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Case Report
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Mycotic Aneurysm of the Ascending Aorta and *Aspergillus Fumigatus* Mediastinitis Early after Cardiac Transplantation

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Abstract

A 66-year old man after orthotopic heart transplantation developed severe infection with *Aspergillus fumigates* covering the entire thoracic cavity with a thick fungal turf. Repeated surgical removal of infectious and necrotic tissue together with innovative topical treatment using voriconazole and chlorhexidine combined with systemic antifungal treatment lead to elimination of the infection. Definite wound closure was achieved by latissimus dorsi muscle flap plasty and standard sterna refixation. To the best of our knowledge, we report the first survival of extensive *A.fumigatus* mediastinitis after heart transplantation due to repeated debridement in combination with novel topical application of antifungal agents.

Keywords: *Aspergillus fumigatus*; Fungal Infection; Heart transplant; Immunosuppression; Mediastinitis; Mycotic aneurysm; Topical treatment; Chlorhexidine; Voriconazole

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Background

Despite treatment options with antifungal drugs and surgery, *Aspergillus* mediastinitis is generally fatal, particularly in immunocompromised patients following orthotopic heart transplantation (OHT), which is associated with the highest risk of postoperative mediastinitis among all cardiothoracic procedures [1,2].

Herein, we describe a patient with early postoperative invasive *A.fumigatus* infection, who was referred with complete sternal dehiscence 43 days after OHT. In this situation, usual surgical debridement and intravenous antifungal treatment were thought to be hopeless due to the massive degree of *Aspergillus* dissemination carrying a mortality rate between 90 and 100% in immunosuppressed patients [1,3]. However, using a combination of innovative surgical and topical antifungal treatment the patient could be cured from this usually fatal complication.

Case Presentation

A 66-year old male patient underwent OHT due to a long-standing history of ischemic heart disease: acute anterior myocardial infarction in 1991; onset of ischemic heart failure in 1993; coronary artery bypass grafting and left ventricular aneurysmectomy in 1994; recurrent myocardial infarctions until 2000; heart failure with a left ventricular ejection fraction of 10% despite repeated percutaneous coronary interventions until 2010; radiofrequency ablation, cardiac resynchronisation, MitraClip procedure, hemofiltration and levosimendan infusions in 2011; finally, in June 2012, installation of an intra-aortic balloon pump and extended cardiac life support with extracorporeal circulation to successfully bridge the patient to a left ventricular assist device (HeartWare®). After full recovery, OHT was performed in July 2013. Basiliximab was administered as inductive immunosuppression, followed by maintenance immunosuppression consisting of tacrolimus, mycophenolat mofetil and prednisone. Co-morbidities included chronic gastritis, amiodarone-induced subclinical hypothyroidism, type-II diabetes mellitus, kidney cysts and chronic prostatitis, which all were well

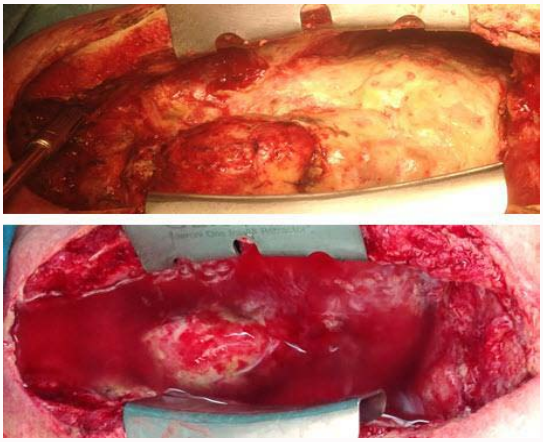

Figure 1: Entire thoracic cavity and heart surface covered with *Aspergillus turf*. Topical application of Chlorhexidin and Voriconazol solution into thoracic cavity.

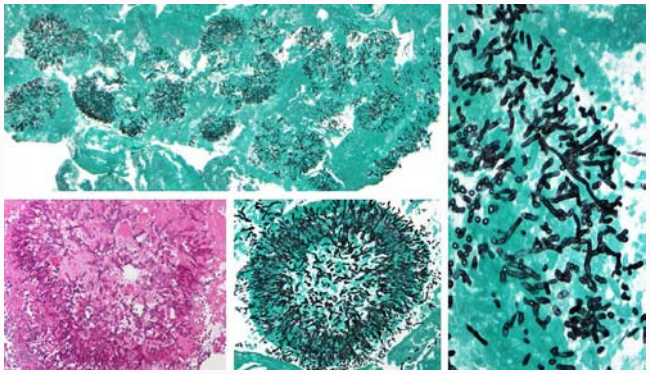

Figure 2: Grocott and HE stain showing fungus ball in the fibrinous tissue taken from the sternum, heart surface, pleura and aorta with septated hypae typical for *Aspergillus fumigatus*.

controlled. The post-transplant period was complicated by bilateral exsudative pleuritis, thrombosis of internal jugular vein, neutropenia and persistent sinus bradyarrhythmia with implantation of a two-chamber pacemaker using the left cephalic vein.

Thirty-seven days after OHT, progressive infection of the median sternotomy wound with a grayish-yellow discharge was noted starting at the epigastrium and resulting in complete skin necrosis and wound dehiscence with direct view on the transplanted heart. However no microorganisms were identified. CT-scan reported pneumomediastinum and a left-sided sero-pneumothorax of 300ml at the site of the previous LVAD, compressing the fibrotic left lower lung lobe.

The patient was referred to our clinic 43 days after OHT pre-treated with meropenem, vancomycin, linezolid, tigecycline, fluconazole and voriconazole. At clinical examination, the fully awake and neurologically normal patient was breathing spontaneously but presented in poor general condition, malnourished (serum albumin 16 g/L) and with renal insufficiency (creatinine 150 µmol/l).

Surgical inspection revealed thick and pervasive, green-yellow membranes covering the entire heart, great vessels, diaphragm, both lungs as well as the entire chest wall (Figure 1). The turf also covered the contained rupture of aorto-aortic anastomosis and the previously constructed end-to-side anastomosis of the LVAD arterial return to the distal native ascending aorta.

Residual parts of the vascular prosthesis were removed. There was imminent rupture of the aorto-aortic anastomosis due to mycotic infection of the native and transplanted ascending aorta, both with positive cultures for *Aspergillus fumigatus*. The aorto-aortic anastomosis was resected including a large proximal segment of the native as well as a large distal segment of the transplanted ascending aorta, which was easily possible due to the excessive length of the entire aorta. Extensive debridement of all anatomical structures of the thoracic cavity was performed and a vacuum-assisted closure dressing (VAC) was applied.

Histopathological examination (Figure 2), cultures as well as sequencing of all specimens including pleural fluid uniformly revealed *A.fumigatus*. Galactomannan test was positive (EIA index 0.1), but bacterial fungal as well as blood cultures revealed no other microorganisms. CT-scan revealed no other organ involvement by invasive aspergillosis.

In lack of a literature report on any similar case with such extensive *Aspergillus* mediastinitis we empirically decided to pursue the following empirical treatment: surgical wound re-opening every third day, sharp and blunt mechanical scrubbing and cleaning of the fungal turf, topical application of voriconazole and chlorhexidine 2%, 20-fold diluted (resulting in chlorhexidine 0.01%), dunking the entire thoracic cavity for 40 min with each drug (Figure 3) and an open chest treatment with VAC between the re-explorations. Pre-emptive systemic antifungal therapy with a combination of caspofungin and voriconazole was started. Following susceptibility testing and determination of minimal inhibitory concentration (MIC 0.125 mg/l), voriconazole was continued at a serum concentration of 4 mg/l - 6 mg/l. The immunosuppressive regimen was tailored and potential organ rejection surveyed by echocardiography. Debridement and topical therapy was performed a total of eight times. As by visible affection of the sternal bone tissue, 5 mm of each sternal side was removed, histopathology confirming *A.fumigatus*.

After the fourth surgical session, consistent with marked visible decrease of the fungal turf overspreading the mediastinal organs, repeated microscopic and microbiological examinations were found to be sterile with regard to *A.fumigatus*. However, colonization with multi-drug resistant *Acinetobacter baumannii* susceptible only to polymyxin B (MIC 0.5 mg/l) was detected in the sixth session. Hence, a diluted colistin-solution was applied topically to the thoracic cavity and infected structures and colistin was administered intravenously for one week. The postoperative course between each surgical session was uneventful the patient remaining isolated but fully mobilized on the regular ward.

After eight surgical revisions revealing clean intrathoracic tissues and negative microbiological findings with respect to *A.fumigatus*, definite wound closure was achieved 26 days after the first revision with a latissimus dorsi muscle flap plasty to fill the persistent left-sided thoracic cavity. Sternal refixation and wound closure were performed according to our infection-prevention protocol (sternal wound irrigation with vancomycin wax and gentamycin solution). Careful reversal of immunosuppression allowed a stable cardiovascular course without any signs of rejection checked by repeated endomyocardial biopsy and echocardiography. The patient was discharged well 47 days after first surgical intervention with uneventful postoperative recovery and wound healing. Oral voriconazole with regular monitoring of liver function was continued for 12 months, cardiac

medication and immunosuppression are continued corresponding to state-of-the-art. One year after wound closure, no findings suspicious for persistent or recurrent fungal infection on chest X-ray and CT-scan and negative serum galactomannan were reported. The patient is in excellent condition with good functional capacity, normal biventricular function, normal coronary angiography and no signs of cardiac rejection.

Discussion

Mediastinitis is a rare but severe complication of heart transplantation, occurring in 1% to 10% of cases with Staphylococcus spp. and Enterobacter spp. As the most common pathogens [4]. Our patient presented with two rare pathogens of mediastinitis namely *Aspergillus fumigatus* and *Acinetobacter baumannii*.

Aspergillus has been recognized as a major opportunistic pathogen and accounts for the most common mycoses in cardiac transplant recipients [1]. Diagnosis can be challenged by discriminating colonization from invasive infection and because strains morphologically identified as putative *A.fumigatus* are recognized as different species by molecular methods with decreased antifungal susceptibility [5]. This may lead to a delay of targeted treatment resulting in an excessive mortality. Despite negative blood cultures in the current patient, invasive infection could be documented by numerous intraoperative specimens from the sternum, native and transplanted aorta including anastomosis, all intrathoracic organs and the thoracic wall, which uniformly showed the characteristic hyphae consistent with *Aspergillus* on microscopic examination, positive serum galactomannan test and the presence of *A.fumigatus* was documented by culture and sequencing. Hence, a diagnosis of invasive aspergillosis could be made in accordance with the definition of the US Centres for Disease Control [6].

A.fumigatus mediastinitis in our patient occurred within the usual time period of onset of invasive aspergillosis reported to be between 36 and 52 days post transplantation [1]. Besides recent cardiac transplantation, the current patient presented with previously reported risk factors for the development of fungal infections such as early postoperative wound problems, renal failure, administration of multiple antibiotics, ventricular assist device before surgery, as well as severe malnutrition and diabetes mellitus [1,3].

Given the unique extent of the disease, the basic principle of therapy [6], i.e. intravenous antifungal treatment, tapering of immunosuppression and surgical re-exploration alone was not thought to be sufficient. With regards to the pathology of invasive aspergillosis resulting in infarction and necrosis of affected organs and poor drug delivery to tissue, our treatment regime was based on the conviction of the necessity to clean large surfaces without blood supply from thick layers of fungal material not only mechanically but also with local antiseptics.

Eventually, a combination of repeated debridements with an open chest treatment, cavity baths with aqueous voriconazole and chlorhexidine, in addition to intravenous administration of voriconazole and caspofungin and lastly a chest wall reconstruction by a muscle flap plasty were necessary and lead to successful recovery of this life-threatening disease.

A combined systemic antifungal therapy was started with caspofungin and voriconazole, the latter guided by testing susceptibility and serum concentration. Voriconazole, a triazole with activity against yeasts and molds including *Aspergillus spp.* [7] performed superior when compared with amphotericin B, and is now recommended as primary treatment of invasive aspergillosis including its uncommon manifestations such as mediastinitis and osteomyelitis [6,8]. Voriconazole was administered systemically in the only two reported surviving cases of *Aspergillus* mediastinitis after OHT [2,4]. Monitoring of its serum levels is recommended in transplanted patients because of impaired renal function and significant interactions with cyclosporine, tacrolimus and sirolimus [1,6]. In the current case, oral voriconazole was continued for 12 months to prevent relapse of infection, which has been reported to occur several months after seemingly successful treatment. The role of combined primary or salvage antifungal therapy is uncertain and warrants a prospective, controlled clinical trial [6].

The use of topical voriconazole in addition to its intravenous administration has recently been found to be effective in cases of *Aspergillus keratitis* and endophtalmitis when administered intravitreally [9-11]. Biocidal activity of chlorhexidine against *A.fumigatus* was reported when applied topically at a concentration of 0.06% for 30 min to 60 min and its stable and lasting adherence on human tissue without being absorbed [12]. In addition, effectiveness of topical chlorhexidine has also been shown in the treatment of fungal keratitis without any adverse effects [13]. Based on this data, we decided to use chlorhexidine in the same way as the voriconazole solution as local antifungal treatment.

After the fourth surgical session, examinations revealed a sterile condition with respect to *A.fumigatus*. However, a super infection with a multi-drug resistant *A.baumannii* was reported. Mediastinits due to *A.baumannii* is rare, with only two reported cases in immunocompetent subjects, successfully treated with ampicillin-sulbactam and a pan-resistant type with tigecycline. [14,15] Notably, only one case of multi-drug resistant *A.baumannii* in sternal wound after OHT has been reported. Favourable outcome was achieved with extensive debridement, systemic colistin and minocycline as well as wound irrigation with 5% chlorhexidine and VAC dressing [16]. Safe and effective topical use of colistin 0.19% has been reported in the treatment of corneal infection by multi-drug resistant Pseudomonas aeruginosa [17]. Hence, we used diluted colistin as described above in combination with intravenous colistin. Lastly, after the completion of topical antimicrobial therapy, the insertion of a latissimus dorsi muscle flap into the thoracic cavity and complete closure of the sternum resulted in a restitutio ad integrum.

Conclusion

Our case report proves that invasive *A.fumigatus* infection, yet accompanied by a super infection with a multi-drug resistant *A.baumannii* can be eliminated with aggressive combined surgical, topical and systemic drug treatment even in an immunocompromised patient.

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