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Radiological abnormalities associated with *Aspergillus* colonization in a cystic fibrosis population

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ABSTRACT

Objective: To determine if sputum colonization with *Aspergillus* species in patients with cystic fibrosis (PWCF) correlates with radiological abnormalities and/or a reduction in pulmonary function (FEV1).
Methods: We prospectively evaluated 32 PWCF utilizing high resolution computed tomography (HRCT) of the thorax and pulmonary function testing (PFT). The cohort was assessed as two groups: *Aspergillus* positive ($n = 16$) and *Aspergillus* negative ($n = 16$) based on sputum culture for *Aspergillus* species. A modified Bhalla scoring system was applied to each HRCT scan by two blinded radiologists.
Results: Aspergillus positive patients had more severe and significant bronchiectasis compared to those *Aspergillus* negative ($p < 0.05$). This was most marked in the right upper and lower lobes (RUL, RLL). Total Bhalla score was clinically significant in both groups and approached statistical significance between groups ($p = 0.063$). No difference in pulmonary function between the groups was detected.
Conclusion: PWCF colonized by *Aspergillus* species have greater radiological abnormalities undetectable by PFTs. Early radiological evaluation of *Aspergillus* colonized PWCF is therefore warranted.

1. Introduction

Cystic fibrosis (CF) is a multisystemic genetic disorder characterized by chronic airway infection, bronchiectasis, pancreatic insufficiency and gastrointestinal dysfunction [1]. Prevalence varies with ethnicity and Ireland has the highest incidence and carrier rate of CF worldwide [2]. Although median survival is variable, males have an unexplained survival advantage [1].

A significant number of PWCF can be affected by the fungus *Aspergillus fumigatus*, a saprotrophic organism found in soil and decaying organic matter. Capable of growth at varying temperatures and with ubiquitous spores, healthy individuals are able to eliminate the fungus while those immunocompromised can be more severely affected.

The pulmonary manifestations of *Aspergillus* include Aspergillomas, invasive Aspergillosis [3–5] or alternatively the organism acts as an allergen inducing a hypersensitivity reaction termed allergic bronchopulmonary aspergillosis (ABPA), a challenging diagnosis in CF [6,7].

Boucher reports that up to 50% of PWCF are colonized with *A. fumigatus* in sputum culture with 10% exhibiting ABPA [1]. In a recent and independently conducted study by our group, we prospectively assessed 50 PWCF for frequencies of *Aspergillus* species in sputum culture and *ABPA*. We found that 30% ($n = 15$) grew *Aspergillus* while 12% had *ABPA* [6] corroborating previous literature. Additionally, we detected that sputum culture did not correlate with the occurrence of ABPA [6].

It has additionally been shown that persistent *A. fumigatus* colonization is an independent risk factor for hospital admissions but not FEV1 decline in PWCF [8,9]. What remains unclear is the extent of radiological change observed in PWCF who are asymptomatically colonized with the fungus (fungal colonization without ABPA).

Computed tomography (CT) has become an important imaging modality in the evaluation of lung disease in patients with CF [10]. Although the last two decades have heralded dramatic improvements in the treatment of disease it has been recognized that PFTs alone may be insufficient in identifying the extent of mild to moderate disease. For this, we require a test that is both accessible and illustrates quantifiable disease severity within the lung parenchyma [11,12]. CT is potentially best placed complemen-

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tary to PFTs for the evaluation of CF associated pulmonary disease [13–15].

The objective of the current study was to determine if asymptomatic *Aspergillus* colonization in PWCF correlates with increased radiological abnormalities and/or is associated with a decline in pulmonary function.

2. Materials and methods

We prospectively evaluated 32 PWCF confirmed by sweat testing (Cl^- >60 mmol/L) and genotyping. Half ($n = 16$) of the cohort were colonized by *Aspergillus* spp. defined as at least two sputum cultures positive for *Aspergillus* spp. at least four weeks apart in the one year prior to study inclusion. All patients were exacerbation free for a six-week period prior to study participation and had no evidence of prior ABPA as defined by consensus conference criteria [16]. The *Aspergillus* colonized group was termed 'asymptomatically colonized' in the absence of any prior episodes of ABPA. For study purposes, we matched this group by age, sex and disease severity to a non-*Aspergillus* CF cohort ($n = 16$). This study was approved by our institutional review board.

All patients had a HRCT scan of the thorax and PFTs performed within one month of the scan date. Sputum was obtained for microbiological evaluation prior to scanning to confirm *Aspergillus* status. Prior to sampling, patients gargled with water and spontaneously expectorated sputum from a deep cough. Sputum was placed into a sterile container and transported to the laboratory. Suitability of sputum samples for study inclusion was confirmed by the presence of ≥10 polymorphonuclear leucocytes (PMN) and ≤25 squamous epithelial cells per low power field on microscopy. Sputum that fit these criteria were considered 'representative' of the airway and processed further.

Serum IgE levels were assessed in both patient groups and where patients were colonized with *Aspergillus* both RAST and serum precipitins specific for *Aspergillus* were evaluated.

HRCT images were obtained on a Siemens 16 slice scanner. All patients were imaged while supine and inspiratory images were obtained from the lung apices to the costophrenic angles. Scanning parameters were 120 kV and 90 mA. Images were reconstructed on mediastinal and lung windows.

A modified version of Bhalla's scoring system for thin section CT in patients with CF was applied to each scan [17,18]. We did not assess for generations of bronchial divisions involved with bronchiectasis/plugging but we did record if mediastinal lymphadenopathy or high attenuation mucus plugging was detected. Scans were reviewed by two radiologists, one with a specialist interest in thoracic radiology. Both radiologists were blinded to the patients *Aspergillus* status when scoring. CT studies were reviewed as described in Table 1.

All lobes were individually assessed for purposes of evaluating severity of bronchiectasis and peribronchial thickening.

Once scores were assigned to each of the parameters, the overall score was calculated by subtracting the patient's individual score from 22. Lower scores therefore indicate greater severity.

We also recorded the presence of mediastinal lymphadenopathy (recorded when one or more lymph nodes with a short axis diameter (SAD) of greater than 1.0 cm were detected).

We evaluated for mucus plug attenuation based on the degree of Hounsfield units within the detected plug. Mucus plugging was defined as tubular structures traced cephalad or caudad on adjacent scans confirming continuity with a bronchus [18].

CT scores were compared to pulmonary function data including percent predicted FEV_1 (forced expiratory volume at one second), FVC (forced vital capacity) and $FEF_{25-75\%}$ (forced expiratory flow between 25–75% of expired vital capacity) to identify any relationships. Of note, no patients from either group had an alteration to their *Aspergillus* colonization status for at least a one year period following the completion of the study.

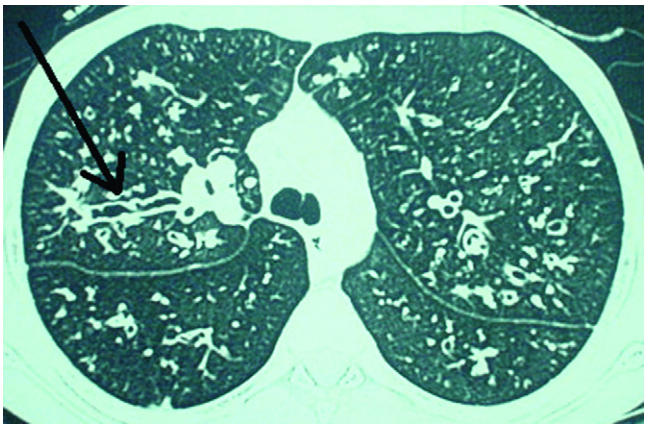

Fig. 1. Saccular bronchiectasis seen in the right upper lobe (denoted by arrow) with a score of 3 for severity of broncheictasis in the right upper lobe (lumen diameter > 3 times that of adjacent vessel diameter).

2.1. Statistical analysis

Descriptive analysis was performed for all variables based on *Aspergillus* colonization status. Continuous data were tested for normality (1-sample Kolmogorov–Smirnoff test). Means and standard deviations (SD) are presented for normally distributed variables and unpaired *t*-testing used to assess for differences between groups. For non-normal variables, medians are presented with inter-quartile ranges (IQR), the Mann–Whitney *U*-test performed when comparing the two groups. For categorical data (within the Bhalla scoring system), proportions are presented and chi-squared or Fischer exact testing performed as appropriate for comparisons between the two groups. All analyses were performed using SPSS (version 16.0) and considered significant at $p < 0.05$.

3. Results

Patients were evaluated in two groups: *Aspergillus* colonized and non-colonized. Demographics are summarized in Table 2. The total Bhalla score for the colonized group was 14.6 ± 1.9 (range 11–18) versus 16.1 ± 2.6 (range 11–21) for those non-colonized. The difference in the total Bhalla scores between the groups approached statistical significance ($p = 0.063$).

Lobar involvement: In total 192 lobes were assessed (96 per group). Bronchiectasis was detected in 96% ($n = 92$) of all lobes in the *Aspergillus* colonized group compared to 81% ($n = 78$) in the non-colonized group (p = ns).

Severity of bronchiectasis: The severity but not extent of bronchiectasis was significantly different between the groups with 75% demonstrating moderate to severe bronchiectasis in the colonized group compared to 56% in the non colonized group ($p < 0.05$, Figs. 1–3). Findings were most marked for the RUL ($p = 0.02$) and RLL ($p = 0.01$) and approached significance for the LUL and lingula (both $p = 0.09$). With regard to the extent of bronchiectasis – 9 or more bronchopulmonary segments were involved in 50% of the *Aspergillus* colonized compared to 31% of the non colonized group ($p = 0.09$).

Other parameters: No significant differences were detected between the groups for peribronchial thickening, extent of mucus plugging, sacculations and abscesses, presence of bullae, emphysema, collapse or consolidation (Fig. 4).