65-Year-Old Woman With a Wheeze

Divya Padmanabhan Menon, MBBS, and Neal M. Patel, MD

A 65-year-old woman sought care from her primary care physician for a 5-month history of a gradually progressive cough, shortness of breath, and wheezing. Her medical history was notable for hypertension and asthma. Her medications included an albuterol rescue inhaler and lisinopril. With the exception of one hospital admission for pneumonia 5 years previously, she was in excellent health. Before the onset of symptoms, she was able to exercise 5 times a week with no limitations on activity. During the 5 months before the current presentation, however, her clinical status had deteriorated such that she was only able to walk one city block before having to rest because of shortness of breath. Her cough was characterized as dry, exacerbated by cold air, more frequent during the day, and occasionally producing grey-green sputum.

She used her albuterol inhaler as frequently as 4 to 5 times a week for dyspnea, with only slight improvement in symptoms. Her primary physician eventually prescribed inhaled corticosteroids in addition to her rescue inhaler, but this regimen only partially alleviated her symptoms. She reported occasional chills and sweats but no fevers. She worked as the chief financial officer of an accounting firm and had traveled to Thailand on a business trip almost 1 year previously. She had no pets and reported no other relevant environmental exposures.

On examination, she appeared to be in no apparent distress and was afebrile, with a heart rate of 80 to 89 beats/min, blood pressure of 130/70 mm Hg, respiratory rate of 16 breaths/min, and oxygen saturation of 94% while breathing room air. Findings on otolaryngologic, cardiac, and gastrointestinal examinations were unremarkable. She had isolated wheezes in multiple lung fields and expectorated trace amounts of brown sputum while in the examination room.

Findings on laboratory tests were remarkable for a white blood cell count of 13.6 × 10^9/L (reference range, 3.4-9.6 × 10^9/L) and an absolute eosinophil count of 6.5 × 10^9/L (reference range, 0.03-0.48 × 10^9/L). Renal and liver function test results were unremarkable. Chest radiography revealed a right upper lobe consolidation and scattered perihilar opacities. A sputum sample was obtained but was of poor quality and could not be cultured. Pulmonary function test (PFT) results identified a moderate obstructive pattern with partial bronchodilator response. Her fractional exhaled nitric oxide level was 30 ppb. Computed tomography (CT) of the chest revealed a right upper lobe consolidation (3 × 3 cm) and a small lingular consolidation (2 × 3 cm), which both appeared inflammatory on the basis of shape, density, and surrounding ground-glass opacities and tree-in-bud changes. A few nodular opacities suggestive of bronchial mucus plugs were also noted. On this noncontrast study, no severe lymphadenopathy was visible.

1. Which one of the following would be the appropriate initial screening test to help support your suspected diagnosis?
   a. IgE level
   b. Antineutrophil cytoplasmic antibody level
   c. Tuberculosis testing (QuantiFERON; Qiagen)
   d. Angiotensin-converting enzyme level
   e. Stool microscopy for ova and parasites

Although the differential diagnosis in this case includes a range of possibilities, subacute respiratory symptoms in a patient with a history of asthma in association with eosinophilia and pathognomonic chest CT findings make allergic bronchopulmonary aspergillosis (ABPA) the most likely diagnosis. Allergic bronchopulmonary aspergillosis is a pulmonary Th2-mediated...
hypersensitivity response to *Aspergillus fumigatus* antigens. Allergic bronchopulmonary aspergillosis is typically diagnosed in patients with a history of asthma or cystic fibrosis. Although the exact prevalence of this condition is unclear, studies estimate a global burden of about 1.4 to 6.8 million cases. Diagnostic criteria (International Society for Human and Animal Mycology) are as follows:

**Presence of**

1. **Predisposing criterion:**
   - Asthma OR cystic fibrosis

2. **Obligatory criteria:**
   - *Aspergillus* skin test positivity or increased IgE levels against *A. fumigatus* AND
   - Increased total IgE concentration (typically >1000 IU/mL, but if the patient meets all other criteria, an IgE value <1000 IU/mL can be counted)

And at least 2 “Other criteria”:

- Radiographic pulmonary opacities consistent with ABPA
- Precipitating serum antibodies to *A. fumigatus* or increased serum *Aspergillus* IgG by immunoassay
- Total eosinophil count >500 cells/µL in glucocorticoid-naive patients.

Antineutrophil cytoplasmic antibody measurement would have utility in diagnosing eosinophilic granulomatosis with polyangitis, which would be part of the differential diagnosis (eosinophilia, history of asthma, fevers, PFT findings) although less likely.

QuantiFERON would be useful in detecting occult tuberculosis (risk factors: travel history, right upper lobe changes, subacute decline, and productive cough). Her CT findings, however, make ABPA a more likely diagnosis.

An increased angiotensin-converting enzyme level may indicate sarcoidosis, a diagnosis that does not correlate with this patient’s clinical picture. Stool ova and parasites may be useful in identifying tropical pulmonary eosinophilia or Loeffler syndrome, which may be a possibility given her travel history. However, only ABPA would support her imaging findings.

The patient’s pathognomonic pulmonary CT findings prompted initiation of targeted anti-ABPA therapy.

2. Which one of following radiologic findings on our patient’s CT images is most likely associated with this condition?
   a. Consolidation and evolving abscess
   b. Bilateral upper lobe consolidation
   c. Lower lobe—predominant tree-in-bud changes
   d. Central bronchiectasis and mucus plugs
   e. Subpleural lobular consolidations

Consolidations and evolving abscesses are seen in multiple conditions such as staphylococcal/Klebsiella pneumonia or pulmonary metastases. Although typical of necrotizing aspergillosis, it is rarely seen in ABPA. Upper lobe consolidations are typical of tuberculosis given mycobacterial propensity for higher oxygen tensions in the upper lung fields. Tree-in-bud opacities are seen in diseases that cause bronchiolar filling such as atypical pneumonias, bronchiolitis, and carcinomatosis.

Lower lobe—predominant tree-in-bud sign is not specific to a particular condition but may be seen in infective bronchopneumonias.

High-resolution CT is the mainstay of radiologic diagnosis of ABPA. Central bronchiectasis (bronchial dilatation extending not more than 50% to 66% of lung fields from the medial lung border) is a classic finding associated with the condition, although up to one-third of patients can have dilatation up to the periphery.

High-attenuation mucus is another CT finding unique to this condition; it indicates mineral deposition within mucus, often causing signal density greater than surrounding musculature (Hounsfield units +33 to +55). This finding, however, is only seen in approximately 1 in 5 patients with ABPA.

Although these finding are typical and often pathognomonic, a multitude of other
findings, including fleeting opacities, tree-in-bud changes, pleuropulmonary fibrosis, effusions, and mosaicism have been described with ABPA. Upper lobe consolidations/cavities/fibrosis and eventual volume loss are also part of the spectrum.

Subpleural lobular consolidations are characteristic of eosinophilic granulomatosis with polyangiitis.

Our patient was referred to the pulmonary medicine department for further management of ABPA and consequent poorly controlled asthma.

3. Which one of the following is the most appropriate first-line therapy for this patient?
   a. Allergen avoidance
   b. Inhaled glucocorticoids
   c. Oral glucocorticoids
   d. Azole antifungals
   e. Liposomal amphotericin B

   The primary aims of ABPA treatment should be symptom mitigation and prevention of progression to chronic disease. Allergen avoidance and inhaled glucocorticoids have a role in long-term maintenance therapy after addressing the acute flare. Current first-line treatment for ABPA is oral glucocorticoids. There is a substantial knowledge gap regarding ideal glucocorticoid regimens, but multiple studies have recommended a slow glucocorticoid taper. Data supporting the safety and efficacy of a “medium-dose corticosteroid regimen” have recently been published and involve the use of 0.5 mg/kg per day for 1 to 2 weeks, then the same dose on alternate days for 6 to 8 weeks, followed by reduction of 5 to 10 mg every 2 weeks until discontinuation.

   Although azole antifungals have been anecdotally used both as monotherapy and in combination with oral glucocorticoids during an initial episode of ABPA, there are no definitive data supporting this practice. Liposomal amphotericin B can have substantial multiorgan toxicity and has no established role in acute ABPA.

   Despite completion of a course of first-line therapy, our patient returned 7 months later with recurrent symptoms. Repeated chest CT and PFT results indicated only marginal improvement compared with previous testing.

4. Which one of the following should you consider for further management?
   a. Oral ketoconazole
   b. Oral itraconazole
   c. Short-course intravenous (IV) methylprednisolone and azole antifungal
   d. Inhaled liposomal amphotericin B
   e. Oral posaconazole

   During treatment, patients are typically followed up every 2 to 3 months with various tests, depending on their clinical status, which may include measurement of serum IgE levels, PFTs, and chest radiography, to assess response to therapy. Decreases in IgE levels of 25% to 50% usually correspond to remission and serve as a goal of treatment. However, in cases of glucocorticoid-dependent ABPA or ABPA recurrence, azole antifungals are typically the next line of treatment.

   Oral ketoconazole’s toxicity does not favor its use as a first choice of azole therapy. Oral itraconazole is often considered second-line treatment in these cases, and a 16-week regimen is commonly used. Therapy can extend for longer depending on the clinical scenario. Hepatotoxicity is a potential concern and liver function should be monitored.

   Azoles, when used in conjunction with glucocorticoids, can help reduce the duration of treatment, the risk of recurrence, and the dose of glucocorticoid. Intravenous methylprednisolone’s use in this scenario, as a once-a-week regimen, is anecdotal only. Randomized controlled trials (RCTs) evaluating the use of inhaled liposomal amphotericin B and oral posaconazole are under way.

   Two years later, the patient returned with corticosteroid-dependent refractory disease. Combination corticosteroid and itraconazole therapy had caused complications including glucocorticoid-induced type 2 diabetes mellitus and a gradual increase in liver enzyme values.
5. Which one of the following medications could be considered at this time given that the disease was refractory to corticosteroids and azoles?
   a. IV liposomal amphotericin B
   b. IV azole antifungals
   c. Anti-IgE monoclonal antibody
   d. Lifelong oral glucocorticoids and IV azoles
   e. Inhaled glucocorticoids and oral azoles

   Substantial clinical toxicity in the absence of established benefit curbs the use of IV amphotericin and azoles for ABPA. Omalizumab is a monoclonal IgG1 antibody that functions as an IgE receptor blocker. The drug has been extensively investigated in asthma, in which its role in aiding in weaning off corticosteroids has been demonstrated. Its use in ABPA needs further investigation, especially with regard to overall applicability and dosing (current clinical experience extrapolates from IgE nomograms used for asthma). Anecdotal evidence on the use of the drug in ABPA is mostly in the setting of refractory disease. Data suggest a lower exacerbation rate and a strong corticosteroid-sparing effect. Moreover, on the basis of data extrapolated from asthma research, investigators have postulated that a decrease in chronic airway remodeling secondary to ABPA potentially decreases the progression to bronchiectatic and fibrotic lung disease. However, RCTs providing definitive indications, dose, and duration of therapy are lacking at this time.

   Lifelong oral glucocorticoids plus IV azoles have concerning adverse effects and are not indicated for this patient at this stage. Inhaled glucocorticoids plus oral azoles may be ineffective in patients with severe refractory disease.

   The patient was seen in the pulmonary clinic for follow-up 3 months later and has been doing well with omalizumab, with no symptoms suggestive of a relapse. She will continue a slow corticosteroid taper and be seen in the clinic for 6-month follow-up.

   **DISCUSSION**
   Allergic bronchopulmonary aspergillosis is challenging to diagnose and treat. The estimated prevalence of ABPA in the general population is 1% to 2%. However, rates as high as 12.9% have been reported among patients in outpatient asthma clinics; this number increases to as high as 39% among patients hospitalized with acute asthma flares. Allergic bronchopulmonary aspergillosis is in the category of allergic bronchopulmonary mycoses; the most common fungi implicated in these cases include Candida, Bipolaris, and Schizophyllum. Typical presenting features of ABPA include malaise, fevers, productive cough, poorly controlled asthma symptoms, and occasional hemoptysis. Although the diagnostic criteria detailed previously are commonly used in clinical practice, there are multiple other diagnostic guidelines with varying sensitivity and specificity, currently, no established diagnostic standard exists. Left untreated, ABPA can lead to multiple complications, including chronic pulmonary aspergillosis with bronchiectasis, pulmonary fibrosis, volume loss, lobar collapse, and progressive pulmonary hypertension.

   Aspergillus spores are ubiquitous, and it has been postulated that in patients with asthma or cystic fibrosis, poor clearance of secretions predisposes them to colonization and subsequent ABPA. However, genetic factors are important in influencing susceptibility. Aspergillus proteases, macrophage-mediated inflammation, and a strong Th2 response precipitate both acute inflammation and chronic airway remodeling.

   Despite anecdotal evidence on the efficacy of oral glucocorticoids as the mainstay of management, very few RCTs evaluating ideal dose and duration of treatment with glucocorticoids exist. However, data from a large recent RCT evaluating “medium-dose” vs “high-dose” corticosteroid regimens found no significant difference in frequency of exacerbations and development of corticosteroid-dependent ABPA. Response rates at 6 weeks and IgE levels were lower in the high-dose group. Given that the exact clinical importance of lower IgE levels is unclear, the authors concluded that this finding did not warrant high-dose regimens. However, lack of response at the 6-week time point
was proposed as an indication to start the high-dose regimen. As expected, the incidence of glucocorticoid-related complications was higher in the high-dose group.3

A recent RCT evaluating prednisolone and itraconazole as therapeutic options for acute ABPA reported better response rates with prednisolone.6 Of note, itraconazole was associated with a better adverse effect profile and a reasonably good response rate, which led the authors to hypothesize that it also may be an effective initial acute ABPA treatment option.

Itraconazole plus corticosteroids is the therapy of choice in patients with recurrent disease. In patients with corticosteroid-dependent ABPA without cystic fibrosis, itraconazole use improved corticosteroid dose requirements, IgE levels, exercise tolerance, or PFT results.7 In stable patients with asthma and ABPA, itraconazole use decreased inflammatory markers (sputum eosinophils, serum IgE, Aspergillus IgG levels).8 The azole arm also had lower flare rates than the placebo arm. Both voriconazole and posaconazole have been used in isolated cases with good clinical response and have a better adverse effect profile than itraconazole. More studies are needed, however, to evaluate the effect of eachazole on corticosteroid dose reduction, overall duration of therapy, and toxicity profiles.

The role of omalizumab in ABPA management is being increasingly appreciated.9 A review of 102 published cases of ABPA treated with omalizumab concluded that the drug helped mitigate symptoms, improve PFTs, and decrease corticosteroid requirements.10 With the increasing use of omalizumab in refractory ABPA, there is interest in developing monoclonal antibodies that target other portions of ABPA’s inflammatory cascade. Anti–interleukin 5 therapy (mepolizumab) has shown promising anecdotal results, demonstrating better symptom control, particularly when used in conjunction with omalizumab.11 Randomized controlled trials evaluating the exact roles of these drugs in ABPA are pending. Inhaled nebulized amphotericin B is also being evaluated as a potential management option—targeted delivery of the medication to the respiratory tract helps substantially limit systemic toxicity.9

Monthly pulsed-dose corticosteroids are another therapeutic option that needs further investigation, although preliminary data supporting their use have been published for both refractory ABPA and cystic fibrosis.12 Chest imaging every 4 to 8 weeks and serial PFTs are recommended for monitoring disease status after medication regimen changes are made.

Despite being a recognized clinical entity for more than half a century and its substantial morbidity and mortality, ABPA remains challenging to diagnose and treat. Early recognition and appropriate therapy can help limit the progression of ABPA to devastating chronic lung disease.

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Correspondence: Address to Neal M. Patel, MD, Department of Critical Care Medicine, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224 (patel.neal@mayo.edu).

REFERENCES


CORRECT ANSWERS: 1. a. 2. d. 3. c. 4. b. 5. c