

Invasive Pulmonary Fungal Infections in Cystic Fibrosis

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Abstract Invasive pulmonary mycosis is after allergic bronchopulmonary aspergillosis (ABPA) a frequent and severe complication of CF lung disease. Among CF caregivers, there is an insecurity when and how to treat infections of the lung parenchyma caused by different fungi in patients with CF. This case series provides a multicenter experience on diagnostic, manifestation, and treatment of non-ABPA cases of pulmonary. Non-ABPA cases of pulmonary mycoses in patients with CF have been collected from the CF Centers in Berlin, Essen, Worms, Frankfurt (Germany), Leeds (UK), and Barcelona (Spain). Non-

ABPA was defined as total serum IgE level <500 kU/L. *Scedosporium* and *Lomentospora* species seem to be more virulent in patients with CF and have been successfully treated with triple antifungal drug regimens in several cases. Rare fungi including yeasts can have pathogenic potential in CF. In this series, antibiotic treatment failure was the main indicator for the initiation of antifungal treatment. For an early and effective treatment of pulmonary mycoses in CF, the identification of biomarkers and of risk factors beyond antibiotic treatment failure is crucial and urgently needed. Furthermore, treatment efficacy studies are necessary for the different causative agents of these infections.

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Introduction

Cystic fibrosis (CF) is a congenital disorder due to defective cystic fibrosis transmembrane conductance regulator (CFTR) protein. Function of this protein is the secretion of chloride ions into the human exocrine glands. Due to the lack of chloride ions, the glands secretions have an increased viscosity with multiple consequences leading to a multiorgan disease with the lung affection contributing the most to the morbidity and mortality [1]. The thickened mucus and the

increasing destruction of the airway mucosa lead to a loss of the mucociliary clearance and chronic colonization of the endobronchial space with bacteria and fungi. Bacterial colonization commonly occurs with staphylococci and later in the course of the disease with gram-negative rods, mostly *Pseudomonas aeruginosa*. Pulmonary exacerbations due to bacteria have been the focus of extensive research in the last decades [2]. Chronic pseudomonal colonization is also associated with a more rapid decline of the lung function [3–5].

Fungi such as *Candida* spp., *Aspergillus* spp. [6] or *Scedosporium*, and *Lomentospora* species are also frequently detected in sputum samples of patients with CF [7]. The pathogenicity of these fungi in patients with CF is variable, not yet evaluated and not completely understood. One entity caused by fungi in CF is allergic bronchopulmonary aspergillosis (ABPA) [8], a common complication of CF lung disease affecting approximately 10% of the CF population [9]. In this condition, a strong and acute immune reaction involving IgE antibodies, antigen-antibody complexes, and *Aspergillus*-specific T cells leads to acute loss of lung function primarily from acute bronchial obstruction [10]. This phenomenon can also be caused by non-*Aspergillus* fungal species and is called allergic bronchopulmonary mycosis (ABPM) [11]. So far atopy has been described as a risk factor for ABPA [10].

Another entity which can be distinguished from ABPA is bronchitis due to fungi, mainly *Aspergillus* spp. [12, 13]. However, compared to bacterial infections, pulmonary mycosis, an acute infection of lung parenchyma due to fungi, has been in the scientific focus to a much lesser extent so far. Since pulmonary exacerbations featuring new infiltrates and acute loss of lung function are most likely caused by bacteria (most common *P. aeruginosa*) [14], the detection and initiation of specific treatment for pulmonary fungal infections remains a challenge and is currently done with an unsatisfactory trial-and-error approach. The clinical failure of antibiotic treatment during acute bronchopulmonary exacerbation with FEV1 drop sometimes in combination with loss of weight has many differential diagnosis. The possibility of new CF-related diabetes manifestation, new non-tuberculous mycobacteria infection, aforementioned ABPA, or infection due to other new bacterial species in the respiratory tract has to be considered. In our opinion

and experience, the suspicion of relevant pulmonary infection due to fungi should also be taken into account in the context of therapeutic failure to antibiotic treatment of exacerbations in CF. This study aims to provide an international six-center experience of non-ABPA/non-ABPM pulmonary mycosis cases stressing on the diagnostic processes, clinical manifestation, and the therapeutic strategies.

Methods

To provide a thorough summary of cases of patients with CF treated in Berlin (Germany) pediatric and adult centers, Barcelona (Spain) pediatric center, and the adult CF centers in Essen, Worms, Frankfurt (Germany), and Leeds (UK), cases for the last 7 years have been collected. A systematic review of the charts and of the results of the examinations has been done. Follow-up data have been collected from the digital quality management system. Some of the cases have been published before elsewhere (indicated by citations in the manuscript), and some of the cases are so far unpublished cases. For this study, non-ABPA/non-ABPM cases have been defined by total serum IgE level <500 kU/L.

Results

Table 1 provides a summary of clinical features, treatment, and outcome of 18 cases featuring invasive pulmonary mycosis in patients with CF. Below is presented a detailed description of eight of these cases, selected as being the most informative regarding the clinical manifestations, the biological diagnosis, and therapeutic strategies.

Detailed Description of Selected Cases

Case 1: A 34-year-old male patient with CF was referred to a tertiary center with a prolonged, therapy-refractory pulmonary exacerbation [15]. Previous multiple antibiotic drug intravenous treatments did not ameliorate the situation. In the further clinical course, the patient presented with spiking fever and rapidly increasing respiratory insufficiency. The CT scan revealed multiple fluffy pulmonary infiltrates

Table 1 Summary of patients treated with antifungals due to pulmonary mycosis

S. no.	Case pulmonary mycoses	Imaging findings	Age, gender, genotype	Effective treatment, duration	Outcome	FEV1 (pre/post)
1.	<i>Arxula adenivorans</i> Invasive pulmonary infection and fungaemia [15]	New infiltrates (chest CT scan)	34 years, M, ND	Conventional amphotericin B 18 mg/d + Flucytosine 9 g 4× daily IV, for 17 days	Temporary remission but persistent colonization by <i>Arxula adenivorans</i>	65%/40%
2.	<i>Scedosporium apiospermum</i> Invasive pulmonary infection [16]	New infiltrates (chest CT scan)	35 years, F, F508 del/R347P	Caspofungin 50 mg once daily IV Posaconazole 300 mg once daily PO for 6 weeks, inhaled liposomal amphotericin B 2 × 50 mg/day for 2 weeks	Rapid improvement of the clinical status	85%/70%
3.	<i>Scedosporium apiospermum</i>	Bronchiectasis and mucus impaction (chest CT scan)	20 years, M, F508 del/S466X	Liposomal amphotericin B IV for 6 weeks	Improved lung function	35%/42%
4.	<i>Scedosporium apiospermum</i> Pulmonary scedosporioma	Lung fungus ball	42 years, F, F508 del/F508 del	Caspofungin 50 mg once daily IV for 3 months, voriconazole 200 mg twice daily PO for 1 year, inhaled amphotericin B twice daily for 1 year	Clinical stabilization, improvement of lung function remission of the lung fungus ball in the imaging	48%/54%
5.	<i>Scedosporium apiospermum</i>	Cloudy peripheral infiltrates (chest CT scan)	25 years, F, F508 del/F508 del	Repetitive treatment for 4 weeks with caspofungin 50 mg once daily IV, voriconazole 200 mg twice daily PO, inhaled amphotericin B once daily for stabilization of this patient on the waiting list for lung transplantation. Peri-transplantation voriconazole 2 × 200 mg/day PO	Clinical stabilization of an end-stage lung disease patient over 1 year on the waiting list for combined lung and liver transplantation. Repetitive multiple drug antibiotic regimens were not sufficient	15%/NA
6.	<i>Candida lusitanae</i>	New infiltrates (chest X-ray)	9 years, F, F508 del/F508 del	Caspofungin IV 40 mg/day for 14 days	Plaques disappeared	31%/NA
7.	<i>Exophiala dermatitidis</i>	Peripheral infiltrates (chest CT scan)	30 years, F, F508 del/R347p	Repetitive treatments with caspofungin 50 mg/day IV, voriconazole 2 × 200 mg PO, and amphotericin B once daily. Peri-transplantation voriconazole 2 × 200 mg/day PO	Stabilization on the waiting list for lung transplantation, successful lung transplantation. After transplantation, eradication of <i>E. dermatitidis</i>	NA
8.	<i>Aspergillus fumigatus</i> / <i>Aspergillus terreus</i>	Bronchiectasis and mucus impaction (chest CT scan)	49 years, F, R553X/I336 K	Liposomal amphotericin B IV for 6 weeks	Improvement of lung function—no eradication	55%/69%

Table 1 continued

S. no.	Case pulmonary mycoses	Imaging findings	Age, gender, genotype	Effective treatment, duration	Outcome	FEV1 (pre/post)
9.	<i>Aspergillus fumigatus</i>	New pneumonic (segmental) infiltrate (chest CT scan)	21 years, M, F508 del/del2,3 (21 kb)	Voriconazole 2 × 200 mg PO for 3 months	Remission of the pulmonary infiltrate	20%/23%
10.	<i>Aspergillus fumigatus</i>	New peripheral cloudy infiltrate (chest CT scan)	20 years, F, F508 del/F508 del	Posaconazole 1 × 300 mg/day for 4 weeks	Clinical stabilization and improvement of lung function	18%/21%
11.	<i>Aspergillus fumigatus</i> (BAL)	New infiltrate left upper lobe (chest CT scan)	4 years, F, W1282X/W1282X	Itraconazole IV for 10 mg/kg/day for 14 days and 2 × 100 mg PO for 4 weeks	Symptoms resolved after 1 month, antibiotic treatment before antifungal treatment was not efficient	NA
12.	<i>Candida albicans</i>	New infiltrate left lower lobe (chest X-ray)	3 years, M, F508 del/1812-1G>A	Fluconazole IV 10 mg/kg/day for 14 days and inhaled amphotericin 24 mg twice a week for 4 months	Symptoms resolved after 1 month	NA
13.	<i>Scedosporium apiospermum</i>	Bilateral pulmonary infiltrates	29 years, F, F508 del/F508 del	Repetitive treatments with caspofungin IV 50 mg/day, voriconazole 2 × 200 mg PO, and amphotericin B twice daily	Successful bridging to lung transplantation over 9 months	31%/37%
14.	<i>Scedosporium minutisporum</i>	Bilateral infiltrates in upper lobes	20 years, M, F508 del/F508 del	Voriconazole IV/PO, caspofungin 50 mg/day, amphotericin B 12.5 mg twice daily for 8 weeks	Stabilization	59%/NA
15.	<i>Exophiala dermatitidis</i>	bronchiectasis	37 years, F, 3659delC/R668C	Voriconazole 2 × 200 mg/day for 12 weeks	Improvement of lung function	63%/71%
16.	<i>Aspergillus fumigatus</i>	Bilateral tree in bud nodularity (Fig. 10)	27 years, M, F508 del/F508 del	Caspofungin IV 50 mg/day for 14 days then voriconazole 200 mg twice daily PO for 12 weeks	Symptom and radiological improvement	24%/31%
17.	<i>Exophiala dermatitidis</i> / <i>Aspergillus fumigatus</i>	Upper lobe consolidation (Fig. 11)	19 years/F, F508 del/F508 del	Caspofungin 50 mg/day IV for 14 days then itraconazole PO for 12 weeks	Radiological resolution	66%/76%
18.	<i>Scedosporium apiospermum</i>	Lingula and right midzone consolidation (Fig. 12)	20 years/F, F508 del/F508 del	Caspofungin IV 50 mg/day for 14 days, then voriconazole 200 mg twice daily PO for 12 weeks	Symptom and radiological improvement	61%/90%

FEV1 forced expiratory volume in one second, pre/post pre-treatment/post-treatment, M male, F female, BAL bronchoalveolar lavage fluid, PO per os, IV intravenous, ND not determined, NA not applicable

(Fig. 1). *Achromobacter* sp. and *Pseudomonas* sp. were detected from sputum samples. Additionally, sputum and blood cultures yielded a yeast which was difficult to identify. First, the yeast was considered as

Stephanoascus ciferrii (now called *Trichomonascus ciferrii*), and later, a consulted reference laboratory identified *Arxula adeninivorans* (now called *Blastobotrys adeninivorans*) as the underlying pathogen

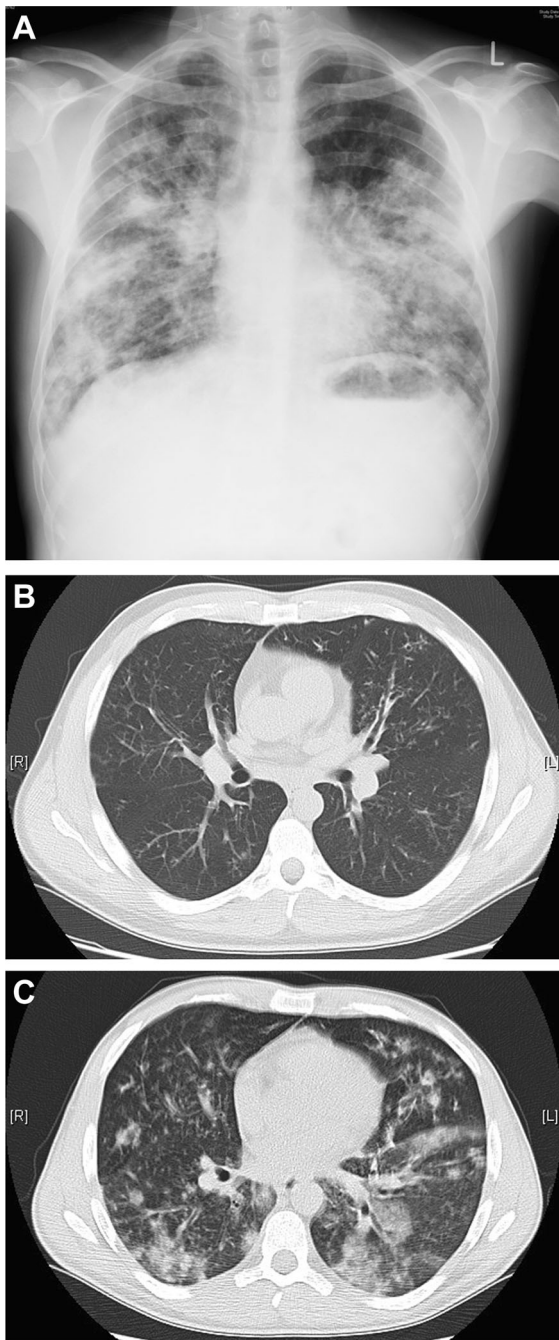


Fig. 1 Chest X-ray of case 1 during the acute exacerbation (a) and chest CT scan before (b) and during (c) the acute exacerbation

(Fig. 2). Meanwhile, an empiric antifungal treatment with caspofungin and voriconazole was started without amelioration. Susceptibility testing at the reference laboratory identified amphotericin B and

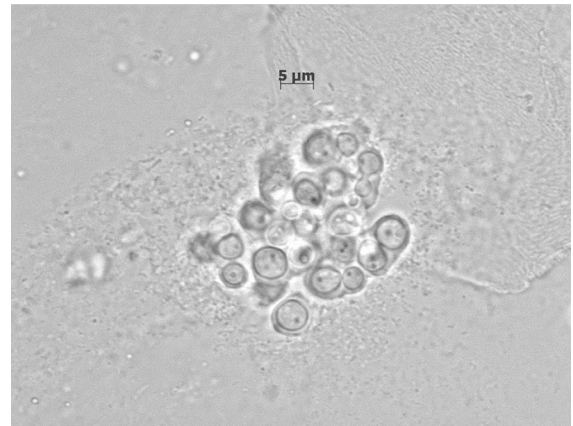


Fig. 2 Direct microscopic examination of bronchoalveolar fluid of case 1 showing atypical yeasts, identified by culture as *Blastobotrys adeninivorans* (*Arxula adeninivorans*)

flucytosine as effective antifungals. Treatment consisting in conventional amphotericin B 18 mg daily and flucytosine 9 g four times daily for 17 days finally controlled the infection and led to a rapid improvement of the clinical situation. Of note, this was the first description of *B. adeninivorans* as a pathogen, causing invasive pulmonary mycosis and fungemia in a patient with CF.

Case 2: A 35-year-old female patient with CF presented with a pulmonary exacerbation which was refractory to antibiotic intravenous therapy [16]. A CT scan demonstrated new pulmonary infiltrates (Fig. 3). Cultures from sputum and bronchoalveolar lavage (BAL) revealed *P. aeruginosa* and *Scedosporium apiospermum* as endobronchial pathogens. *Scedosporium apiospermum* being considered as a fungal pathogen causing—or participating with *Pseudomonas* to—pneumonia in this patient with CF, an empiric treatment with initially intravenous caspofungin and oral voriconazole was started. Voriconazole caused after a 2-week treatment course adverse drug reactions, so the regimen was adapted to intravenous caspofungin and oral posaconazole. This treatment led to stabilization, but not to a sufficient improvement of the clinical status. Finally, inhaled liposomal amphotericin B was added as a third antifungal, resulting in a rapid improvement of the clinical situation.

Case 4: A 42-year-old female patient with CF and chronic pseudomonal colonization presented with a pulmonary exacerbation. Multiple broad-spectrum

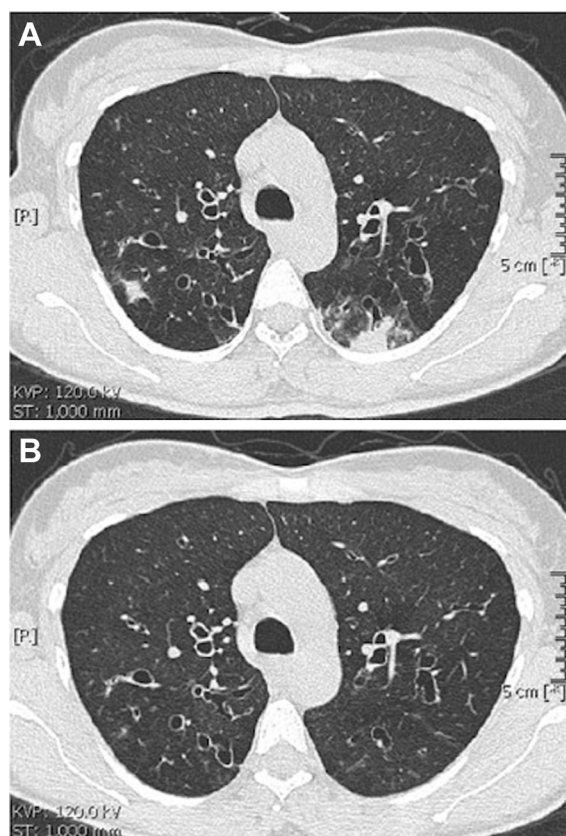


Fig. 3 Chest CT scan of case 2 during (a) and after (b) acute exacerbation (treatment). **a** CT scan with bilateral bronchiectasis and round infiltrates in the *right* and *left upper lobe* in the dorsal area. **b** CT scan with complete remission of both infiltrates

antipseudomonal treatments did not result in amelioration. Chest CT imaging revealed a fungus ball in the upper lobe of the right lung (Fig. 4). The detection of *S. apiospermum* from sputum and the experimental detection of CD4+ lymphocytes specific to *S. apiospermum* in peripheral blood led to the diagnosis of *Scedosporium* pulmonary mycetoma which was successfully treated with a triple antifungal drug regimen consisting in intravenous caspofungin for 3 months, together with oral voriconazole and inhaled liposomal amphotericin B twice daily for a year. This treatment resulted into remission of the radiological findings and clinical improvement.

Case 5: A 25-year-old female patient with CF, end-stage lung disease, liver cirrhosis, and treatment-refractory pulmonary exacerbations was on the waiting list for double organ transplantation. However, the patient had to remain on the list for combined liver and

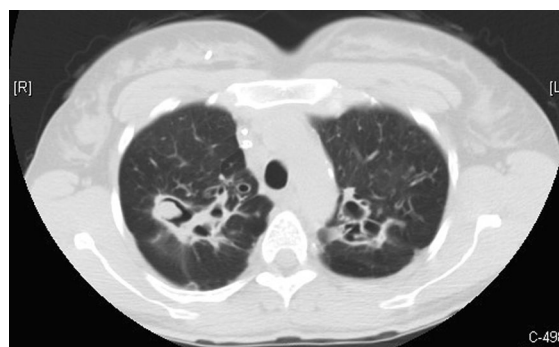


Fig. 4 Chest CT scan of case 4 showing a lung fungus ball in the right upper lobe

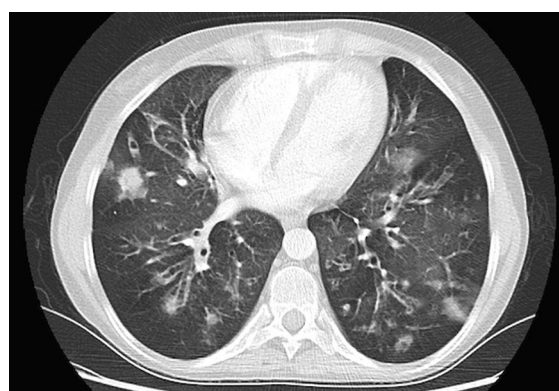


Fig. 5 Chest CT scan of case 5 showing peripheral round infiltrates in the lung

lung transplantation for more than 1 year. The recurrent pulmonary exacerbations could not be controlled with multiple drug antibiotic treatment regimen (Fig. 5). The detection of *S. apiospermum* from cultures of respiratory secretions and the cloudy infiltrates in the lung led to the diagnosis of a coinfection with *S. apiospermum* and *P. aeruginosa*. The addition of triple antifungal therapy led to higher grade of infection control and finally to the possibility of a successful combined transplantation. *Scedosporium apiospermum* was not detected again after transplantation.

Case 6: An eight-year-old female patient with CF was referred to our center for further evaluation of a chronic exacerbation with dramatic loss of lung function. She was previously treated with several antipseudomonal antibiotic regimens and with non-tuberculous mycobacteria (NTM) effective polychemotherapy due to the detection of *Mycobacterium avium*. The initial workup included a bronchoscopy

featuring BAL and comprehensive microbiological workup for bacteria, fungi, and NTM. Additionally, a chest CT scan was performed (Fig. 6), and blood values including differential blood count, markers of inflammation, liver enzymes, kidney function test, and antibodies (total serum IgE level, anti-*Aspergillus*-specific serum IgE level, anti-*Aspergillus*- and *Candida*-specific serum IgG levels) were determined. The bronchoscopy revealed multiple whitish plaques in the left upper lobe bronchus (Fig. 7). In fungal cultures grew a unique species which was identified as *Candida lusitanae*. Treatment was performed with caspofungin intravenously for 14 days. In a second bronchoscopy, the endobronchial plaques have

vanished after the treatment and the patient's clinical status was improved significantly. However, *C. lusitanae* could be detected from sputum samples even after this treatment, enabling recurrent fungal infections.

Case 7: A 30-year-old female patient with CF first presented to a tertiary treatment center with a severe pulmonary exacerbation and global respiratory failure in addition to a new infiltrate of the lung. During the clinical course, the patient's status worsened despite broad antipseudomonal antibiotic treatment which at the end required extracorporeal membrane oxygenation (ECMO) and additional multiple anti-infective treatment regimens. Chronic colonization with *P. aeruginosa* and *Exophiala dermatitidis* was already known at this point. Besides antibiotic treatment, this patient repeatedly benefitted from antifungal treatment, which allowed clinical stabilization, and the patient could be bridged to lung transplantation. In total, before lung transplantation, three fungal exacerbations could be treated successfully. The first fungal exacerbation was diagnosed 4 years before transplantation. Peri-transplantation the antifungal treatment was done with posaconazole. After transplantation, *E. dermatitidis* was not detected any more, neither in sputum nor in BAL (after 6 months of follow-up).

Case 9: A 21-year-old male patient with CF, chronic pseudomonal colonization, and previously diagnosed end-stage lung disease presented with an acute pneumonia (Fig. 8). Antibiotic treatment did not result in a clinical improvement. The detection of

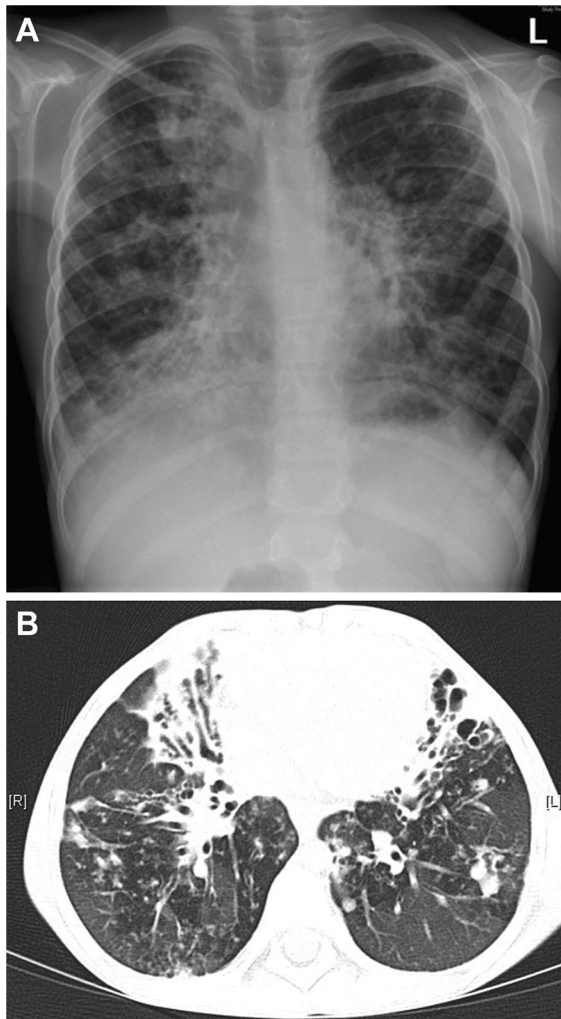


Fig. 6 Chest X-ray and CT scan of case 6 during the prolonged exacerbation

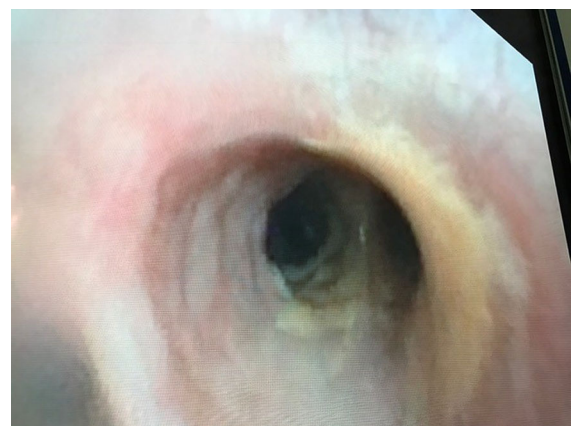


Fig. 7 Bronchoscopic examination of case 6 showing bronchus with plaques in the left upper lobe



Fig. 8 Chest CT scan of case 9 showing an infiltrate in the right lung

Aspergillus fumigatus in the sputum and BAL as well as a new significant infiltration in the right lung led to the decision of an antifungal treatment with voriconazole (2×200 mg daily) for 3 months resulting in a complete remission of the pneumonia and improvement of the clinical situation.

Case 10: A 20-year-old female patient with CF, chronic pseudomonal colonization, and previously diagnosed end-stage lung disease with global respiratory insufficiency and chest pain on the right site presented with a pulmonary exacerbation. The patient received two antibiotic treatment regimens with broad-spectrum antipseudomonal antibiotics without clinical improvement. The lack of amelioration and the new peripheral infiltrate (Fig. 9) alongside with the detection of *A. fumigatus* from sputum resulted into the initiation of an antifungal treatment with posaconazole (300 mg daily—tablets) for 4 weeks. This treatment resulted into a steady improvement of the clinical situation.



Fig. 9 Chest CT scan of case 10 showing an infiltrate in the right lung

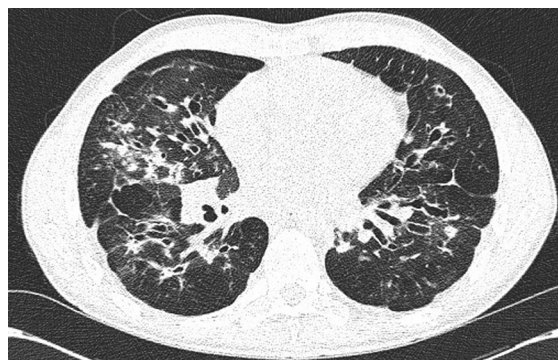


Fig. 10 Chest CT scan of case 16 showing bilateral tree in bud nodularity

Aspergillus cases required multiple antifungal drug treatments. Cases due to *Aspergillus* sp. were treated with either voriconazole, posaconazole, itraconazole or liposomal amphotericin B in a single-drug approach (Figs. 8–11).

Summary

In summary, all reported cases (1–18) share the same point of departure: a therapy-refractory pulmonary exacerbation. Due to the very high frequency of bacterial pulmonary exacerbations, empiric antibiotic treatments were performed first in all the cases. The detection of the causative fungi was possible in these cases due to the utilization of mycological culture media. To find an effective treatment regimen was a challenge in some cases (e.g., cases 1 and 2). The non-

Discussion

This study shows that severe pulmonary fungal infections can occur in patients with CF. The evaluated cases show that it is possible to conduct specific and effective antifungal treatments when facing pulmonary mycosis in CF. A major challenge remains the early detection of a pulmonary mycosis in CF, particularly regarding the much more frequent bacterial exacerbations which can cause a similar clinical picture and sometimes even similar imaging findings (e.g., infiltrates). At present, the

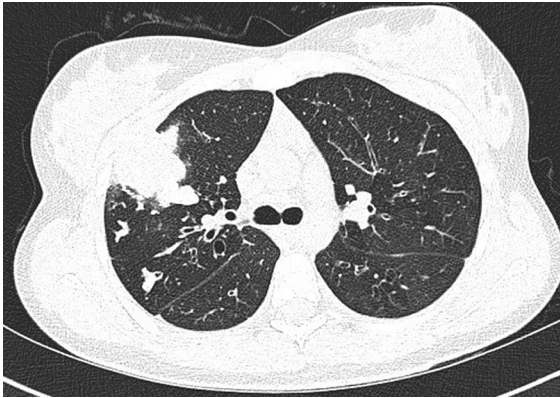


Fig. 11 Chest CT scan of case 17 showing an upper lobe consolidation

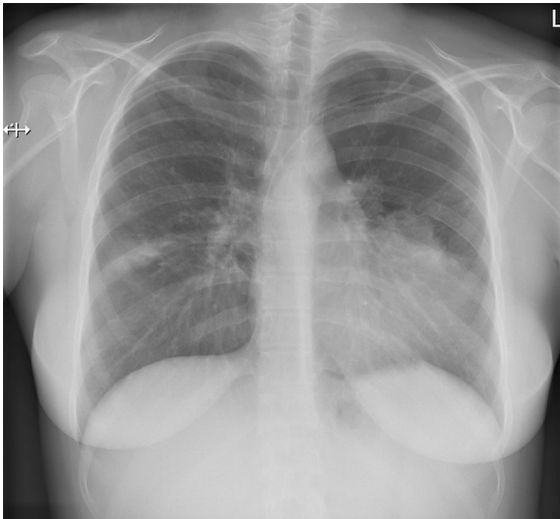


Fig. 12 Chest X-ray showing lingula and right midzone consolidation

patients generally undergo days to weeks of antibiotic treatment before the diagnosis of a pulmonary mycosis can be achieved and a specific treatment can be initiated. Baxter et al. [17] proposed a classification of *Aspergillus* colonization and infection based on the simultaneous detection of IgG and IgE antibodies, *Aspergillus* galactomannan, culture detection of the fungus, and PCR detection of fungal DNA. The clinical accuracy of this approach must be confirmed in further studies. For other indications, the detection of antigen-specific T helper cells (CD4+) in peripheral blood has been established as a very sensitive and early diagnostic tool for the detection of fungal infections [18, 19]. This method

has not been established yet for the chronically infected and multiple pathogens-bearing situation in the CF lung, but seems very promising and may contribute to an early detection of pulmonary mycosis.

In our point of view, the goal should be the capability to identify very early the patients at risk to prevent the loss of valuable days or even weeks of effective treatment in the early phase of an acute exacerbation and to prevent unnecessary side effects of antibiotics. In this context, one area of future research should be the identification of biomarkers allowing an early detection of fungal infections. Another strategy would be the empirical identification of risk factors and the development and validation of a score (taking into account clinical features as well as radiological, microbiological, and immunological data) which would indicate a certain probability of a pulmonary mycosis.

Additionally, we present two cases in which the patients could be successfully bridged to transplantation with repetitive effective antifungal treatment adjunct to repetitive multiple drug antibiotic treatment. We believe that this challenging clinical situation should be regarded as a clinical entity because it underlines the significance of managing pulmonary mycoses, especially on the waiting list for lung transplantation. Antifungal treatment was crucial for several of the analyzed patients with end-stage lung disease [20]. With the current diagnostic possibilities, we believe the empiric addition of antifungal treatment is mandatory in this clinical setting. Post-transplantation, the significance of pathogenic fungi is even higher due to the immunosuppression. Treatment is more complicated due to drug interactions between azoles and immunosuppressants.

An unresolved clinical problem is the frequent detection of multiple fungal pathogens alongside with bacteria from sputum samples from patients with CF [21, 22]. Since the treatment approaches for *Candida*, other yeasts, and filamentous fungi differ substantially regarding the choice of the antifungal drugs and duration of the treatment, identification of the fungal pathogen causing pulmonary mycoses and susceptibility testing are crucial.

Here, we could present the experience of six CF centers narrating the successful treatment of pulmonary mycoses in 18 cases. Multidrug treatment regimens have proven successful for the treatment of

infections caused by *Scedosporium* species, *Lomentospora prolificans*, *B. adenivorans*, *A. fumigatus*, *C. lusitanae*, or *E. dermatitidis*. Nevertheless, there is an urgent need for prospective data in larger patient cohorts to confirm, for example, the superior effectiveness of multiple antifungal drug treatment compared to single-drug treatment regimen.

One limitation of this study is the selection of patients with severe pulmonary exacerbations. In these cases, a fungal pathogen was successfully identified and a specific treatment could be conducted. It must be stated though that we have done many more empiric antifungal treatments when facing therapy-refractory pulmonary exacerbations with just little or even no effect. Therefore, this case series must be understood as a biased selection of our experiences. Another limitation is that the gold standard for diagnosing fungal lung tissue infections is not feasible in this patient group, because the invasive procedures bronchoscopy and thoracoscopy required for a lung biopsy would put the patients at a high risk of bleeding and pneumothorax. By common definition, the gold standard for the diagnosis of a lung tissue fungal infection is histological proof of hyphal structures in tissue and the cultural or molecular confirmation of their presence [23].

In conclusion, pulmonary mycosis in CF has been shown to be a significant clinical problem in the management of CF. *Scedosporium* species and *L. prolificans* seem to be more virulent than *Aspergillus* species in CF as much more *Aspergillus* than *Scedosporium* species and *L. prolificans* are detected in respiratory samples, but comparatively little infections are caused by *Aspergillus* spp. In a patient cohort with coinfections being the normal case, the differentiation of colonizing and infectious agents at a certain point of time is not resolved yet. Multicentric epidemiological data and the detection of antigen-specific T cells may contribute to resolve this problem. Also, a scientific evaluation of the antifungal treatment regimens in a prospective, multicentric, randomized manner in CF is still an unmet need.

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Authors' Contribution All authors were involved in the manuscript design and in data collection. CS, JFR wrote the paper, and all authors edited the paper.

Compliance with Ethical Standards

Conflict of interest None of the authors has any potential financial or non-financial conflicts of interests related to this manuscript.

Human and Animal Rights There was no research involving human participants or animals.

References

1. Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med*. 1992;326:1187–91.
2. Flume PA, Mogayzel PJ, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med*. 2010;182:298–306.
3. Elkin S, Geddes D. Pseudomonal infection in cystic fibrosis: the battle continues. *Expert Rev Anti Infect Ther*. 2003;1:609–18.
4. Zemanick ET, Emerson J, Thompson V, McNamara S, Morgan W, Gibson RL, et al. Clinical outcomes after initial *pseudomonas* acquisition in cystic fibrosis. *Pediatr Pulmonol*. 2015;50:42–8.
5. Konstan MW, Morgan WJ, Butler SM, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr*. 2007;151:134–9.
6. Ziesing S, Suerbaum S, Sedlacek L. Fungal epidemiology and diversity in cystic fibrosis patients over a 5-year period in a national reference center. *Med Mycol*. 2016;54:781–6.
7. Middleton PG, Chen SC-A, Meyer W. Fungal infections and treatment in cystic fibrosis. *Curr Opin Pulm Med*. 2013;19:670–5.
8. Mastella G, Rainisio M, Harms HK, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis. A European epidemiological study. *Epidemiologic registry of cystic fibrosis*. *Eur Respir J*. 2000;16:464–71.
9. Maturu VN, Agarwal R. Prevalence of *Aspergillus* sensitization and allergic bronchopulmonary aspergillosis in cystic fibrosis: systematic review and meta-analysis. *Clin Exp Allergy*. 2015;45:1765–78.
10. Agarwal R. Allergic bronchopulmonary aspergillosis. *Chest*. 2009;135:805–26.
11. Pihet M, Carrère J, Cimon B, Chabasse D, et al. Occurrence and relevance of filamentous fungi in respiratory secretions of patients with cystic fibrosis—a review. *Med Mycol*. 2009;47:387–97.
12. Baxter CG, Dunn G, Jones AM, et al. Novel immunologic classification of aspergillosis in adult cystic fibrosis. *J Allergy Clin Immunol*. 2013;132:560–6.
13. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. *Thorax*. 2015;70:270–7.
14. Elborn JS. Cystic fibrosis. *Lancet*. 2016;388:2519–31.
15. Roehmel JF, Tintelnot K, Bernhardt A, et al. *Arxula adenivorans* causing invasive pulmonary mycosis and fungaemia in cystic fibrosis. *Lancet*. 2015;385:1476.

16. Schwarz C, Thronicke A, Staab D, Tintelnot K. *Scedosporium apiospermum*: a fungal pathogen causing pneumonia in a patient with cystic fibrosis. *JMM Case Rep*. 2015;2:1–5.
17. Baxter CG, Moore CB, Jones AM, Webb AK, Denning DW. IgE-mediated immune responses and airway detection of *Aspergillus* and *Candida* in adult cystic fibrosis. *Chest*. 2013;143:1351–7.
18. Bacher P, Schink C, Teutschbein J, et al. Antigen-reactive T cell enrichment for direct, high-resolution analysis of the human naive and memory Th cell repertoire. *J Immunol*. 2013;190:3967–76.
19. Bacher P, Steinbach A, Kniemeyer O, Hamprecht A, Assenmacher M, Vehreschild MJGT, et al. Fungus-specific CD4 + T cells for rapid identification of invasive pulmonary mold infection. *Am J Respir Crit Care Med*. 2012;11:293–9.
20. Luong M-L, Chaparro C, Stephenson A, et al. Pretransplant *Aspergillus* colonization of cystic fibrosis patients and the incidence of post-lung transplant invasive aspergillosis. *Transplantation*. 2014;97:351–7.
21. Chotirmall SH, McElvaney NG. The International Journal of Biochemistry and Cell Biology. *Int J Biochem Cell Biol*. 2014;52:161–73.
22. Liu JC, Modha DE, Gaillard EA. What is the clinical significance of filamentous fungi positive sputum cultures in patients with cystic fibrosis? *J Cyst Fibros*. 2013;12:187–93.
23. De Pauw B, Walsh TJ, Donnelly JP, 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. *Clin Infect Dis*. 2008;46:1813–21.