“Fleeting Pulmonary Infiltrates in Allergic Bronchopulmonary Aspergillosis” Misdiagnosed as Tuberculosis

Shital Patil¹, Rajesh Patil²

Departments of ¹Pulmonary Medicine and ²Internal Medicine, MIMSR Medical College, Latur, Maharashtra, India

Abstract

Allergic bronchopulmonary aspergillosis (ABPA) is underdiagnosed and underevaluated routinely because of clinical and radiological overlap with tuberculosis (TB), especially in tropical setting with high TB burden countries like India. ABPA is the best-recognized manifestation of Aspergillus-associated hypersensitivity to Aspergillus antigens in patients with long-standing atopic asthma. ABPA with varied clinical presentation has been reported to occur in 20% of asthmatic patients admitted to hospitals and in 5% of all rhinitis cases. In this case report, we documented middle age male with known asthma case for many years with constitutional symptoms such as cough, fever, and shortness of breath diagnosed as TB and received anti-TB treatment for 4 weeks. Finally, we confirmed as a case of ABPA and documented complete clinical and radiological response to medical treatment with antifungals and systemic corticosteroids.

Keywords: Allergic bronchopulmonary aspergillosis, fleeting pulmonary infiltrates, tuberculosis

Introduction

Allergic bronchopulmonary aspergillosis (ABPA), the most widely studied Aspergillus-related allergic phenomenon, is an immune-mediated inflammatory syndrome caused by hypersensitivity to a ubiquitous fungus, Aspergillus fumigatus.¹ The clinical, radiological, and histological manifestations of bronchopulmonary aspergillosis depend not only on the number and virulence of the infective organism but also on the patient’s immune response.² ABPA is still under-recognized and under diagnosed in India, in spite of its relatively high prevalence. Many factors may contribute to this situation. Most common being the misdiagnosis with tuberculosis (TB) due to striking radiological similarity between ABPA and TB, and the patient goes on receiving anti-TB drugs for long periods. In some Indian studies, ABPA was misdiagnosed as TB in as high as 17%–50% cases.³

Case Report

A 48-year-old gentleman, known case of bronchial asthma since 15 years presented with a history of cough with minimal sputum production, shortness of breath Grade IV, and low-grade intermittent fever since 1 month.

He was taking inhalation treatment in the form of inhaled bronchodilators and inhaled corticosteroids since 15 years with a history of 3–4 exacerbations per year with hospitalization for same.

His X-ray done at general hospital was showing left upper zone airspace filling in heterogeneous opacity [Figure 1]. He was diagnosed as TB and started on empirical anti-TB treatment. His clinical response to antibiotics, bronchodilators, and anti-TB treatment was not satisfactory and his breathlessness worsened and referred to pulmonary medicine department Intensive Care Unit for respiratory care and further expert management.

On examination we documented

• Respiratory rate - 24/min, accessory muscles of respiration working
• PsO₂-90% room air (improved to 96% at nasal oxygen 3 L/min)
• Heart rate - 102/min
• Blood pressure - 100/60 mmHg

Case Report

A 48-year-old gentleman, known case of bronchial asthma since 15 years presented with a history of cough with minimal sputum production, shortness of breath Grade IV, and low-grade intermittent fever since 1 month.

He was taking inhalation treatment in the form of inhaled bronchodilators and inhaled corticosteroids since 15 years with a history of 3–4 exacerbations per year with hospitalization for same.

His X-ray done at general hospital was showing left upper zone airspace filling in heterogeneous opacity [Figure 1]. He was diagnosed as TB and started on empirical anti-TB treatment. His clinical response to antibiotics, bronchodilators, and anti-TB treatment was not satisfactory and his breathlessness worsened and referred to pulmonary medicine department Intensive Care Unit for respiratory care and further expert management.

On examination we documented

• Respiratory rate - 24/min, accessory muscles of respiration working
• PsO₂-90% room air (improved to 96% at nasal oxygen 3 L/min)
• Heart rate - 102/min
• Blood pressure - 100/60 mmHg

Address for correspondence:
Dr. Shital Patil, Department of Pulmonary Medicine, MIMSR Medical College, Latur, Maharashtra, India.
E-mail: drsvpatil1980@gmail.com

How to cite this article: Patil S, Patil R. "Fleeting pulmonary infiltrates in allergic bronchopulmonary aspergillosis” Misdiagnosed as tuberculosis. Int J Mycobacteriol 2018;7:186-90.
• Respiratory system evaluation - Bilateral wheeze and coarse crepitation's bilaterally
• Ear nose throat evaluation - Bilateral nasal turbinate hypertrophy.

**Investigations**
- Hemoglobin - 13.8 g%
- Total white blood cells - 16000/mm³
- Eosinophil percentage - 9% (of total differential cell count)
- Absolute eosinophil count - 1276/mm³
- Sputum eosinophil count - 8%
- Sputum for acid-fast bacilli - negative by Ziehl–Neelson stain
- Sputum for Gene Xpert Mycobacterium tuberculosis (MTB)/rifampicin - Negative for MTB genome
- Sputum culture for mycobacterium TB - Negative after 4 weeks in liquid media (middlebrook 7H9 media)
- Serum IgE level - 1036 ng/ml
- Serum precipitins - positive serum antibodies (precipitins) against Aspergillus species
- Sputum culture for fungus - yields A. fumigatus in fungal culture.

**Final diagnosis**
Final diagnosis confirmed as ABPA.

We confirmed as a case of ABPA and started on antifungals and steroids including itraconazole and omnacortil. We documented radiological and clinical response in 1st month [Figure 2], which is rare in TB where radiological response is delayed.

Patient received itraconazole as 100 mg twice daily for 16 weeks and omnacortil in tapering doses for 24 weeks. We started omnacortil at dose of 2 mg/kg and tapered gradually it over 24 weeks. We observed near total resolution of all radiological shadows at 3 months of treatment [Figure 3].

We collected all the details of case during our hospitalization, and we observed “classical fleeting pulmonary infiltrates” and other radiological signs as shown in Figures 4-9.

High-resolution computed tomography (HRCT) thorax was showing airspace consolidation with air-bronchogram involving right posterior segment [Figure 4] and bilateral centrilobular nodules and lingular segment [Figure 5].

HRCT thorax documented changing (fleeting) pulmonary infiltrates involving right lower lobe [Figure 6] and left upper lobe [Figure 7].

HRCT thorax of this presentation documented finger in glove appearance [Figure 8] and central bronchiectasis (CB) [Figure 9].

**Discussion**
ABPA was first described in 1952 when Hinson, Moon, and Plummer described three patients with recurrent wheezing, pulmonary infiltrates, eosinophilia in blood and sputum, and brown plugs or flecks in expectorated mucus. Clinically, it presents as increasingly severe asthma or cystic fibrosis (CF) exacerbations. There are no specific clinical or physical examination findings to ABPA. Symptoms can range from recurrent pulmonary exacerbations with cough, wheeze, and shortness of breath to systemic features with fever, anorexia, and malaise. Physical examination findings can
range from a normal examination to digital clubbing, auscultatory fine crackles, or bronchial breath sounds.[1,4]

However, it was not until 1977 that Rosenberg et al. in Chicago proposed a set of diagnostic criteria.[1,5]

**Primary criteria (1–6 suggestive, +7 definite)**
1. Episodic bronchial obstruction
2. Peripheral eosinophilia
3. Positive immediate skin test to *Aspergillus*
4. Positive precipitin test to Aspergillus
5. Increased total serum IgE
6. History of transient or fixed lung infiltrates
7. Proximal bronchiectasis.

**Secondary (supportive) criteria**

1. Brown plugs/flecks in sputum
2. Positive late (6–12 h/Arthus) skin test to Aspergillus.

Since then, as laboratory and clinical medicine have continued to advance, diagnostic criteria for ABPA have been modified, especially in light of improved and more specific serologic and radiographic testing.[1,6]

**Modified ISHAM working group 2013 criteria for the diagnosis of allergic bronchopulmonary aspergillosis**[1,8]

1. Predisposing asthma or CF
2. Obligatory criteria
   a. IgE >1000 IU/mL and
   b. Positive immediate skin test or increased IgE antibody to *Aspergillus*
3. Supportive (>2) criteria
   a. Eosinophilia >500
   b. Precipitins or increased IgG antibody to Aspergillus
   c. Consistent radiographic opacities

Mendelson *et al.* described the chest radiographic findings in various stages of ABPA.[7]

The active stage is characterized radiographically by transient and recurrent infiltrates that may clear with or without glucocorticoid therapy, although steroid therapy does hasten the clearing of opacities. Consolidation is believed to be one of the most common findings, and the occurrence of eosinophilic pneumonia has also been pathologically demonstrated [Table 1].[8]

| Stage | Description | Radiologic findings |
|-------|-------------|---------------------|
| I     | Acute phase | Normal; pulmonary infiltrates and mucoid impaction, predominantly in the upper lobes |
| II    | Remission   | Significant resolution of pulmonary infiltrates and clearance of mucoid impaction |
| III   | Exacerbation| Reappearance of infiltrates and/or mucoid impaction in previously involved, as well as new areas |
| IV    | Glucocorticoid-dependent ABPA | Significant resolution of pulmonary infiltrates and mucoid impaction, although fixed pulmonary opacities may be encountered |
| V     | End-stage (fibrotic) ABPA | Evidence of bronchiectasis, pulmonary fibrosis, pulmonary hypertension |

Tram-line shadows and band-like (toothpaste) shadows showing sometimes “V,” inverted “V,” or “Y” shaped shadows and finger-in-glove opacities may occur. They are the most characteristic finding of ABPA and represent mucoid impaction in dilated bronchi with occlusion of the distal end. These shadows are often transient, disappearing with the expulsion of secretions either spontaneously or following treatment.[9] CB is believed to be a characteristic finding in ABPA although there are no uniform criteria for the diagnosis of CB. Depending on the proximity of the dilated bronchi from the hilum at a point midway between the hilum and the chest wall, bronchiectasis is arbitrarily defined as central if confined to the medial two-thirds or the medial half of the lung.[1] Bronchiectasis can, however, extend to the periphery as well, and peripheral bronchiectasis has been described in 26%–39% of the lobes involved by bronchiectasis. The bronchiectasis in ABPA usually involves the upper lobes although, rarely, there may be involvement of the lower zones without involvement of the upper lobes.[1]

Systemic steroids have been shown to be an effective first-line treatment for APBA in both asthma and CF.[1] Agarwal *et al.* described a more aggressive approach with treatment dose of 0.75 mg/kg/day for 6 weeks, then 0.5 mg/kg/day for 6 weeks, followed by a tapering dose of 5 mg every 6 weeks for a total duration of 6–12 months.[1,9] Recently, Agarwal *et al.* performed a randomized controlled trial in patients with asthma and ABPA comparing the efficacy and safety of the two regimens.[1,10] The 0.5 mg/kg/day regimen was referred to as the “medium dose,” while the 0.75 mg/kg/day regimen was referred to as a “high-dose” regimen. Previous studies had looked at each regimen individually and there was some suggestion that high dose would be superior in the prevention of exacerbations.[1,9] This study was the first randomized controlled trial to compare two steroid regimens and determined that the medium dose oral glucocorticosteroids (prednisolone) were effective and safer than the high dose in the treatment of ABPA.[1,10]

Adding an antifungal agent to the regimen may have a steroid-sparing effect, reducing the need for steroids to control inflammation.[1,11] Azoles are used to reduce the antigen burden arising from fungal colonization of the airway. It is then expected that the reduction in antigenic stimulation would result in decreased inflammation and reduced disease severity and progression.[1,11] Itraconazole is an orally administered triazole that has fewer side effects and a wider spectrum of activity compared to ketoconazole. There have been open-label case series that suggests benefit in the treatment of ABPA in patients with and without CF.[11]

There are two randomized controlled trials using itraconazole in ABPA. Stevens *et al.* in 2000 published findings from their randomized, double-blind trial of treatment with either 200 mg of itraconazole twice daily or placebo for 16 weeks in patients.[12] These patients met immunologic and pulmonary function test criteria for corticosteroid-dependent ABPA.
A response was defined as at least a 50% reduction in steroid dose, a 25% reduction in serum IgE concentration, and either an improvement of 25% in exercise tolerance testing or pulmonary function testing or a resolution of pulmonary infiltrates on imaging. There was also a follow-on open-label arm of the trial where all patients received itraconazole 200 mg daily (a lower dose than in the placebo-controlled trial) for 16 weeks. The study demonstrated that, in patients with corticosteroid-dependent ABPA, adding itraconazole can lead to clinical improvement without significant risk of toxicity. In addition, the lower dose used in the open-label trial showed benefit as well.\[12\]

Prevalence of ABPA presenting as hemoptysis is 31%.\[13\] ABPA is frequency misdiagnosed as pulmonary TB. Almost half are initially misdiagnosed as pulmonary TB.\[9\]

**Conclusion**

ABPA has diverse clinical presentation ranging from typical bronchial asthma to tropical infectious pulmonary diseases such as pneumonia and TB. A high index of suspicion is must while managing these cases, especially in tropical countries like India where burden of TB is high. All possible measures should be taken to rule out TB. ABPA is easily managed with antifungals and steroids, if diagnosed early and will have successful treatment outcome before it reaches fibrosis stage.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Agarwal R. Allergic bronchopulmonary aspergillosis. In: Jindal SK, Shankar PS, Raoof S, Gupta D, Aggarwal AN, Agarwal R, editors. Textbook of Pulmonary and Critical Care Medicine. 1st ed. New Delhi: Jaypee Publications; 2010. p. 947-70.
2. Agarwal R. Allergic bronchopulmonary aspergillosis: Lessons learnt from genetics. Indian J Chest Dis Allied Sci 2011;53:137-40.
3. Behera D, Guleria R, Jindal SK, Chakrabarti A, Panigrahi D. Allergic bronchopulmonary aspergillosis: A retrospective study of 35 cases. Indian J Chest Dis Allied Sci 1994;36:173-9.
4. Tracy MC, Okorie CU, Foley EA, Moss RB. Allergic bronchopulmonary aspergillosis. J Fungi (Basel) 2016;2. pii: E17.
5. Rosenberg M, Patterson R, Mintzer R, Cooper BJ, Roberts M, Harris KE, et al. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med 1977;86:405-14.
6. 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.
7. Mendelson EB, Fisher MR, Mintzer RA, Halwig JM, Greenberger PA. Roentgenographic and clinical staging of allergic bronchopulmonary aspergillosis. Chest 1985;87:334-9.
8. McCarthy DS, Simon G, Hargreave FE. The radiological appearances in allergic broncho-pulmonary aspergillosis. Clin Radiol 1970;21:366-75.
9. Agarwal R, Gupta D, Aggarwal AN, Behera D, Jindal SK. Allergic bronchopulmonary aspergillosis: Lessons from 126 patients attending a chest clinic in North India. Chest 2006;130:442-8.
10. Agarwal R, Aggarwal AN, Dhooria S, Singh Sehgal I, Garg M, Saikia B, et al. A randomised trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. Eur Respir J 2016;47:490-8.
11. 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.
12. Stevens DA, Schwartz HJ, Lee JY, Moskovitz BL, Jerome DC, Catanzaro A, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med 2000;342:756-62.
13. Kumar R. Allergic bronchiopulmonary aspergillosis. Review of 29 cases. Indian J Tuberc 2000;47:237.