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Atypical Presentation of Allergic Bronchopulmonary Aspergillosis: An Unusual Cause of Difficult-to-Treat Asthma

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Abstract

Allergic Bronchopulmonary aspergillosis (ABPA) commonly presents with persistently uncontrolled asthma, despite of the therapy with highest possible anti-asthma medications. Most common cause of ABPA is *Aspergillus fumigatus*. Hence, ABPA is one of the important differential diagnoses of difficult-to-treat asthma. Atypical presentation of ABPA misleads the diagnosis and asthma remains uncontrolled. Here we present such a case of 28-year-old non-smoker, normotensive male office worker who presented with persistent cough with scanty white, mucoid expectoration and gradually progressive breathlessness with bilateral crackles for last two years. Diagnosis of asthma was made based on clinical evidences and spirometry. Anti-asthma treatment was started and gradually stepped up. Further evaluation was done due to lack of clinical improvement, and diagnosis of ABPA was made from bilateral reticulonodular lesions on HRCT thorax, increased levels of serum IgE and *Aspergillus fumigatus* specific IgE, and positive aspergillin skin test. Oral prednisolone and itraconazole were started with anti-asthma medications.

Keywords: Allergic bronchopulmonary aspergillosis, *Aspergillus fumigatus*, asthma, difficult- to-treat, itraconazole, oral prednisolone

Introduction

According to Global Initiative for Asthma (GINA) guideline, patient who do not reach an acceptable level of control with highest possible step four treatment, i.e., high dose inhaled corticosteroids (ICS), inhaled long acting beta₂ agonist (LABA), montelukast, and oral sustained release theophylline, can be considered to have difficult-to-treat asthma. Incorrect diagnosis, non-compliance and incorrect technique of inhalation are most common causes for persistent uncontrolled asthma. Thereafter allergic bronchopulmonary aspergillosis (ABPA) should be excluded. Classical presentation makes the diagnosis of ABPA easy, but atypical clinicoradiological presentation makes the confusion. It was first described by Hanson *et al.* in 1952.[1] From India, first three cases of ABPA were reported in 1971.[2] The prevalence of ABPA in an asthmatic population is probably between 1-2% and as high as 14% in corticosteroid dependent asthma.[3,4] *Aspergillus fumigatus* is the commonest cause of ABPA but other species are also responsible.

Case Report

A 28-year-old nonsmoker, male office worker, presented with persistent cough with scanty, mucoid expectoration and gradually progressive breathlessness for last two years. There was no diurnal or seasonal variation of cough or breathlessness. History of intermittent fever along with increased severity of symptoms was present. Past history revealed that since childhood he was suffering from recurrent

cough and cold, nasal itching, and obstruction, especially in summer. No history of food or drug allergy and atopic dermatitis were revealed. Family history of asthma or atopy was not documented. Past history of tuberculosis was not present. He complained of retrosternal burning sensation, especially at night. Spirometry before presenting to us revealed obstructive ventilatory defect with partial reversibility to bronchodilator. Therefore, the patient was diagnosed as having asthma and medium dose ICS plus inhaled LABA was advised. Despite adequate compliance and correct inhaler technique, his asthma was uncontrolled; inhaled salbutamol was taken more than twice a week.

On general survey at presentation, only mild pallor was seen. His respiratory rate was 24 breaths/minute, and pulse rate 120 beats/minutes. Examination of the respiratory system revealed barrel shaped chest. There were bilateral hyperresonant percussion note, diminished vesicular breath sound, and bilateral crackles with occasional wheezing.

Absolute eosinophil count was 1,500/cmm. Sputum smear for acid fast bacilli and sputum culture for *Mycobacterium tuberculosis* were negative. Chest X - ray (CXR), posteroanterior view showed bilateral hyperinflated lung with reticular shadows. Spirometry in our institution showed mixed pattern with partial reversibility to inhaled salbutamol, although his effort was not adequate. The patient was advised high dose ICS, inhaled LABA, and once daily 10 mg montelukast, and the treatment was gradually stepped up by addition once daily 400 mg sustained release theophylline within two months, as his symptoms were not under control. We also advised once daily 40 mg esomeprazole and 30 mg sustained release domperidone, and once daily mometasone nasal spray (two sprays in each nostril). But our all efforts were in vain. High resolution computed tomogram (HRCT) of thorax revealed bilateral reticulonodular pattern with patchy consolidation [Figure 1]. Further investigations showed total serum immunoglobulin E (IgE) level was 1979.1 U/L and *Aspergillus fumigatus* specific serum IgE was positive (1.39 U/L). Skin prick test with aspergillin antigen was positive. From these, the diagnosis of ABPA was suggested, although diagnosis was confused with diffuse parenchymal lung disease (DPLD) due to atypical presentation and HRCT pattern. Bronchoalveolar lavage fluid analysis showed only eosinophils. Oral prednisolone at dose of 0.5 mg/kg/day along with oral itraconazole 200 mg twice daily was added. Patient gradually improved within one month. Follow up CXR and spirometry showed significant improvement after six weeks. Oral prednisolone after six weeks was tapered off at the rate of 5 mg/week over six weeks. Total duration of oral prednisolone was planned for six months. Itraconazole was continued as 200 mg twice daily for eight weeks, then 200 mg once daily for another eight weeks. On six month follow up, his asthmatic symptoms were well controlled, and CXR was normal.

Discussion

First confirmation of the diagnosis of asthma, then identification of the cause of the persisting symptoms, assessment of adherence with therapy and technique of inhalation therapy should be done. Lastly physician should search for alternative etiology of asthma like symptoms, and definitely ABPA is an important differential diagnosis for difficult-to-treat asthma.

ABPA is a hypersensitivity reaction to colonized *Aspergillus* in bronchi. Because of this hypersensitivity, eosinophilic infiltration of the lung parenchyma, bronchial wall and mucus plugging of the bronchi occur, which manifest as eosinophilic pneumonia, bronchiectasis, asthma like symptoms and subsequent fibrosis.[5]

Aspergillus after entering the airway releases gliotoxin, which causes epithelial damage and ciliary dysfunction. After that, it colonizes within the airways by adhering with fibronectin of extracellular matrix.[6] Fungal metabolites induce type I, type III and type IV hypersensitivity responses. Type I response leads to increased level of non-specific and *Aspergillus* specific IgE. Type III reaction results in high level of both total and *Aspergillus* specific IgG and IgA.[7] Type IV response leads to granuloma formation.[8]

Diagnosis of ABPA is made by diagnostic criteria laid down by Rosenberg *et al.*[7] There are eight major criteria like asthma, fleeting pneumonia, positive aspergillin skin test, eosinophilia, precipitin antibodies in serum, serum IgE level >1000 mg/mL, central bronchiectasis on HRCT thorax, presence of *Aspergillus fumigatus* specific IgG and IgE antibodies in serum, and three minor criteria like presence of

Aspergillus hyphae in sputum, expectoration of black mucus plug, and delayed skin reaction to Aspergillus antigen for the diagnosis of ABPA. These criteria may not be evident during remission or in fibrotic stage.

ABPA is divided into five stages, stage I - acute, stage II - remission, stage III - exacerbation, stage IV - corticosteroid dependent asthma, stage V- fibrotic end stage disease. Important HRCT findings are fleeting pneumonia in upper lobe, central bronchiectasis, and endobronchial mucus plugging.

Acute exacerbation of ABPA can be treated with oral prednisolone, and itraconazole along with step 4 management of GINA guideline. Oral prednisolone may be continued till good clinical response, radiological clearing of the shadows and a significant fall in the IgE level is achieved.[9]

Classical presentation of ABPA in difficult-to-treat asthma makes its diagnosis easy. In our case, due to irregular therapy, classical symptoms of asthma were altered and an irreversible component of airway obstruction was developed. Classical HRCT features of ABPA like fleeting pneumonia, and central bronchiectasis were absent in our case, whereas bilateral reticulonodular shadows confused us with the diagnosis of DPLD. But, persistent peripheral blood eosinophilia gave the initial clue for the diagnosis of ABPA, which was confirmed by high level of total and aspergillus specific IgE, positive aspergillin skin test, and eosinophil predominance on BAL fluid study. Therefore, the dose of steroid should not be increased inadvertently, rather should search for the ABPA in case of difficult-to-treat asthma, if compliance and correct inhaler technique are ensured.

Footnotes

Source of Support: Nil

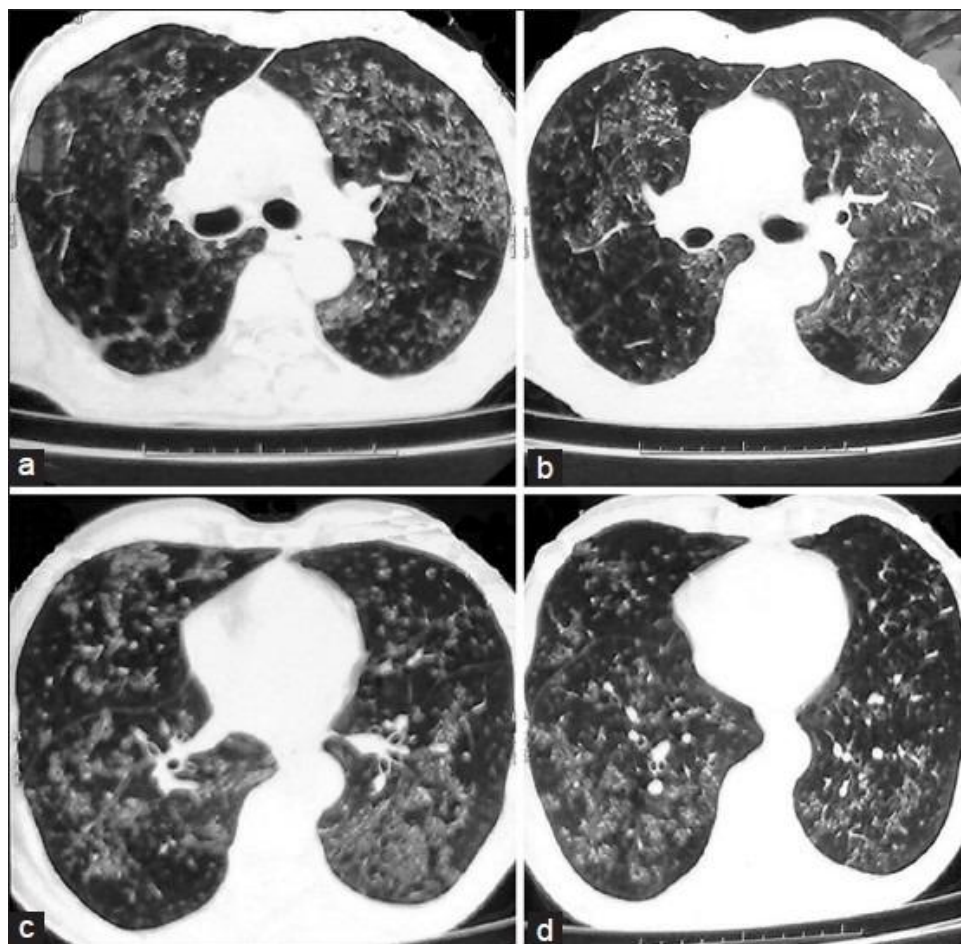
Conflict of Interest: None declared.

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Figures and Tables

Figure 1



HRCT scan of thorax showing bilateral reticulonodular opacities

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