INTRODUCTION

Aspergillus species are ubiquitous, widely distributed fungi, commonly occurring in soil, water, dust, and decaying vegetation [1]. These species are a major cause of nosocomial invasive fungal infections in patients with highly immunocompromised conditions [2, 3]. Wound infections occur much less frequently but have been reported after cardiac and abdominal surgery [3-6]. Hospital reservoirs of Aspergillus include unfiltered air, contamination of conditioning filters, and dust generated during hospital construction activity [4]. In this report we describe three cases of Aspergillus flavus sternal wound infections following open-heart surgery in the Cardiosurgery Unit of the Perugia Regional Hospital. All three cases occurred during a 3-month period coinciding with hospital construction. In this period there were renovation activities in the operating room adjacent areas.

CASE REPORTS

Three hundred and nine patients who had undergone cardiac surgery at Cardiosurgery Unit of the Perugia Regional Hospital between 1 January 2000 and 31 December 2000 were studied. We have defined nosocomial SSIs (Surgical Site Infections), according to the CDC definitions, which involve skin, subcutaneous tissue, deep soft tissue, and organs or spaces manipulated during an operative procedure [7]. Patients with Aspergillus SSI were identified with evidence of Aspergillus species testing sample from a normally sterile site or histopathologic evidence of typical fungal elements [3]. Three patients developed nosocomial SSI by Aspergillus species. The demographic, surgical, and clinical characteristics of the three patients are summarized in table 1. The first and the second patients underwent aortic valve replacement (AVR), and the third coronary artery bypass graft (CABG). Preoperative antibiotic prophylaxis consisted of intravenous imipenem-cilastatin for all three patients (first dose 500 mg one hour before surgery, followed every 6 hours for two days). This prophylaxis scheme was in accordance with internal cardio surgery equip prophylaxis protocol. The median interval between surgery and the onset of signs of infection was 48 days (range, 36-59). The median duration of symptoms before diagnosis (from symptoms onset to diagnosis) was 164 days (range, 154-174). The initial symptoms developed insidiously, with only moderate systemic symptoms. All three patients felt fatigue, malaise, and continuous low-grade fever. Later, after 2-3 months, in all three cases there was local tenderness, and formation of sterno-cutaneous fistula. Both the culture and the microbiology smears obtained from the fistula were negative (both for bacteria and fungi) in patients 1 and 2; whereas a swab of the fistula of patient 3 yielded A. flavus, but it was thought to be an environmental contamination from surgeons. Initially all three patients were treated for a bacterial infection, with local dressing and antibiotic therapy. After 4-5 months from symptoms onset, they
were referred to the Infectious Disease Department. At admission to the Infectious Disease Department, the patients had already radiographic signs of osteomyelitis. Laboratory findings revealed an increase in the Erythrocyte Sedimentation Rate (ESR) and in the C-reactive Protein (CRP). All three patients had mild anemia, whereas white blood cells were normal (see Table 1).

In patients 1 and 2, sternal wound swabs and blood cultures did not yield pathogens, despite discontinuation of antibiotic therapy. In both of them CT scan revealed sternal osteomyelitis with hypertrophic inflammatory tissue formation, which involves sternum, ribs, and intercostals muscles. Therefore, the patients underwent an extensive surgical debridement operation, followed by plastic reconstructive procedures. In both of the cases, the cultures and the microbiology smears, obtained from surgical sample, identified *A. flavus* (identification by macroscopic and microscopic characters). Patient 1 was put on a regimen of liposomal amphotericin B (AmBisome; 3 mg/Kg q.d.) for four weeks and then itraconazole (200 mg orally q.d.) for sixty days. Patient 2 started intravenous treatment with liposomal amphotericin B (AmBisome; 3 mg/Kg q.d.) for eighteen days, followed by ninety days of itraconazole (200 mg orally q.d.). For the third patient, the culture of the purulent fluid yielded *A. flavus* colonies, and the microbiology examination showed numerous septate hyphae. Treatment with amphotericin B lipid complex (ABLC, Abelcet; 5 mg/Kg q.d.) was started immediately and continued for twenty days, and then itraconazole at 200 mg twice daily orally for ninety days. The antifungal agents were well tolerated by all three patients, with clinical and laboratory improvement. The tests normalized in 90, 69, and 77 days for the patient 1, 2, and 3, respectively. All three strains of *Aspergillus flavus* were susceptible to itraconazole, amphotericin B, and fluconazole in E-test examination. Unfortunately patient 2 died at four months, after the end of treatment, for non-infectious cause: cardiac arrhythmia. At the present, at sixteen months after the cessation of treatment, patient 1 and 3 are cured.

## DISCUSSION

The estimated prevalence of sternal wound infections after cardiac surgery is 1-4% [8]. In these patients Gram-positive cocci (*Staphylococcus aureus* and *Staphylococcus epidermidis*) are the most common pathogens [5, 8]. Fungal infections are rarely observed and have received little attention in literature [5]. In spite of this, in the last years these infections, both by yeasts and moulds, have been increasing. Our study confirms the relevant role of moulds as a cause of severe surgical site infections, also in immunocompetent patients, especially in peculiar environmental conditions. In fact all three patients had undergone surgery during a period of hospital construction. Unfortunately, during

### Table 1 - Demographic, clinical, and surgical characteristics of 3 patients with sternal wound infections due to *Aspergillus flavus*.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, sex</td>
<td>74, M</td>
<td>63, M</td>
<td>56, M</td>
</tr>
<tr>
<td>Disease</td>
<td>Aortic insufficiency</td>
<td>Aortic stenosis</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Others diseases</td>
<td>Renal failure</td>
<td>COPD</td>
<td>Diabetes, Asthma, Hypertension</td>
</tr>
<tr>
<td>Operation</td>
<td>AVR</td>
<td>AVR</td>
<td>CABG</td>
</tr>
<tr>
<td>Time of onset after operation (days)</td>
<td>36</td>
<td>59</td>
<td>49</td>
</tr>
<tr>
<td>Diagnostic delay (days)</td>
<td>174</td>
<td>154</td>
<td>165</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>131</td>
<td>81</td>
<td>73</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>9.2</td>
<td>4.7</td>
<td>7.5</td>
</tr>
<tr>
<td>Hb, mg/dl</td>
<td>7.8</td>
<td>11.6</td>
<td>11.3</td>
</tr>
<tr>
<td>WBC count, cells/mm³</td>
<td>7,410</td>
<td>6,590</td>
<td>8,500</td>
</tr>
<tr>
<td>% Neutrophils</td>
<td>69.9</td>
<td>71</td>
<td>78</td>
</tr>
</tbody>
</table>

Note: COPD = Chronic Obstructive Pulmonary Disease; AVR = Aortic Valve Replaced; CABG = Coronary Artery Bypass Graft; ESR = Erythrocyte Sedimentation Rate; CRP = C-Reactive Protein.
this period, no microbiologic environmental studies were carried out, but the association between *Aspergillus* infection and construction activities is well-known [6].

Our patients received several courses of antibiotic therapy before the correct diagnosis was made. In two of three cases, an *Aspergillus* infection was not suspected before extensive surgical debridement was performed. There was a long delay in the diagnosis and thus also in the therapy and recovery of patients. *Aspergillus* infection must be considered in the differential diagnosis of slowly progressive, but destructive wound infections, and of culture-negative mediastinitis that can occur after cardiac surgery [7, 8]. Moreover, these infections are refractory to therapy, and so relapse is quite common [8]. Treatment of sternal wound infection due to *Aspergillus* species is based on a combined surgical and medical approach [2, 8]. However, one of our patients was successfully treated with medical therapy alone. Amphotericin B in desoxycholate or liposomal encapsulate preparations remains the standard treatment [8]. Initially, the more effective amphotericin B was chosen for induction therapy, and then itraconazole was used for the need to prolong treatment out of the hospital. This approach was demonstrated to be valid in all three evaluated cases. In contrast to other case-reports, no relapse occurred. We think that the increased cost related to a longer hospitalization for iv treatment with amphotericin B was balanced by the lack of a need for further hospitalization and more surgery (i.e. for relapse), as described in other case reports [8].

The role of the operating room air, as a source of infection and the need for special ventilation systems in the operating room have been subjects of debate. Usually the largest source of airborne microbial contamination is the staff in the operating room; but in the case of *Aspergillus* infections the reservoir and airborne transmission is normally due to heavy contamination of the operating room close to hospital renovation activities. For these reasons, it’s very important to underline the need for implementing environmental control according to CDC guidelines for environmental infection control, and the use of an active infection surveillance system to promptly identify particular epidemic infections.

**Key words:** fungal infections, *Aspergillus* spp., surgical site infection.

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### SUMMARY

In this report we describe three cases of *Aspergillus flavus* sternal wound infection following cardiac surgery. All three cases occurred in a 3-month period coinciding with hospital renovation activities. The patients were successfully treated with combined surgical and medical therapy.

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### RIASSUNTO

Riportiamo tre casi di infezioni della ferita chirurgica organo/spazio post-cardiochirurgia causate da *Aspergillus flavus*. I tre casi riportati si sono verificati nell’arco di tre mesi, in un periodo in cui erano effettuati lavori di restauro all’interno dell’Ospedale. I tre pazienti sono stati trattati con successo con associazione di terapia chirurgica e medica.

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### REFERENCES


[3] Lutz B.D., Jin J., Rinaldi M.G. et al. Outbreak of invasive *Aspergillus* infection in surgical patients, associ-