CLINICAL CASE REPORTS

The Role Of Fungi In Cystic Fibrosis: Actors Or Bystanders? - Two Cases Report

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ABSTRACT

Introduction: Fungal infections increasingly contribute to morbidity in patients with cystic fibrosis (CF). Despite their rising incidence, there is considerable controversy surrounding the treatment and eradication of these infections in CF.

Case presentation: We present two CF patients: the first patient was largely asymptomatic despite intermittent detection of *Scedosporium spp*, while the second case experienced frequent pulmonary exacerbations (PEx) with persistent detection of both *Aspergillus fumigatus* (*A. fumigatus)* and *Scedosporium spp*. Both patients showed improvement after initiating the modulator therapy. Case 1 achieved complete eradication of fungal colonization, while case 2 remained sensitized to *A. fumigatus* but experienced fewer fungal exacerbations.

Discussion: These case reports underscore the variable clinical significance of fungal infections in CF and highlight the ongoing uncertainty regarding their role in disease progression. Further research is essential to elucidate their impact on CF and develop more tailored treatment strategies.

Keywords: antifungal agents; cystic fibrosis; fungi; hypersensitivity; pulmonary aspergillosis

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INTRODUCTION

Cystic fibrosis (CF) is a genetic disorder that affects multiple organ systems, particularly the respiratory and digestive systems. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which lead to the production of abnormally thick and sticky mucus in the airways, pancreas, and other organs.[1] This mucus obstructs the airways and impairs the clearance of bacteria and other microorganisms, leading to recurrent infections and chronic inflammation in the lungs.

CF is the most common genetic disorder among Caucasians and its prevalence varies significantly according to the geographic location. The highest incidence was observed in individuals of Northern European descent. Globally, it is estimated that approximately 162,428 individuals [range: 144,606–186,620] are living with CF across 94 countries, of whom around 105,352 (65%) have been formally diagnosed.[2]

Despite significant advances in treatment and management, CF remains a life-limiting disease, with a median predicted survival age of approximately 40 years. The clinical course of CF can vary widely, and patients may experience a range of symptoms and complications including respiratory distress, malnutrition, pancreatic insufficiency, and diabetes.

The respiratory system is one of the most frequently implicated in CF, and chronic infections are major contributors to morbidity and mortality. The thick and sticky mucus that characterizes CF provides an ideal environment for bacteria and other microorganisms to grow and thrive, leading to recurrent respiratory infections. These infections trigger an exaggerated and prolonged inflammatory response in the airway, leading to tissue damage and scarring. Chronic inflammation and lung damage can lead to respiratory failure and other complications. The management of respiratory infections in CF is a key component of patient care and involves aggressive and targeted use of antibiotics, airway clearance techniques, and other therapies aimed at preventing or minimizing lung damage.

In recent years, fungal respiratory infections have emerged as significant contributors to the morbidity and disease progression in patients with CF. However, the extent of fungal infection in the airways remains unclear, and the prevalence and clinical significance of fungal communities in sputum are not well understood.[3,4] The complex pathogenesis involves a combination of genetic, environmental and microbiological factors, with thick CF mucus that promotes fungal colonization.[2] Additionally, the use of antibiotics and other CF therapies can disrupt the respiratory microbiome, further promoting fungal growth and exacerbating the underlying lung disease.

Despite the increasing incidence of fungal infections in CF, there is considerable controversy surrounding their treatment and eradication.[3] This is partly due to the lack of guidelines for managing fungal infections in this disease. Given the potential of these infections to exacerbate lung disease and worsen clinical outcomes, further research is needed to guide clinical practice and improve patient care. In this report, we present two pediatric CF cases of fungal infections and discuss their clinical implications and management strategies.

Case 1

Presentation: A six-year-old girl presented to the pediatric pulmonology consultation with four episodes of pneumonia over four years, each requiring antibiotic treatment and poor weight gain since twelve months of age. Despite treatment with inhaled corticosteroids and antihistamines, the patient continued to suffer from a persistent, productive cough that was non-seasonal. Additionally, she reported frequent mucus passage in her stools, although steatorrhea was not observed. Family history was unremarkable.

Upon physical examination, the patient presented with a thoracic deformity, digital clubbing, nasal turbinate hypertrophy, and occasional crackles in the lungs during auscultation.

Diagnosis: A sweat test was positive, with chloride levels of 110 mmol/L and 130 mmol/L. Genetic testing confirmed the diagnosis of cystic fibrosis (CF) at six years of age, revealing the presence of the F508del mutation in both CFTR alleles. Comprehensive evaluations indicated additional CF-related complications, including hepatic steatosis on abdominal ultrasound and low levels of vitamins A and D, suggestive of malabsorption and nutritional deficiencies. Pancreatic insufficiency was also detected, with fecal elastase levels < 15 µg/g. Initial thoracic CT revealed bronchial wall thickening, tubular bronchiectasis, and laminar and subsegmental atelectasis (**Figure 1**).

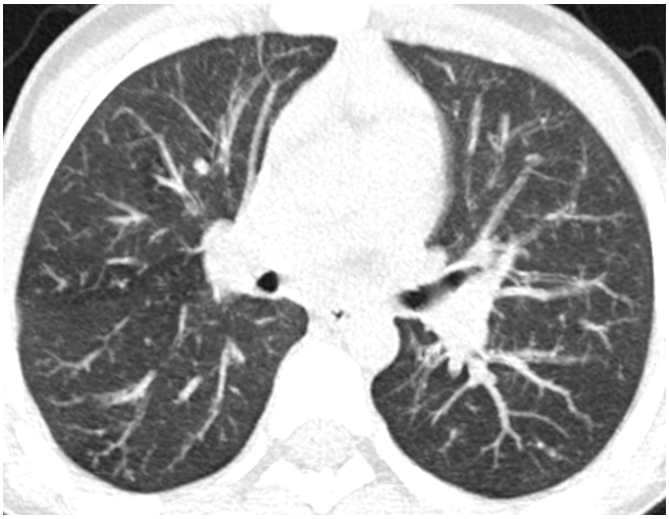

Figure 1 - Thoracic CT revealing thickening of the bronchial walls, tubular bronchiectasis, and laminar and subsegmental atelectasis

Initial Treatment: The patient began treatment with pancreatic enzyme replacement therapy (pancreatin), inhaled dornase alfa, and salbutamol, accompanied by respiratory physiotherapy and swimming exercises.

Progression and Complications: She experienced mild and sporadic pulmonary exacerbations (PEx), during which *Serratia marcescens* and *Achromobacter species* were intermittently identified. These exacerbations responded well to the oral outpatient antibiotic treatment. At age seven, *Aspergillus fumigatus (A. fumigatus)* was first detected in her sputum, and from age eight onwards, *Scedosporium spp.* were intermittently identified. Despite these fungal detections, the patient did not exhibit any clinical signs of fungal infections such as persistent or worsening cough or brown/black plugs in sputum. There was no eosinophilia, and both the total and specific IgE levels for *A. fumigatus* were consistently negative. Despite the occasional identification of *Scedosporium spp*, there was no increase in the frequency of pulmonary exacerbations, and her lung function remained stable, with a recent FEV1 (Forced Expiratory Volume in one second) of 85%. Accordingly, the patient did not require antifungal therapy or corticosteroids.

Advanced Treatment: At the age of nine years, the patient started combination therapy with lumacaftor/ivacaftor, resulting in a significant improvement in overall health, control of cough and gastrointestinal symptoms, reduced frequency of exacerbations and antibiotic courses. Prior to lumacaftor/ivacaftor initiation, the patient's FEV1 was 83% predicted. After one year of lumacaftor/ivacaftor therapy, FEV1 increased to 103% predicted.

At age 11, she transitioned to elexacaftor/tezacaftor/ivacaftor (ETI) therapy, which further stabilized her condition with FEV1 further improving to 126% predicted. Her chloride level was last measured at 37 mmol/L, and since starting this regimen, there has been no further detection of fungal species in her sputum. No adverse effects were observed.

Case 2

Presentation and Diagnosis: A newborn girl was diagnosed with cystic fibrosis through the neonatal screening program. Genetic testing revealed a heterozygous F508del mutation, characterized by a deletion in exon 16 and a duplication in exon 19, with no additional mutations identified after whole CFTR gene sequenced.

Since birth, elevated sweat chloride levels (Cl^- 113 mmol/L) have consistently been observed. The patient also presented with severe pancreatic insufficiency (fecal elastase <15 µg/g) in the first few months of life, as well as progressive respiratory insufficiency, requiring noninvasive ventilation during sleep and oxygen therapy.

Progression and Complications: The patient developed chronic bacterial colonization of the respiratory tract during the first year of life (*Table 1 – Bacterial colonization*), associated with frequent pulmonary exacerbations (PEx). The first eradication of *Pseudomonas aeruginosa* was achieved at six months of age.

She was started on continuous inhaled antibiotic therapy with tobramycin before the age of 2, in addition to standard baseline treatment with pancreatin, inhaled dornase alfa, and daily respiratory physiotherapy. At 4 years of age, the inhaled antibiotic was switched to colistimethate sodium, and by age 5, she transitioned to alternating cycles of aztreonam and colistin.

Pulmonary exacerbations were intermittently caused by *Stenotrophomonas maltophilia, Serratia marcescens,* and *Pseudomonas aeruginosa*. In the first six years of life, she required an average of 2.5 intravenous antibiotic courses per year, in addition to multiple oral antibiotic treatments. Due to the COVID-19 pandemic, spirometry to assess lung function was not yet feasible during this period.

Table 1 - Chronic bacterial colonization during the first 6 years of life and after ETI initiation.

Age of life	***Chronic bacterial colonization***
<12 months	***Pseudomonas aeruginosa, Stenotrophomona maltophilia,*** *Meticillin-Sensitive Staphylococcus aureus (MSSA),* ***Haemophilus*** *influenzae, Moraxella*
2 years	***Pseudomonas aeruginosa,*** *MSSA*
3 years	*MSSA****, Pseudomonas aeruginosa, Haemophilus*** *influenzae*
4 years	*MSSA,* ***Stenotrophomona maltophilia****, Enterobacter Cloacae,* ***Haemophilus*** *influenzae, Achromobacter xylosoxidans, Moraxella catarrhalis*
5 years	*MSSA,* ***Stenotrophomonas maltophilia,*** *S. aureus*
6 years	*MSSA, Pseudomonas putida, S.aureus, Haemophilus parainfluenzae,* ***Stenotrophomonas maltophilia****, Enterobacter cloacae*
9 – 10 years	***Haemophilus*** *influenzae*

Fungal infection with *Aspergillus fumigatus* was first detected at 5 years of age. One year later, the patient experienced a clinical exacerbation characterized by anorexia and cough with brownish sputum plugs, fulfilling diagnostic criteria for Allergic Bronchopulmonary Aspergillosis (ABPA). The diagnosis was supported by the following findings: specific IgE to *A. fumigatus* of 49.78 kUA/L, anti-*Aspergillus* IgG of 67 mg/L, a peak total IgE of 2404 kU/L, and an eosinophil count of 690/µL. Thoracic computed tomography (CT) revealed pulmonary infiltrates and segmental collapse (**Figure 2**). Over the course of corticosteroid and itraconazole treatment (two and four months respectively), a favorable clinical response was observed with reduction in exacerbations and a progressive decline in total IgE levels to 656 kU/L.

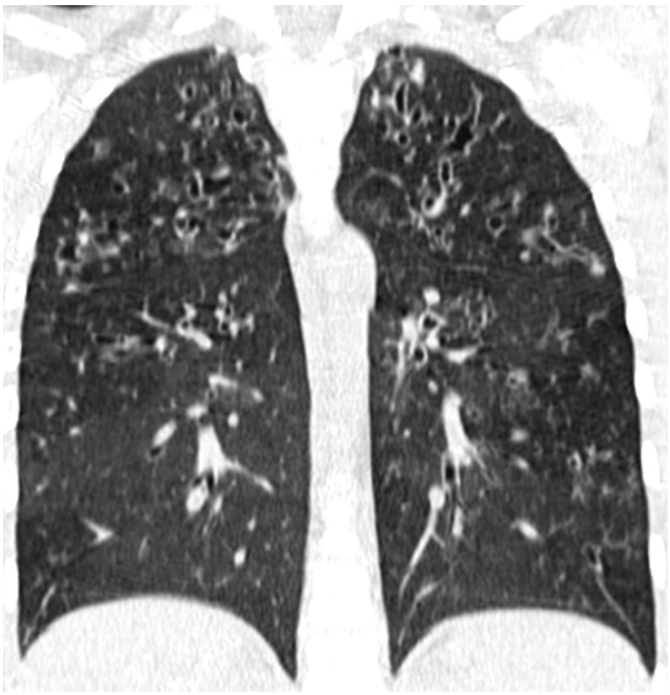

Figure 2 - CT thoracic - Multiple varicose and cystic type bronchiectasis, scattered bilaterally with a central predominance. Presence of endoluminal content at the level of the bronchial structures in the left upper lobe and both lower lobes.

The patient's first lung function assessment with spirometry was performed six months after the ABPA episode, revealing an FEV_1 of 0.93 L (77% predicted) and an FVC of 1.08 L (80% predicted).

Subsequent respiratory cultures showed persistent colonization with *Scedosporium* spp., accompanied by continued elevation of total IgE levels. These findings prompted multiple courses of antifungal therapy (voriconazole and terbinafine) as well as repeated corticosteroid treatment. Although a modest improvement in lung function was observed [FEV_1 1.09 L (82%), FVC 1.30 L (88.4%)], clinical exacerbations recurred upon discontinuation of corticosteroids.

Chronic bacterial colonization of the respiratory tract also persisted during this period, with an increase in pulmonary exacerbations to approximately four/five episodes per year.

Advanced Treatment: At 8.5 years of age, the patient experienced a marked clinical improvement following the initiation of CFTR modulator therapy with elexacaftor/tezacaftor/ivacaftor (ETI). Her lung function improved significantly, with FEV_1 rising to 1.68 L (105.9% predicted), and pulmonary exacerbations became well controlled. This clinical stability allowed for the discontinuation of both corticosteroid therapy and continuous inhaled antibiotic treatment. Over the subsequent three years, she remained free from any antibiotic courses.

Despite the clinical improvement, the patient continued to show markers of sensitization to *A. fumigatus*, with a total IgE of 1809 kU/L, IgG anti-*Aspergillus* of 89.4 mg/L, and specific IgE to *Aspergillus fumigatus* at 22.6 kUA/L. ImmunoCAP® ISAC testing further identified specific IgE sensitization to Asp f 1 (6.2 ISU-E) and Asp f 6 (4.5 ISU-E).

DISCUSSION

The prevalence of fungal identification in respiratory samples from patients with cystic fibrosis (CF) has increased significantly over recent decades. This rise has been attributed to several factors, including prolonged use of inhaled antibiotics and corticosteroids, an aging CF population, and improvements in sample processing and microbiological detection methods.[4,5]

Therefore, fungal diseases are now common in CF, with a wide variety of fungal species identified in the respiratory secretions of CF patients.[6] Multiple factors contribute to the increased susceptibility of CF airways to fungal infections, including the CFTR defect, which leads to impaired mucociliary clearance, thickened mucus, immune dysfunction, and structural lung changes such as bronchiectasis. These alterations predispose patients to colonization, particularly by *Aspergillus fumigatus*.[7]

Aspergillus species, especially *A. fumigatus*, are the most frequently isolated fungi in the respiratory tracts of CF patients. These ubiquitous, spore-forming saprophytes can exacerbate lung disease and accelerate structural damage, especially in children.[7,8] In some cases, *A. fumigatus* causes allergic bronchopulmonary aspergillosis (ABPA), a hypersensitivity-mediated lower airway disorder. However, other fungi, such as *Candida albicans* and *Scedosporium* species, have also been implicated. The broader term "allergic bronchopulmonary mycosis" (ABPM) has been proposed to encompass these reactions, including those driven by *Scedosporium*, which may contribute to disease progression.

Diagnosing ABPA in patients with CF is challenging, as many

of its diagnostic criteria overlap with common manifestations of CF-related lung disease, making accurate diagnosis difficult.[9,10] Despite the high prevalence of fungal infections in CF, there is no clear consensus on the clinical significance of *Aspergillus* colonization or the need for routine screening and treatment in the absence of ABPA.[8]

Scedosporium species are the second most common filamentous fungi found in CF airways. While generally well tolerated, they can cause bronchitis and allergic manifestations such as ABPM.[7]

While the presence of fungal species in the respiratory secretions of CF patients has been associated with worse clinical outcomes, including lung function decline and increased exacerbations, the role of fungi in CF disease progression remains unclear. Whether fungi serve as markers of disease progression or act as independent contributors to accelerated lung damage is still debated.[5]

A significant subset of CF patients exhibit evidence of type 2 (T2) inflammation, demonstrated by blood and airway eosinophilia, elevated total IgE, and allergen sensitization. This T2 inflammatory state contributes to disease severity and exacerbation frequency.[13] The advent of CFTR modulator therapy has revolutionized CF management, but its impact on pre-existing T2 inflammation remains unclear.[13]

The two cases presented in this study illustrate the variability in the impact of fungal infections on CF progression, highlighting the challenges in their management.

In **Case 1**, the patient exhibited relatively well-controlled disease, with only mild, sporadic pulmonary exacerbations and occasional identification of *Serratia marcescens* and *Achromobacter* species. However, the persistent presence of *Scedosporium* species from age 8 onwards did not correlate with the clinical symptoms of fungal infection. There was no increase in the frequency of pulmonary exacerbations or a decline in lung function, suggesting that *Scedosporium* colonization in this case may not have been clinically significant. The cessation of fungal sputum identification following the initiation of Elexacaftor/Tezacaftor/Ivacaftor therapy further supports the notion that better-controlled disease may reduce fungal colonization.

In contrast, **Case 2** involved a patient with a more severe clinical course, characterized by frequent exacerbations and persistent lung function impairment despite intensive and targeted therapies, including systemic and inhaled corticosteroids, antifungals and antibiotics. The patient met diagnostic criteria for ABPA and responded well to systemic corticosteroids and itraconazole. While corticosteroids remain the mainstay of ABPA treatment, their long-term efficacy is uncertain, and side effects are considerable. Azole antifungals like itraconazole are recommended for targeting *A. fumigatus*.[10]

Despite antifungal and corticosteroid therapy, this patient showed continued *Scedosporium* colonization and elevated total IgE levels, with recurrent exacerbations, suggesting that hypersensitivity to *Scedosporium* may have contributed to disease progression. Omalizumab was considered but deferred due to the opportunity to initiate modulator therapy. Following CFTR modulator initiation, the patient experienced a marked clinical improvement, with no further hospitalizations and significantly fewer pulmonary exacerbations.

While CFTR modulators do not directly address T2 inflammation, they improve mucociliary clearance and reduce mucus production, thereby decreasing fungal colonization. Indirectly, this may help reduce IgE levels.[13] One study demonstrated that CFTR modulators reduce exaggerated reactive oxygen species (ROS) production in CF immune cells infected with *Aspergillus*, suggesting a potential immunomodulatory effect.[11] Other studies have reported decreased *Aspergillus* colonization following initiation of ivacaftor.[12]

In our cases, a temporal relationship was observed between CFTR modulator therapy and reduced fungal colonization, though with variable clinical outcomes. **Case 1** showed complete eradication of fungal colonization, while **Case 2** maintained sensitization to *A. fumigatus* but experienced fewer exacerbations. These findings highlight ongoing uncertainties regarding the role of fungal infections in CF and the potential immunomodulatory and antimicrobial effects of modulator therapy.

Further research is needed to clarify the clinical impact of fungal colonization on CF progression and to inform more tailored management strategies.

CONCLUSION

These cases underscore the need for greater awareness and understanding of fungal infections in CF patients, emphasizing the importance of a personalized approach to patient care. The concept of ABPM provides a useful framework for managing CF patients with fungal diseases, although further research is needed to determine whether early fungal infections independently contribute to accelerated lung disease progression.

The successful use of modulator therapy in both cases demonstrates the potential benefits of this new class of drugs in managing CF patients with fungal infections, and warrants further investigation in larger studies.

CONSENT

Written informed consent was obtained from the patients for the publication of this report in accordance with the journal's patient consent policy.

AUTHORSHIP

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