

## Endobronchial fusariosis in a child following bilateral lung transplant

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### ARTICLE INFO

#### Keywords:

Endobronchial  
Fusariosis  
Lung transplantation  
Nebulized amphotericin  
Pediatric

### ABSTRACT

We present a case of endobronchial fusariosis following bilateral sequential lung transplantation for idiopathic pulmonary arterial hypertension in a 13 years old boy who was treated successfully with posaconazole and nebulized amphotericin B. We discuss the role of nebulized amphotericin B in treating invasive pulmonary fungal disease in children. To our knowledge, this is the first pediatric case of endobronchial fusariosis reported in the literature.

### 1. Introduction

Invasive fungal disease (IFD) causes significant morbidity and mortality in the lung transplant population; however, the epidemiologic data in children have been sparse with a variable prevalence reported as ranging from 0% to 20%. *Aspergillus* and *Candida* infections are the most common infections in children following lung transplantation. Endobronchial fusariosis is very rare. To our knowledge, this is the first pediatric case of endobronchial fusariosis reported in the literature.

### 2. Case

A 13 year old boy underwent bilateral sequential lung transplantation in July 2016 for idiopathic pulmonary arterial hypertension diagnosed 2 years earlier. At routine surveillance bronchoscopy few weeks post-transplantation, *Aspergillus* species was grown from a bronchoalveolar lavage (BAL) sample. There was no evidence of radiological or endobronchial changes and treatment with posaconazole modified release tablet was started as a prophylaxis (100 mg daily). Routine post-transplant immunosuppression regimen included tacrolimus (2 mg daily), mycophenolate mofetil (MMF) (250 mg twice daily)

and prednisolone (0.3 mg/kg daily). Post-transplantation course was also complicated by steroid-induced diabetes mellitus (DM), stenosis of left main bronchial anastomosis and drug-induced neutropenia likely related to trimethoprim-sulphamethoxazole, and valganciclovir administered for *Pneumocystis jirovecii* and cytomegalovirus (CMV) prophylaxis, respectively. CMV reactivation eight-month post-transplantation (while on valganciclovir) was treated with two weeks of intravenous ganciclovir (5 mg/kg bd) and then valganciclovir (450 mg daily) as maintenance therapy.

A surveillance bronchoscopy one month later (nine months post-lung transplantation) revealed white plaques at the left main bronchus anastomotic site and this was defined as day 0. (Fig. 1) Broncho-alveolar lavage (BAL) washings revealed fungal elements on cytology and *Fusarium* species grew on Sabouraud agar. Clinically, the patient was asymptomatic but severely neutropenic (count of  $0.0 \times 10^9/L$ ). His trough posaconazole level was 0.91 mg/L. Given the risk of anastomotic breakdown and consequent disseminated fusariosis in a severely neutropenic patient, we increased the posaconazole dose to 300 mg daily whilst awaiting antifungal susceptibility results. We aimed for a trough level of posaconazole of  $> 2$  mg/L. The patient was also commenced on daily granulocyte-colony stimulating factor (G-CSF) and trimethoprim-

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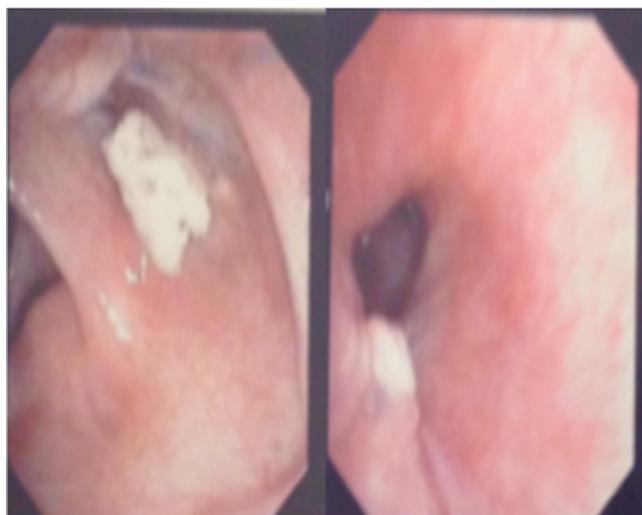
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<https://doi.org/10.1016/j.mmcr.2019.01.002>

Received 7 November 2018; Received in revised form 8 January 2019; Accepted 11 January 2019

Available online 14 January 2019

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**Fig. 1.** Photo of the endo-bronchial white plaque seen at the lower left lobe anastomotic site during a surveillance bronchoscopy.

sulphamethoxazole was changed to atovaquone/proguanil to reverse the neutropenia. Histopathology revealed changes suggestive of early rejection (A1B1), so we were unable to reduce the immunosuppression any further. The isolate was later identified as *Fusarium mundagarra* using DNA sequencing (Plant Pathology Unit, Royal Botanic Gardens Sydney). Drug susceptibility testing was performed using Sensititre™ YeastOne™ (CLSI-compatible) at the Mycology Reference Laboratory at the Royal North Shore Hospital, New South Wales, Australia and showed minimum inhibitory concentrations of 1 mg/L for amphotericin B, posaconazole and voriconazole,  $\geq 8$  mg/L for the echinocandin class.

Five weeks later, the patient remained asymptomatic, had stable lung function, was mildly neutropenic ( $0.8 \times 10^9/L$ ) and his posaconazole trough level was 2.3 mg/L. His chest computed tomography (CT) demonstrated progressive focal stenosis of the distal left main-stem bronchial anastomotic site. There were no features suggestive of lung parenchymal fungal disease and blood cultures remained sterile. Follow-up bronchoscopy demonstrated persistent white plaques at the anastomotic site; but now there was also evidence of bleeding from the friable endobronchial surface and displacement of the staple/suture suggestive of some anastomotic dehiscence. A trans-bronchial biopsy yielded inadequate tissue to assess for fungal invasion. *Fusarium mundagarra* grew again from BAL sample and the antifungal susceptibility testing showed increased MICs; 8 mg/L to amphotericin B and 2 mg/L to both posaconazole and voriconazole. Given the progression of endobronchial disease, posaconazole dosing was increased to 500 mg daily to achieve a target area under the concentration-time curve over MIC (AUC/MIC) ratio of  $> 100$  (trough level  $> 3.8$  mg/L) and nebulized liposomal amphotericin B (Ambisome) 25 mg thrice weekly was added. The patient initially developed cough and bronchospasm with nebulized liposomal amphotericin B; however, this was successfully managed with salbutamol pre-treatment. Whilst *Fusarium mundagarra* was grown again from a BAL sample taken two months post-commencement of dual antifungal therapy; subsequent BAL samples were culture negative at the 5 and 8 month mark. Eight months from commencing nebulized amphotericin B and increased posaconazole dose the surveillance bronchoscopy showed no evidence of white plaques and the anastomotic site looked healthy. In addition, his neutrophil count had recovered to  $> 1.0 \times 10^9/L$  three months post commencement of G-CSF and so the dose was reduced to thrice weekly. Seventh month post commencement of G-CSF the patient was able to maintain a neutrophil count above  $2 \times 10^9/L$ , and so the G-CSF ceased. He is being monitored closely for potential recrudescence and is continuing on the same antifungal regimen indefinitely. His progress is summarised in

**Fig. 2.**

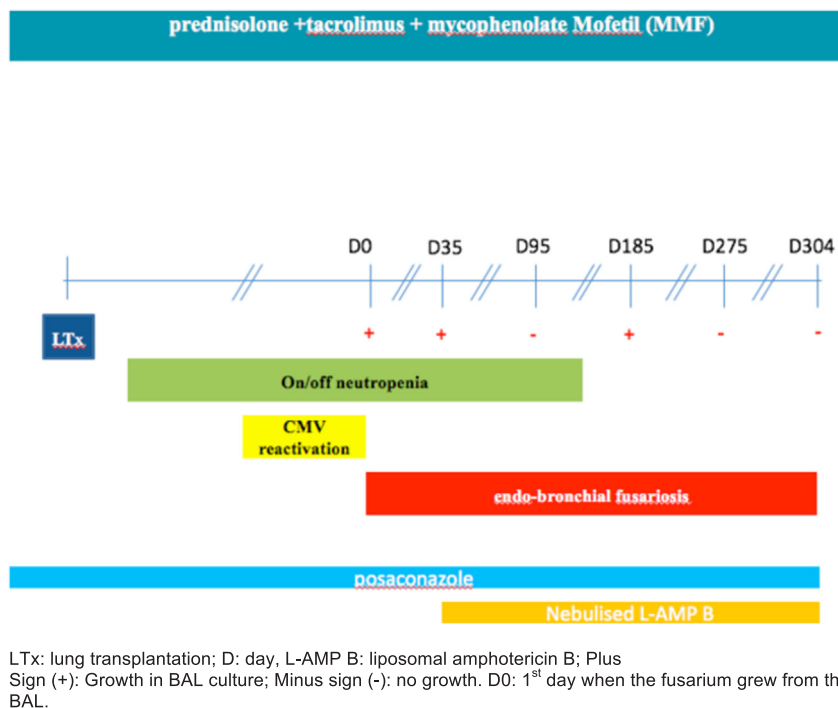
### 3. Discussion

Invasive fungal disease (IFD) causes significant morbidity and mortality in the lung transplant population; however, the epidemiologic data in children have been sparse with a variable prevalence reported as ranging from 0% to 20% [1]. *Aspergillus* and *Candida* species are the most common causes of IFD in this setting; however, endobronchial fusariosis following lung transplantation has rarely been reported [1,2]. There are only 10 cases of endobronchial fusariosis reported in the adult lung transplant population with a 70% mortality rate [2,3]. Here, we present the first pediatric case of endobronchial fusariosis that was successfully eradicated. Disseminated fusariosis usually occurs in immunocompromised patients with severe and persistent neutropenia; however, one third (3/10) of the reported adult cases of endobronchial fusariosis post lung-transplantation developed disseminated fusariosis in the setting of normal neutrophil counts [2]. Overall, outcome of fusariosis in immunocompromised patients appears proportional to the ongoing level of immunosuppression [4]. Factors that have been associated with increased mortality include disseminated infection, persistent neutropenia and corticosteroid use [2,4].

*Fusarium mundagarra* is one of six novel species of *Fusarium* isolated from natural ecosystems in Australia in the last few years. Carnarvon Gorge is the geographic origin of the first recognized isolate in central Queensland, Australia. It is considered as a part of the *Fusarium redolens* species complex [5]. There are no clinical antifungal breakpoints or epidemiological cut-off values to guide therapy for this species [6].

Management of fusariosis in immunocompromised patients can be challenging given the intrinsic resistance of *Fusarium* species to most antifungal agents [4]. *In vitro* susceptibility testing has shown intrinsic resistance to fluconazole, itraconazole and the echinocandin class, while susceptibility to amphotericin B, voriconazole and posaconazole is unpredictable [4]. Despite the early diagnosis, invasive fusariosis is associated with high morbidity and up to 70% mortality [4]. There are no comparative studies to compare clinical efficacy with the *in vitro* susceptibility of different antifungal agents for treatment of *Fusarium* species. The current recommendations in lung transplant recipients are voriconazole or liposomal amphotericin B as first-line therapy and posaconazole for refractory disease [2,4]. Antifungal combination for fusariosis has not been evaluated either in animal models or in humans [4]. From first principles, antifungal therapy should be combined with surgical resection where possible and reduction of immunosuppression when possible [4]. Antifungal choice should take into account the known characteristics of the fungal isolate, *in vitro* susceptibility results and host-specific factors [4]. Our patient was on posaconazole for *Aspergillus* colonization and he was tolerating it very well. We optimized the dose of posaconazole according to the AUC/MIC ratio to maximize time dependent killing. *In vitro* and *In vivo* modelling studies have indicated that the AUC/MIC is the pharmacokinetic/dynamic target for posaconazole treatment response; however studies looking at this relationship is limited to *Aspergillus* and *Mucorales* infections where the target is defined as  $> 100$  [7,8]. Nebulized liposomal amphotericin B (Ambisome) was added when the patient didn't show any signs of improvement. His tacrolimus dose was reduced when possible, and G-CSF was given to reverse the severe neutropenia.

There is convincing evidence for using nebulized amphotericin B for IFD prophylaxis in adult lung transplant recipients but very little evidence for its use for IFD treatment [1,9,10]. A 10 year observational study showed significant reduction of *Aspergillus species* colonization and infection among lung-transplant recipients receiving prophylactic nebulized liposomal amphotericin B [9]. Several comparative studies showed no significant differences between deoxycholate and lipid formulation of amphotericin in reducing the incidence of IA, when used as single agents [10,11]. Although it has been a widely studied agent for antifungal prophylaxis, the optimal dosages, formulations, and duration



**Fig. 2.** Summary of the patient BAL cultures and the antifungal agents used for treatment during the course of his disease. LTx: lung transplantation; D: day, L-AMP B: liposomal amphotericin B; Plus Sign (+): Growth in BAL culture; Minus sign (-): no growth. D0: 1<sup>st</sup> day when the fusarium grew from the BAL.

of therapy remains undetermined [10]. Studies using daily administration of amphotericin B products for short durations (up to 2 weeks) followed weekly or fortnightly for 1–3 months have generally proved to be successful as prophylaxis [10]. Studies showed that inhaled deoxycholate (conventional) amphotericin B achieves high concentrations in the lower airway of transplanted lungs, but concentration at the anastomotic sites and in the native lung are lower [10]. The concentration of inhaled amphotericin B (in BAL aliquots) and amphotericin B lipid complex (measured in epithelial lining fluid) remained above the generally reported MIC of *Aspergillus* for at least 7 days which enables once-weekly administration [10,12].

The limitation of this route of administration is that it does not protect against extra-pulmonary infections, especially early post-operative pleural space infection with *Candida* species. In addition, emerging species with reduced amphotericin susceptibility in lung transplant recipients on lifetime nebulized amphotericin B prophylaxis has been reported [9]. Systemic absorption of nebulized amphotericin B is minimal and quite safe compared with systemic antifungal therapy; however, it can cause cough, dyspnea, bronchospasm, wheezing and nausea in a small proportion which may affect compliance [10,12]. A recent retrospective study comparing adverse events of the inhaled deoxycholate with lipid formulations of amphotericin B observed no difference in the rates of adverse events concluding that both the nebulized deoxycholate and lipid (Abelcet) amphotericin B can be safely used [13].

Although there has been increased use of nebulized amphotericin B (both deoxycholate and lipid formulations) in children for IFD prophylaxis in the lung-transplantation setting, there are still limited data on its efficacy and safety in children. An international multicenter survey of antifungal prophylaxis in pediatric lung transplantation reported that most centers use either voriconazole or nebulized amphotericin B as a mono-therapy for IFD prophylaxis [14]; however, the updated international guidelines [1] could not give any recommendations for effective, safe anti-fungal prophylaxis in children and no specific recommendations were made regarding nAmB given the absence of published data.

In regards to using nebulized amphotericin B for treatment of IFD in

lung transplant recipients, the updated guidelines from the International Society for Heart and Lung Transplantation for management of fungal infections recommend azole therapy, with therapeutic drug monitoring to ensure maximal efficacy, as a primary monotherapy for *Aspergillus* endobronchial fungal infections but did not give any specific recommendations for the addition of nebulized amphotericin B to the standard azole regimens for treatment of pulmonary fungal infections [1]. Evidence for an additive benefit of nebulized amphotericin B in the treatment of invasive aspergillosis is limited however; nebulized amphotericin B could be used in combination with systemic antifungal drugs, depending on the severity of IFD, or possibly in situations in which large cavitory lesions might render the penetration of systemic agents difficult [1]. There is a single case report of a complex airway infection involving an endobronchial prosthesis that was treated with a combination of systemic voriconazole and nebulized amphotericin [1]. There are not enough published data to give any specific recommendations for using nebulized amphotericin B in the treatment of IFD in children following lung transplantation [1].

Although our patient showed clinical improvement after adding nebulized liposomal amphotericin, we are not certain that adjunctive nebulized amphotericin contributed to bronchoscopic and microbiological cure above the optimal posaconazole therapy and reduced immunosuppression. It is also possible that *fusarium mundagarra* is a less virulent species compared to the more well-known *fusarium solani*. There is, however, an argument in our case that given the high rates of dissemination following endobronchial fusariosis in lung transplant recipients, nebulized amphotericin in addition to a systemic anti-fungal agent was at least able to contain the infection until some level of immune reconstitution could be achieved. This case suggests that adjunctive nebulized amphotericin should be considered in similar cases where there is slow response to or progress on systemic antifungal therapy.

In conclusion, *Fusarium* species are an important but uncommon pathogen post-lung transplantation with a potentially high mortality rate. Treatment is difficult because of high levels of intrinsic resistance of *Fusarium* species to many antifungal agents and reduction of immunosuppression is essential for achieving a good outcome.

Multicenter, observational studies and randomized trials are needed to ascertain the optimal prophylactic and therapeutic strategies for fungal infections in pediatric lung transplant recipients [10].

### Acknowledgements

The Mycology Reference Laboratory at the Royal North Shore Hospital who helped with identification of the clinical isolates and with the anti-fungal susceptibility.

### Conflict of interest

None to declare.

### Funding source

None.

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