Aspergillus Aortitis After Cardiac Surgery
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OBJECTIVES The aim of this study was to describe the clinical characteristics of Aspergillus aortitis in a small series of consecutive patients.

BACKGROUND Aspergillus infection of the ascending aorta after cardiopulmonary bypass surgery has rarely been reported and has always resulted in death.

METHODS Aspergillus aortitis was confirmed by pathologic and microbiologic analysis in eight men (61 ± 8 years) of 9,375 consecutive patients who underwent cardiac surgery between 1975 and 2000.

RESULTS Patients presented with Aspergillus aortitis after aortic valve replacement (n = 5), coronary revascularization (n = 2), or both (n = 1). Initial symptoms appeared between the immediate postoperative period and up to two years after surgery. All patients had prolonged fever. Ante-mortem diagnosis was established in only three patients for whom transthoracic echocardiography was suggestive of aortic pseudoaneurysm and was confirmed by thoracic computed tomography or aortography. All patients had negative peripheral blood cultures. Seven patients died at short-term follow-up, and the one surviving patient was promptly treated by surgery and antifungal drugs. Pathologic examination confirmed Aspergillus aortitis with multi-organ dissemination without heart involvement in all patients except for two, in whom aortic valve endocarditis was found. Fungal cultures confirmed the presence of Aspergillus fumigatus in all patients.

CONCLUSIONS Aspergillus aortitis is typically found after aortic valve or coronary surgery. It commonly leads to lethal multi-organ dissemination without involvement of the intracardiac structure. This entity should be considered in patients with persistent fever and negative blood cultures after open-heart surgery involving significant aortic wall damage, irrespective of the postoperative period. (J Am Coll Cardiol 2003;41:152–6) © 2003 by the American College of Cardiology Foundation

Mycotic cardiovascular invasion is an uncommon infectious disease that generally follows cardiopulmonary bypass surgery. Its prevalence, nevertheless, has grown in the last decade due to wider use of this type of surgery and to the increased number of patients who are immunocompromised or treated with long-term antibiotics (1–4).

Aspergillus cardiovascular infection usually presents as endocarditis, which is difficult to diagnose and has a high mortality (3). Aspergillus infection of the ascending aorta in the absence of endocarditis is more exceptional and follows an inevitably lethal course (5–10). This analogous entity was first described by Hadorn in 1960 (11) and has subsequently been published in scarce case reports (8–19). In almost all reported cases, diagnosis has been made at necropsy because of late recognition or non-recognition (5,10–13,20). The clinical features of this entity have never been reported in a series of patients.

The aim of the present study was to describe the clinical-pathologic characteristics and therapeutic implications of Aspergillus aortitis in a series of consecutive patients.

METHODS

Patients. Between January 1975 and January 2000, eight consecutive patients (all male; mean [±SD] age 61 ± 8 years) from 9,375 were diagnosed with Aspergillus infection of the ascending aorta after cardiopulmonary bypass surgery. All patients had Aspergillus infection diagnosed in our institution, except for one patient who died after surgery in our center, with subsequent necropsy performed at another institution. In addition, one patient underwent surgery in another hospital and was diagnosed in our department. The following patient data were collected: type of cardiac surgery, antibiotic therapy before and after surgery, interval from intervention to clinical onset, symptoms and physical examination, complementary tests if performed (e.g., trans-thoracic echocardiography [TTE] and transesophageal echocardiography [TEE], thoracic computed tomography [CT], aortography), fungal cultures, pathologic examination, clinical evolution, and therapy after initial surgery.

Histology and microbiology. Definitive diagnosis of Aspergillus aortitis was established in all patients from biopsy or autopsy materials. All specimens were stained with hematoxylin-eosin and periodic acid-Schiff techniques. Gomori’s methenamine silver staining was performed in cases with non-conclusive diagnoses. Aspergillus infiltration was diagnosed by standard criteria (21–23) that, briefly, consisted of presentation with typical Aspergillus spp hyphae, 5 to 10 μm in width, septated and branched with numerous
septae distributed at regular intervals (Fig. 1). Hyphal branches had the same caliber as the parent from which they arose, usually at acute angles. Viable hyphae were often basophilic, whereas macerated or necrotic hyphae were hyaline or eosinophilic. A presumptive histopathologic diagnosis of *Aspergillus* was made in all specimens. Although typical *Aspergillus* spp hyphae have a characteristic appearance on histopathologic sections, it is not always possible to reliably distinguish them from the hyphae of other angio-invasive *Hyphomycetes*.

For the microbiologic diagnosis, all samples were cultured in habitual media for bacteria, fungi, and mycobacteria. A filamentous fungus grew in Sabouraud and Sabouraud-chloramphenicol plates. The definitive identification of *Aspergillus fumigatus* in all cases was made by macroscopic examination in the specific medium (Czapek) and microscopic examination with lactophenol blue.

### RESULTS

**Clinical presentation.** All patients were male, and their clinical characteristics are summarized in Table 1. Ascending aortic infection occurred after valvular replacement (n = 5), aortocoronary bypass (n = 2), or both (n = 1). Valvular replacement was performed with both mitral and aortic valve mechanical prostheses in two patients and with a biologic aortic valve prosthesis in three patients. A triple aortocoronary graft and aortic valve replacement (AVR) with a biologic prosthesis was performed in one patient, and a single aortocoronary graft to the left anterior descending coronary artery was performed in another patient and triple aortocoronary grafts were performed in the remaining patient. Five patients underwent surgery in 1987, which coincided with construction work in the cardiac surgical intensive care unit, which was sited very close to the surgical suite. The two rooms shared the air supply. Epidemiologic investigation began when two patients died in the immediate postoperative period and necropsy revealed an *Aspergillus* infection of the ascending aorta. High concentrations of *Aspergillus fumigatus* were found in the ventilation system and on the surgical suite floor. Cardiac surgery was immediately suspended for three weeks until the following envi-

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**Figure 1.** Microscopic examination (hematoxylin-eosin stain, ×10, before 80% reduction for publication) showing invasive aortic aspergillosis. The hyphae in this necrotic nodule radiate from a central focus, forming a micro-colony. Typical hyphae appeared as septate filaments of uniform width, with a progressive and dichotomous pattern of branching.
Table 1. Clinical Characteristics and Outcomes of 8 Patients With *Aspergillus* Infection of the Ascending Aorta

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Age (yrs)</th>
<th>Surgery</th>
<th>Year of Diagnosis</th>
<th>Concurrent Construction</th>
<th>Clinical Onset (months)</th>
<th>Symptoms</th>
<th>Peripheral Blood Cultures</th>
<th>Imaging Techniques</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>CR</td>
<td>1995</td>
<td>No</td>
<td>6</td>
<td>Persistent fever*, emboli</td>
<td>–</td>
<td>TTE (–), TEE (–), CT (+)</td>
<td>Postmortem diagnosis: massive brain embolism</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>MAVR</td>
<td>1987</td>
<td>Yes</td>
<td>PP</td>
<td>Persistent fever, mediastinitis</td>
<td>–</td>
<td>TTE (–)</td>
<td>Postmortem diagnosis: fatal aortic rupture</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>CR + AVR</td>
<td>1992</td>
<td>Yes</td>
<td>PP</td>
<td>Persistent fever, emboli</td>
<td>–</td>
<td>TTE (–)</td>
<td>Postmortem diagnosis: massive brain embolism</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>CR</td>
<td>1995</td>
<td>No</td>
<td>24</td>
<td>Persistent fever, emboli</td>
<td>–</td>
<td>TTE (–), TEE (–)</td>
<td>Postmortem diagnosis: massive brain embolism</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>MAVR</td>
<td>1987</td>
<td>Yes</td>
<td>PP</td>
<td>Persistent fever, chest pain</td>
<td>–</td>
<td>TTE (+), CT (+)</td>
<td>Antemortem diagnosis: fatal aortic prosthetic dehiscence after surgery</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>AVR</td>
<td>1987</td>
<td>Yes</td>
<td>PP</td>
<td>Persistent fever, emboli</td>
<td>–</td>
<td>TTE (+), aortography (+)</td>
<td>Antemortem diagnosis: alive after early aortic surgery</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>AVR</td>
<td>1987</td>
<td>Yes</td>
<td>3</td>
<td>Persistent fever, heart failure</td>
<td>–†</td>
<td>TTE (+), aortography (+)</td>
<td>Antemortem diagnosis: fatal uncontrollable intraoperative bleeding</td>
</tr>
<tr>
<td>8</td>
<td>38</td>
<td>AVR</td>
<td>1987</td>
<td>Yes</td>
<td>PP</td>
<td>Persistent fever, renal failure</td>
<td>–</td>
<td>TTE (–)</td>
<td>Postmortem diagnosis: multi-organ failure</td>
</tr>
</tbody>
</table>

*Fever ≥ 7 days despite antibiotic treatment. †Blood culture positive with blood sample taken directly from the aortic pseudoaneurysm.

AVR = aortic valve replacement; CR = coronary revascularization; CT = computed tomography; MAVR = mitral-aortic valve replacement; PP = postoperative period; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

†Fever ≥ 7 days despite antibiotic treatment. †Blood culture positive with blood sample taken directly from the aortic pseudoaneurysm.
The single surviving patient had *Aspergillus* aortitis diagnosed and treated early by resection of the pseudoaneurysm, together with ascending aortic reconstruction using a tubular prosthesis and prolonged antifungal therapy (amphotericin B for 1 week before and 7 months after surgery and subsequent treatment with oral itraconazole for 18 months). At 12-year follow-up, there had been no recurrences of infection.

**DISCUSSION**

**Predisposing factors.** *Aspergillus* aortitis is considered a primary infection due to aortic surgical damage such as that which presents after cannulating for cardiopulmonary bypass surgery (3,8–10,12,18). However, all our patients developed an infection of the ascending aorta after aortotomy for AVR or for aortocoronary bypass graft implantation. This suggests that significantly greater aortic wall damage than that seen during other cardiopulmonary bypass interventions is crucial for the infection. Similarly, the fungal infection occurred after the aforementioned interventions in all the reported cases of which we are aware (8–20).

Interestingly, male gender was predominant in this series as well as in all of the reviewed published data (8–19); this may be explained by female hormones playing a protective role (estradiol was described as an inhibitor of *Aspergillus* growth in vitro) (2). However, this finding is controversial because coronary and aortic valve surgery is more prevalent in males than in females, and in addition, there was a limited number of *Aspergillus* aortitis cases in this series. Other important extensively known factors are the presence of construction work in areas near cardiac surgical rooms and immunosuppression (1,2,8,9). Interestingly, none of the patients were immunocompromised or received long-term antibiotic treatment. This suggests that the most important alteration of host defenses is probably the surgical procedure itself.

**Hypothetical pathophysiologic mechanism.** Surgical trauma such as aortotomy could damage the aortic wall, which could be contaminated by airborne fungal spores and initiate an inflammatory response. As a consequence of this inflammatory process, the aortic wall could be disintegrated and weakened by the subsequent formation of an aneurysm. All the patients developed ascending aortic aneurysms, which were probably the origin of mycotic emboli in the systemic circulation and infectious multi-organ invasion. Interestingly, none of the six patients who underwent valve surgery developed a cardiac infection, including two patients with mitral replacement at their primary surgery. This was probably the consequence of the infection source’s being located at the supracoronary sinus level, distal to blood flowing from the heart, and therefore driving the hyphae away from this structure.

**Diagnostic and prognostic implications.** *Aspergillus* aortitis presents with clinical manifestations similar to other fungal cardiovascular infections (8,9). In the few reported cases, the course of this entity invariably led to death in all patients regardless of the treatment administered (8–20). Negative blood cultures, leading to a delayed diagnosis, could play a role in the normally fatal outcome in these settings (10,12,18). Early diagnosis of *Aspergillus* aortitis is also made more difficult because the localization of the infection in the ascending aorta and the lack of endocarditis vegetation; this condition is therefore often undetected by both TTE and TEE. In addition, prolonged latency from surgery to clinical onset is another factor that delays the consideration of *Aspergillus* aortitis until late in the diagno-

![Figure 2.](image)
sis. In view of this, this condition should be suspected, and precise techniques for ascending aortic visualization, such as CT, magnetic resonance imaging, and contrast aortography, should be performed in any patient who has undergone aortic valve or cardiac surgery and presents with persistent fever and negative blood cultures, irrespective of the post-operative period. This approach was adopted in the single surviving patient who had *Aspergillus* aortitis diagnosed early and was promptly treated.

The management of this entity requires an aggressive medical and surgical approach (7,18,24,25). Prompt therapy with high doses of amphotericin B, preferably lipid preparations because of their reduced toxicity, is indicated. Hypothetically, antifungal therapy before surgery might reduce the potential infectious load and the recurrences of this disseminating disease (24).

**Study limitations.** The retrospective nature of this study is a limitation that is impossible to overcome owing to the nature of this entity. Although all patients underwent TTE, TEE was performed in only two patients because this imaging technique was not available when the others were diagnosed. This procedure would have been valuable in detecting vegetation in the valve early in the two patients who presented with aortic valve endocarditis concurrently, and it might have changed their fatal outcome.

**Conclusions.** *Aspergillus* aortitis typically presents in patients with significant surgical aortic wall damage, such as in those undergoing aortic valve or coronary bypass surgery, and it normally leads to fatal multi-organ dissemination without cardiac involvement. A late diagnosis, due to inadequate ascending aortic visualization by echocardiography and the prolonged latency from surgery to clinical onset, could be partly responsible for this fatal course. Alternative imaging techniques should be considered in any patient presenting with persistent fever and negative blood cultures after open-heart surgery involving significant aortic wall damage.

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**REFERENCES**