

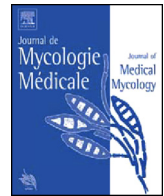


Available online at

ScienceDirect
www.sciencedirect.com

Elsevier Masson France

EM|consulte
www.em-consulte.com



Case report

Successful control of exacerbation of Allergic Bronchopulmonary Aspergillosis due to *Aspergillus terreus* in a cystic fibrosis patient with short-term adjunctive therapy with voriconazole: A case report

M. Hassanzad^a, V. Mortezaee^b, F. Bongomin^c, M. Poorabdollah^a, S. Sharifynia^d,
M. Maleki^b, N. Hedayati^e, A.A. Velayati^d, M.T. Hedayati^{b,*}

^a (PRDRC) Pediatric Respiratory Diseases Research Center, Shahid Beheshti University of Medical Sciences, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Tehran, Iran

^b Invasive Fungi Research Center (IFRC)/ Department of Medical Mycology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

^c Department of Medical Microbiology and Immunology, School of Medicine, Gulu University, Gulu, Uganda

^d (CTERC) Clinical Tuberculosis and Epidemiology Research Center, Shahid Beheshti University of Medical Sciences, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Tehran, Iran

^e Student Research Committee, Invasive Fungi Research Center, Mazandaran University of Medical Sciences, Sari, Iran

ARTICLE INFO

Article history:

Received 13 November 2018

Received in revised form 31 January 2019

Accepted 4 February 2019

Available online xxx

Keywords:

Allergic bronchopulmonary aspergillosis

Cystic fibrosis

Voriconazole

Short-course

Lung

Itraconazole

ABSTRACT

A 12-year-old boy with cystic fibrosis (CF) and a history of glucocorticoid-dependent allergic bronchopulmonary aspergillosis (ABPA) was referred to our hospital. The ABPA was diagnosed when he was 8 years old and he had been treated with several course of oral glucocorticoids for recurrent exacerbations. He was readmitted when aged 12 with a history of worsening shortness of breath and chest tightness. A recurrence of ABPA was diagnosed based on eosinophilia and elevation of *Aspergillus* specific IgE and IgG, and total IgE. Thoracic high-resolution computed tomography (HRCT) showed central bronchiectasis with parenchymal infiltrates. The treatment started with itraconazole and oral corticosteroid. After 2 months of treatment, he was re-admitted to the hospital due to a progressive worsening of respiratory symptoms. Chest HRCT revealed the a sub segmental atelectasis in the left lung. Microscopic examination of sputum and BAL samples demonstrated septate hyphae consistent with *Aspergillus* species. Sputum and BAL culture yielded *Aspergillus ochraceus* and *Aspergillus terreus*, which were both sensitive to itraconazole and voriconazole. The treatment was switched to voriconazole and the patient showed significant clinical, serological and mycological improvement after three months. This case shows that voriconazole may be used as an alternative for treatment of ABPA due to *Aspergillus terreus*.

© 2019 Elsevier Masson SAS. All rights reserved.

1. Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity lung disorder characterized by airway inflammation, elevated levels of *Aspergillus* specific IgE and IgG, elevated total

IgE and positive skin sensitivity to *Aspergillus* allergens/proteins [1,2]. *Aspergillus fumigatus* was reported as the most common etiologic agent of ABPA, however other species of *Aspergillus* are rarely implicated [3]. ABPA typically occurs in patients with asthma or cystic fibrosis (CF) with a 2–15% rate in CF patients [4,5]. The global burden of ABPA in CF patients is estimated at about 7000 cases annually [6]. Glucocorticoids are the mainstay of management of ABPA; however, the use of antifungals (usually itraconazole) in patients with slow or poor response to steroids, frequent relapses, steroid-dependent ABPA, or steroid toxicity has been recommended by a consensus expert panel [5].

Here, we report an unusual case of ABPA exacerbation due to two different non-*fumigatus Aspergillus* species that was successfully controlled by short-term course of voriconazole therapy after a failed itraconazole treatment.

Abbreviations: Cystic Fibrosis, CF; Allergic Bronchopulmonary Aspergillosis, ABPA; Enzyme-Linked Immunosorbent Assay Method, ELISA; High-Resolution Computed Tomography, HRCT; Central Bronchiectasis, CB; β -tubulin, BenA; Forced Expiratory Volume, FEV1; Forced Vital Capacity, FVC; Bronchoalveolar Lavage Liquid, BAL; International Unit Per Millilitre, IU/ml; Clinical and Laboratory Standard Institute, CLSI; Minimum Inhibitory Concentration, MIC; Itraconazole, ITC; Amphotericin B, AMB; Posaconazole, POS; Voriconazole, VOR; Caspofungin, CAS; Minimum Effective Concentration, MEC.

* Corresponding author.

E-mail address: hedayatim@gmail.com (M.T. Hedayati).

<https://doi.org/10.1016/j.mycmed.2019.02.001>

1156-5233/© 2019 Elsevier Masson SAS. All rights reserved.

Please cite this article in press as: Hassanzad M, et al. Successful control of exacerbation of Allergic Bronchopulmonary Aspergillosis due to *Aspergillus terreus* in a cystic fibrosis patient with short-term adjunctive therapy with voriconazole: A case report. Journal De Mycologie Médicale (2019), <https://doi.org/10.1016/j.mycmed.2019.02.001>

2. Case report

In this report, a 12-year-old boy with ABPA was presented. The CF was diagnosed at age 1.5 years old by positive sweet chloride concentration, homozygous genotype for CFTR mutation (p.F508del/p.F508del) and pancreatic insufficiency. Since childhood, he showed symptoms of moderate lung problems, severe cough, chest tightness and antibiotic therapy (3–4 times per year). At the age of 6 years, he showed a respiratory colonization with *Pseudomonas aeruginosa* and *Aspergillus flavus*. ABPA was diagnosed at age 8 years according to Rosenberg & Patterson ABPA diagnostic criteria [1,2]. The laboratory and clinical parameters were a FEV1 baseline of 47%, positive *Aspergillus* skin prick test, total IgE value of 1001 IU/ml, *Aspergillus* specific IgG level of 32 IU/ml, *Aspergillus* specific IgE value of 0.65 IU/ml and eosinophil count of 1000 cell/ μ L. Corticosteroid therapy was started by an initial dose of 1.0 mg/kg/day (maximum 50 mg) of prednisolone for 1 week, and then continued by 2.0 mg/kg/day for 2 weeks, and then taper during the next 2 months. The symptoms went down and the spirometric parameters increased. Between the age of 10 and 12 years, he showed recurrence of ABPA symptoms several times, during which the exacerbation of ABPA was controlled by increase of prednisone dosage. At the age of 12 years, he was re-admitted to the Pediatric Respiratory Diseases Research Center, Masih Daneshvari hospital, Tehran, Iran, in July 2016, with weight loss, and a marked increase in productive cough, chest pain, a history of worsening shortness of breath and chest tightness for 14 days. The *Aspergillus* specific IgE value (measured by ImmunoCap[®] method) and total IgE and *Aspergillus* specific IgG values (measured by enzyme-linked immunosorbent assay) were 17.2 IU/ml, 1013 IU/ml and 101.9 IU/ml, respectively. He also had a raised peripheral eosinophil count (1600 cells/ μ L). There was a positive skin reaction to *Aspergillus* allergen. In the high-resolution computed tomographic scan (HRCT), the patient revealed central bronchiectasis. Three consecutive sputum samples were obtained from the patient. The light brown plugs were macroscopically observed in sputum samples. The direct microscopic examination of sputum following 0.5% pancreatin homogenization revealed septate hyphae with acute angle branching. Culture of sputum samples revealed *Aspergillus ochraceus* belong to *Aspergillus* section *Circumdati*. No antifungal susceptibility testing was done on this isolate.

According to observed clinical and laboratory findings, a diagnosis of exacerbation of ABPA in patient was confirmed. Antifungal therapy with itraconazole (200 mg) twice daily and inhaled fluticasone and oral corticosteroid (prednisone) was commenced. Patient took initial dose of prednisolone as 0.5 mg/kg/day (maximum 50 mg) for 2 weeks, and then continued with 1.0 mg/kg/day for 2 weeks plus itraconazole (200 mg/day) and then tapered during the next 2 months. Two months after

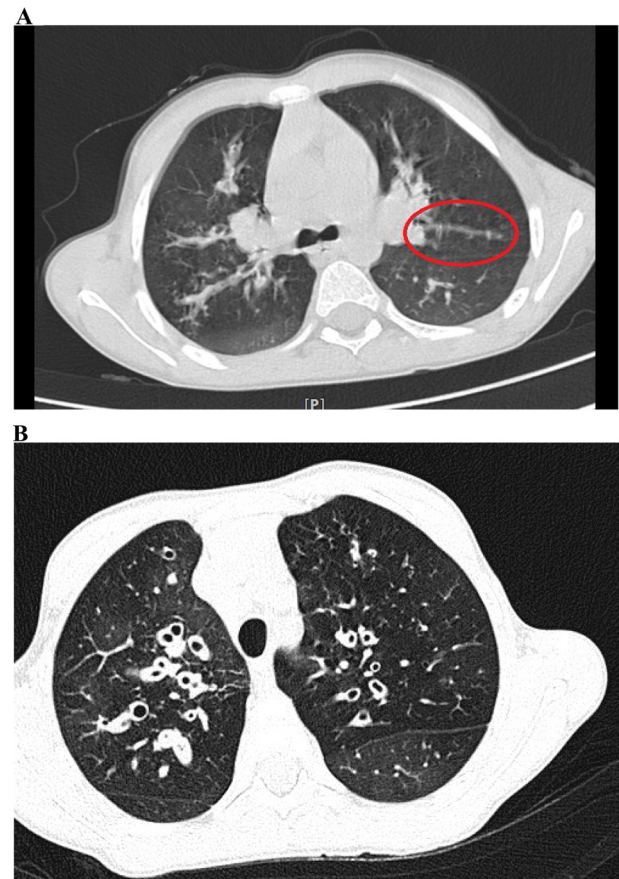


Fig. 1. Sub segmental atelectasis in the left lung (A) and bilateral central bronchiectasis (B) with peribronchial wall thickness along with some mucus impaction in favour of cystic fibrosis is seen.

discontinuing of itraconazole and corticosteroid therapy, the patient was re-admitted to hospital with increased cough, high production of sputum with brown plugs, shortness of breath, chest pain, and fever despite coverage with broad-spectrum antibiotics.

A repeat chest HRCT revealed central bronchiectasis and sub segmental atelectasis in the left lung (Fig. 1). The forced expiratory volume (FEV₁) was 51% and forced vital capacity (FVC) was 58% predicted. The patient showed a raised level of *Aspergillus* specific IgE and IgG and total IgE (26.4 IU/ml; 160.3 IU/ml; 1200.5 IU/ml, respectively) as well as the increased peripheral eosinophil count (2153 cell/ μ L). A repeat skin prick test showed sensitivity to *Aspergillus* allergens. Bronchoscopy was performed for control of lung atelectasis, bronchial washing and sampling. Three samples of

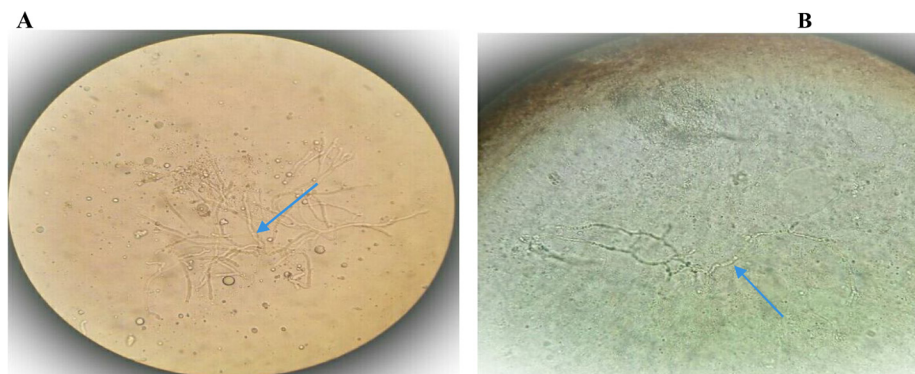


Fig. 2. Direct microscopic examinations of sputum (A) and bronchoalveolar lavage (B) samples from our patient. Numerous septate hyphae with acute angle branching is observed in both preparations, consistent with the identification of *Aspergillus* species.

sputum were collected in three consecutive working days and two bronchoalveolar lavage liquid (BAL) samples were taken within a week. All collected samples were cultured on malt extract agar (Quelab, Canada). Direct microscopy examination on sputum and BAL fluid samples revealed septate hyphae similar to the previous samples from this patient (Fig. 2). Culture of BAL samples revealed two types of colonies, one yellow-orange and the other cinnamon to brown in colour. A molecular approach was used for confirmation of the isolates at species level. DNA extraction was performed and the partial beta-tubulin region was amplified using forward primer BT2a and reverse primer BT2b as previously described [7]. The polymerase chain reaction (PCR) products underwent sequencing to identify *Aspergillus* species and the sequence results deposited in GenBank using BankIt sequence submission tool. Two species of *Aspergillus* *A. terreus* (accession number: MG254194) and *A. ochraceus* (accession number: MG254195) were identified.

In vitro antifungal susceptibility testing was performed using broth microdilution method according to the Clinical & Laboratory Standards Institute (CLSI) M38-A2 protocol [8]. The minimum inhibitory concentrations (MICs) of itraconazole (ITC, Janssen Research Foundation, Belgium), amphotericin B (AMB, Bristol-Myers Squibb, The Netherlands), posaconazole (POS, Schering-Plough, NJ, USA) and voriconazole (VOR, Pfizer, NY, USA), and the minimum effective concentration (MEC) of caspofungin (CAS, MerckSharp & Dohme, Haarlem, The Netherlands), were determined for the isolates. The obtained MIC of AMB for *A. terreus* and *A. ochraceus* isolates were $> 16 \mu\text{g/mL}$ and $1 \mu\text{g/mL}$, respectively. Both isolates of *A. ochraceus* and *A. terreus* were susceptible to CAS, VOR, ITR and POS. The MIC of POS against *A. terreus* and *A. ochraceus* isolates were low ($0.0625 \mu\text{g/mL}$ and $0.125 \mu\text{g/mL}$, respectively). The MIC of VOR for *A. terreus* was $0.25 \mu\text{g/mL}$ and for *A. ochraceus* isolate was $0.125 \mu\text{g/mL}$. The MIC of ITC for both isolates of *A. terreus* and *A. ochraceus* were $0.5 \mu\text{g/mL}$. Both isolates of *A. terreus* and *A. ochraceus* were susceptible to CAS. Patient failed ITC therapy despite both *A. terreus* and *A. ochraceus* isolates being susceptible to ITC in the in vitro test. We decided to manage the exacerbation of ABPA with oral VOR (200 mg) twice daily plus an initial dose of prednisolone 0.5 mg/kg/day (maximum 50 mg) for 1 week, then continued with 1.0 mg/kg/day for 2 weeks and then tapered during the next 1 month. One month after treatment with VOR, our patient showed a significant decrease in *Aspergillus* specific IgE (10.3 IU/mL) and *Aspergillus* specific IgG (58.8 IU/mL), and total IgE (641.5 IU/mL). There was no evidence of *Aspergillus* species on direct microscopic examination and culture of sputum samples. The peripheral eosinophil count decreased ($1209 \text{ cell}/\mu\text{L}$) and the FEV1 increased from 51 to 68% of predicted value. Four months after stopping of VOR therapy, the sputum sample was negative for fungi. Twelve months after VOR therapy, the patient was stable.

3. Discussion

This report showed a successful control of ABPA exacerbation with short-term VOR plus corticosteroids therapy in a CF patient with previously failed ITC therapy. *A. fumigatus*, *A. niger*, and *A. terreus* are commonly implicated species in ABPA. However, *A. ochraceus* is a rare cause of ABPA. The first case report of ABPA due to *A. ochraceus* was presented by Novey and Wells in 1978 [9]. Nakahara et al. [10] reported an ABPA cases without CF caused by *A. terreus* with extensive collapse of the left upper lobe, which is unusual for radiographic results. In contrast to Nakahara et al. [10], our patient showed a sub segmental atelectasis in the lung. Another report of ABPA due to *A. terreus* was presented by Laham et al. [11].

ABPA is a progressive diseases associated with significant morbidity. Early detection and treatment can prevent the development of bronchiectasis or pulmonary fibrosis that otherwise occurs in the later stages of the disease. The management of the disease includes environmental control measures, corticosteroids, and antifungals [12]. Glucocorticoids are used as the first-line of therapy in ABPA, and antifungals reserved in those with recurrent exacerbations and glucocorticoid-dependent disease [4]. Our patient was prescribed oral prednisolone in combination with inhaled fluticasone and ITC therapy.

Antifungal agents are generally considered an adjunct but not primary therapy for ABPA [12]. Antifungals reduce the fungal burden and control inflammation in the airways of CF patients. Eradication of *Aspergillus* thought to modify the disease progression by reducing the level of hypersensitivity reaction in the bronchi [12]. Systemic triazole antifungals (ITC, VOR, POS and isavuconazole) are all active against *Aspergillus* species [13]. Adjunctive ITC is considered as the first-line therapy in ABPA, due to a lower side effect [14]. However, ITC is associated with 40% failure rates as seen in our patient [15]. There are few data on the use of VOR for ABPA. VOR and POS have been shown to reduce the severity of ABPA in patients with CF [15]. Our patient showed tolerance to VOR, and a significant improvement in serological parameters, pulmonary function and clinical manifestations. In agreement with our result, Hilliard et al. [16] reported a significant improvement in serological parameters and lung function by VOR monotherapy in 11 CF children with ABPA. Glackin et al. [17] found that treatment with VOR lead to a significant drop in IgE values as well as a decrease in dose of corticosteroids. Schelstraete et al. [18] suggested that VOR monotherapy appears to be an alternative treatment strategy in CF patients with ABPA when oral corticosteroids are not suitable.

4. Conclusion

This case presentation showed that other species of *Aspergillus* than *A. fumigatus* can be involved in ABPA. It could be recommended VOR as an alternative adjunctive therapy along with corticosteroid for ABPA patients who failed or may not tolerate ITC. The antifungal susceptibility test is helpful in choosing an alternative medicine, in patients who failed to respond to initial therapy.

Ethical statement

Informed consent was obtained from all individual participants included in the study.

Authors' contribution

Conceptualisation and design of the study: Dr. Vida Mortezaee, Dr. Maryam Hassanzad.

Sample collection: Dr. Vida Mortezaee, Maedeh Maleki.

Acquisition of data: Dr. Vida Mortezaee, Dr. Somayeh Sharifynia, Dr. Mihaan Poorabdollah.

Analysis and interpretation of data: Dr. Felix Bongomin, Prof. Mohammad Taghi Hedayati, Dr. Vida Mortezaee.

Drafting of manuscript: Dr. Vida Mortezaee, Maryam Hassanzad.

Revising it critically for important intellectual content: Prof Ali Akbar Velayati, Prof. Mohammad Taghi Hedayati, Dr. Felix Bongomin.

Manuscript editing: Dr. Felix Bongomin, Dr. Vida Mortezaee.

Final approval of the version to be submitted: Prof. Mohammad Taghi Hedayati.

Patient consent

Obtained.

Ethics committee code

IR.MAZUMS.REC.95.235.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

This research was supported by Invasive Fungi Research Center (IFRC) (fund number: 2060), Mazandaran University of Medical Sciences, Sari, Iran. We thank of Milad Medical Laboratory, Isfahan, Iran, and our colleagues from Paediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, who provided insight and expertise that greatly assisted the research.

References

- [1] Rosenberg M, Patterson R, Mintzer R, Cooper BJ, Roberts M, Harris KE. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. *Ann Intern Med* 1977;86:405e14.
- [2] Patterson R, Greenberger PA, Halwig JM, Liotta JL, Roberts M. Allergic bronchopulmonary aspergillosis. Natural history and classification of early disease by serologic and roentgenographic studies. *Arch Intern Med* 1986;146:916e8.
- [3] Denning DW, Pashley C, Hartl D, Wardlaw A, Godet C, Del Gaudio S, et al. Fungal allergy in asthma – state of the art and research needs. *Clin Transl Allergy* 2014;4:14.
- [4] Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy* 2013;43:850–73.
- [5] Stevens DA, Moss RB, Kurup VP, Knutsen AP, Greenberger P, Judson MA, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis* 2003;37:S225–64.
- [6] Bongomin F, Gago S, Oladele R, Denning D. Global and multi-national prevalence of fungal diseases – estimate precision. *J Fungi* 2017;3:57.
- [7] Glass NL, Donaldson GC. Development of primer sets designed for use with the PCR to amplify conserved genes from filamentous ascomycetes. *Appl Environ Microbiol* 1995;61:1323–30.
- [8] CLSI. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi; approved standard, 2nd ed., Wayne, PA: Clinical and Laboratory and Standards Institute; 2008 [CLSI document M38-A2].
- [9] Novey HS, Wells ID. Allergic bronchopulmonary aspergillosis caused by *Aspergillus ochraceus*. *Am J Clin Pathol* 1978;70:840–3.
- [10] Nakahara Y, Katoh O, Yamada H, Sumida I, Hanada M. Allergic bronchopulmonary aspergillosis caused by *Aspergillus terreus* presenting lobar collapse. *Int Med* 1992;31:140–2.
- [11] Laham MN, Carpenter JL. *Aspergillus terreus*, a pathogen capable of causing infective endocarditis, pulmonary mycetoma, and allergic bronchopulmonary aspergillosis. *Am Rev Respir Dis* 1982;125:769–72.
- [12] Agarwal R, Sehgal IS, Dhoria S, Aggarwal AN. Developments in the diagnosis and treatment of allergic bronchopulmonary aspergillosis. *Exp Rev Respir Med* 2016;10:1317–34.
- [13] Nett JE, Andes DR. Antifungal agents: spectrum of activity, pharmacology, and clinical indications. *Infect Dis Clin* 2016;30:51–83.
- [14] Denning DW, Van Wye JE, Lewiston NJ, Stevens DA. Adjunctive therapy of allergic bronchopulmonary aspergillosis with itraconazole. *Chest* 1991;100:813–9.
- [15] Chishimba L, Niven RM, Cooley J, Denning DW. Voriconazole and posaconazole improve asthma severity in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization. *J Asthma* 2012;49:423–33.
- [16] Hilliard T, Edwards S, Buchdahl R, Francis J, Rosenthal M, Balfour-Lynn I, et al. Voriconazole therapy in children with cystic fibrosis. *J Cyst Fibros* 2005;4:215–20.
- [17] Glackin L, Leen G, Elnazir B, Greally P. Voriconazole in the treatment of allergic bronchopulmonary aspergillosis in cystic fibrosis. *Irish Med J* 2009;102:29.
- [18] Schelstraete P, Haerynck F, De Baets F. Voriconazole treatment in CF patients with ABPA and/or invasive aspergillosis. *J Cyst Fibros* 2010;1:S53.