Changing Pulmonary Infiltrates in ABPA Misdiagnosed as Recurrent Pneumonia: A Case Report and Review of the Literature

Tekrarlayan Pnömoni Olarak Yanlış Tanı Konan ABPA Olgusunda Değişen Pulmoner İnfiltratlar: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Abstract

Pneumonia is the most common respiratory problem in tropical countries like India. Allergic bronchopulmonary aspergillosis (ABPA) is routinely underdiagnosed and under evaluated as a result of clinical and radiological overlap with many other respiratory conditions, including pneumonia and tuberculosis. ABPA is the best-recognized manifestation of the fungus Aspergillus, associated with hypersensitivity to Aspergillus antigens in patients with longstanding atopic asthma. ABPA has been reported to occur in 20% of asthmatic patients admitted to hospitals and in 5% of all rhinitis cases, with varied clinical presentations. This report is a description of the case of a middle-aged male with known asthma for several years and constitutional symptoms, such as a cough, fever, and shortness of breath, who was diagnosed and treated for recurrent pneumonia. The case was eventually confirmed as ABPA, and a complete clinical and radiological response to medical treatment with antifungals and systemic corticosteroids was documented.

Key words: ABPA, Recurrent pneumonia, fleeting pulmonary infiltrates.

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 underdiagnosed in India, in spite of its relatively high prevalence. Many factors may contribute to this situation. However, the clinical presentation of ABPA may be indistinguishable from pneumonia or pulmonary tuberculosis, especially in developing countries where the prevalence of pulmonary tuberculosis is still high (3).
CASE
A 44-year-old man, with known bronchi asthma for 15 years, presented with a cough with minimal sputum production, shortness of breath (Grade IV), and a low-grade intermittent fever for 15 days.
He had been using inhaled bronchodilators and inhaled corticosteroids as inhalation treatment for 15 years, with a history of infrequent exacerbation and hospitalization for the same conditions.
An X-ray done at a general hospital indicated heterogeneous opacity filling the left upper zone air space (Figure 1). He was diagnosed with community-acquired pneumonia and empirical antibiotic treatment with amoxicillin and levofloxacin was initiated. The clinical response to antibiotics and bronchodilators was not satisfactory, his breathlessness worsened, and the patient was referred to the pulmonary medicine department intensive care unit for respiratory care and further expert management.
The patient reported experiencing similar episodes 1 year earlier that were diagnosed as community-acquired pneumonia and treated with empirical antibiotics; however the treatment provided only partial relief of symptoms. Underlying bronchial asthma may lead to misleading symptoms and an incorrect diagnosis.

Respiratory system evaluation- bilateral wheeze and coarse crackles
Ear/nose/throat evaluation- bilateral nasal turbinate hypertrophy

Test results:
Hemoglobin-13.8 gm%
Total white blood cell count- 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 with Zeihl-Neelsen stain
Sputum for GeneXpert Mycobacterium tuberculosis/rifampicin (MTB/RIF) (Cepheid, Inc., Sunnyvale, CA, USA)- negative for MTB genome
Sputum culture for Mycobacterium tuberculosis-negative after 4 weeks in liquid media (Middlebrook 7H9 media)
Serum immunoglobulin E (IgE) level - 1036 ng/mL
Serum precipitins- positive serum antibodies (precipitins) for Aspergillus species
Sputum culture for fungus- Aspergillus fumigatus identified in fungal culture
Final diagnosis- confirmed as ABPA

This case was confirmed as ABPA and the patient was started on antifungals and steroids: itraconazole and omnacortil. We documented radiological and clinical response in the first month (Figure 2), which is rare in tuberculosis where radiological response is often delayed.

Examination findings:
Respiratory rate- 24/per minute, functional accessory muscles of respiration
Partial oxygen saturation- 90% room air (improved to 96% at nasal oxygen 3 L/minute)
Heart rate – 102/minute
Blood pressure- 100/60 MmHg

Figure 1: Showing left upper zone air space heterogeneous opacity

Figure 2: Response to treatment after one month

This patient received itraconazole at a dose of 100 mg twice daily for 16 weeks and omnacortil at dose of 2 mg/kg, which was tapered gradually over 24 weeks.
Near total resolution of all radiological shadows was observed after 3 months of treatment (Figure 3). The classic sign of fleeting pulmonary infiltrates, as well as other radiological signs were observed (Figures 4-9). A high-resolution computed tomography image of the thorax showing air space consolidation with air-bronchogram involving the right posterior segment (Figure 4), bilateral centrilobular nodules and lingular segment (Figure 5).

A high-resolution computed tomography image of the thorax documented changing (fleeting) pulmonary infiltrates involving the right lower lobe (Figure 6) and left upper lobe (Figure 7). A high-resolution computed tomography of the thorax documented the finger-in-glove sign (Figure 8) and central bronchiectasis (Figure 9).

**DISCUSSION**

ABPA was first described in 1952 when Hinson, Moon, and Plummer wrote of 3 patients with recurrent wheezing, pulmonary infiltrates, eosinophilia in the blood and sputum, and brown plugs or flecks in expectorated mucus. Clinically, ABPA presents like increasingly severe asthma or exacerbation of cystic fibrosis (CF) (4). There are no specific clinical or physical examination findings. The symptoms can range from recurrent pulmonary exacerbations with cough, wheezing, and shortness of breath, to systemic features, including fever, anorexia, and malaise. Physical examination findings can range from normal results to the observation of digital clubbing, auscultatory fine crackles, or bronchial breath sounds (4).

Two differential diagnoses for ABPA include bacterial pneumonia and pulmonary tuberculosis, which should be
given great care in India and other areas where there is a high prevalence (3). It was not until 1977 that Rosenberg, Patterson et al. (5) proposed a set of diagnostic criteria.

![Figure 8: Finger in glove appearance](image)

![Figure 9: Central bronchiectasis](image)

**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 serological and radiographic testing (6).

**Modified International Society for Human and Animal Mycology Working Group 2013 criteria for diagnosis of ABPA (6)**

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

Mendelson et al. (7) described chest radiographic findings in various stages of ABPA.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Radiological findings</th>
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<tbody>
<tr>
<td>I</td>
<td>Acute phase</td>
<td>Normal, pulmonary infiltrates and mucoid impaction, predominantly in the upper lobes</td>
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<tr>
<td>II</td>
<td>Remission</td>
<td>Significant resolution of pulmonary infiltrates and clearance of mucoid impaction</td>
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<tr>
<td>III</td>
<td>Exacerbation</td>
<td>Reappearance of infiltrates and/or mucoid impaction in previously involved, as well as new, areas</td>
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<tr>
<td>IV</td>
<td>Glucocorticoid dependent ABPA</td>
<td>Significant resolution of pulmonary infiltrates and mucoid impaction, although fixed pulmonary opacities may be encountered</td>
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<tr>
<td>V</td>
<td>End-stage (fibrotic) ABPA</td>
<td>Evidence of bronchiectasis, pulmonary fibrosis, pulmonary hypertension</td>
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**ABPA: Allergic bronchopulmonary aspergillosis**

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 (8).

Tram-line shadows, band-like (toothpaste) shadows showing sometimes V-shaped, inverted V-, or Y-shaped shadows, and finger-in-glove opacities may occur. These 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 (8). Central bronchiectasis (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 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% to 39% of lobes affected 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. Agarwal et al. (9) described a more aggressive approach with a 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 to 12 months. Recently, Agarwal et al. (10) performed a randomized controlled trial with patients who had a diagnosis of asthma and ABPA comparing the efficacy and safety of the 2 regimens. 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 the high dose would be superior in the prevention of exacerbation (9). This study was the first randomized, controlled trial to compare 2 steroid regimens, and it was determined that the medium dose of oral glucocorticosteroids (prednisolone) was both effective and safer than the high dose in the treatment of ABPA (10).

Adding an antifungal agent to the regimen may have a steroid-sparing effect, reducing the need for steroids to control inflammation (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. Itraconazole is an orally administered triazole that has fewer side effects and a wider spectrum of activity compared with ketoconazole. There have been open-label case series that suggest benefit in the treatment of ABPA in patients with and without CF (11).

There are 2 randomized controlled trials in the literature using itraconazole in ABPA. Stevens et al. (12) in 2000 published findings from their randomized, double-blind trial of treatment with either 200 mg of itraconazole twice daily or a placebo for 16 weeks in patients. These patients met immunological 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 of the 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. Additionally, the lower dose used in the open-label trial showed a benefit as well (12).

CONCLUSION
ABPA has a diverse clinical presentation, ranging from typical bronchial asthma to tropical infectious pulmonary diseases, like pneumonia and tuberculosis. All possible measures should be taken to rule out ABPA, especially in a scenario with recurrent pneumonia, for example, with changing pulmonary infiltrates. A high index of suspicion is necessary while managing these cases, particularly in tropical countries, like India, where pneumonia is a frequently encountered respiratory issue. ABPA is easily managed with antifungals and steroids if diagnosed early, and the treatment outcome will likely be successful if diagnosed before it reaches the fibrosis stage.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS

YAZAR KATKILARI
REFERENCES


