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Case Report

Aspergillus mediastinitis after cardiac surgery

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SUMMARY

Background: Mediastinitis is a serious complication after cardiac surgery. While bacteria are the more common pathogens, fungal infections are rare. In particular, several cases of postoperative Aspergillus mediastinitis have been reported, the majority of which had an extremely poor outcome.
Methods: A case of mediastinitis in a 42-year-old patient due to *Aspergillus fumigatus* after cardiac surgery is described. Two main risk factors were found: cardiogenic shock requiring veno-arterial extracorporeal life support and failure of primary closure of the sternum. A full recovery was attained after surgical drainage and antifungal therapy with liposomal amphotericin B, followed by a combination of voriconazole and caspofungin. The patient was followed for 18 months without relapse.
Results: This is an extremely rare case of postoperative Aspergillus mediastinitis exhibiting a favourable outcome. Based on a systematic review of the literature, previous cases were examined with a focus on risk factors, antifungal therapies, and outcomes.
Conclusion: The clinical features of postoperative Aspergillus mediastinitis may be paucisymptomatic, emphasizing the need for a low index of suspicion in cases of culture-negative mediastinitis or in indolent wound infections. In addition to surgical debridement, the central component of antifungal therapy should include amphotericin B or voriconazole.

1. Introduction

Mediastinitis is a feared complication of open heart surgery. Most commonly due to *Staphylococcus spp* or *Enterobacteriaceae*, non-bacterial pathogens are rare. Several cases of postoperative Aspergillus mediastinitis have been described in the literature in immunocompetent patients or after heart transplantation. The patient outcome after such a complication is extremely poor despite antifungal therapy and surgery.[1]

The third reported case of postoperative Aspergillus mediastinitis in an immunocompetent adult patient who had a favourable outcome is described herein. A review of the literature showed that successful treatment is exceedingly rare and that the optimal antifungal therapy needs to be determined.

2. Case report

A 42-year-old woman with a history of three open heart surgeries for mitral and aortic valve replacements was admitted to the intensive care unit (ICU) after her fourth double valve replacement. Anaesthetic interventions were uneventful, including antibiotic prophylaxis with cefamandole. Veno-arterial extracorporeal life support (ECLS) was initiated immediately after surgery due to biventricular failure. The patient's postoperative course was complicated by cardiac tamponade on postoperative day (POD) 1, requiring surgical drainage; primary closure of the sternum was not possible due to significant myocardial oedema, necessitating a latex patch sutured to the skin. She received a 7-day course of imipenem for ventilator-associated pneumonia due to extended-spectrum beta-lactamase-producing *Enterobacter cloacae* . After a week, she was successfully weaned off ECLS, and sternal closure was achieved on POD 16, under imipenem and vancomycin prophylaxis. During this procedure, samples from the surgical site were systematically

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sent for bacteriological and mycological analyses (POD 16); however there were no clinical or biological signs of an underlying infectious process.

All surgical samples including sternal and pericardial tissues were positive for hyphae under direct visualization, compatible with *Aspergillus spp*. Cultures returned positive for several colonies of *Aspergillus fumigatus*; no bacteria were isolated. An extensive search for possible environmental contamination did not reveal any source in the operating room or in the ICU. An external fan that was used to cool the patient during a summer heat wave was suspected to be the source of contamination. The fan was not cultured due to the delay from the time it was used for the patient. No other patient undergoing cardiac surgery since the year prior to this case and to date has developed postoperative mediastinitis or another invasive Aspergillus infection.

Intravenous (IV) liposomal amphotericin B at 3 mg/kg daily was started on POD 17 for 7 days, followed by IV voriconazole at 2.5 mg/kg twice daily (POD 23), adjusted according to plasma levels. Ten days after the initiation of treatment (POD 27), cultures from the surgical drains were still positive for fungi, therefore IV caspofungin (70 mg on the first day followed by 50 mg daily) was added to IV voriconazole (POD 28) for an additional period of 21 days.

A whole body computed tomography scan showed no sign of secondary localization of invasive aspergillosis; endocarditis was

Table 1
Main characteristics of patients with mediastinitis due to *Aspergillus spp* after cardiac surgery

Ref.	Age (years) and sex	Surgical procedure	Immuno-deficiency	Risk factors	Delay between surgery and diagnosis	*Aspergillus* species	Antifungal treatment and duration	Outcome (Time between diagnosis and death/cure)
[8]	51, M	Heart transplantation	Yes	Immunosuppressive agents	NA	*A. fumigatus*	None	Death (Unknown)
[9]	64, M	Valvular surgery	No	Urgent surgery, COPD	12 days	*A. flavus*	Amphotericin B	Death (19 days)
[10]	46, M	Valvular surgery	No	-	NA	*A. fumigatus*	NA	Death (Unknown)
	72, F	Coronary artery bypass graft	No	-	NA	*A. flavus*	NA	Cure (Unknown)
[11]	61, M	Heart transplantation	Yes	COPD, immunosuppressive agents	5 weeks	*A. fumigatus*	Voriconazole 200 mg twice daily indefinitely	Cure (13 months of treatment)
[12]	51, F	Heart transplantation	Yes	Multiple redo-surgeries, immunosuppressive agents	2 months	*A. fumigatus*	Liposomal amphotericin B 5 mg/kg daily + caspofungin 35 mg daily Then voriconazole 400 mg daily 6 months total	Cure (6 months)
[13]	3, F	Repair of congenital cardiomyopathy	No	Multiple redo-surgeries	5 months	*A. fumigatus*	IV caspofungin 6 months + oral voriconazole 8 months	Cure (14 months)
	6 mo, F		No	Multiple redo-surgeries, ECMO, delayed sternal closure	<1 month	*Aspergillus spp*	None (post-mortem diagnosis)	Death (16 days)
	1 mo, M		No	Multiple redo-surgeries, delayed sternal closure	1 month	*A. fumigatus*	Liposomal amphotericin B + caspofungin 1 week after	Death (23 days)
[14]	60, M	Coronary artery bypass graft	No	Diabetes mellitus	2 months	*A. fumigatus*	NA	Cure (4 weeks)
[15]	61, M	Heart transplantation	Yes	Redo-surgery, septic shock, immunosuppressive agents	1 month	*A. fumigatus*	NA	Death (Unknown)
[16]	63, M	Aortic dissection	No	Delayed sternal closure, hemodynamic instability	34 days	*A. fumigatus*	NA	Death (43 days)
[17]	68, M	Pulmonary endarterectomy	No	Pulmonary hypertension, candidemia prior to surgery	8 days	*A flavus*	Liposomal amphotericin B 3 mg/kg daily + voriconazole 4 mg/kg daily	Death (26 days)
[18]	57, M	Coronary artery bypass graft	No	Diabetes mellitus, redo-surgery	6 days	*A. fumigatus*, *A. flavus*	Caspofungin	Death (Unknown)
	57, F	Heart transplantation	Yes	Immunosuppressive agents, haemodialysis, COPD	49 days	*A. fumigatus*, *A. terreus*	Caspofungin + voriconazole	Cure (Unknown)
[19]	55, F	Heart transplantation	Yes	Redo-surgery, immunosuppressive agents, haemodialysis, cardiogenic shock	5 weeks	*A. calidoustus*	Posaconazole 11 days + voriconazole 10 days + amphotericin B 42 days	Cure (4 months)
Present case	42, F	Valvular surgery	No	Multiple redo-surgeries, delayed sternal closure, cardiogenic shock	16 days	*A. fumigatus*	Liposomal amphotericin B 3 mg/kg daily Then IV voriconazole 200 mg twice daily + caspofungin 50 mg daily Then voriconazole 200 mg twice daily	Cure (18 months)

M, male; F, female; NA, not available; COPD, chronic obstructive pulmonary disease; IV, intravenous; ECMO, extracorporeal membrane oxygenation.

ruled out by transoesophageal echocardiography. Initially, the beta-D-glucan test was negative, but this became positive (200 pg/ml) 2 weeks later (POD 30); galactomannan antigenemia was negative. Galactomannan, beta-D-glucan, and surgical drains were tested twice weekly for fungi, and the drains were progressively removed after two consecutive negative cultures, with the last drain removed after 18 days of combined therapy (POD 47). Since the patient continued to improve clinically, caspofungin was discontinued (POD 50) and IV voriconazole was transitioned to oral treatment (POD 52) for a total of 3 months. Microbiological monitoring with serial beta-D-glucan testing remained negative during the 18-month follow-up period. The patient experienced no relapse during this period and recovered fully.

3. Discussion

Mediastinitis is a rare complication occurring in 1–2% of cases after sternotomy for cardiac surgery and carries a high mortality rate. Diagnostic criteria include positive culture from mediastinal tissue or fluid, evidence of mediastinitis on gross anatomic or histopathological examination, and at least one of the following signs or symptoms: fever, chest pain, and sternal instability, with either purulent drainage from the mediastinal area or mediastinal widening on imaging.

The most common pathogens are *Staphylococcus spp* and *Enterobacteriaceae*, and fungal pathogens are extremely rare, predominantly *Candida spp*. Nevertheless, invasive aspergillosis is an emerging entity in non-immunocompromised patients, especially after major cardiovascular and ophthalmological surgeries.[1] In the literature, postoperative Aspergillus mediastinitis has been reported in only 16 cases, including six in immunocompromised patients after heart transplantation and 10 in immunocompetent patients (Table 1 [8–19]). The diagnosis is often delayed and has relied on direct visualization and culture until recently. Although galactomannan and beta-D-glucan tests are non-specific and cannot be used for diagnosis, they can be useful for monitoring fungal infections.[2]

Only two previous cases of postoperative Aspergillus mediastinitis in immunocompetent adults have had a favourable outcome. Interestingly, immunocompromised patients appear to have better outcomes (4/6 surviving) than immunocompetent patients (2/10 surviving), suggesting a delay in reaching a diagnosis and the need for earlier treatment. Although the patient presented here was not immunosuppressed in the traditional sense, it is well established that critically ill patients are prone to healthcare-associated infections due to transient immunosuppression following major surgery. Given the exceedingly poor outcomes of this type of infection, delineating the optimal medical therapy is crucial, regardless of the immune status.

In patients with a favourable outcome, antifungal therapy has consisted of voriconazole or amphotericin B monotherapy, with some cases in which caspofungin was added in combination. In the case presented here, liposomal amphotericin B was the first-line drug, analogous to the treatment of Aspergillus endocarditis, in which both liposomal amphotericin B and voriconazole are the therapeutic options.[3,4] As endocarditis was ruled out, voriconazole was selected due to its efficacy against *Aspergillus spp*.[3] However, persistently positive surgical drain fungal cultures led to the coverage being reinforced with caspofungin. Indeed, caspofungin was chosen as adjuvant therapy because of the presence of a mechanical cardiac valve and the effect of caspofungin on biofilms,[5] although the requirement for an antifungal combination is not proven. While long-term treatment with oral voriconazole is recommended in Aspergillus endocarditis, the treatment duration in the present patient was relatively short because of the lack of signs of recurrence. The short and long-term follow-up confirmed the effectiveness of this strategy. However, further studies are needed to better determine the optimal treatment duration and choice of antifungal therapy, since the currently available data are restricted to isolated reports.

In this patient, the maintenance of chest opening for over 2 weeks appeared to be the most probable entry site of infection, despite the latex patch applied to the sternal wound. Contamination of the surgical site by airborne spores may also have been favoured by air-mixing due to the external fan. Neither the high-efficiency particulate air-filtering systems nor the areas adjacent to the cardiac surgery ward seemed to have contributed to this contamination. Invasive Aspergillus outbreaks, however, have been described after cardiac surgery due to high levels of airborne Aspergillus spores. In addition, the severity of organ dysfunction, reflected by the need for prolonged ECLS and mechanical ventilation, has been found to be a risk factor for aspergillosis.[6] Transient immunodeficiency after major cardiac surgery and early re-operation for cardiac tamponade may also have contributed to the onset of Aspergillus mediastinitis. Although broad-spectrum antibiotic therapy has been identified as a risk factor for Candida infection, this is not a risk factor for invasive aspergillosis.[7]

In summary, the clinical features of postoperative Aspergillus mediastinitis may be paucisymptomatic, emphasizing the need for a low index of suspicion in cases of culture-negative mediastinitis or in indolent wound infections with no other bacterial growth. Besides surgical debridement, guidelines for optimal therapy are needed. Based on the few favourable outcomes, the central component of antifungal therapy should include amphotericin B or voriconazole.

Ethical approval: No ethical approval was required.

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