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Case Report

Break-Through Invasive Pulmonary *Aspergillus* Infection in a Lung Transplant Recipient

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Abstract

Current available evidence is equivocal on the effectiveness of anti-fungal prophylaxis against development of invasive fungal infections in lung transplant recipients. We present the case of a lung transplant recipient with breakthrough invasive pulmonary *Aspergillus* infection despite being on targeted anti-fungal prophylaxis with isavuconazole in the setting of augmentation of immunosuppression for acute cellular rejection. Breakthrough invasive fungal infections are important to recognize as they are associated with significant morbidity and mortality risk. To our knowledge, our case is among the handful reports of breakthrough invasive *Aspergillus* infection in the lung transplant population while on isavuconazole, antifungal prophylaxis.

Keywords: *Case Report; Lung Transplant; Pulmonary Aspergillosis; Breakthrough Invasive Fungal Infections (b-IFI); Isavuconazole*

Abbreviations

LTR: Lung Transplant Recipient; IA: Invasive Aspergillosis; b-IFI: Breakthrough Invasive Fungal Infection; ISA: Isavuconazole; BAL: Bronchoalveolar Lavage; CMV: Cytomegalovirus

Background

Invasive and breakthrough fungal infections in lung transplant recipients are important to recognize and carry high mortality risk. Antifungal prophylaxis is employed in lung transplant recipients to prevent invasive fungal disease with isavuconazole being one of the approved agents for both prophylaxis and treatment. To our knowledge, our case is among the few reports of breakthrough invasive *Aspergillus* infection in the lung transplant population while on isavuconazole antifungal prophylaxis.

Objectives:

1. Describe the case of break through invasive *Aspergillus* infection in a lung transplant recipient receiving prophylaxis with isavuconazole.

2. Review the current antifungal prophylaxis strategies employed after lung transplant and the evidence to support their use.
3. Discuss possible explanations for mechanisms of breakthrough *Aspergillus* infections with isavuconazole use and possible strategies to mitigate risk.

Case Report

We present the case of a fifty-seven year old male recipient of a bilateral lung transplant for idiopathic pulmonary fibrosis presenting with a one-week history of dyspnea, low-grade fevers and productive cough. Patient was on a maintenance immunosuppression regimen of prednisone, tacrolimus and sirolimus after initial induction with alemtuzumab. Eight weeks prior to this current presentation he was treated with anti-thymocyte globulin (ATG) for allograft dysfunction due to persistent acute cellular rejection (A2B0). Infectious workup performed at that time including BAL fluid fungal culture and galactomannan (GM) were negative. He had no history of fungal colonization or infection prior to or after his transplant performed eighteen months ago. With a history of elevated transaminases due to non-alcoholic fatty liver disease, he was prescribed isavuconazole (ISA) as part of our centre's hybrid approach to anti-fungal prophylaxis in lung recipients receiving ATG.

Physical exam findings were notable for coarse breath sounds and expiratory wheezing worse on the left than the right. His spirometry showed decline in FEV1 by 16% compared to his effort a month prior. Further evaluation was conducted including a chest CT showing narrowing of the left main-stem bronchus and a nodular soft tissue mass near the anastomotic site measuring up to 10 mm (Figure 1). Bronchoscopy revealed an inflamed, friable mucosa with extrinsic compression of the left main-stem bronchus due to an endo-bronchial lesion adjacent to the anastomosis. Needle aspiration of the mass showed septate, acute-angle branching fungal hyphae (Figure 2).

The BAL fungal culture and biopsy culture both grew *Aspergillus fumigatus*. BAL fluid *Aspergillus* GM was 1.06. On susceptibility testing, the MIC for ISA was 2 µg/ml. The patient was diagnosed with breakthrough-Invasive pulmonary *Aspergillus* infection given the consis-

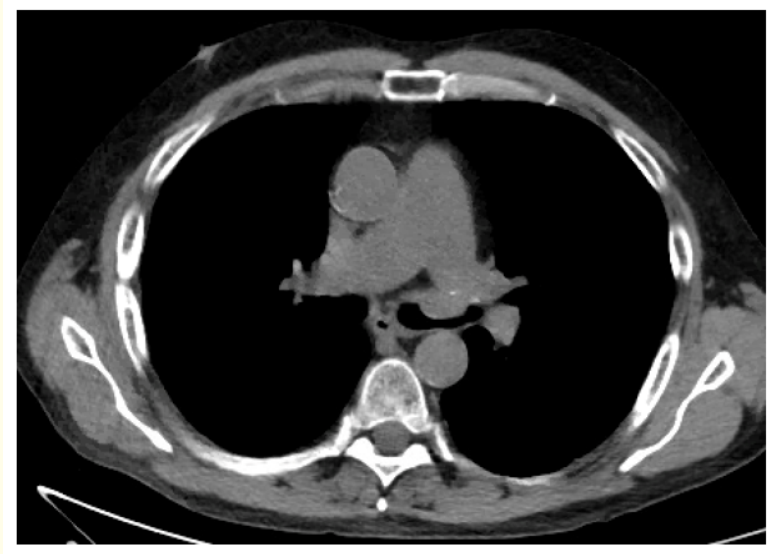

Figure 1: *CT image of a mass in the left main-stem bronchus.*

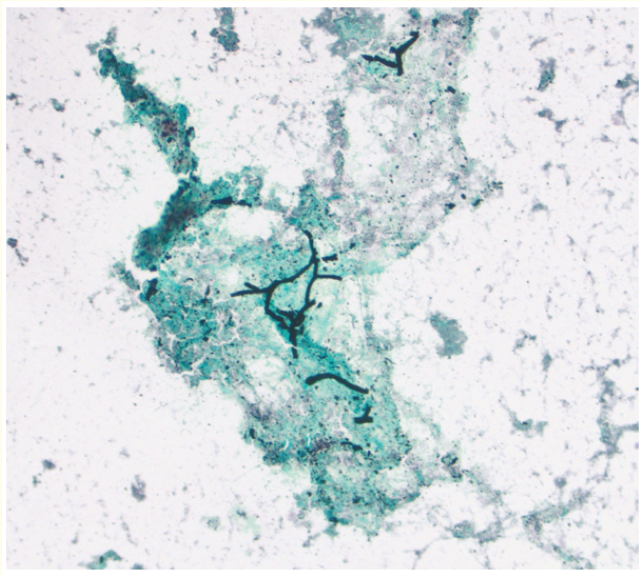

Figure 2: *Biopsy specimen showing fungal hyphae with acute-angle branching.*

tent clinical, histo-pathological, culture and radiographic findings. He was started on oral voriconazole with therapeutic drug monitoring and close monitoring of transaminases in combination with aerosolized liposomal amphotericin. He reported a gradual improvement in his dyspnea and cough. After twelve weeks of therapy, he exhibited improvement in lung function on spirometry. Follow-up bronchoscopy revealed resolution of the endo-bronchial mucosal abnormalities noted on initial exam and BAL *Aspergillus* GM was 0.42 with a negative fungal culture. Repeat chest imaging showed the peri-bronchial nodule to be less than 5 mm in size. Duration of treatment was extended with voriconazole as single-agent till complete resolution was seen after six months of effective therapy.

Discussion

The ISHLT classifies antifungal prophylaxis strategies in lung transplant recipients (LTR) as universal, targeted or pre-emptive; based on whether antifungal agents are offered to all, those with risk factors or those patients with fungal colonization. Current available evidence is equivocal on the value of anti-fungal prophylaxis against development of invasive fungal infections in lung transplant recipients [1,2]. Much of the support for post-lung transplant antifungal prophylaxis has been extrapolated from robust data from the hematopoietic stem-cell transplant and liver transplant populations. With lack of randomized control trial (RCT) data in the lung transplant population there is a variation in practice amongst lung transplant centers with respect to strategy, agents and duration of anti-fungal prophylaxis [3].

Invasive fungal infections are associated with high mortality risk and poor outcomes after lung transplantation [4]. Breakthrough invasive fungal infections (b-IFIs) are a feared complication in immunosuppressed patients on systemic antifungal therapy, as they carry an extremely poor prognosis with high reported mortality [5]. They are defined as invasive fungal infections occurring during exposure for at least seven days to antifungal therapy, with either a prophylactic or therapeutic intent [6-8]. Majority of reports on b-IFIs in the literature have been about patients with profound neutropenia from hematological malignancies and patients after hematopoietic stem cell transplant.

We describe the case of a LTR who developed breakthrough pulmonary invasive aspergillosis (IA) infection despite being on targeted ISA fungal prophylaxis in the setting of augmented immunosuppression for acute cellular rejection. ISA has been used for the treatment and prophylaxis of invasive molds, including *Aspergillus* and mucor. Despite its emergence as an alternative agent, with an attractive pharmacokinetic (PK) profile there are few reports of treatment failure for ISA or specific adverse outcomes in specific populations like LTRs.

In the lung transplant population, Baker., *et al*. presented their experience with non-candida breakthrough invasive fungal infections in 30 patients among 815 lung transplant recipients between 2007 and 2014. Their retrospective series included b-IFI with the use of voriconazole, micafungin, posaconazole and aerosolized amphotericin prophylaxis [9]. Of note, since these data of lung transplant patients came from 2007-2014, they were before the 2015 FDA approval of ISA. Samanta., *et al*. reported a 3% b-IFI incidence (10 cases) in three hundred lung transplant recipients receiving antifungal prophylaxis. Five patients developed b-IFI on prophylactic ISA, of whom four received therapeutic drug monitoring and had serum trough levels of 1.6 μg/ml or greater. The same number of patients on voriconazole prophylaxis developed b-IFI [10].

B-IFI maybe explained by decreased susceptibility of *Aspergillus* to anti-fungal agent or sub-therapeutic drug levels. For our patient, the ISA MIC was 2 μg/ml, and we did not perform drug-level monitoring while on ISA. Our experience with this patient brings to the forefront the lack of guidelines for the use of ISA MIC values and trough level monitoring in clinical practice given the absence of meaningful associations between these parameters and clinical outcomes [11]. The European Society for Clinical Microbiology and Infectious Disease does suggest ISA drug level monitoring in certain clinical situations, including treatment failure [12]. Being a relatively newer agent more clinical evidence is needed about the utility of ISA drug level monitoring in certain select populations like LTRs or clinical scenarios that do increase risk of altered PK like critical illness or need for extra-corporeal life support.

Conclusion

Caution is advised when there are changes in immunosuppression. Maintaining a high index of suspicion for invasive fungal infection, despite the use of antifungal therapy, can ensure prompt diagnosis and effective treatment.

Informed Consent

Written consent for publication was obtained from the patient's family prior to submission. Patient deceased at time of write-up/report.

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Authors' Contributions

MD: Involved in patient care, diagnostics, procedures, management decisions, reviewed and edited manuscript.

AS: Idea, Involved in patient care, diagnostics, procedures, management decisions, drafting and editing manuscript, submission, corresponding author.

Bibliography

1. Marinelli T., *et al*. "Antifungal prophylaxis in adult lung transplant recipients: Uncertainty despite 30 years of experience. A systematic review of the literature and network meta-analysis". *Transplant Infectious Disease* 24.3 (2022): e13832.

2. Pennington KM., *et al*. "Antifungal prophylaxis in lung transplant recipients: A systematic review and meta-analysis". *Transplant Infectious Disease* 22.4 (2020): e13333.

3. Pennington KM., *et al*. "Antifungal prophylaxis in lung transplant: A survey of United States' transplant centers". *Clinical Transplantation* 33.7 (2019): e13630.

4. Hosseini-Moghaddam SM., *et al*. "Incidence and outcomes of invasive fungal infection among solid organ transplant recipients: A population-based cohort study". *Transplant Infectious Disease* 22.2 (2020): e13250.

5. Fung M., *et al*. "Breakthrough Invasive Fungal Infections on Isavuconazole Prophylaxis and Treatment: What Is Happening in the Real-World Setting?" *Clinical Infectious Diseases* 67.7 (2018): 1142-1143.

6. Cornely OA., *et al*. "Defining breakthrough invasive fungal infection-Position paper of the mycoses study group education and research consortium and the European Confederation of Medical Mycology". *Mycoses* 62.9 (2019): 716-729.

7. De Pauw B., *et al*. "Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group". *Clinical Infectious Diseases* 46.12 (2008): 1813-1821.

8. Donnelly JP., *et al*. "Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium". *Clinical Infectious Diseases* 71.6 (2020): 1367-1376.

9. Baker AW., *et al*. "Invasive Fungal Infection After Lung Transplantation: Epidemiology in the Setting of Antifungal Prophylaxis". *Clinical Infectious Diseases* 70.1 (2020): 30-39.

10. Samanta P., *et al*. "Isavuconazole is as effective as and better tolerated than voriconazole for antifungal prophylaxis in lung transplant recipients". *Clinical Infectious Diseases* (2020).

11. Desai AV., *et al*. "Exposure-Response Relationships for Isavuconazole in Patients with Invasive Aspergillosis and Other Filamentous Fungi". *Antimicrobial Agents and Chemotherapy* 61.12 (2017).

12. Ullmann AJ., *et al*. "Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline". *Clinical Microbiology and Infection* 24.1 (2018): e1-e38.

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