

Pulmonary Masses in Allergic Bronchopulmonary Aspergillosis: Mechanistic Explanations

Ritesh Agarwal MD DM, Rajagopala Srinivas MD, Ashutosh N Aggarwal MD DM, and Akshay K Saxena MD

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a disorder caused by hypersensitivity to *Aspergillus* antigens, and is currently the best recognized manifestation of *Aspergillus*-associated hypersensitivity disorders. ABPA occurs in 1–2% of patients with bronchial asthma and 2–15% of patients with cystic fibrosis.¹ Patients with ABPA may present with recurrent asthma exacerbations, expectoration of dark brown mucus plugs, hemoptysis, or systemic symptoms such as fever, anorexia, malaise, or weight loss. The Rosenberg criteria² are most widely used for diagnosis and include 8 major and 3 minor criteria. The major criteria (easily remembered by the mnemonic ARTEPICS) are:

- A - Asthma
- R - Radiographic fleeting pulmonary opacities
- T - Skin test positive (type 1 reaction) for *Aspergillus fumigatus*
- E - Eosinophilia
- P - Precipitating antibodies (Immunoglobulin G [IgG]) in serum
- I - Immunoglobulin E (IgE) in serum elevated (> 1,000 IU/mL)
- C - Central bronchiectasis
- S - Serum-specific IgG and IgE against *A. fumigatus*

If 6 of the 8 primary criteria are met, the diagnosis is certain.

The minor criteria are *Aspergillus* in sputum, expectoration of brownish-black mucus plugs, and delayed skin reaction to *Aspergillus* antigen (type 3 reaction).

Patients with ABPA present with diverse radiographic manifestations, including finger-in-glove and toothpaste opacities, air-fluid levels from dilated bronchi, and tram-line shadows from edematous bronchial walls.³ High-resolution CT characteristically shows central bronchiectasis, mucus-filled bronchi (bronchoceles), consolidation, and tree-in-bud appearance of centri-lobular nodules.⁴ Pulmonary masses in ABPA are uncommon but have been described in the literature.^{5–8} Proximal bronchoceles (often inseparable from the hilum) may simulate hilar mass.⁹

We report 3 patients with pulmonary masses and ABPA. We also discuss mechanisms by which ABPA might lead to such parenchymal lesions.

Case Summaries

Patient 1

A 38-year-old female who was known to be asthmatic since childhood was referred to our chest clinic with a 2-month history of worsening breathlessness, vague right upper chest pain, and streaky hemoptysis. She had a history of anorexia and weight loss of 4 kg, without fever or cough. Her asthma was well-controlled with medications (budesonide 200 µg plus formoterol 6 µg, 1 puff twice daily, and albuterol 100 µg, 2 puffs as needed) prior to 2 months before this presentation. She had never been hospitalized for an asthma exacerbation. Physical examination showed decreased breath sounds in the right infraclavicular region, and no wheeze. A chest radiograph showed a right-upper-lobe mass, which was confirmed on computed tomography (CT) (Fig. 1). Fiberoptic bronchoscopy was normal, and bronchoalveolar lavage fluid (BALF) was negative for acid-fast bacilli, fungi, and malignant cells, but showed eosinophilia of 7%. CT-guided fine-needle-aspiration cytology was planned, but, in view of her asthma, hemoptysis, and BALF eosinophilia, we did the work-up for ABPA. A skin test for *A. fumigatus* was

Ritesh Agarwal MD DM, Rajagopala Srinivas MD, Ashutosh N Aggarwal MD DM are affiliated with the Department of Pulmonary Medicine, and Akshay K Saxena MD is affiliated with the Department of Radiodiagnosis, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

The authors report no conflicts of interest related to the content of this paper.

Correspondence: Ritesh Agarwal MD DM, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India. E-mail: riteshgpi@gmail.com.

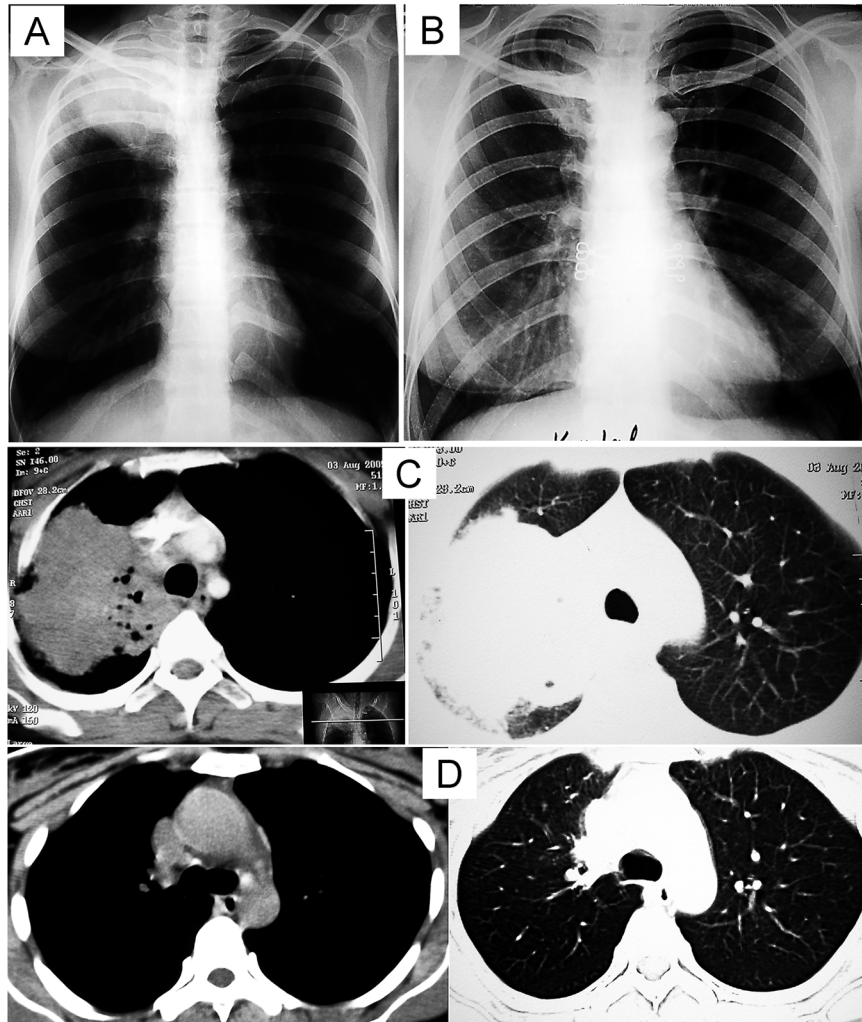


Fig. 1. Patient 1. Chest radiograph (A) at presentation, shows large right-upper-lobe mass, and (B) after 6 weeks of prednisolone, shows resolution of the mass. Computed tomogram (lung [left] and mediastinal window [right]) (C) at presentation, confirms the right-upper-lobe mass and shows air bronchograms, and (D) after 6 weeks of prednisolone, confirms resolution.

positive (types 1 and 3). Her total IgE count was 21,400 IU/mL (normal is < 100 IU/mL). IgE specific to *A. fumigatus* was 27.3 kilounits of antibody per liter (kUA/L) (normal is < 0.35 kUA/L). Absolute eosinophil count was 1,850/ μ L. Precipitins to *A. fumigatus* were positive. Spirometry showed mild obstruction and substantial bronchodilator reversibility. We started her on prednisolone 40 mg/d, with which she had complete resolution of all her symptoms. Six weeks later her IgE was 4,950 IU/mL, and a chest radiograph and CT (see Fig. 1) showed complete resolution. Prednisolone was tapered and stopped after a total course of 9 months. She is doing well on follow-up at 1 year.

Patient 2

A 38-year-old male presented to the chest clinic with right-sided dull aching chest pain for 2 months. He

denied any fever, cough, expectoration, wheeze, hemoptysis, or weight loss. Chest radiograph showed a large mass in the right mid-zone, which was confirmed on CT (Fig. 2). The CT also revealed characteristic high-attenuation areas within the mass. There was no adenopathy or pleural effusion. Bronchoscopy revealed thick inspissated secretions from the right main bronchus. *Aspergillus* skin test was strongly positive for type 1 and type 3 reactions. His total serum IgE was elevated (4,900 IU/mL), as was his IgE specific for *A. fumigatus* (16.2 kUA/L). *Aspergillus* precipitins were positive. Absolute eosinophil count was 768/ μ L. Spirometry and bronchodilator reversibility were normal. BALF was negative for acid-fast bacilli, but culture revealed growth of *A. fumigatus*. We started him on oral prednisolone at 40 mg/d, with which he had complete resolution of all his symptoms. After 6 weeks his IgE was 2,050 IU/mL, and

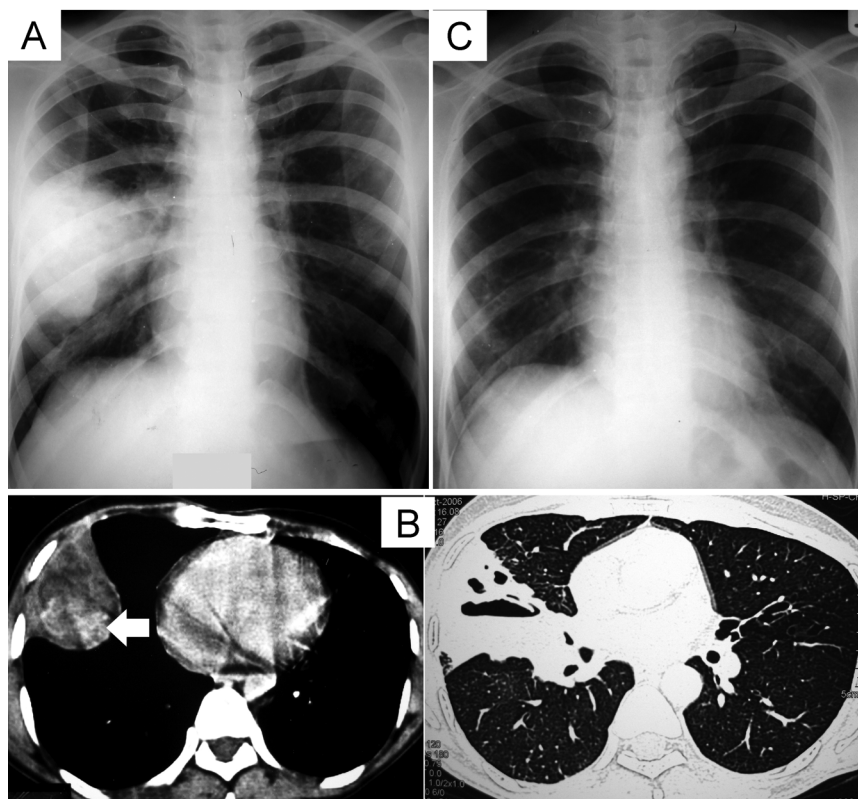


Fig. 2. Patient 2. A: Chest radiograph at presentation, shows a mass in the right mid-zone. B: Noncontrast computed tomogram at presentation. The mediastinal window (left) confirms a pleura-based mass in the lateral segment of the right middle lobe, with hyperdense attenuation (arrow). The high-resolution sections of the lung window (right), done following bronchoscopy, confirms the mass and shows an air-fluid level that developed secondary to bronchoalveolar lavage. There is also evidence of central bronchiectasis in the left lung. C: Chest radiograph after 6 weeks of prednisolone shows complete disappearance of the pulmonary mass. There are few linear opacities suggesting fibrosis in the right mid-zone.

radiograph showed substantial resolution (see Fig. 2). Prednisolone was tapered, and he is doing well on follow-up at 9 months.

Patient 3

A 26-year-old male who was known to be asthmatic presented to the chest clinic with worsening dyspnea, hemoptysis, and expectoration of brownish plugs for 2 weeks. He denied any fever, cough, expectoration, wheeze, or weight loss. He did not smoke or drink alcohol. Physical examination was normal. Chest radiograph showed a large mass in the right mid-zone area. High-resolution CT (Fig. 3) revealed bilateral bronchiectasis, extensive mucus plugging, and hyperdense mucus (90 Hounsfield units). Serum IgE was 3,120 IU/mL, serum IgE specific to *A. fumigatus* was 8.93 kUA/L, and *Aspergillus* skin test was strongly positive (types 1 and 3). Spirometry revealed severe obstruction, with substantial bronchodilator reversibility. Bronchoscopy was normal, BALF showed eosinophilia (8%), and culture revealed growth of *A. fumigatus*. Oral

prednisolone at 40 mg/d completely resolved all of his symptoms. After 6 weeks his IgE was 1,128 IU/mL, and radiograph showed complete resolution (see Fig. 3). Prednisolone was tapered, and he is doing well on follow-up at 6 months.

Discussion

ABPA is a complex immune hypersensitivity reaction that manifests when the bronchi become colonized by *Aspergillus*,¹⁰ which causes chronic inflammation, then bronchiectasis, fibrosis, and, ultimately, respiratory failure.¹¹ Although there are 200 species of *Aspergillus*, only a few have been reported to cause ABPA: *A. fumigatus*, *A. flavus*, and *A. niger*.

A wide spectrum of radiographic changes can be seen in patients with ABPA,^{4,12} including transient migratory radiographic opacities secondary to eosinophilic pneumonia.³ High-resolution CT characteristically shows central bronchiectasis, mucus-filled bronchi, consolidation, and centri-lobar nodules.⁴ Other manifestations include seg-

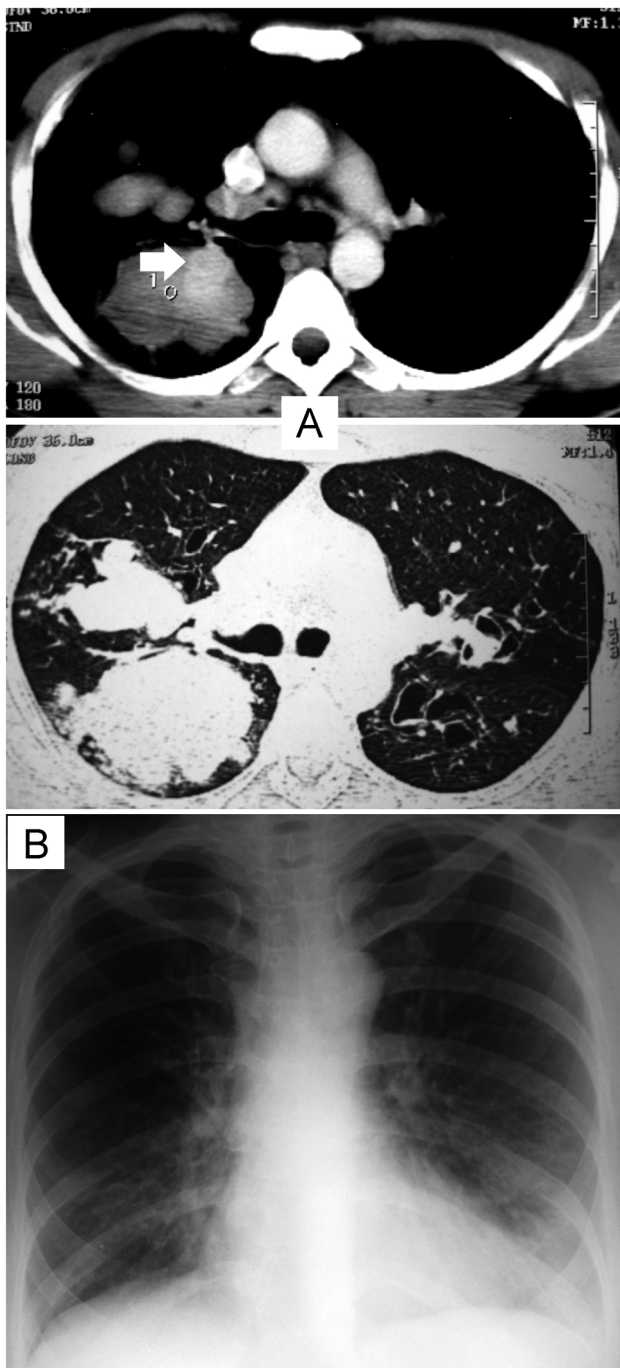


Fig. 3. Patient 3. A: Computed tomogram at presentation. The mediastinal window (above) shows multiple bronchoceles and areas of high-attenuation (arrow). The lung window (below) shows areas of central bronchiectasis in the left lung. B: Chest radiograph after 6 weeks of prednisolone shows complete disappearance of the mass.

mental or lobar collapse, pleural effusions, and spontaneous pneumothorax.⁴ A characteristic radiographic finding in ABPA is high-attenuation mucus (ie, the mucus plug is visually denser than the normal skeletal muscle, or the

mucus-plug density is 100–170 Hounsfield units), which is attributable to contained calcium salts, metals (the ions of iron and manganese), and/or hemorrhagic products.^{13,14} High-attenuation mucus occurred in 2 of our patients. The presentation of ABPA as large pulmonary masses (as seen in our patients) is distinctly uncommon.^{5–8}

These masses are usually attributed to mucus plugging of bronchi and distal accumulation of secretions,^{5–7} as seen in Patient 2, or large bronchoceles (mucus-filled dilated bronchi), which appear as masses but with no proximal obstruction, as seen in Patient 3.⁸ Another mechanism, which we saw in Patient 1, is probably inflammatory eosinophilic parenchymal consolidation, without endobronchial involvement, appearing as pseudotumor. Although we did not confirm it with surgical lung biopsy, we hypothesize that an eosinophilic organizing pneumonia due to adjoining intense bronchial inflammation led to pseudotumor formation. The finding of BALF eosinophilia suggests this possibility. Unlike the other reported cases in the literature, another interesting feature in Patient 1 was the absence of central bronchiectasis,⁸ which further strengthens the suspicion of an inflammatory pseudotumor due to an intense immune reaction, which had probably not had enough time for bronchiectasis to set in. Though bronchoceles are classically seen in ABPA, reversible bronchoceles are almost pathognomonic of ABPA.¹⁵

Many a solitary pulmonary mass or nodule is malignant, and recognition of subtle radiographic clues and epidemiologic markers of benign lesions can be important to rapidly evaluate such patients. The presence of hyperdense mucus is invaluable in several ways.¹³ It is the most characteristic (if not pathognomonic) finding of ABPA, and occurs in almost 19% of these patients.¹⁴ The high-attenuation calcium salts generally indicate chronicity and negate an acute event. And, high-attenuation mucus is sufficiently specific for ABPA to allow a confident screen for the same.

Teaching Points

ABPA can present as pulmonary mass lesions and must be considered in the differential diagnosis of—particularly but not restricted to—patients with a history of asthma. High-attenuation density within these masses can help narrow the differential diagnosis. It is important to consider ABPA in the diagnostic algorithm of pulmonary masses, because treatment with glucocorticoids is associated with excellent outcomes, as seen in our patients.

REFERENCES

1. Greenberger PA. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 2002;110(5):685–692.
2. 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(4):405-414.
3. Thompson BH, Stanford W, Galvin JR, Kurihara Y. Varied radiologic appearances of pulmonary aspergillosis. *Radiographics* 1995; 15(6):1273-1284.
 4. Shah A. Allergic bronchopulmonary and sinus aspergillosis: the roentgenologic spectrum. *Front Biosci* 2003;8:e138-e146.
 5. Cote CG, Cicchelli R, Hassoun PM. Hemoptysis and a lung mass in a 51-year-old patient with asthma. *Chest* 1998;114(5):146-148.
 6. Sanchez-Alarcos JM, Martinez-Cruz R, Ortega L, Calle M, Rodriguez-Hermosa JL, Alvarez-Sala JL. ABPA mimicking bronchogenic cancer. *Allergy* 2001;56(1):80-81.
 7. Otero González I, Montero Martínez C, Blanco Aparicio M, Valiño López P, Vereá Hernando H. [Pseudotumoral allergic bronchopulmonary aspergillosis]. *Arch Bronconeumol* 2000;36(6):351-353. *Article in Spanish.*
 8. Coop C, England RW, Quinn JM. Allergic bronchopulmonary aspergillosis masquerading as invasive pulmonary aspergillosis. *Allergy Asthma Proc* 2004;25(4):263-266.
 9. Agarwal R, Reddy C, Gupta D. An unusual cause of hilar lymphadenopathy. *Lung India* 2006;23(2):90-92.
 10. Greenberger PA. Allergic bronchopulmonary aspergillosis. In: Grammer LC, Greenberger PA, editors. *Patterson's allergic diseases*. 6th ed. Philadelphia: Lippincott Williams Wilkins; 2002: 529-554.
 11. Neeld DA, Goodman LR, Gurney JW, Greenberger PA, Fink JN. Computerized tomography in the evaluation of allergic bronchopulmonary aspergillosis. *Am Rev Respir Dis* 1990;142(5):1200-1205.
 12. 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(2):442-448.
 13. Agarwal R, Aggarwal AN, Gupta D. High-attenuation mucus in allergic bronchopulmonary aspergillosis: another cause of diffuse high-attenuation pulmonary abnormality. *Am J Roentgenol* 2006; 186(3):904.
 14. Agarwal R, Gupta D, Aggarwal AN, Saxena AK, Chakrabarti A, Jindal SK. Clinical significance of hyperattenuating mucoid impaction in allergic bronchopulmonary aspergillosis: an analysis of 155 patients. *Chest* 2007;132(10):1183-1190.
 15. Lemire P, Trepanier A, Hebert G. Bronchocele and blocked bronchiectasis. *Am J Roentgenol* 1970;110(4):687-693.