Post-surgical invasive aspergillosis: An uncommon and under-appreciated entity

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Summary  Objective: Post-surgical invasive aspergillosis (PSIA) is an unusual and underes- timated complication of surgery. It may occur after colonization of surgical sites by airborne Aspergillus conidia during surgery, or in the immediate postoperative.  Methods: We reviewed 7 cases of PSIA (1997–2006) and checked the air levels of Aspergillus conidia in the operating rooms and/or areas surrounding 5/7 patients.  Results: PSIA accounted for 8.4% (n = 83) of all cases of invasive aspergillosis. Patients had no classic predisposing conditions (wound infection (n = 4), mediastinitis (n = 2), and endotipitis with endocarditis (n = 1)). PSIA occurred sporadically after heart, thoracic, and vascular prosthetic surgery. Aspergillus fumigatus was involved in all cases. Median time from surgery to diagnosis was 25 days. Galactomannan was only positive (>1 ng/mL) in 2 patients (endotipitis with endocarditis and mediastinitis). Mortality was 100% in cases of organ/space post-surgical infections. Although the air of operating rooms taken before surgery was free of Aspergillus, airborne Aspergillus conidia levels were high (>95 CFU/m³) in the rooms of 2 patients.  Conclusions: PSIA represented almost 10% of all cases of invasive aspergillosis. Our cases were not linked to high levels of Aspergillus conidia in the operating rooms but to postoperative contamination by environmental isolates present in high counts.

Introduction

Invasive pulmonary aspergillosis affects patients with different degrees of immunosuppression.1-4 However, post-surgical invasive aspergillosis (PSIA) is an unusual and underestimated complication of surgery that involves mainly immunocompetent patients whose prominent predisposing condition is a breach of the integrity of skin and...
mucosal barriers. PSIA infects surgical sites, it often goes unnoticed at first, and is believed to be caused by an external source of *Aspergillus* conidia contaminating the tissues of surgical sites during or after surgery. Information on PSIA is usually available as single case reports. A denominator of the overall number of cases of IA is not often provided and the significance of PSIA in comparison with the overall number of cases of IA in a large tertiary hospital is unknown. We review the 7 cases of PSIA that occurred in our hospital during a 7-year period.

**Material and methods**

**Institutional information**

Ours is a large 1750-bed tertiary teaching hospital serving a population of approximately 715,000 inhabitants.

Our institution attends patients at risk of acquiring IA, including solid organ and bone marrow transplant recipients, patients with haematological malignancies or HIV infection, and patients undergoing major surgery.

**Air sampling for airborne *Aspergillus* conidia**

Our heart-surgery intensive care unit and operating rooms for major surgery have systems to guarantee the absence of fungal propagules (high-efficiency particular air [HEPA] filtration and positive pressure). The air in these areas is monitored monthly for the presence of filamentous fungal conidia.6,7 Samples were collected using the Merck Air Sampler MAS 100® (Darmstadt, Germany), drawing a final air volume of 200 L per sample. Conidia are cultured on Sabouraud–chloramphenicol agar plates, which are incubated at 35 °C for 7 days and checked daily. The results are reported as CFU/m³ of air analyzed. If fungal spores are shown to be present, a cleaning protocol is performed and additional analysis is warranted. Surgical activity is stopped until air cultures have been shown to be negative for *Aspergillus*.

**Study period, definition of cases, and microbiological data**

We retrospectively reviewed the clinical charts of all patients with PSIA diagnosed from November 1999 to December 2006.

Proven PSIA was defined as the isolation of *Aspergillus* from normally sterile sites using procedures that guarantee sterility and/or provide evidence of fungal invasion of tissue by *Aspergillus* spp. Probable PSIA involved isolation of *Aspergillus* (and no other bacterial pathogen) from surgical sites or wounds with a poor outcome, despite administration of standard antibacterial treatment.5

Clinical samples (biopsy, abscess aspirates, blood samples, or other samples) were cultured onto bacterial and fungal culture media. Fungal culture plates were incubated at 30–37 °C for a minimum of 7 days. Species were identified using standard morphological procedures.

Determination of galactomannan in serum was requested by an infectious diseases clinician and performed using Platelia® (BioRad, Marnes-la-Coquette, France). We used 2 different cutoffs (>0.5 ng/mL and ≥1.0 ng/mL) to consider a determination as positive. In those cases with multiple determinations, only the first result was evaluated, as the results of the subsequent samples were the same as the first one.

**Results**

We recorded 7 cases of PSIA (3 proven and 4 probable), representing 8.4% of all cases of invasive aspergillosis (n = 83) in our institution. The clinical forms of the infection were: wound infections 4 (57.1%), mediastinitis 2 (28.6%), and endotracheal 1 (14.3%). Cases of PSIA had a sporadic distribution and occurred exclusively in patients with no classic predisposing conditions for invasive aspergillosis (Table 1). The mean time from surgery to the first *Aspergillus* isolation was 25 days (range 11–376). *Aspergillus* was isolated in all patients (Table 1); however, the infection was histopathologically confirmed in only 1 patient. In the remaining cases, biopsies were not submitted for histopathology analysis.

Treatment involved surgical debridement and concomitant antifungal therapy in six patients. Patients with good outcome received antifungal therapy for a mean of 45 days after surgery.

Five of the 7 patients with PSIA underwent surgery in operating rooms with HEPA filtration to keep the air free from *Aspergillus* conidia. In these cases, the air of the operating rooms was free from *Aspergillus* in the month before surgery (Table 1). No information on the presence of *Aspergillus* in the air surrounding the other 2 patients is available, as it was not possible to examine the operating room. However, 2 of these patients developed mediastinitis and, after surgery, stayed in HEPA-filtered rooms with normally high levels of *Aspergillus* conidia.

**Patient 1** underwent tracheal resection and anastomosis and developed shortness of breath and difficulty breathing 5 days after surgery. She was diagnosed with upper airway obstruction and taken to the operating room where endoscopy revealed partial wound dehiscence and evidence of infection. Although the samples taken did not yield bacterial or fungal isolates, empirical antimicrobial treatment with vancomycin and cefotaxime was started. Two weeks later she again developed shortness of breath and a new endoscopy showed overall wound dehiscence. She underwent resection and reconstruction of the trachea and tissue culture yielded *Aspergillus fumigatus*.

**Patient 2** was admitted for pacemaker placement. In the postoperative period, she developed a hematoma around the wound of the pacemaker pocket site in the chest wall. She was discharged on day 22, and 38 days after surgery she was re-admitted with erythema and swelling around the area of the pacemaker pocket requiring incision and drainage. Purulent material was submitted to the microbiology laboratory and the culture yielded *A. fumigatus* with no co-pathogen. The infected pacemaker pocket and wires were removed. There was no evidence of relapse in the following 4 years.

**Patient 3** underwent surgery for placement of an aortic stent via aortic dissection. Sternal closure was delayed until day +2 and his postoperative period was complicated by hemodynamic instability. Outcome was poor with sternal...
Table 1  Summary of the clinical and predisposing conditions of the 7 patients with post-surgical invasive aspergillosis included in the study.

<table>
<thead>
<tr>
<th>Case</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Underlying condition</th>
<th>Comorbid conditions</th>
<th>Infection type</th>
<th>Surgery/minutes</th>
<th>Time from surgery to diagnosis</th>
<th>Aspergillus in operating rooms</th>
<th>Aspergillus in ward of admission</th>
<th>Galactomannan (in ng/mL) 0.5/1</th>
<th>Species involved</th>
<th>Antifungal treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2000</td>
<td>7</td>
<td>F</td>
<td>Congenital tracheal stenosis</td>
<td>BSA, re-surgery</td>
<td>Wound infection</td>
<td>Tracheoplasty/100</td>
<td>25 days</td>
<td>NEG</td>
<td>NP</td>
<td>NEG/NEG</td>
<td>A. fumigatus</td>
<td>AMB—ITC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cure</td>
</tr>
<tr>
<td>2</td>
<td>2000</td>
<td>79</td>
<td>F</td>
<td>Heart disease</td>
<td>DM, chronic renal insufficiency</td>
<td>Wound infection</td>
<td>Implantation pacemaker/ND</td>
<td>39 days</td>
<td>ND</td>
<td>NP</td>
<td>NEG/NEG</td>
<td>A. fumigatus</td>
<td>ITC</td>
<td>Cure</td>
</tr>
<tr>
<td>3</td>
<td>2000</td>
<td>63</td>
<td>M</td>
<td>Aortic dissection</td>
<td>BSA, chronic renal insufficiency, reintervention</td>
<td>Mediastinitis</td>
<td>Cardiovascular/360</td>
<td>34 days</td>
<td>NEG</td>
<td>95 CFU/m&lt;sup&gt;3&lt;/sup&gt;</td>
<td>POS/POS</td>
<td>A. fumigatus</td>
<td>—</td>
<td>Death</td>
</tr>
<tr>
<td>4</td>
<td>2002</td>
<td>70</td>
<td>M</td>
<td>Lung cancer HCV cirrhosis (TIPS)</td>
<td>BSA, re-intervention</td>
<td>Wound infection</td>
<td>Thoracotomy/biopsy/180</td>
<td>376 days</td>
<td>NEG</td>
<td>NP</td>
<td>NEG/NEG</td>
<td>A. fumigatus</td>
<td>ITC</td>
<td>Cure</td>
</tr>
<tr>
<td>5</td>
<td>2003</td>
<td>75</td>
<td>F</td>
<td>HCV cirrhosis</td>
<td>BSA</td>
<td>Endotipsis with endocarditis</td>
<td>Mediastinitis with mediastinitis</td>
<td>32 days</td>
<td>ND</td>
<td>NP</td>
<td>POS/POS</td>
<td>A. fumigatus</td>
<td>VRC</td>
<td>Attributable Death</td>
</tr>
<tr>
<td>6</td>
<td>2003</td>
<td>57</td>
<td>F</td>
<td>Chronic renal insufficiency</td>
<td>BSA, DM, obesity, DM</td>
<td>Wound infection</td>
<td>Aortofemoral bypass/195</td>
<td>23 days</td>
<td>NEG</td>
<td>NP</td>
<td>NEG/NEG</td>
<td>A. fumigatus</td>
<td>ITC—VRC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Cure</td>
</tr>
<tr>
<td>7</td>
<td>2006</td>
<td>57</td>
<td>M</td>
<td>Ischemic heart disease</td>
<td>DM, BSA, re-intervention</td>
<td>Mediastinitis</td>
<td>Cardiovascular/285</td>
<td>11 days</td>
<td>NEG</td>
<td>200 CFU/m&lt;sup&gt;3&lt;/sup&gt;</td>
<td>NEG/NEG</td>
<td>A. fumigatus</td>
<td>CAS A. flavus</td>
<td>Attributable Death</td>
</tr>
</tbody>
</table>

AMB: amphotericin B; BSA, broad-spectrum antimicrobials; CAS, caspofungin; DM, diabetes mellitus; F, female; HCV, hepatitis C virus; ITC, itraconazole; M, male; NEG, negative (<0.5 or 1.0 ng/ml); ND, no data; NP, patient located in non-protected area out of our air sampling program; POS, positive (>0.5 or 1 ng/ml); TIPS, transjugular intrahepatic portosystemic shunt; VRC, voriconazole.

<sup>a</sup> Sequential treatment: amphotericin B at 3 mg/kg/day for 10 days after itraconazole at 200 mg/day for 20 days po.

<sup>b</sup> Sequential treatment: itraconazole at 200 mg/day for 40 days after voriconazole at 200 mg/day for 40 days, due to poor outcome and A. fumigatus isolated in surgical wound (amputation).

<sup>c</sup> Presence of airborne Aspergillus conidia in the air of the operating room within ±30 days from the day of surgery.

<sup>d</sup> Presence of airborne Aspergillus conidia in the air of the ward within ±30 days from the day of admission to the ward.
wound dehiscence. Only *A. fumigatus* was repeatedly isolated form the wound, but histopathology of biopsy samples was negative for *Aspergillus*. He died on day +43 despite repeated debridement. Highly abnormal levels of *Aspergillus conidia* (95 CFU/m³) were observed in the intensive care unit after surgery the same day of the patient admission, whereas the samples taken in days +2, +23, +43, and +50 were free of conidia.

**Patient 4** underwent a biopsy procedure via thoracotomy for diagnosis of a pulmonary nodule. He was diagnosed with lung cancer and received only palliative therapy. One year later, he developed erythema and swelling around the biopsy scar, requiring incision and drainage of a persistent pleural fistula. Purulent material was submitted to the microbiology laboratory and the culture yielded *A. fumigatus* with no co-pathogen. The patient died 1 year later due to progression of the cancer.

**Patient 5** received a transjugular intrahepatic portosystemic shunt (TIPS) in 1997 for the control of her portal hypertension. From 1997 to 2003, she required repeated endovascular transjugular procedures for TIPS dysfunction. In January 2003, she experienced a new episode of esophageal variceal bleeding with TIPS obstruction that required a new endovascular procedure. In the immediate postoperative period, the patient developed *Staphylococcus epidermidis* bacteremia that cleared after treatment with vancomycin, but the patient remained febrile 27 days after the procedure, despite negative blood cultures. She developed an episode of chorioretinitis. In order to evaluate the role of the TIPS in the infection, blood samples were taken from the portal vein near the TIPS using a transjugular approach, and from peripheral veins. Cultures of portal blood revealed heavy growth of *A. fumigatus*. Blood obtained from peripheral veins proved to be sterile. Transesophageal echocardiography (TEE) revealed vegetations compatible with endocarditis in the mitral valve. Clinical outcome and situation of the patient were poor, and valve replacement was initially rejected. Antifungal therapy with voriconazole was added. A new TEE showed enlargement of the vegetations in the mitral valve, which was surgically removed. Cultures of the mitral valve were positive for both *A. fumigatus* and *S. epidermidis*. Ten days after the valve replacement, the patient died of multiorgan failure. An autopsy was denied and histopathological diagnosis of IA was not possible.

**Patient 6** was admitted for iliofemoral bypass venous graft. She was discharged on day 4, and 10 days after surgery she was re-admitted with erythema and swelling around the surgical wound and ischemic involvement of the lower extremities. She received treatment with amoxicillin and clavulanic acid and, 23 days after surgery, underwent above-knee amputation. A biopsy sample was submitted to the microbiology laboratory and the culture yielded *A. fumigatus* with mixed flora, but these microorganisms were not isolated in other samples and were considered contaminants. The patient progressed well and was discharged. She was re-admitted 73 days after surgery with erythema, swelling, and purulent secretion around the surgical site. Purulent material was drained and sent to the microbiology laboratory: the culture yielded *A. fumigatus* and *Staphylococcus aureus*. She received treatment with amoxicillin, clavulanic acid, and itraconazole (dose adjusted to renal function).

**Case 7** underwent coronary aortic bypass surgery. Sternal closure was delayed until day 4 after surgery, and his postoperative period was complicated with hemodynamic instability. He had persistent fever and received empiric antibiotics until day 6 after surgery with meropenem and vancomycin. On day 10, he developed sternal erythema and swelling with wound necrosis. Only *A. fumigatus* and *Aspergillus flavus* were repeatedly isolated from the wound. Proven diagnosis of invasive aspergillosis was achieved by the visualization of branched fungal elements compatible with *Aspergillus* invading the tissues in the wound biopsies. He died despite repeated debridement and therapy with caspofungin. The air of the operating rooms before surgery (days −30 before the surgery and the same day of the surgery) was free of *Aspergillus*. The air of the intensive care unit was sampled in the days −30, 0, +6, +23, and +27 after surgery. *Aspergillus conidia* were observed in the air the same day of admission (200 CFU/m³) and the day +6 after (60 CFU/m³); the remaining samples taken were negative for *Aspergillus*.

**Discussion**

PSIA is an infrequent but severe complication of surgery, affecting 2 of every 10,000 surgical procedures. It represented almost 10% of the total number of cases of IA occurring at our hospital during the study period. Pasqualotto et al. recently collected a large number of cases of PSIA after different surgical procedures. They showed that PSIA occurred mainly in immunocompetent patients whose main risk factor was surgery. The retrospective collection of cases from multiple sources in the literature made it impossible for the authors to compare cases of PSIA with all the episodes of IA or per 10,000 surgical procedures. The surgical procedures with the highest risk of PSIA were cardiac surgery, ophthalmological surgery, and dental surgery. In our series, PSIA occurred exclusively in patients who had undergone thoracic, cardiac, and vascular prosthetic procedures.

The most common clinical presentation of the infection in our patients was superficial or deep wound infection, and none of them were immunocompromised or taking corticosteroids. Half of the cases of surgical wound aspergillosis reported in the literature occurred in solid-organ transplant recipients. Onset is generally during the first 2 weeks after surgery (mean 17 days). Outcome was favorable in patients with wound infection after antifungal treatment and surgical debridement, and survival 2 years after the episode was 100%. Clinical presentation at accessible and visible sites may partially explain the good outcome of the disease in this specific group of patients.

Deep organs may be involved after exposure of deep tissue during surgical procedures. Endotipsitis is an emerging infectious disease to be considered in patients with a TIPS and a bloodstream infection that is not clearly attributable to another source. Our patient with TIPS infection by *Aspergillus* also had disseminated disease with associated endocarditis. To our knowledge, this is the first report of endotipsitis caused by *Aspergillus*.

*Aspergillus* mediastinitis in surgical patients has been described in association with deep sternal wound
infection. Our 2 cases had signs of wound infection, although the first isolation of Aspergillus was not considered significant by the clinicians. The infection progressed and compromised deep sites in the mediastinum. Given the poor outcome of mediastinitis after cardiac surgery, a differential diagnosis of aspergillosis should be made in slowly progressive and destructive wound infections with no other isolated bacterial pathogens. In these patients, the presence of A. flavus as a cause of the infection is not uncommon and may account for 41.2% of cases with no other isolated bacterial pathogen. In these patients, A. fumigatus is the predominant species causing IA and colonizing patients in our hospital. The high number of cases of invasive aspergillosis caused by A. fumigatus may be due to its higher frequency of isolation in the air of Madrid.

The duration of antifungal treatment and the agent of choice for patients with PSIA remain unresolved. After reviewing several case reports, Pasqualotto and Denning recommended that, once as much infected tissue as possible has been debrided, antifungal treatment should be administered for no less than 3 months beyond the last evidence of active disease. Although no prospective studies show the superiority of voriconazole in patients with PSIA, new IDSA guidelines recommend its use. Our patients with wound infections received a mean of 6 weeks of antifungal treatment, mainly with itraconazole, after debridement. Outcome was favorable after 1 year of follow-up.

Many studies have associated PSIA with the dissemination of Aspergillus conidia in the operating room. We had 2 patients with mediastinitis and PSIA who were in rooms with abnormally high levels of Aspergillus conidia in the air (95 and 200 CFU/m3). Previous studies performed by our team showed that the common concentration of filamentous fungi conidia in the hospital air is 35.8 CFU/m3. In the absence of genotypical characterization of the clinical and environmental strains, we can only suggest an airborne infection, although this suggestion should be considered with caution. However, in a previous study, we observed a correlation between high levels of Aspergillus conidia and the development of IA. A shortcoming of our study is the lack of histopathologic evidence to confirm invasion by septate hyphae in several cases.

In conclusion, PSIA is an uncommon but not anecdotic complication of surgery in our hospital. PSIA should be suspected in wound infections that do not improve despite broad-spectrum antibiotic treatment.

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