

A rare cause of acute respiratory failure – allergic bronchopulmonary aspergillosis

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Summary

Allergic bronchopulmonary aspergillosis (ABPA) is a complex immune hypersensitivity reaction to *Aspergillus fumigatus*, usually complicating the course of patients with asthma and cystic fibrosis. The common radiological manifestations encountered are fleeting pulmonary opacities, bronchiectasis and mucoid impaction. Uncommon radiological findings encountered in ABPA include pulmonary masses, perihilar opacities simulating hilar adenopathy, miliary nodules and pleural effusions. Herein, we describe a 22-year-old female patient who presented with acute hypoxaemic respiratory failure secondary to left lung collapse, which necessitated rigid bronchoscopy for management. On further evaluation, she was diagnosed to have ABPA. This is the first documented report of ABPA presenting as acute hypoxaemic respiratory failure secondary to lung collapse.

Introduction

Aspergillus can affect the respiratory system in diverse fashion, which includes simple colonisation, aspergilloma, hypersensitivity pneumonitis, IgE-dependent asthma, allergic bronchopulmonary aspergillosis (ABPA), chronic necrotising pulmonary aspergillosis and invasive pulmonary aspergillosis, invasive airway aspergillosis and severe asthma with fungal sensitisation [Soubani AO. The clinical spectrum of pulmonary aspergillosis. *Chest* 2002; **121**: 1988–99; Shah A. *Aspergillus*-associated hypersensitivity respiratory disorders. *Indian J Chest Dis Allied Sci* 2008; **50**: 117–28; Denning DW. Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitisation – the fungal asthma sensitization trial (FAST) study. *Am J Respir Crit Care Med* 2008; **179**: 11–8]. ABPA, currently the best recognised manifestation of *Aspergillus*-associated hypersensitivity disorders is a complex pulmonary disorder induced by hypersensitivity to antigens of *Aspergillus fumigatus* that colonise the

bronchial tree (Agarwal R. Allergic bronchopulmonary aspergillosis. *Chest* 2009; **135**: 805–26). It complicates the course of almost 13% of asthmatics attending Chest Clinics and 8% of patients with cystic fibrosis (Agarwal R. Allergic bronchopulmonary aspergillosis. *Chest* 2009; **135**: 805–26; Agarwal R. *Aspergillus* hypersensitivity and allergic bronchopulmonary aspergillosis in patients with bronchial asthma: systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2009; **13**: 936–44). Most patients present with poorly controlled asthma, recurrent asthma exacerbations, expectoration of dark brown mucous plugs, haemoptysis or systemic features such as fever, anorexia and weight loss. The Rosenberg-Patterson criteria are the most widely used for diagnosis and include eight major (asthma, fleeting pulmonary opacities on chest radiograph, type I skin test reaction to *A. fumigatus* antigen, eosinophilia, serum precipitins against *A. fumigatus*, elevated serum total IgE levels, central bronchiectasis, and elevated levels of serum IgG and/or IgE against *A. fumigatus*) and three minor criteria (growth of *A. fumigatus* in sputum, expectoration of brownish-black mucous plugs and type III skin reaction to *A. fumigatus* antigen). If six of the eight primary criteria are met, the diagnosis is said to be made with certainty (Rosenberg M. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. *Ann Intern Med* 1977; **86**: 405–14; Patterson R. Allergic bronchopulmonary aspergillosis. *Nat-*

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ural history and classification of early disease by serologic and roentgenographic studies. *Arch Intern Med* 1986; **146**: 916–8).

The radiological findings generally encountered in ABPA include central bronchiectasis, mucous impaction and centrilobular nodules with a tree-in-bud pattern (Agarwal R. Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest clinic in north India. *Chest* 2006; **130**: 442–8). The uncommon radiological manifestations noted in ABPA include presentation as large pulmonary masses (Agarwal R. Pulmonary masses in allergic bronchopulmonary aspergillosis: mechanistic explanations. *Respir Care* 2008; **53**: 1744–8), pleural effusions (O'Connor TM. Allergic bronchopulmonary aspergillosis: a rare cause of pleural effusion. *Respirology* 2001; **6**: 361–3) and miliary nodules (Agarwal R. Case report: A rare cause of miliary nodules – allergic bronchopulmonary aspergillosis. *Br J Radiol* 2009; **82**: e151–4). The exact mechanism by which bronchial wall damage evolves and gives rise to bronchiectasis and pulmonary fibrosis is poorly understood (Wark P. Pathogenesis of allergic bronchopulmonary aspergillosis and an evidence-based review of azoles in treatment. *Respir Med* 2004; **98**: 915–23; Rapaka RR. Pathogenesis of allergic bronchopulmonary aspergillosis in cystic fibrosis: current understanding and future directions. *Med Mycol* 2008; 1–7). However, if the disease is not recognised, the chronic inflammatory process can progress inexorably and result in irreversible pulmonary dysfunction because of bronchiectasis and/or pulmonary fibrosis, and ultimately respiratory failure and cor pulmonale.

Allergic bronchopulmonary aspergillosis is most often a non-acute respiratory syndrome that lingers on for years without diagnosis, and seldom presents as a life-threatening condition. In fact, presentation as acute hypoxaemic respiratory failure is not previously reported. Herein, we report a case of ABPA presenting as acute respiratory failure secondary to unilateral whole lung collapse, and review the mechanisms that can cause such a presentation.

Case report

A 22-year-old female patient with no respiratory illness in the past presented to our Chest Clinic with complaints of cough with minimal mucoid expectoration and worsening dyspnoea of 7 days duration. The breathlessness had progressively worsened over 7 days and at presentation, the patient was dyspnoeic at rest. There was no history of haemoptysis, chest pain, wheeze, fever, anorexia or weight loss. On examination, the heart rate

was 110 beats per minute, respiratory rate 35 breaths per minute and blood pressure was 100/70 mmHg. There was no pallor, icterus, cyanosis, clubbing, lymphadenopathy or pedal oedema. Jugular venous pressure was normal. Auscultation of the chest revealed absence of breath sounds on the left side. Rest of the physical examination was unremarkable. Chest radiograph revealed homogenous opacity on the whole of the left lung with volume loss and mediastinal shift to the left side suggesting a left lung collapse (Fig. 1). Pulse oximetric saturation was 75% on room air. Arterial blood gas analysis was suggestive of type I respiratory failure (pH – 7.45, PaO₂ – 45 mmHg, PaCO₂ – 18 mmHg, HCO₃ – 20 mEq l⁻¹). Fiberoptic bronchoscopy performed under oxygen supplementation revealed thick secretions in the left main bronchi; however, the procedure had to be abandoned as a result of hypoxaemia. Subsequently, under total intravenous anaesthesia, rigid bronchoscopy was performed. The left main bronchus was intubated with the rigid bronchoscope and thick secretions and mucous plug were noted in the left main bronchus extending to carina. Bronchial lavage was performed and the secretions were aspirated and sent for cytology. The underlying bronchus was normal; there was no underlying foreign body or adenoma. A postprocedure chest radiograph showed evidence of residual left lower lobe collapse (Fig. 2); however, a chest radiograph carried out 2 weeks later was normal (Fig. 3). Bronchial fluid sent for cytology showed numerous eosinophils, Charcot-Leyden crystals and septate hyphae conforming to the morphology of



Figure 1 Chest radiograph showing left lung collapse.

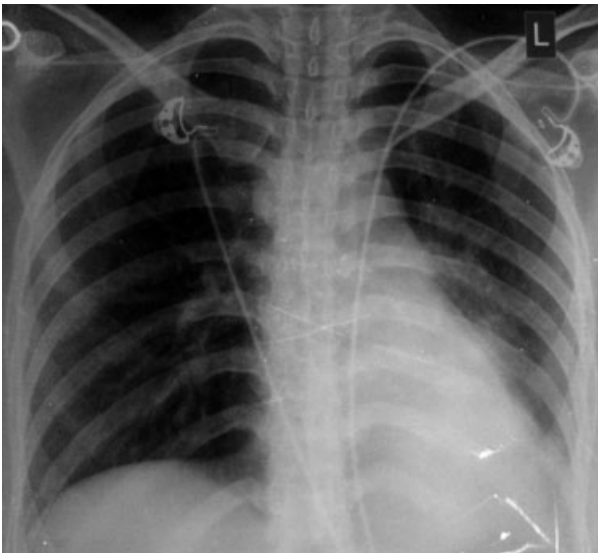


Figure 2 Chest radiograph performed after rigid bronchoscopy shows near total expansion of the left lung with no evidence of parenchymal opacities.

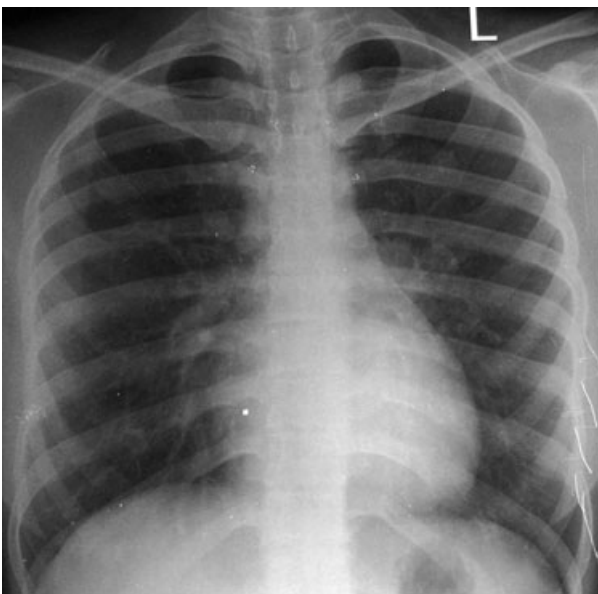


Figure 3 Chest radiograph performed 2 weeks after rigid bronchoscopy showed a normal film.

Aspergillus (Fig. 4). In lieu of the cytology report, a work-up for allergic bronchopulmonary aspergillosis was carried out. Skin test with *Aspergillus* antigen showed immediate cutaneous hyperreactivity [diameter of antigen was 11 millimeters more than the control (performed with intradermal phosphate-buffered saline)]. Both total and *Aspergillus fumigatus*-specific IgE levels

were raised—3800 IU ml⁻¹ (normal, 0–120 IU ml⁻¹) and 16.1 kUA l⁻¹ (normal, <0.35 kUA l⁻¹) respectively. The absolute eosinophil count was 670 µl⁻¹, and *A. fumigatus* precipitins were positive. Bronchial fluid was sent for bacterial and fungal cultures. Bacterial cultures were sterile, whereas fungal culture grew *Aspergillus fumigatus*. High resolution computed tomographic scan (Fig. 5) and spirometry were normal. Serology for HIV-1 and 2 was non-reactive. A final diagnosis of allergic bronchopulmonary aspergillosis was made, and the patient was initiated on prednisolone 30 mg day⁻¹. At 6 weeks follow-up, the patient was asymptomatic and total IgE levels were 1500 IU ml⁻¹. Prednisolone was subsequently tapered and stopped after 5 months of therapy. Sweat chloride values were within normal limits. Spirometry was normal and there was no bronchodilator reversibility.

Discussion

Allergic bronchopulmonary aspergillosis is a pulmonary disorder attributed to hypersensitivity reactions to *Aspergillus* sp. mainly *A. fumigatus*. The clinical, radiological and histological manifestations of bronchopulmonary aspergillosis are a complex interplay between the number and virulence of the organisms and the patient's immune response. Clinically, symptomatic ABPA manifests with low-grade fever, wheezing, bronchial hyperreactivity, haemoptysis or productive cough. Patients can also present with episodes of systemic illness with fever, weight loss and malaise. A classic scenario is an asthmatic that is poorly controlled with medications despite a good compliance with drugs (Agarwal R. Allergic bronchopulmonary aspergillosis. *Chest* 2009; **135**: 805–26). There are several interesting findings in the index case. The case presents ABPA in the most unusual fashion as acute hypoxaemic respiratory failure caused by left lung collapse. Furthermore, there was no history of pre-existing respiratory illness specifically bronchial asthma and no documented central bronchiectasis on high-resolution computed tomography.

Mucoid impaction is a pulmonary disease characterised by obstruction of the larger bronchi with mucous plugs and was first described by Shaw in 1951 (Shaw RR. Mucoid impaction of the bronchi. *J Thorac Surg* 1951; **22**: 149–63). The disease has also been described as plastic bronchitis (Leggat PO. Plastic bronchitis. *Dis Chest* 1954; **26**: 464–73). Semantically, in mucoid impaction of the bronchi, the casts have a predilection for the upper lobes and tend to be located in segmental or second-order bronchi, whereas plastic bronchitis

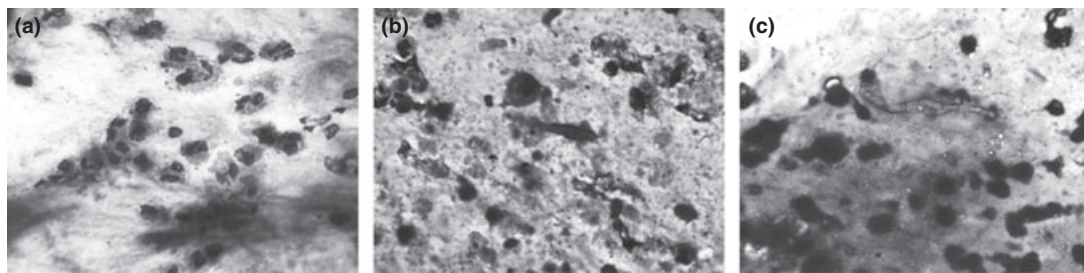


Figure 4 Smear from bronchoalveolar lavage fluid showing numerous eosinophils (a), Charcot-Leyden crystals (b) and septate fungal hyphae with acute angle branching consistent with morphology of *Aspergillus* (c) (MGG $\times 100\times$).

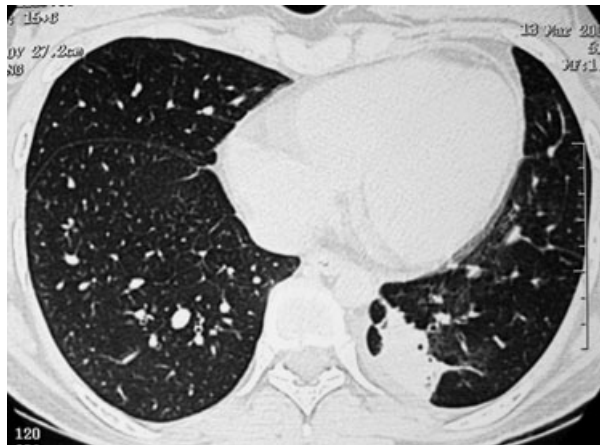


Figure 5 High-resolution computed tomographic scan shows no evidence of central bronchiectasis.

tends to affect the central airways and lower lobes (Borbely BR. Left lung atelectasis in a smoker. *Chest* 1994; **105**: 1833–5). However, the pathogenesis is similar as the composition of the casts seen in these two entities is indistinguishable (Borbely BR. Left lung atelectasis in a smoker. *Chest* 1994; **105**: 1833–5). Mucous impaction leading to segmental and subsegmental collapse is a common finding in ABPA. The mucus impaction in ABPA can be of normal density or high density (Agarwal R. Clinical significance of hyperattenuating mucoid impaction in allergic bronchopulmonary aspergillosis: an analysis of 155 patients. *Chest* 2007; **132**: 1183–90). High-attenuation mucoid impaction, defined as mucus that is visually denser than the paraspinal skeletal muscle, is a pathognomonic finding encountered in patients with ABPA (Agarwal R. Clinical significance of hyperattenuating mucoid impaction in allergic bronchopulmonary aspergillosis: an analysis of 155 patients. *Chest* 2007; **132**: 1183–90; Agarwal R. High-attenuation mucus in allergic bronchopulmonary aspergillosis: another cause of diffuse high-attenuation pulmonary abnormality. *AJR Am J*

Roentgenol 2006; **186**: 904). In the index case, there was mucous impaction of the left main bronchus, which presented as acute hypoxaemic respiratory failure.

Allergic bronchopulmonary aspergillosis is generally a chronic disease and is rarely life-threatening. In fact, there is only a single documented case of severe life-threatening presentation of ABPA as hypercapnic respiratory failure (Skowronski E. Life-threatening allergic bronchopulmonary aspergillosis in a well child with cystic fibrosis. *Med J Aust* 2005; **182**: 482–3). Respiratory failure in ABPA is generally encountered in chronic cases with extensive bronchiectasis and underlying pulmonary fibrosis and manifests as chronic type 2 respiratory failure (Agarwal R. Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest clinic in north India. *Chest* 2006; **130**: 442–8; Agarwal R. Clinical significance of hyperattenuating mucoid impaction in allergic bronchopulmonary aspergillosis: an analysis of 155 patients. *Chest* 2007; **132**: 1183–90; Lee TM. Stage V (fibrotic) allergic bronchopulmonary aspergillosis. A review of 17 cases followed from diagnosis. *Arch Intern Med* 1987; **147**: 319–23). These patients can also present with repeated episodes of acute-on-chronic respiratory failure. However, there is no documented report of ABPA presenting as hypoxaemic acute respiratory failure. Type 1 respiratory failure can occur in ABPA because of left lung collapse as seen in the index case. It is also encountered in patients with ABPA without extensive central bronchiectasis who present with acute severe asthma (Agarwal R. *Aspergillus* hypersensitivity and allergic bronchopulmonary aspergillosis in patients with acute severe asthma in a respiratory intensive care unit in North India. *Mycoses* 2009; MYC1680 [pii] 10.1111/j.1439-0507.2008.01680.x [doi]). Theoretically, it can also occur in cases with ABPA that present with extensive pulmonary consolidation although we are yet to document such a case despite our wide experience with managing such patients (Agarwal R. Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest

clinic in north India. *Chest* 2006; **130**: 442–8; Agarwal R. Clinical significance of hyperattenuating mucoid impaction in allergic bronchopulmonary aspergillosis: an analysis of 155 patients. *Chest* 2007; **132**: 1183–90). Finally, acute respiratory failure can also occur in a subset of patients with ABPA whose course of illness is complicated by invasive aspergillosis (Gupta K. *Aspergillus* endocarditis in a known case of allergic bronchopulmonary aspergillosis: an autopsy report. *Cardiovasc Pathol* 2009; in press).

Allergic bronchopulmonary aspergillosis is most commonly known to complicate the course of pre-existing bronchial asthma. However, ABPA may occasionally develop in an individual without pre-existing bronchial asthma. We have performed a systematic MEDLINE search for the occurrence of ABPA without bronchial asthma (Agarwal R. Case report: A rare cause of miliary nodules – allergic bronchopulmonary aspergillosis. *Br J Radiol* 2009; **82**: e151–4). In total, they included 36 cases reported across the globe; two cases demonstrated bronchodilator reversibility and one showed airway hyperresponsiveness to methacholine challenge. Majority of the cases demonstrated hypersensitivity to *A. fumigatus*, but three cases showed hypersensitivity to *Helminthosporium*, and one case each to *A. niger*. Because of the absence of bronchial asthma, these cases are often mistaken initially for other pulmonary disorders (Agarwal R. Case report: A rare cause of miliary nodules – allergic bronchopulmonary aspergillosis. *Br J Radiol* 2009; **82**: e151–4). In the index case, the patient is asymptomatic after stopping glucocorticoids, and spirometry with bronchodilator reversibility was normal.

It has been documented that non-asthmatic presentation of ABPA can manifest as lobar or complete lung collapse rather than pulmonary infiltrates (Berkin KE. Lung collapse caused by allergic bronchopulmonary aspergillosis in non-asthmatic patients. *Br Med J (Clin Res Ed)* 1982; **285**: 552–3). However, in this study, all patients presented over days to weeks rather than the acute presentation noted in our case (Berkin KE. Lung collapse caused by allergic bronchopulmonary aspergillosis in non-asthmatic patients. *Br Med J (Clin Res Ed)* 1982; **285**: 552–3).

Finally, this patient had no documented central bronchiectasis on HRCT, and this entity is referred to as serologic ABPA (Agarwal R. Allergic bronchopulmonary aspergillosis. *Chest* 2009; **135**: 805–26). Serological ABPA is generally encountered in asthma clinics where there is an active screening policy for ABPA, and ABPA is diagnosed in the immunological stage before central bronchiectasis develops. In other situations, ABPA can present with unusual radiological forms (Agarwal R. Pulmonary masses in allergic bronchopulmonary aspergillosis: mechanistic explanations. *Respir Care* 2008; **53**: 1744–8) exemplified by the index case where not enough time has elapsed for central bronchiectasis to set in.

In conclusion, ABPA can present in unusual clinical forms, and must be considered in the radiological differential diagnosis of patients with lung collapse, particularly but not restricted to, those with a history of asthma. A high index of suspicion should be maintained especially in high prevalence areas because treatment with glucocorticoids is associated with excellent outcomes.