A Rare Case of Aspergillus Mediastinitis After Coronary Artery Bypass Surgery: A Case Report and Literature Review

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Conflict of interest: None declared

Patient: Male, 74-year-old
Final Diagnosis: Aspergillus fumigatus infection
Symptoms: Anemia • elevated inflammatory marker • fever • mediastinal fluid collection • sternal disruption
Medication: —
Clinical Procedure: —
Specialty: Cardiac Surgery • Infectious Diseases

Objective: Rare disease
Background: Mediastinitis is a serious complication after cardiac surgery; it is a deep sternal wound infection following sternotomy, with clinical evidence and/or microbiological involvement and sternal osteomyelitis. The most common pathogens are Staphylococcus spp (S. aureus), followed by gram-negative organisms. Establishing an etiological diagnosis of fungal mediastinitis is often a challenging issue, given the nonspecific clinical presentation.

Case Report: A 74-year-old man was diagnosed with a three-vessel coronary artery disease in a university hospital. The patient had as clinical background hypertension, a body mass index (BMI) of 29.78 kg/m², and no diabetes mellitus. After an uneventful coronary artery bypass surgery, he presented clinical and radiological mediastinitis manifestations on the 9th postoperative day. He was treated with a range of antibiotics, with no clinical improvement until the 33rd postoperative day. Then, mediastinal fluid and biopsied tissue were collected and he was started on voriconazole due to growing Aspergillus spp. On the 93rd postoperative day, he had clinical improvement and, after several exams, was released from the hospital. We present the first report of Aspergillus fumigatus mediastinitis after cardiac surgery in Brazil, successfully treated with voriconazole.

Conclusions: Aspergillus infection should be considered in the differential diagnosis of mediastinitis after coronary surgery, especially in a clinical case of unexplained sepsis, negative blood culture, and no clinical improvement despite antibiotic therapy. This case report highlights that the mediastinal fluid and biopsy tissue culture can be useful for the diagnosis of fungal mediastinitis.

Keywords: Aspergillus • Mediastinal Diseases • Voriconazole

Abbreviations: BMI – body mass index; WBC – white blood cell; RBC – red blood cells; CRP – C-reactive protein; ICU – Intensive Care Unit; POD – postoperative day; IV – intravenous

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**Background**

Mediastinitis is a deep sternal wound infection following sternotomy, with clinical evidence and/or microbiological involvement and sternal osteomyelitis, with an incidence varying from 0.5 to 5.6% [1-3].

According to the European Association for Cardio-Thoracic Surgery expert consensus, the diagnosis of mediastinitis after sternotomy requires at least one of the following criteria: 1) a positive culture of fluid or mediastinal tissue; 2) a histopathological lesion compatible and 3) signs and symptoms such as fever, chest pain or sternal instability.

Postcardiac surgery wound infections are mostly caused by *Staphylococcus* or *Enterobacteriaceae* species [2,3]. Herein, we report the first case of mediastinitis caused by *Aspergillus* after coronary artery bypass graft surgery in Brazil.

**Case Report**

A 74-year-old man was admitted to a university hospital in a Brazilian Midwest Region state with precordial pain and typical angina, showing tightness and irradiation to the left upper limb. The patient had hypertension, a body mass index (BMI) of 29.78 kg/m², and no diabetes mellitus. A cardiac catheterization procedure diagnosed three-vessel coronary artery disease, and the patient underwent coronary artery bypass surgery.

Initial laboratory test results revealed no anemia and normal hemogram parameters: white blood cell (WBC) count, $7.2 \times 10^3/\mu L$ (normal range: 4.5 to $11 \times 10^3/\mu L$); neutrophils, 66%; red blood cells (RBCs), $5.22 \times 10^6/\mu L$ and C-reactive protein (CRP), 3.16 mg/L (normal range: 0 to 5 mg/L). Cardiac enzyme levels were normal (creatine kinase: 13.28 U/L; troponin I: 12.5 pg/mL). The creatinine level was 1.26 mg/dL (0.5-1.2 mg/dL), and blood urea nitrogen was 37.3 mg/dL (16-40 mg/dL). The coagulogram and blood glucose level (88 mg/dL) did not show abnormalities. Blood and urine cultures were negative.

The surgery was uneventful. On the 9th postoperative day (POD), the patient presented with sternal instability, fever (axillary temperature 39.2ºC), anemia (hemoglobin, 11 g/dL), leukocytosis (WBCs, $5.22 \times 10^3/\mu L$ and C-reactive protein (CRP), 3.16 mg/L (normal range: 0 to 5 mg/L). Cardiac enzyme levels were normal (creatine kinase: 13.28 U/L; troponin I: 12.5 pg/mL). The creatinine level was 1.26 mg/dL (0.5-1.2 mg/dL), and blood urea nitrogen was 37.3 mg/dL (16-40 mg/dL). The coagulogram and blood glucose level (88 mg/dL) did not show abnormalities. Blood and urine cultures were negative.

The surgery was uneventful. On the 9th postoperative day (POD), the patient presented with sternal instability, fever (axillary temperature 39.2ºC), anemia (hemoglobin, 11 g/dL), leukocytosis (WBCs, $24.8 \times 10^3/\mu L$ and an elevated inflammatory marker (CRP, 262 mg/L). Chest computed tomography showed sternal disruption, and mediastinal fluid collection suggested mediastinitis (Figure 1). With the diagnosis of infection, therapy with meropenem IV (3000 mg/day) and teicoplanin IV (1.200 mg/day) was introduced empirically.

No clinical improvement was observed until the 23rd POD, and antibiotic therapy was changed to polymyxin B IV (100 mg/day), amikacin IV (500 mg/day) and linezolid IV (1200 mg/day), due to a negative blood culture. On the 27th POD, owing to persistent fever (axillary temperature 38.8ºC) despite antibiotic therapy and suspected candidemia, treatment with micafungin IV (100 mg/day) was introduced empirically.

On the 33rd POD, the patient underwent a new surgical procedure for sternal resuscitation. Mediastinal fluid and biopsied...
Postoperative Aspergillus mediastinitis is a rare event, mostly associated with heart transplants, valve surgery, and tetralogy of Fallot repair surgery [5-8].

The diagnosis of invasive aspergillosis is a major challenge. This condition can mimic other diseases, and the diagnosis is often delayed. Diagnostic dilemmas can delay appropriate therapy of mediastinitis and influence the outcome [9].

Postoperative invasive aspergillosis may occur as a result of host susceptibility and may be caused by Aspergillus spores from the air during surgery. However, postoperative contamination due to a high number of spores in the environment, contaminated grafts, paranasal sinuses and hematogenous dissemination is also possible [10,11]. Intrahospital outbreaks caused by Aspergillus species were also described [12,13]. Risk assessment and implementation of preventive measures (eg, environmental control strategies, air surveillance, inpatients, immunocompromised patients in high-efficiency particulate air filter rooms, and antifungal prophylaxis in high-risk patient groups) showed that this reduces the incidence of invasive fungal infection [12,14].

Mediastinal infections are usually indolent and, in some cases, occur several months after heart surgery [6,15]. Previous studies have shown that patients with mediastinitis are hospitalized longer than patients without this complication [3,4].

In our case, the diagnosis of mediastinitis was readily suspected, but fungal culture was not requested at the onset of the symptoms. Because of the persistent signs and symptoms of infection and considering that the classical postcardiac surgery wound infections are mostly caused by Staphylococcus or Enterobacteriaceae species [1,2], several classes of antibiotics were administered.

Of note, cardiovascular infection by Aspergillus is difficult to diagnose, considering that this fungus is infrequently isolated from blood cultures and some surgical specimens are not sent to the laboratory for fungal culture [8,16].

Mycfungin was ineffective in our patient because echinocandins are not recommended as first-line agents and are reserved for the salvage setting or in combination with another antifungal class. Voriconazole is most suitable for the treatment of invasive aspergillosis [17]. In the present case, the use of voriconazole was effective. However, it is important to remember that due to the non-linear pharmacokinetics of this drug, it is poorly soluble in water and may cause renal toxicity. An alternative to this problem would be the use of a liposomal solution that increases solubility, reduces toxicity, and enhances the antifungal action [18]. Unfortunately, this pharmaceutical formulation was not available in our institution.

The main risk factors for mediastinitis include diabetes mellitus, chronic obstructive pulmonary disease, obesity, bilateral internal mammary artery use, advanced age, smoking, mechanical ventilator assist devices, and prolonged ICU stay [1,2,19]. In our case, the preoperative risk factors for Aspergillus mediastinitis were obesity and advanced age, and the postoperative risk factor was prolonged use of ventilator support in the ICU.

Invasive aspergillosis occurs more frequently in severely immunocompromised patients; however, cases of surgical site infection have been reported in both immunocompetent and immunocompromised individuals [9,16].

Some tools are very important and help diagnoses. Procalcitonin levels seem to be able to distinguish between fungal and bacterial infection [20]. Galactomannan is another biomarker used for clinical suspicion of invasive fungal infections. However, they were not available at our hospital due to lack of reagents.

In reviews based on PubMed (http://www.ncbi.nih.gov/) and SciELO (https://scielo.org/) database searches using the keywords “mediastinitis,” “Aspergillus” and “coronary artery bypass,” only 3 cases of Aspergillus mediastinitis were reported from 2000 to July 2020 after coronary artery bypass graft surgery [8,12,13]. All these cases were of immunocompetent patients, aged over 50 years, of which 2 patients had diabetes mellitus. Among them, 2 patients progressed well, even without antifungal treatment; the third patient died, despite caspofungin treatment. The good outcome of our case might have been partly due to the correct treatment with voriconazole, which proved to be effective.
**Conclusions**

Aspergillus infection should be considered in the differential diagnosis of mediastinitis after coronary surgery, especially in a clinical case of unexplained infection and negative blood culture. This case report highlights that the mediastinal fluid and biopsy tissue culture can be useful for the diagnosis of fungal mediastinitis and helps reduce mortality. In addition, it highlights how the indiscriminate use of antifungal and antibiotic without defining the etiological agent can prolong hospitalization and contribute to microbial resistance.

**References:**

1. Abu-Omar Y, Kocher GJ, Bosco P, et al. European Association for Cardio-Thoracic Surgery expert consensus statement on the prevention and management of mediastinitis. Eur J Cardiothorac Surg. 2017;51(1):10-29
2. Diez C, Koch D, Kuss O, et al. Risk factors for mediastinitis after cardiac surgery: a retrospective analysis of 1700 patients. J Cardiothorac Surg. 2007;2:23
3. Sánchez MPBO, Santos CA, et al. Risk factors for mediastinitis after coronary artery bypass grafting surgery. Rev Bras Cir Cardiovasc. 2011;26(1):27-35
4. Baláje V, Houbraken J, Pérez-Díaz R, et al. Aspergillus species identification in the clinical setting. Stud Mycol. 2007;59:39-46
5. Caballero MJ, Mongardon N, Hauwache H, et al. Aspergillus mediastinitis after cardiac surgery. Int J Infect Dis. 2016;46:16-19
6. Caron J, Conti M, Pietro R, et al. Atypical presentation of Aspergillus mediastinitis infection in a heart transplant patient: The importance of combined medical and surgical treatment. Exp Clin Transplant. 2019;17(5):695-98
7. Forestier E, Remy V, Lesens O, et al. A case of Aspergillus mediastinitis after heart transplantation successfully treated with liposomal amphotericin B, caspofungin and voriconazole. Eur J Clin Microbiol Infect Dis. 2005;24(5):347-49
8. Ghotaslou R, Parvizi R, Safaei N, Yousefi S. A case of Aspergillus flavus mediastinitis after heart surgery. Madani Heart Center, Tabriz, Iran. Prog Cardiovasc Nurs. 2008;23(3):133-35
9. Kartik M, Kanala A, Sunilnadikuda, et al. Invasive mediastinal aspergillosis in an immunocompetent male with invasion of left atrium and hilar structures. Indian J Crit Care Med. 2017;21(6):408-11
10. Hedayati MT, Pasqualotto AC, Warn PA, et al. Aspergillus flavus: Human pathogen, allergen and mycotoxin producer. Microbiology (Reading, England). 2007;153:1677-92
11. Jensen J, Guine J, Torres-Narona M, et al. Postsurgical invasive aspergillosis: An uncommon and under-appreciated entity. J Infect. 2010;60(2):162-67
12. Lutz BD, Jin J, Rinaldi MG, et al. Outbreak of invasive Aspergillus infection in surgical patients, associated with a contaminated air-handling system. Clin Infect Dis. 2003;35;37(6):786-93
13. Pérez T, Muñoz P, Guine J, et al. Outbreak of invasive aspergillosis after major heart surgery caused by spores in the air of the Intensive Care Unit. Clin Infect Dis. 2012;54(3):e24-31
14. Alvare-Moreno CA, Combariza JF. Risk of invasive fungal infections during hospital construction: How to minimize its impact in immunocompromised patients. Curr Opin Infect Dis. 2019;32(4):322-29
15. Acuña M, Farfán F, Cofré F, Benadof D. [Aspergillus fumigatus mediastinitis in an immunocompetent pediatric patient after heart surgery]. Rev Chilena Infectol. 2016;33(1):75-78 [in Spanish]
16. Pasqualotto AC, Denning DW. Post-operative aspergillosis. Clin Microbiol Infect. 2006;12(11):1060-76
17. Cadena J, Thompson GR 3rd, Patterson TF. Invasive Aspergillosis: Current strategies for diagnosis and management. Infect Dis Clin North Am. 2016;30(1):125-42
18. Veloso DFMC, Benedetti NigM, Ávila RI, et al. Intravenous delivery of a liposomal formulation of voriconazole improves drug pharmacokinetics, tissue distribution, and enhances antifungal activity. Drug Deliv. 2018;25(1):1585-94
19. Vandecasteele SJ, Boelaert JR, Verrelst P, et al. Diagnosis and treatment of Aspergillus flavus sternal wound infections after cardiac surgery. Clin Infect Dis. 2002;35(7):887-90
20. Cortegiani A, Misseri G, Ippolito M, et al. Procalcitonin levels in candidemia versus bacteremia: A systematic review [published correction appears in Crit Care. 2019;23(1):322]. Crit Care. 2019;23(1):190

**Ethics Approval**

The study was approved by the local Research Ethics Committee – Plataforma Brasil (CAAE: 95838818.0.0000.0021).

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