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Case Report

Emergence of persistent *Aspergillus terreus* colonisation in a child with cystic fibrosis

Katie Dunne [a,b,c,1], Anna-Rose Prior [a,1], Kate Murphy [b], Niall Wall [a], Geraldine Leen [a], Thomas R. Rogers [c], Basil Elnazir [a], Peter Greally [a], Julie Renwick [a,b,*,2], Philip Murphy [a,b,2]

[a] The National Children's Hospital, Tallaght Hospital, Tallaght, Dublin 24, Ireland
[b] Department of Clinical Microbiology, Trinity Centre for Health Science, Tallaght hospital, Trinity College Dublin, Dublin 24, Ireland
[c] Department of Clinical Microbiology, Trinity College Dublin, St James's Hospital, Dublin 8, Ireland

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1. Introduction

Cystic Fibrosis (CF) is the most common inherited life shortening condition affecting Caucasians. CF is characterised by mutations in the CF transmembrane conductance regulator (CFTR) gene, which codes for an ATP-driven pump that transports sodium and chloride ions across epithelial surfaces [1]. CF is a multiple organ disease; however up to 95% of morbidity and mortality is due to pulmonary infection. The CF lung has impaired mucociliary clearance and a build-up of thick mucus which creates an ideal environment to facilitate microbial colonisation. Excessive neutrophil recruitment and enhanced inflammation ensue which causes airway epithelial cell damage, decline in lung function and eventual respiratory failure.

Isolation of filamentous fungi, in particular *Aspergillus spp.* is common in respiratory secretions from CF patients [2]. *Aspergillus terreus* is the third most common filamentous fungus isolated from CF adult airway samples, being detected in 1.9 to 6.2% of CF patients [3,4]. In our clinic, 3 of 159 paediatric CF patients tested were *A. terreus* positive which is in line with the published literature on adults with CF (unpublished data). *A. terreus* has been reported to cause ABPA [5,6], infective endocarditis [6], pulmonary mycetoma [6] and invasive aspergillosis (IA) [7]. Until recently *Aspergillus* species identification was not thought to be therapeutically important; however different species within the genus can exhibit varying levels of antifungal drug resistance [8] and virulence in *in vivo* infection models [9]. Invasive disease caused by *A. terreus* can be as severe as IA caused by *Apergillus fumigatus* however *A. terreus* is inherently resistant to Amphotericin B [10]. Additionally IA caused by *A. terreus* is associated with long-term persistence of conidia and liver degeneration [11]. For these reasons *A. terreus* has the potential to cause complications post-transplant for people with CF. Here we present a case of a child with CF with a polymicrobial community in the airways among which *A. terreus* emerged and persisted as a dominant species.

2. Case

A 10-year-old boy with advanced CF lung disease diagnosed at 10 weeks old presented with a decline in pulmonary function. He had significant clinical manifestations of his disease, including chronic colonisation/infection with *Pseudomonas aeruginosa* and *Staphylococcus aureus* for more than 6 years necessitating multiple courses of antibiotic therapy, as well as gastrointestinal manifestation resulting in a body mass index (BMI) below the 0.4th centile and the requirement for gastrostomy feeding. His forced

* Corresponding author: Department of Clinical Microbiology, Trinity Centre for Health Science, Tallaght hospital, Trinity College Dublin, Dublin 24, Ireland
[1] These authors contributed equally to this work.
[2] Joint senior author.

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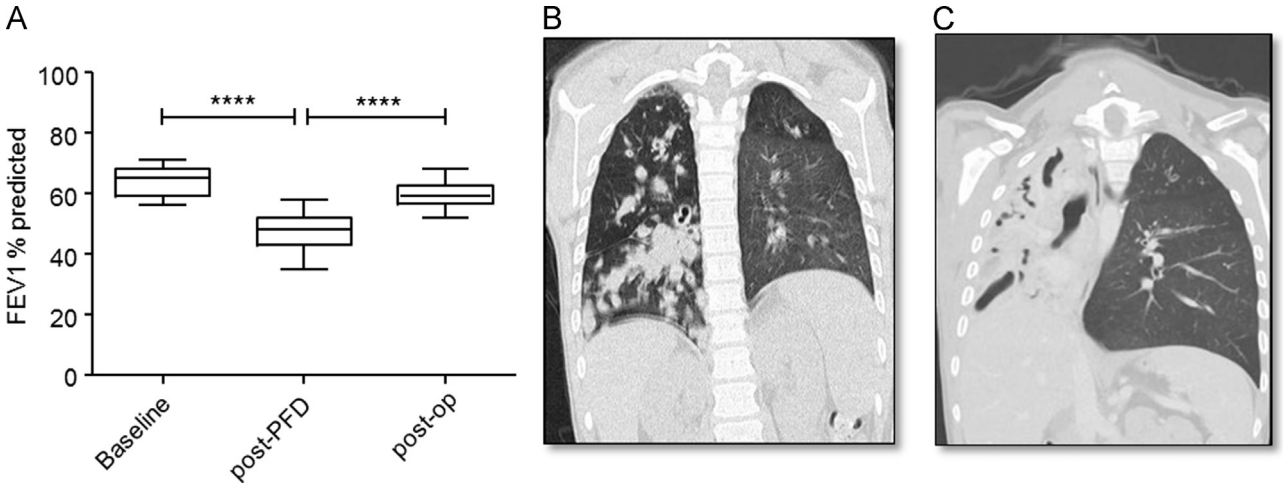

Fig. 1. Evidence of pulmonary function decline (A) Histogram depicting ranges of FEV_1 scores before initial decline in lung function (baseline), after pulmonary function decline (post-PFD) and post-pneumonectomy (post-op). Chest CT scan in month 19 (B) and in month 45 (C) revealed progressive obstruction of the right lung. $^{****}p < 0.0001$; 1-way ANOVA.

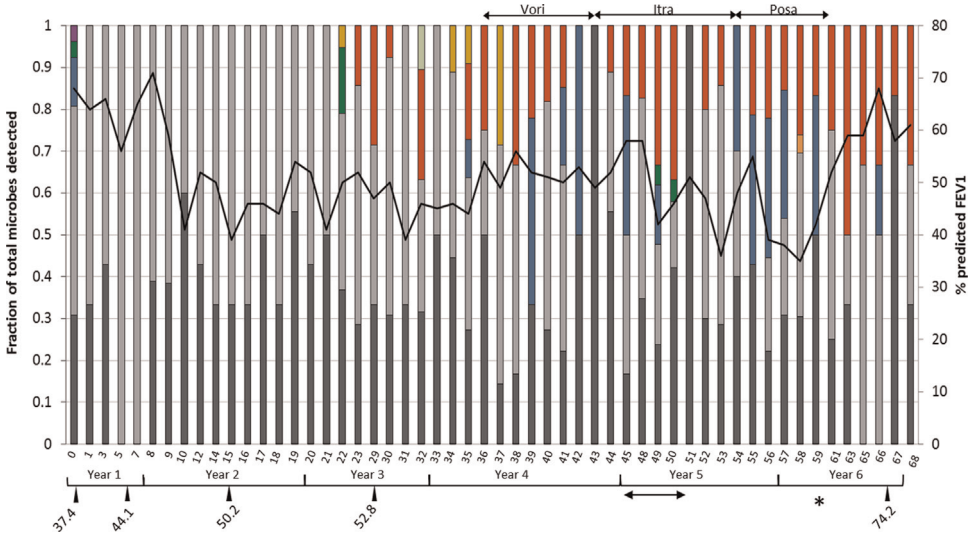

Fig. 2. Microbiological culture results and associated FEV_1 scores. A 100% stacked column histrogram presenting the microrganisms cultured from the patients airways as a fraction of the total microbial community detected by culture. *P. aeruginosa* (dark grey), *S. aureus* (light grey), *Stenotrophomonas* (blue), *A. fumigatus* (dark green), *Streptococcus pneumoniae* (purple), *Candida* (gold), *A. terreus* (red), *A. flavus* (light green) and *Escherichia coli* (orange) all colonised the airways of this patient. The secondary *y*-axis depicts the FEV_1 scores (black line) at the time of each sample collection over a six year period (*x*-axis represents months). The star (*) represents the time of right lung pneumonectomy. The doubled-ended arrow below the timeline shows the period of time that *A. terreus* was mis-identified as *P. variotii*. Periods of antifungal drug treatment are represented by doubled-ended arrows above the stacked columns; vori=voriconazole, itra=itraconazole, posa=posaconazole. Anti-*A. fumigatus* IgG levels (mg/L) are represented by drop-down arrows from the timeline. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

expiratory volume in 1 s (FEV_1) was found to have significantly declined between months 8 and 10 from a score of 56–71% predicted to a score of 35–58% predicted (1 way ANOVA; $p < 0.0001$) (Fig. 1A). This coincided with an anti-*A. fumigatus* IgG level (ImmunoCap) of 44.1 mg/L (above the 40 mg/L threshold [12]) (Fig. 2), high total IgG, high total IgA and high anti-*A. fumigatus* IgE levels (ImmunoCap) (Table S1). Ten months prior to pulmonary function decline (PFD), *A. fumigatus* was detected once by culture of patient sputum on malt extract agar (Fannin) and then once again thirteen months after PFD. Fourteen months after PFD *A. terreus* was detected by culture from sputum samples. The patient subsequently remained persistently colonised with *A. terreus* (Fig. 2) and only cultured *A. fumigatus* on 2 more occasions over the 68 months (Fig. 2). The patient also tested positive for *A. flavus* on one occasion in month 32. Following six consecutive isolations of *A. terreus* from the patient's sputa, treatment with voriconazole was commenced. Due to significant side effects, this was changed to itraconazole 7 months later, and after a further 11 months this was switched to posaconazole. Susceptibility of six of the *A. terreus* isolates to the azoles was measured using the TREK Sensititre YeastOne method. Isolates were classed as resistant (R), intermediate (I) or sensitive (S) to the azoles based on published epidemiological cutoff values (ECVs) (Table S2) [13]. Despite good *in vitro* susceptibility to the azoles, *A. terreus* was not eradicated during therapy. Of note sera levels of voriconazole, itraconazole and posaconazole ranged from 0.2–1.4 mg/L, 0.34–1.44 mg/L and 0.41–0.4 mg/L, respectively (reference ranges: >2 mg/L, >0.5 mg/L and 5–15 mg/L for voriconazole, itraconazole and posaconazole, respectively). The patient's lung function continued to worsen and radiological appearances declined (Fig. 1B and C).

Twenty-two months after *A. terreus* was first identified, a fungus with a different morphological appearance was cultured on malt extract agar. In contrast to the typical cinnamon brown colonies of *A. terreus* cultured in month 40 (Fig. 3A), this isolate had