Case Report

Successful treatment of allergic bronchopulmonary aspergillosis with posaconazole in a child with cystic fibrosis: Case report and review of the literature

Nurhayat Yakut[1], Eda Kepenekli Kadayifci[1], Ela Erdem Eralp[2], Yasemin Gokdemir[2]

[1]*Department of Pediatrics, Division of Pediatric Infectious Diseases, Marmara University School of Medicine, Istanbul, Turkey,*
[2]*Department of Pediatrics, Division of Pediatric Pulmonology, Marmara University School of Medicine, Istanbul, Turkey*

ABSTRACT

Allergic bronchopulmonary aspergillosis (ABPA) is recognized as a rare, progressive, allergic disorder in patients with cystic fibrosis (CF) and asthma. Treatment of ABPA mainly includes systemic corticosteroids (CSs) and antifungal agents. Here, we report posaconazole treatment in a 9-year-old male child with ABPA and also review the literature on antifungal management of ABPA. The child with CF was admitted to the emergency room with complaints of fever, productive cough, and acute dyspnea. Auscultation of the lungs revealed obvious bilateral fine crackles and bilateral rhonchus. He was started with intravenous meropenem and amikacin for acute exacerbation. The patient was diagnosed with ABPA because of his failure to respond to antibiotherapy, elevated serum immunoglobulin (Ig) E, specific IgE, to *Aspergillus fumigatus* levels and sputum growth of *A. fumigatus*. He was successfully treated with posaconazole with marked clinical and laboratory improvement and no adverse effects. CSs and antifungal agents are the mainstay of therapy in patients with ABPA based on observational studies in children. Posaconazole is a useful treatment option for patients with ABPA.

KEY WORDS: Allergic bronchopulmonary aspergillosis, antifungal therapy, posaconazole

Address for correspondence: Dr. Nurhayat Yakut, Fevzi Cakmak Mahallesi Muhsin Yazıcıoğlu Cad. No: 41, Ustkaynarca, Pendik, Istanbul, Turkey.
E-mail: nurhayatyakut@gmail.com

Submitted: 23-Jun-2019 **Revised:** 20-Aug-2019 **Accepted:** 09-Sep-2019 **Published:** 27-Feb-2020

INTRODUCTION

Aspergillus fumigatus is the main fungus isolated from the airways of patients with cystic fibrosis (CF). Allergic bronchopulmonary aspergillosis (ABPA) is a rare, progressive, allergic fungal lung disease that affects the respiratory tract in patients with asthma or CF.[1] ABPA was described first by Hinson *et al*. in 1952. ABPA occurs in 5%–15% of patients with CF. Treatment of ABPA includes systemic oral corticosteroids (CSs) to control the host immune response and antifungal agents to decrease the burden of microorganism. Here, we report the case of treatment of ABPA with posaconazole in a child with CF and we also review on antifungal management of ABPA.

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_288_19

CASE REPORT

A 9-year-old male child with the diagnosis of CF presented with complaints of fever, productive cough, and acute dyspnea. CF was diagnosed at 2 months following presentation of persistent cough. On admission,

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Yakut N, Kadayifci EK, Eralp EE, Gokdemir Y. Successful treatment of allergic bronchopulmonary aspergillosis with posaconazole in a child with cystic fibrosis: Case report and review of the literature. Lung India 2020;37:161-3.

he was hypoxic, tachypneic, and dyspneic. His oxygen saturation was 92% while breathing room air and his respiratory rate was 30 breaths per minute. His body temperature was 38.5°C. Auscultation of the lungs revealed obvious bilateral fine crackles and bilateral rhonchi. His other examination findings were normal. The admitting diagnosis was an acute exacerbation of his CF. He was started with intravenous meropenem and amikacin to cover pseudomonal infective exacerbation of his CF, physiotherapy, and supplementary oxygen. Serum immunoglobulin (Ig) E level was 3554 IU/mL (normal: 0.3–215 IU/mL), specific IgE to *Aspergillus fumigatus* was 74.5 KU/L (normal: <0.35 kU/L), a peripheral blood eosinophilia was 0.6 × 10^3/μL (normal 0.0–0.7 × 10^3/μL), and a sputum culture grew *A. fumigatus*. X-ray and computed tomography (CT) scan of the chest demonstrated cystic and tubular bronchiectasis in the bilateral upper-lung field and peribronchial nodular opacities bilaterally [Figures 1 and 2]. The patient was diagnosed with ABPA. He was started methyl prednisolone 1 mg/kg/day and itraconazole. Methyl prednisolone and itraconazole were continued for 2 months. Because of his failure to respond to itraconazole, the drug was discontinued, and he was then started on voriconazole. Voriconazole was discontinued after 1 month of the treatment because of severe photosensitivity. Voriconazole was then substituted with posaconazole 200 mg orally thrice daily, and the cough and sputum production improved significantly. On the 2nd month of the treatment, chest X-ray was also markedly improved [Figure 3]. He was discharged with posaconazole therapy. On follow-up, within 2 months of initiating posaconazole treatment, his IgE levels decreased to 1183 IU/mL and specific IgE to *A. fumigatus* to 44 KU/L. On the 3rd month of the treatment, his IgE levels were 706 IU/mL and specific IgE levels to *A. fumigatus* were 35.7 KU/L.

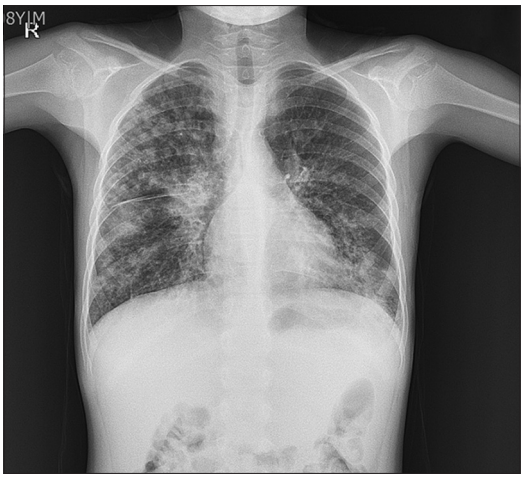

Figure 1: Diffuse peribronchial nodular opacities bilaterally

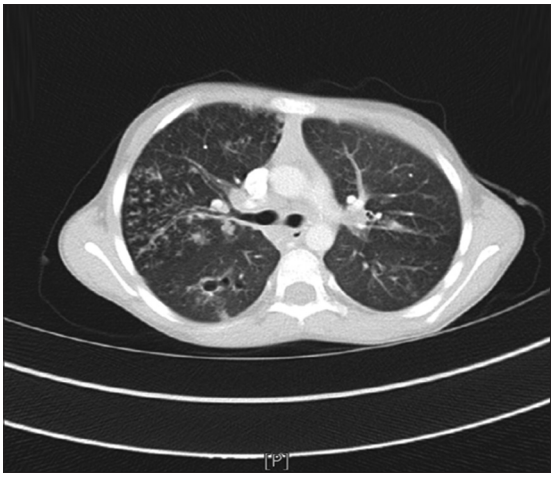

Figure 2: Cystic and tubular bronchiectasis in the bilateral upper lung

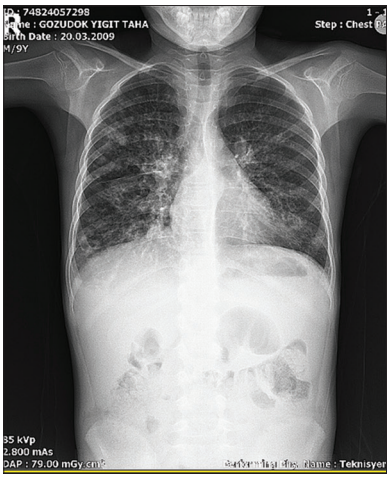

Figure 3: Improved peribronchial nodular opacities bilaterally

DISCUSSION

ABPA is a hypersensitivity pulmonary disease that affects children with asthma or CF. Diagnostic criteria of ABPA vary between asthma and CF patients. The clinical and pathological course of ABPA is variable, including recurrent exacerbations and chronic persistent symptoms. ABPA is usually a progressive disease. If left untreated, it can cause recurrent pulmonary consolidation, bronchiectasis, pulmonary fibrosis, and lung destruction.[2] Defining optimal treatment practices for ABPA is controversial. Treatment for allergic fungal diseases involves the use of CSs, antifungal agents, and monoclonal antibodies. The most commonly antifungal agents used for ABPA are amphotericin B and the azoles, including itraconazole, voriconazole, posaconazole, and ketoconazole.[3] The first reported use of an antifungal agents for ABPA was published in 1967. Since then, many different antifungal agents have been used to eradicate or suppress *A. fumigatus*. Although itraconazole has been used for many years, recently azole resistance has been recognized related to prolonged therapeutic exposure. In a retrospective study, Skov *et al*.[4] reported that high-dose itraconazole as monotheraphy or in combination with CS may be an efficient treatment for ABPA in patients with CF. However, the only randomized controlled study that used itraconazole for treatment of *A. fumigatus* in CF

patients demonstrated no significant benefit.[5] A recent randomized study of itraconazole versus prednisolone by Agarwal *et al*.[6] conducted on patients with ABPA complicating asthma reported that itraconazole is also effective compared to prednisolone with less adverse effects. Voriconazole, with superior oral bioavailability to itraconazole, is approved for primary therapy of invasive aspergillosis syndromes; furthermore, its use can lead to drug interactions and adverse effects, such as skin rash and photosensitization. In a case series, Glackin *et al*.[7] reported that total serum IgE level was decreased with voriconazole therapy in CF patients. An uncontrolled, retrospective study in 21 patients with CF showed an improvement in lung function in two children with voriconazole therapy.[8] In another study, Agarwal *et al*.[9] showed that voriconazole is effective and safe treatment option in acute-stage ABPA. While posaconazole is a new triazole that is recommended as an alternative therapy for invasive aspergillosis syndromes, the data about posaconazole usage in patients with ABPA are limited. In a systematic review, 38 studies including patients with ABPA were retrieved. Azoles were used in 29 of the studies. Posaconazole was used in one observational study.[3,10] In this review, Moreira *et al*. reported that antifungal treatment in ABPA improves symptoms, frequency of exacerbations, lung function, inflammatory biomarkers, and pulmonary infiltrates in most of the studies.[3] A case series by Chishimba *et al*.[10] outlined that both voriconazole and posaconazole are effective alternative treatment options for ABPA. In another study, Periselneris *et al*.[11] showed that there was a significant reduction in *Aspergillus* IgE with posaconazole compared to other triazoles in ABPA. The use of isavuconazole in ABPA is less well studied. However, a recent case reported by Jacobs *et al*.[12] showed that a patient with ABPA was successfully treated with isavuconazole without serious adverse effect. In our case, because of patient's failure to respond to itraconazole and severe photosensitization associated with voriconazole, both drugs should be subsequently discontinued. Our patient's clinical condition and inflammatory biomarkers were improved with posaconazole treatment. In a review, researched evidence about the effect of antifungal treatment for ABPA in patient with CF reported that there are no randomized controlled studies to evaluate the use of antifungal treatment for ABPA in patients with CF.[13] Furthermore, multicenter, larger, prospective studies are required to determine the effect of posaconazole treatment on disease outcomes and on future effective treatment options.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. 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.
2. Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. Eur Respir J 2011;37:865-72.
3. Moreira AS, Silva D, Ferreira AR, Delgado L. Antifungal treatment in allergic bronchopulmonary aspergillosis with and without cystic fibrosis: A systematic review. Clin Exp Allergy 2014;44:1210-27.
4. Skov M, Høiby N, Koch C. Itraconazole treatment of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Allergy 2002;57:723-8.
5. Aaron SD, Vandemheen KL, Freitag A, Pedder L, Cameron W, Lavoie A, *et al*. Treatment of aspergillus fumigatus in patients with cystic fibrosis: A randomized, placebo-controlled pilot study. PLoS One 2012;7:e36077.
6. Agarwal R, Dhooria S, Singh Sehgal I, Aggarwal AN, Garg M, Saikia B, *et al*. A randomized trial of itraconazole vs prednisolone in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. Chest 2018;153:656-64.
7. Glackin L, Leen G, Elnazir B, Greally P. Voriconazole in the treatment of allergic bronchopulmonary aspergillosis in cystic fibrosis. Ir Med J 2009;102:29.
8. 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.
9. Agarwal R, Dhooria S, Sehgal IS, Aggarwal AN, Garg M, Saikia B, *et al*. A randomised trial of voriconazole and prednisolone monotherapy in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. Eur Respir J 2018;52: pii: 1801159.
10. 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.
11. Periselneris J, Nwankwo L, Schelenz S, Shah A, Armstrong-James D. Posaconazole for the treatment of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. J Antimicrob Chemother 2019;74:1701-3.
12. Jacobs SE, Saez-Lacy D, Wynkoop W, Walsh TJ. Successful treatment of allergic bronchopulmonary aspergillosis with isavuconazole: Case report and review of the literature. Open Forum Infect Dis 2017;4:ofx040.
13. Elphick HE, Southern KW. Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. Cochrane Database Syst Rev 2016;11:CD002204.