorta showed fragments of mycelia present within the vasa vasorum. Fungi were not demonstrated in the infarcted areas of the liver or spleen. No cultures were done at the time of autopsy and identification of the fungus was made on morphology alone. In tissue the unequivocal diagnosis of aspergillosis is difficult in the absence of characteristic sporeheads. However, these do not occur in tissue except perhaps in pulmonary cavities. In the presence of hyphae, mucor-

mycosis and candidiasis must both be considered. However, in mucormycosis the hyphae are long, nonseptate and markedly irregular. The hyphae of *Candida* stain more evenly, are smaller and show less lateral branching. Small, deeply staining, rounded spores are usually present in great numbers in *Candida* infections.

Discussion

This patient exhibited clinical and pathological features of myxomatous degeneration of the aortic valve.^{3,20} The increased incidence of endocarditis in such patients has been described.^{20,29} It is more likely that development of *Aspergillus* endocarditis was related to the changed milieu produced by antibiotic therapy pre and postoperatively.

Aspergillus is an ubiquitous fungus and can be isolated from the soil and vegetation, and in man from the respiratory tract and auditory canal.^{19,22} In the laboratory,

Table 1.—PROVEN POSTOPERATIVE ASPERGILLUS ENDOCARDITIS

Reference	Operation	Symptoms Emboli				Antibiotics					Diagnosis			Findings at Autopsy	Comment	
		Fever	Peripheral	Large Artery	Cerebral	P	S	M	C	O	Tissue Examination	Culture Postmortem	Day of Death Postoperative			
19	M	+	+	+	+	14	14	-	-		+	+	70	Thrombi on ventricular side of sewing ring of S-E valve.	Blood cultures for bacteria x10 negative.	
17	A	+	+	+	+	26	26				1/30	+	+	120	3 cm thrombus located 3 mm distal to aortic valvuloplasty.	Treated antemortem by amphotericin B.
12	M	+	+	-	+	18	10	10				+	+	46	A large thrombus obliterated Hufnagel valve. Thrombi in left atrium.	Blood cultures for bacteria x6 negative.
15	M	+	+	+	+	5	19	28	+	5	+	+	+	270	Huge verrucous mass from posterior leaflet extending to left atrium.	Blood cultures for bacteria and fungi negative.
Present Case	A	+	+	+	+	-	5	-	15	5	+	-	-	36	Large verrucous masses on aortic and ventricular side of S-E valve.	

M=Mitral valve replacement, A=Aortic valve replacement or valvuloplasty, P=Penicillin, S=Streptomycin, M=Methicillin, C=Cephalothin, B=Bicillin, O=Other, 1/30=Once in 30 days, S-E=Starr-Edwards.

Table 2.—UNPROVEN POSTOPERATIVE ASPERGILLUS ENDOCARDITIS

Reference	Operation	Symptoms Embolism						Diagnosis				Vegetations at Autopsy	Comments
		Fever	Peripheral	Large Artery	Cerebral	Pulmonary	Antibiotics Postoperative	Tissue Examination	Culture Post or Antemortem	Day of Death Postoperative			
1	VSD	+	?	-	-	+	+	-	+	+	173	+	Possible contaminant Staphylococcus isolated. No mycelia seen in vegetations.
1	VSD	+	+	-	-	-	+	-	+	+	105	-	Staphylococcus isolated. No mycelia in tissue. Aspergillus possible contaminant.
25	A	+	+	-	-	-	-	-	+	+		-	Staphylococcus isolated. Aspergillus possible contaminant.

VSD: Ventricular septal defect closure with Teflon patch.

A: Aortic valve replacement.

it is commonly found as a contaminant of cultures. The portal of entry into the heart can be endogenous from the respiratory tract or exogenous at the time of surgery, cardiac catheterization or infusion therapy. There is evidence that endocarditis may be produced by *Candida* introduced at the site of intravenous catheter infusions^{14,24} or from polyethylene catheter emboli.²⁸ It is possible that *Aspergillus* may gain entry to the blood stream in the same manner.

A review of all cases of postoperative endocarditis showed four proven and three unproven instances of *Aspergillus* endocarditis (Tables 1 and 2). In the latter group^{1,25} *Staphylococcus* was obtained in culture at first. These patients showed no evidence of invasion of tissue with *Aspergillus* and were probably not cases of *Aspergillus* endocarditis (Table 2).

Clinical evidence of peripheral emboli were seen in all proven cases whether operation was on the mitral or aortic valve. Usual emboli were in the larger vessels. An aortic "saddle embolus" was seen in one case and diagnosis was made from examination of the embolus.¹⁵ Saddle emboli were also reported in patients developing *Aspergillus* and *Candida* endocarditis without prior operations.^{4,16,30} Cerebral symptoms due to embolization of vegetations were present in almost all patients with postoperative *Aspergillus* endocarditis (Table 1) and in many of the patients developing it without prior cardiovascular operations.^{4,16,30} In postoperative cases, diagnosis can be suspected when episodes of systemic embolization occur in the presence of fever and negative cultures for bacteria (Table 1).

The treatment of well established *Aspergillus* endocarditis has not been successful. Amphotericin B has been tried^{4,15} without success, though clinical circumstances prevented the administration of a full dosage. In view of relatively good results obtained in endocarditis due to *Candida* by remov-

ing the infected prosthesis¹¹ or by substituting a homograft⁵ for the prosthesis, it may be worthwhile to reoperate in all cases of *Aspergillus* endocarditis. A better salvage rate can be expected than the present 100% mortality seen in conservative therapy of *Aspergillus* endocarditis.

Conclusions

From this experience and a review of the literature, we believe that reoperation is indicated in a patient with clinical evidence of endocarditis, negative blood cultures, valve dysfunction and/or peripheral embolization. The efficacy of antifungal drugs as "surgical coverage" is still unknown.

Resumo

Desta experiência e de uma revisão da literatura, acreditamos que a re-operação é indicada num paciente com evidência clínica de endocardite, hemoculturas negativas, disfunção valvular e/ou embolização periférica. A eficácia das drogas fungicidas como "cobertura cirúrgica" é ainda desconhecida.

Riassunto

Di questa esperienza e la rivista della letteratura, siamo d'opinione che la re-operazione è indicata in pazienti con evidenza clinica d'endocardite, con culture negative del sangue, con disfunzione valvolare ed embolismo periferico. L'efficacia di medicinali anti-fungosi come "provvidenza chirurgica" non è ancora stabilita.

Resumen

De nuestra experiencia y revisión de la literatura, consideramos necesario el operar de nuevo en aquel paciente con evidencia clínica de endocarditis, hemocultivo negativo, disfunción valvular y/o embolia periférica. La eficacia de drogas fungicidas utilizadas como "protección quirúrgica" es todavía desconocida.

Zusammenfassung

Auf Grund seiner Erfahrungen und der Literatur glaubt der Autor, dass eine Operation wiederholt werden muss an Patienten, die klinische Symptome von Endokarditis, negative Blutkulturen, Störungen in der Funktion der Herzklappen und/oder periphere Embolusbildung zeigen. Ob antifungale Medikamente ein "chirurgisches Equivalent" darstellen, ist noch nicht bekannt.

Résumé

La réintervention chirurgicale est indiquée chez le malade qui présente cliniquement les symptômes d'endocardite, hémocultures négatives, malfonction valvulaire et/ou embolisation périphérique. L'efficacité de la thérapeutique fongicide reste encore à être prouvée.

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