Aspergillus clavatus Endocarditis Involving a Normal Aortic Valve Following Coronary Artery Surgery

Steven M. Opal, L. Barth Reller, Gerald Harrington, and Preston Cannady, Jr.

From the Infectious Disease Service, Department of Medicine, Fitzsimons Army Medical Center; and the University of Colorado Health Sciences Center, Denver, Colorado

Aspergillus species causing endocarditis on a native heart valve is a rare occurrence with an exceedingly high mortality. This report describes a 60-year-old man who developed Aspergillus clavatus endocarditis of the aortic valve 18 months after coronary artery bypass surgery. The aortic valve was angiographically normal on cardiac catheterization performed before coronary artery surgery. Despite aortic valve replacement and amphotericin B therapy, the patient died as a result of Aspergillus species aortitis with occlusion of the coronary ostia and bypass grafts. Coronary artery surgery may be complicated by this highly lethal infection, which is difficult to diagnose and treat.

Aspergillus species endocarditis is an uncommon infectious disease that generally follows prosthetic valve surgery [1, 2]. The difficulties in the diagnosis and management of this disease are well known [1, 3, 4] and are primarily related to the infrequency of isolation of this fungal organism from blood cultures. The diagnosis of Aspergillus species endocarditis is frequently made at autopsy or after surgical intervention for valvular dysfunction or systemic emboli.

Aspergillus infection of the aortic valve and proximal aorta has been previously described in two cases, both following aortocoronary bypass surgery. The first patient developed an aspergilloma at the site of the saphenous vein graft [5]; the second patient developed fatal Aspergillus species aortitis 19 months after surgery [6].

This report describes a fatal episode of endocarditis following coronary artery surgery caused by Aspergillus clavatus. This species has not previously been reported to cause infective endocarditis. The patient died despite early and aggressive surgical and medical therapy. In vitro antifungal susceptibility testing demonstrated the organism to be resistant to amphotericin B and flucytosine.

Case Report

A 60-year-old man developed vague abdominal and retrosternal chest discomfort 18 months after a triple-vessel coronary artery bypass grafting. Cardiac catheterization performed before coronary artery surgery revealed moderately severe coronary artery lesions but no evidence of a pressure gradient across the aortic valve or valvular regurgitation. The patient had an uneventful course following coronary artery surgery except for an infection of a superficial sternal wound two weeks after surgery. Enterobacter agglomerans was isolated from cultures of the wound, which resolved after 14 days of intravenous cefamandole and local wound care. The patient then remained asymptomatic until one week prior to his last admission, when abdominal and chest pains developed.

His past history included chronic peptic ulcer disease, vagotomy and pyloroplasty at age 46, and cimetidine and antacid therapy on an intermittent basis for recurrent dyspepsia. Tetracycline and sodium indanyl carbenicillin had been prescribed two weeks prior to admission for acute prostatitis. He denied alcohol use and took no other medications. There was no history of immunocompromised states, recurrent infections, or respiratory illnesses.

Physical examination revealed a previously undetected murmur of aortic regurgitation and an elevated oral temperature of 38.0°C. The remainder of the physical examination was unremarkable except for a tender, slightly enlarged prostate.

Laboratory data included normal complete blood count, electrolytes, and urinalysis. Electrocardiogram and chest radiographs were unremarkable.
Figure 1. Postmortem examination of proximal aorta and prosthetic aortic valve demonstrating extensive vegetations in the proximal aorta with occlusion of coronary and saphenous vein bypass ostia.

Blood cultures on six separate occasions were negative despite being incubated for six weeks in tryptic soy broth, with subculturing on Sabouraud's agar. Echocardiography performed on the day of admission demonstrated thickening of the aortic valve leaflets without other abnormalities.

During the ensuing 10 days, aortic regurgitation became progressively more severe, and congestive heart failure developed. The patient remained febrile, but no systemic emboli or other evidence of endocarditis was noticed. A repeat echocardiogram demonstrated a prolapsing aortic valve leaflet with vegetations. Intravenous nitropresside was begun for afterload reduction, and empiric antimicrobial therapy was begun with intravenous ampicillin, 12 g/day, and gentamicin, 3 mg/kg per day.

Cardiac catheterization confirmed severe aortic valve regurgitation and a normal aortic root. Coronary angiography defined patent saphenous vein grafts, except for the right coronary artery graft, which was totally occluded. Left ventricular end-diastolic pressure was 32 mm Hg. The cardiac index was 1.8 liters/min per square meter.

The patient was taken to cardiac surgery, where a 1-cm vegetation was found on the right coronary cusp. A small annular abscess containing a "currant jelly-like" material was detected at the base of the right cusp. The aortic valve was replaced with a Carpentier-Edwards porcine heterograft. The annular abscess was obliterated. The aortic root and ascending aorta appeared normal at the time of surgery.

Histologic examination of the excised valve revealed numerous septate, dichotomously branching hyphae compatible with Aspergillus species. Therapy with amphotericin B was begun intravenously, and therapy with ampicillin and gentamicin was discontinued. Fungal cultures from aortic valve tissue confirmed the presence of A. clavatus. This organism is distinguished morphologically from other Aspergillus species by its elongated, clavate vesicle with numerous, uniseriate sterigmata [7].

The patient recovered rapidly from aortic valve surgery. Treatment consisted of digoxin, diuretics, heparin, and amphotericin B. Amphotericin was
given at a dose of 0.6 mg/kg per day. The patient remained afebrile and asymptomatic until the 16th postoperative day when acute dyspnea and chest pain developed. Physical examination suggested congestive heart failure, but no evidence of pericardial effusion or valvular dysfunction was found. Serum creatine phosphokinase levels were elevated and an MB band was present. The patient suffered cardiopulmonary arrest and could not be resuscitated.

Postmortem examination demonstrated the aortic valve heterograft to be in normal position and functioning normally. The entire proximal aorta distal to the heterograft was encased in extensive, verrucous vegetations. The vegetations were so extensive as to occlude the coronary ostia as well as the ostia of the saphenous vein bypass graft (figure 1). Histologic sections confirmed the presence of Aspergillus hyphae invading the aortic intima (figures 2 and 3). Death was attributed to A. clavatus aortitis with occlusion of the ostia of the coronary arteries and aorto-coronary-saphenous vein bypass grafts.

Table 1. Clinical characteristics and results for patients with Aspergillus endocarditis.

<table>
<thead>
<tr>
<th>Year [reference], no. of patients</th>
<th>Antemortem diagnosis (%)</th>
<th>Positive blood cultures (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974 [1], 40</td>
<td>22</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>1980 [3], 13</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1981 [4], 15</td>
<td>20</td>
<td>6</td>
<td>6</td>
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</tbody>
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Comments

Aspergillus species endocarditis is an uncommon infection causing exceedingly high mortality. This fungal infection was first identified in 1950 [8] and is most commonly recognized as a cause of prosthetic valve endocarditis [1, 2, 9]. Aspergillus infection of native heart valves has rarely been described. Vishniavsky et al. [10] found reports of 15 patients with Aspergillus species endocarditis involving normal heart valves. Most of these patients were considered immunocompromised, and the infection proved to be fatal in every case. Our patient had a normal aortic valve—angiographically documented—prior to his coronary artery surgery. There was no evidence of any defect in host defenses in this patient.

A major contributing factor to the high fatality rate in Aspergillus species endocarditis is the difficulty in making the correct diagnosis. The majority of cases described in previous reports have been identified at postmortem examination. Blood cultures are rarely positive despite prolonged incubation in appropriate media. The rarity of positive blood cultures is illustrated in table 1. Aspergillus species grow readily in routine culture media, including tryptic soy broth. The difficulty in culturing the organism from the blood of infected patients presumably reflects its infrequent presence in the circulation at any time.

When the disease is recognized clinically, fever, murmurs, splenomegaly, and emboli in large vessels have generally led to the correct diagnosis. Other peripheral physical findings associated with infectious endocarditis are rarely present [1].

Fungal aortitis has been reported in eight patients following cardiac surgery [11, 12, 13]. These infections generally occur along suture lines at aortotomy sites. Four of these infections were identified as
caused by \textit{Aspergillus} species. All such infections proved fatal, regardless of the treatment administered.

There have been two previous case reports of \textit{Aspergillus} species endocarditis or aortitis following coronary artery surgery. The first patient was reported by Whiting et al. in 1973 \cite{5}. An aspergilloma was found to be occluding a saphenous vein bypass graft 12 months after surgery. The patient recovered after excision of the infected vein graft and placement of a second bypass graft through a separate aortotomy site. No antifungal therapy was given to this patient.

A second patient was described with supravalvar obstruction secondary to \textit{Aspergillus} species aortitis 19 months after coronary artery bypass surgery \cite{6}. This infection was unrecognized until an autopsy was performed. The vegetations along the aortic wall impinged upon the aortocoronary bypass ostia but did not occlude them. Unfortunately, no fungal cultures were available from either of these two patients to identify the causative organism precisely.

It is interesting to speculate upon the route of inoculation of aspergilli in these infections. It is generally assumed that prosthetic valve endocarditis due to \textit{Aspergillus} species is the result of contamination of the valve at the time of its insertion \cite{14}. It is conceivable that the proximal aorta may become contaminated during coronary artery surgery. The 12–19-month incubation period before symptoms develop from such contamination is remarkable. Alternatively, infection may arise from seeding of the aortic tissue during transient fungemia from \textit{Aspergillus} species. This seems unlikely because of the rarity of isolation of this fungal organism from the blood. \cite{1, 3, 4}.

The management of \textit{Aspergillus} species endocarditis requires an aggressive medical and surgical approach. No patient has been successfully treated with medical therapy alone. Surgical extirpation of all involved tissues appears to be essential to offer any chance of survival \cite{1, 4, 15}.

Carrizosa et al. \cite{16} have developed an animal model for \textit{Aspergillus} species endocarditis that supports the necessity of surgical excision in the treatment of this infection. In this model, amphotericin and flucytosine alone or in combination are capable of reducing the number of viable \textit{Aspergillus} colonies from infected heart tissue. However, no antifungal agent or combination of agents was capable of sterilizing the vegetations. Amphotericin B is known to penetrate valvular vegetations poorly \cite{17}, which may help explain these findings.

Antifungal therapy for \textit{Aspergillus} species endocarditis generally includes amphotericin B therapy. Flucytosine has variable activity in vitro and has been used in combination with amphotericin to treat this infection. Rifampin and amphotericin have synergistic activity in vitro against aspergilli, and this combination may be of potential clinical utility \cite{18}. The imidazoles have been largely ineffective against \textit{Aspergillus} species. Clinical experience is at present insufficient to recommend any regimen other than amphotericin B. Combination therapy with flucytosine is appealing, but demonstration of its efficacy awaits further clinical trial.

Our patient is unique in that \textit{A. clavatus} has not, to our knowledge, been previously described as a cause of endocarditis. The organism continued to grow and invade the proximal aortic wall despite amphotericin B therapy. In vitro antifungal susceptibility testing using the agar-dilution method \cite{19} demonstrated this isolate to be highly resistant to amphotericin B with an MIC of >32 µg/ml. The organism was also resistant to flucytosine with an MIC of >128 µg/ml. No in vitro evidence of synergism could be detected with various concentrations of amphotericin and flucytosine. The actual cause of death was coronary occlusion secondary to aortitis that developed in the presence of therapeutic doses of intravenous amphotericin B.

If the current mortality of \textit{Aspergillus} species endocarditis is to be reduced significantly, clinical methods in both diagnosis and treatment need to be improved. Serologic techniques in the diagnosis of this disease have received little attention and deserve additional investigation. The search for more effective, nontoxic, antifungal agents continues. Therapeutic regimens that utilize potentially synergistic combinations of drugs active against \textit{Aspergillus} organisms should be considered. In vitro sensitivity testing of antifungal drugs requires further development to insure accuracy, reproducibility, and close correlation with clinical response. Surgery is mandatory in the successful management of this disease and necessitates the excision of all tissues infected with \textit{Aspergillus} organisms.

References

3. Walsh TJ, Hutchins GM, Bulkley BH, Mendelsohn G. Fun-
Aspergillus clavatus Endocarditis