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Case report

A differential comes up short in a patient with shortness of breath

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A B S T R A C T

Chronic obstructive pulmonary disease (COPD) exacerbation and allergic bronchopulmonary aspergillosis (ABPA), in spite of sharing common features such as airway inflammation, airflow obstruction, and mucus hypersecretion, differ significantly from each other. We report a case of ABPA that was unsuccessfully treated as a COPD exacerbation. The history of non-exertional progressive dyspnea, absence of a symptom-free interval, and hemoptysis combined with a minimal, distant smoking history and prior employment at a fertilizer plant favor a diagnosis other than COPD exacerbation. The patient's disease progression and delay in diagnosis testify to the sway of cognitive biases. This case serves as a reminder that generating a thorough differential diagnosis early in a patient's care prevents misdiagnoses and hastens the initiation of definitive therapy.

1. Introduction

When building a differential diagnosis, it is essential to create a list of both likely diagnoses and life-threatening diseases. If the list is not sufficiently robust the provider may fall prey to cognitive biases and the diagnosis may be missed. Dyspnea and wheeze are symptoms commonly encountered by general internists and often patients carry inadequate diagnoses that convey a framing bias to all future practitioners. We report a case of delayed diagnosis of allergic bronchopulmonary aspergillosis (ABPA) that had been previously treated as chronic obstructive pulmonary disease (COPD) exacerbation for nearly a decade following multiple hospital admissions and subsequent disease progression.

2. Case report

A 41-year-old male with bronchiectasis, chronic sinusitis, and obstructive lung disease presented to the emergency department in acute on chronic hypoxic respiratory failure. Chart review showed multiple encounters for shortness of breath and cough, with increasing admission frequency over the preceding 2 months. On each occasion he was given a diagnosis of COPD exacerbation and treated with steroids and azithromycin or doxycycline. Symptoms between admissions were poorly controlled despite adherence to albuterol, montelukast, and ranitidine. The patient initially noted dyspnea 12 years prior and had been on 2.5 L/minute home oxygen for the preceding 8 years. The patient reported dyspnea unrelated to exertion and dry cough. Over the last few months, patient denied remission of symptoms and had no history of atopy. Patient admitted night sweats, chills, and a 4.5-kg. unintentional weight loss with suspected exposure to tuberculosis while imprisoned. Patient declared a 5-pack year smoking history with quit date 10 years prior to admission and denied alcohol and illicit drug use. Prior to incarceration the patient worked at a fertilizer factory. Family history and surgical history were non-contributory.

On examination, the patient was afebrile with normal vital signs. The patient was a thin white male in respiratory distress with prolonged expiratory phase, diffuse expiratory wheeze and cough. No crackles were heard, and the patient did not exhibit clubbing.

A pulmonary function test administered 6 years before presentation demonstrated reduced flow and capacity with mid flow-loop obstruction, which was responsive to bronchodilator, and mildly reduced diffusion capacity. Previous results also included a normal alpha-1 antitrypsin level and a non-diagnostic bronchial alveolar lavage (BAL) that disclosed moderate polymorphonuclear neutrophils with normal respiratory flora.

Laboratory testing revealed a white blood cell count of 11.75 K/μL comprised of 93% neutrophils but also an eosinophil count of 0.04 K/μL. The complete metabolic panel was normal.

A chest radiograph showed no acute pulmonary radiologic findings (Fig. 1). Due to chronic course and relapses, the pulmonology team performed flexible fiberoptic bronchoscopy with BAL from the right middle lobe of lung. BAL cytology resulted with eosinophilia but microbiology stains, PCRs and cultures were negative.

Computed-tomography (CT) showed mild centrilobar emphysema with a few subpleural blebs in the right upper lung and signs of central bronchiectasis. Also, there was minimal apical scarring bilaterally (Fig. 2).

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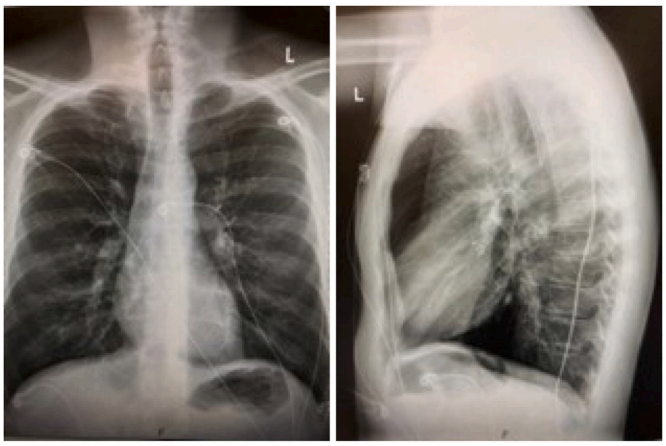

Fig. 1. A radiograph of the chest showed no acute cardiopulmonary findings. The hilar vasculature appeared normal.

The serum specific IgE against *A. fumigatus* was positive (4.23 kU/L) and serum total IgE (3868 kU/L) was markedly elevated. Serum precipitins (specific IgG) against Aspergillus spp. were negative. *A. fumigatus* and *A. terreus* by PCR and fungal blood cultures were negative. Table 1 below summarizes the findings in our case and how the findings differ from the minimum essential diagnostic criteria proposed by Greenberger [1].

A diagnosis of ABPA was made as our case met three of the minimum essential criteria despite not performing a skin prick test and a negative history of asthma. The patient was treated with itraconazole and prednisone. On follow up, the patient reported improvement of cough, sputum, and dyspnea.

3. Discussion

Despite similar symptoms, COPD exacerbation and ABPA differ as ABPA is a form of hypersensitivity associated with the destruction of the airways in response to *Aspergillus* exposure [2]. ABPA is characterized by recurrent exacerbations of dyspnea, cough, and thick sputum [3]. Wheezing may be present, and bronchial obstruction, fever, and hemoptysis may occur.[2]Aspergillus species require moisture and organic material to grow. The substrates for Aspergillus species include decomposing organic matter, such as decaying vegetation, mulches, and fertilizer [1]. The mold-allergic patient with asthma or ABPA will experience acute respiratory symptoms of asthma or develop an episode of ABPA pulmonary eosinophilia after exposure to an especially moldy environment [1].

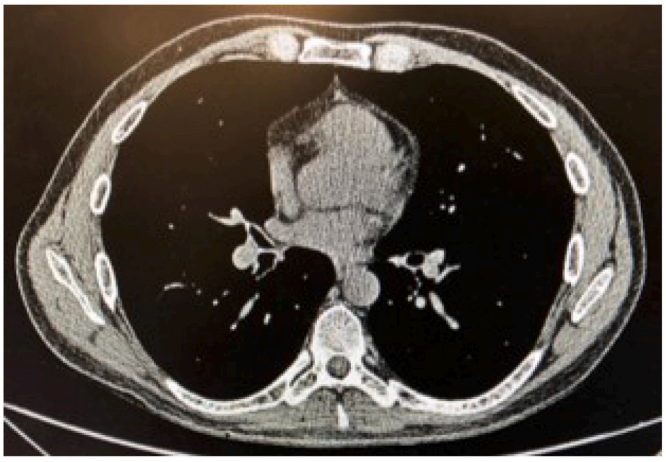

Fig. 2. CT of the chest showed mild centrilobar emphysema with a few subpleural blebs in the right upper lung and signs of central bronchiectasis.

Table 1
Greenberger's Minimum Essential Criteria for the diagnosis of ABPA in the presented case.

Diagnostic Criteria	Findings in the present case
1. Asthma	–
2. Immediate cutaneous hypersensitivity reaction to *A. fumigatus*	-*
3. Total serum IgE elevated more than 1000 ng/ml (417 kU/L)	+
4. Elevated IgE and/or IgG antibodies to *A. fumigatus*	+
5. Central bronchiectasis in absence of distal bronchiectasis	+

*A skin prick test to show immediate cutaneous reactivity to *A. fumigatus* was not performed, ABPA - allergic bronchopulmonary aspergillosis.

The current diagnostic practice hinges on data gathering and hypothesis testing. Yet, physicians too are susceptible to cognitive bias during this process. One prevalent limitation is premature closure evidenced above by accepting a diagnosis before it is vetted [4]. In some cases, the differential diagnosis is too narrow, and the provider fails to consider other illnesses that could account for the patient's complaint [5]. As a result, clinicians can misdiagnose dangerous disease processes. A thorough differential diagnosis must be generated at the time of a chief complaint or core history questions will go unasked raising the risk of cognitive error–accounting for nearly 1 in 5 adverse events in healthcare [6]. In the Harvard Medical Practice Study of 30,195 hospital records, diagnostic errors accounted for 17% of adverse events [6]. A more recent follow-up study of 15,000 records from Colorado and Utah reported that diagnostic errors contributed to 6.9% of the adverse events [7]. This fact demands that internists employ strategies to offset cognitive biases and limitations. Experimental studies show that the reflective practice of early differential diagnosis generation enhances diagnostic accuracy in complex situations [8].

Respiratory complaints are great fodder for errors given similar presentations of a variety of diseases. Caution is needed to avoid premature closure to prevent error. In our case, the patient was repeatedly treated for COPD despite the history of a non-exertional type of progressive dyspnea, absence of a completely symptom-free interval, constant need of medication between exacerbation, hemoptysis, minimal distant smoking history, and occupational exposure. We acknowledge that ABPA can co-exist with COPD. However, multiple courses of acute therapy along with appropriate maintenance medications for COPD did not provide the improvement typically witnessed when COPD is the lone culprit for dyspnea. This, in addition to the patient's recovery after treatment for ABPA, supports delayed diagnosis of the primary illness.

A broad differential diagnosis is a tool that helps clinicians make accurate diagnoses despite our limitations. Reducing missed or delayed diagnoses by generating a thorough differential diagnosis early in a patient's care can alleviate some of the burden of respiratory (and all) diseases. This is a fast, cost-effective habit that can significantly enhance patients' quality of life. The high prevalence and morbidity of airway disease translate into a substantial cost to the healthcare system [9]. Drug costs are the main expenses that are associated with the treatment of asthma, whereas COPD and bronchiectasis have a greater economic impact due to high hospitalization rates [9]. These costs magnify with delayed diagnosis and readmission.

4. Conclusion

Establishing forced consideration of a variety of possible diagnoses, as is done when generating a differential, is an efficient strategy that can mitigate diagnostic errors and reduce the costs/burdens of delayed/prolonged care. As a result, internists must identify premature closure as a powerful cognitive bias when addressing common respiratory

symptoms and utilize a broad differential diagnosis as a cognitive debiasing strategy. In adult patients with episodic dyspnea with wheeze, ABPA should be considered as a reason for acute on chronic hypoxic respiratory failure.

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Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Duy Ha: Writing - original draft, Writing - review & editing. **Steven McKee:** Writing - review & editing, Supervision.

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