Asthma Mimics

Case related questions.

Scenario:
Mrs. H is a 57-year-old woman with a history of asthma and congestive heart failure (CHF) with preserved ejection fraction who presents for consultation due to worsening shortness of breath. She reports having asthma for many years with occasional emergency department visits but no prior hospitalizations and typically has one exacerbation per year. However, her breathing has worsened for the past year, and she has experienced significant exertional dyspnea in addition to a chronic cough productive of clear sputum. She feels that her breathing is stable at home, but her symptoms get worse when she goes out. She takes albuterol and has been on prednisone for much of the past year without relief. She smoked 1 pack of cigarettes daily for 25 years but quit two months ago. On exam, her body mass index is 30.4, her oxygen saturation is 97% on room air, and she has audible wheezing. No pulmonary function tests (PFTs) are available.

Question 1: What are some clues in her presentation that asthma may not be the only explanation for Mrs. H's respiratory symptoms?

Question 2: What common conditions might be mistaken for asthma in this patient, and what initial testing might you order?

Scenario cont.:
Her chest x-ray is completed, and you note clear lungs with no evidence of hyperinflation. Her spirometry demonstrates a forced vital capacity (FVC) of 2.50L (z-score -2.6), low forced expiratory volume in 1 second (FEV1) 1.70 (z-score -2.8), and forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio 68% (z-score -2.1).

The tech noted the following: "Albuterol sulfate nebulizer was given but post-bronchodilator studies were not done as the patient had anxiety about getting stuck in traffic, so she asked to stop the test and get on the road." You note that there is flattening of the inspiratory limb of the flow-volume loop (FVL).

Question 3: Does her spirometry raise concern for any conditions that may mimic asthma?

Question 4: When should you consider inducible laryngeal obstruction (ILO) and how would you diagnose this?

Scenario cont.:
You refer her to otolaryngology and a laryngoscopy is performed. There is no abnormal vocal cord motion even though she is audibly wheezing during the study.

Question 5: What else should you consider, given the audible wheeze?

Scenario cont.:
Her previous FVL was potentially truncated on the inspiratory limb, so you order a computerized tomography (CT) scan of the chest with inspiratory and expiratory views. The report notes that the airway caliber is normal, and there is no significant reduction in caliber on expiration. In the interim, you advise her to taper her steroids and start a combined high-dose inhaled corticosteroid (ICS) and long-acting beta agonist. She returns to see you and tells you her symptoms are unchanged, except she thinks her cough has worsened slightly, and she is coughing up balls of mucus.

Question 6: What other diagnosis should you consider, and what diagnostic workup do you recommend?

Scenario cont.:
You order a CBC with differential, IgE level, specific IgE to *Aspergillus* on immunoassay, specific IgG antibodies, and a CT scan.

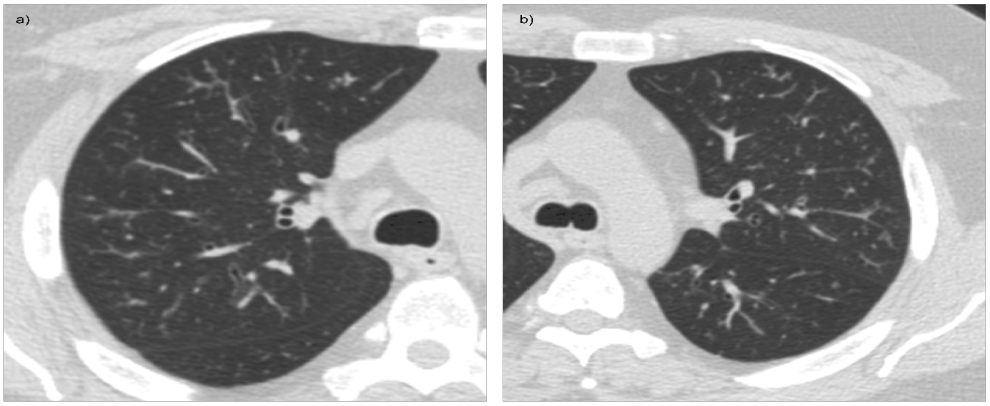
Question 7: While you are busy ordering her studies, she asks how you would treat allergic bronchopulmonary aspergillosis (ABPA) if she had it. What do you tell her?

Scenario cont.:
Her studies return and are notable for the following: absolute eosinophil count of 1200, IgE 482, *A. fumigatus*-specific IgE ≤ 0.35 kU/L, negative serum *A. fumigatus* IgG. She has not yet had her CT scan due to insurance pre-authorization issues.

Question 8: Does she have ABPA?

Question 9: She does have eosinophilia. What conditions should you consider that cause eosinophilia and pulmonary disease?

Scenario cont.:
Her CT scan (below) demonstrates some areas of air trapping with tiny, peripheral-predominant nodules.



Question 10: Which uncommon diagnosis should you consider?

Asthma Mimics

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Educational Objectives:

1. Review the diagnostic criteria for asthma
2. Recognize signs and symptoms that suggest an asthma mimic
3. Develop a diagnostic plan for common conditions that mimic asthma

Scenario:
Mrs. H is a 57-year-old woman with a history of asthma and congestive heart failure (CHF) with preserved ejection fraction who presents for consultation due to worsening shortness of breath. She reports having asthma for many years with occasional emergency department visits but no prior hospitalizations and typically has one exacerbation per year. However, her breathing has worsened for the past year, and she has experienced significant exertional dyspnea in addition to a chronic cough productive of clear sputum. She feels that her breathing is stable at home, but her symptoms get worse when she goes out. She takes albuterol and has been on prednisone for much of the past year without relief. She smoked 1 pack of cigarettes daily for 25 years but quit two months ago. On exam, her body mass index is 30.4, her oxygen saturation is 97% on room air, and she has audible wheezing. No pulmonary function tests (PFTs) are available.

Question 1: What are some clues in her presentation that asthma may not be the only explanation for Mrs. H's respiratory symptoms?

Global Initiative for Asthma (GINA)[1] defines asthma as a heterogeneous disease often characterized by chronic airway inflammation, defined by a history of respiratory symptoms (such as wheeze, shortness of breath, chest tightness, and cough) that vary over time and intensity, together with variable expiratory airflow limitation.

Abnormal or unresolved issues for our patient:

- Chronic but not episodic symptoms
- Productive cough
- Smoking history
- History of CHF

Clinical Features Favoring and Not Favoring Asthma in Those with Episodic Symptoms[2]:

Favoring:

- At least two of the following: wheeze, breathlessness, chest tightness, cough (+/- sputum). Especially if: worse at night or early morning, symptoms w/exercise, exposure to allergens, or cold air, symptoms following aspirin or beta-blocker use
- History of atopy
- Widespread wheeze on exam
- Low forced expiratory volume in 1 second (FEV1) or peak expiratory flow (PEF) that is otherwise unexplained
- Symptoms rapidly relieved by short acting beta agonist (SABA) or by inhaled corticosteroid (ICS)-formoterol
- Peripheral eosinophilia otherwise unexplained

Not Favoring:

- Chronic productive cough without wheezing or breathlessness
- No wheezing on exam while symptomatic
- Symptoms worse when talking on the phone, associated throat tightness or change in voice
- Normal spirometry or PEF when symptomatic
- No significant increase in FEV1 after bronchodilator
- No response to trial of asthma treatment
- Symptoms beginning later in life, particularly in those who smoke
- Clinical features to suggest an alternate diagnosis

An important note: studies have shown poor inhaler technique can lead to poor asthma outcomes. It is important to confirm that the patient is properly using their inhaler while also considering other underlying causes.

Question 2: What common conditions might be mistaken for asthma in this patient, and what initial testing might you order?

Chronic obstructive pulmonary disease (COPD) is commonly confused with asthma. Prior asthmatics who are long-term smokers are also at risk for developing COPD. Again, symptoms in asthma are typically variable while symptoms in COPD are persistent.

Tests that can help guide your diagnosis include:

- Pulmonary function testing, including pre- and post-bronchodilator spirometry which can be normal in asthma but not in COPD, low diffusing capacity suggests emphysema and possible COPD
- Chest imaging with emphysema and/or features of pulmonary hypertension suggests COPD

- Complete Blood Count (CBC) – blood eosinophilia supports diagnosis of eosinophilic airway inflammation in asthma but may also be present in COPD including during exacerbations
- Bronchodilator reversibility is more characteristic of asthma than COPD, however it can also be observed in COPD

A (non-exhaustive) list of other diagnoses to consider is seen in Table 1.[3]

Table 1. Differential Diagnosis in a Patient with Suspected Asthma

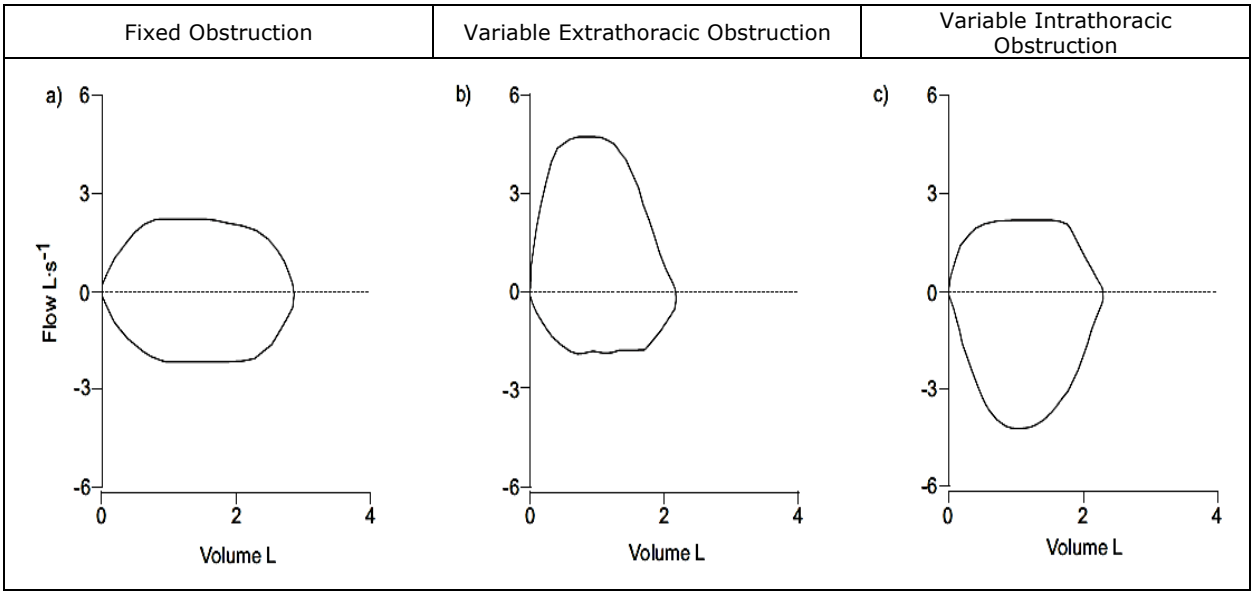
Predominant symptom	Consider these diagnoses
Cough	○ Upper airway cough syndrome ○ Rhinosinusitis ○ Nasal polyposis ○ Gastroesophageal reflux disease/ laryngopharyngeal reflux ○ Post viral tussive symptoms ○ Chronic bronchitis ○ Eosinophilic bronchitis ○ Cough due to angiotensin-converting enzyme (ACE) inhibitors ○ Bronchiectasis
Wheeze	○ Inducible laryngeal obstruction ○ Bronchiectasis ○ COPD ○ Bronchogenic carcinoma ○ Foreign body aspiration ○ Tracheobronchomalacia
Dyspnea	○ COPD ○ Heart failure ○ Pulmonary embolism ○ Interstitial lung disease

Scenario cont.:
Her chest x-ray is completed, and you note clear lungs with no evidence of hyperinflation. Her spirometry demonstrates a forced vital capacity (FVC) of 2.50L (z-score -2.6), FEV1 1.70 (z-score -2.8), and FEV1/FVC ratio 68% (z-score -2.1). The tech noted the following: "Albuterol sulfate nebulizer was given but post-bronchodilator studies were not done as the patient had anxiety about getting stuck in traffic, so she asked to stop the test and get on the road." You note that there is flattening of the inspiratory limb of the flow-volume loop (FVL).

Question 3: Does her spirometry raise concern for any conditions that may mimic asthma?

Flattening of the inspiratory limb of the FVL suggests variable extrathoracic obstruction, as demonstrated in Figure 1. Causes of this include inducible laryngeal obstruction (ILO) which was previously referred to as vocal cord dysfunction (VCD), tracheobronchomalacia, and polychondritis. Keep in mind that a blunted inspiratory loop can also be seen with suboptimal effort or inability to perform the test correctly.

Figure 1. Examples of Variable and Fixed Obstruction on Flow Volume Loops



Question 4: When should you consider ILO and how would you diagnose this?

ILO describes an inappropriate, transient, and reversible narrowing of the larynx in response to external triggers.[4] It should be suspected in patients with episodic dyspnea, often associated with throat tightness, cough, hoarseness, and/or stridor. Triggers of ILO include exercise, inhaled irritants, laryngopharyngeal reflux, neurologic injury, and psychosocial disorders and stress. Also remember, ILO can be misdiagnosed as asthma but can also be seen with asthma.

Flexible laryngoscopy is necessary for diagnosis and typically shows adduction of the vocal cords most commonly during inspiration, >50% closure of the cords, or "posterior chinking".

Scenario cont.:
You refer her to otolaryngology and a laryngoscopy is performed. There is no abnormal vocal cord motion even though she is audibly wheezing during the study.

Question 5: What else should you consider, given the audible wheeze?

Consider evaluation for subglottic airway obstruction and tracheobronchomalacia.

Scenario cont.:
Her previous FVL was potentially truncated on the inspiratory limb, so you order a computerized tomography (CT) scan of the chest with inspiratory and expiratory views. The report notes that the airway caliber is normal, and there is no significant reduction in caliber on expiration. In the interim, you advise her to taper her steroids and start a combined high-dose ICS and long-acting beta agonist. She returns to see you and tells you her symptoms are unchanged, except she thinks her cough has worsened slightly, and she is coughing up balls of mucus.

Question 6: What other diagnosis should you consider, and what diagnostic workup do you recommend?

Refractory asthma and a productive cough should raise the possibility of allergic bronchopulmonary aspergillosis (ABPA). ABPA is caused by hypersensitivity to *Aspergillus fumigatus* and is a complication of asthma and cystic fibrosis. Some estimates suggest it complicates up to 6% of chronic asthma.[5]

The diagnostic criteria for ABPA are as follows[6]:

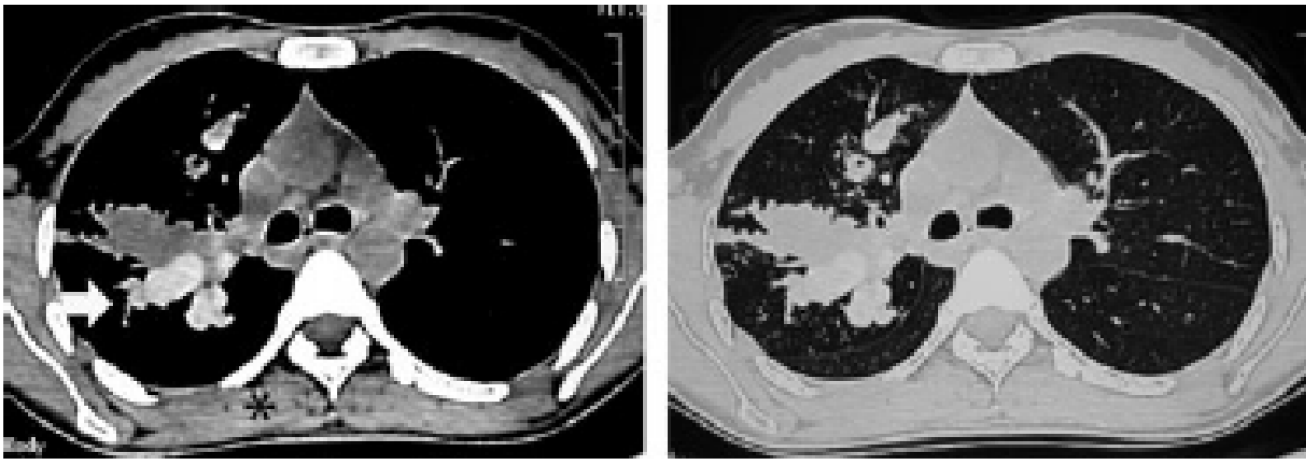
1. Predisposing conditions (asthma, cystic fibrosis, chronic obstructive lung disease, bronchiectasis) or a compatible clinico-radiological presentation.

2. Essential components: (Both MUST be present)
    a. *A fumigatus*-specific IgE ≥0.35 kU/L
    b. Serum total IgE ≥ 500 IU-mL

3. Other components: (any two)
    a. Positive Immunoglobulin G against *A. fumigatus*
    b. Blood eosinophils ≥500 cells/uL (could be historical)
    c. Thin-section chest computed tomography consistent with ABPA (bronchiectasis, mucous plugging and high-attenuation mucous) or fleeting opacities on chest radiograph consistent with ABPA

4. Important considerations:
    a. Expectoration of mucous plugs, finger-in-glove and fleeting opacities on chest radiograph, lung collapse, and others
    b. A positive type 1 skin test is acceptable when *Aspergillus* IgE is unavailable
    c. Serum total IgE<500 IU-mL may be acceptable if all other criteria are fulfilled
    d. *A. fumigatus*-specific IgG can be detected using lateral flow assays or enzyme immunoassays. The cut-offs for *A. fumigatus*-specific IgG must be developed for specific populations.
    e. **High-attenuation mucus is pathognomonic of ABPA and confirms ABPA diagnosis even if all other criteria are not fulfilled** (Figure 2)
    f. Elevated IgE against the recombinant *Aspergillus* antigens f1, f2 and f4 supports the diagnosis of ABPA and could be used as another component for diagnosing ABPA

Figure 2. Presence of High Attenuation Mucus in Mediastinal Window and Corresponding Lung Window



Left: High attenuation mucus (bold arrow)
Images reproduced from Agarwal, et al.[7]

Scenario cont.:
You order a CBC with differential, IgE level, specific IgE to *Aspergillus* on immunoassay, specific IgG antibodies, and a CT scan.

Question 7: While you are busy ordering her studies, she asks how you would treat ABPA if she had it. What do you tell her?

1. Corticosteroids are the mainstay of the initial treatment of acute ABPA (newly diagnosed or exacerbation).[7] This is based on the results of case series demonstrating clearing of radiographic opacities, a decrease of >50% in IgE, and normalization of eosinophils. The optimal dosing of prednisone is unknown. A common regimen is prednisone 0.5mg/kg daily for 14 days, tapered and completed over months.[6]

2. Antifungals can be considered in some circumstances. Oral antifungal triazoles have similar effects as systemic steroids, but a slower time course to improvement.[6] A 4-month course of oral itraconazole can be considered as an alternative initial treatment for acute APBA. They should also be considered inn those unable to taper oral steroids and can be used in addition to oral steroids for treatment of recurrent ABPA exacerbations. While voriconazole may be effective, it has poorer patient tolerance.

3. Inhaled corticosteroids are often used during and after steroid tapers. Itraconazole can increase the serum concentration of certain inhaled steroids.

4. Biologic agents should not be used as first-line therapy but do have a role in treatment-dependent ABPA. Most data exists for Omalizumab, but dupilumab, mepolizumab, and tezepelumab have also been used. A systematic review and metanalysis of case series and one early-terminated randomized control trial of omalizumab use in ABPA found reduced exacerbation frequency and oral corticosteroid use after initiation of omalizumab.[6,8]

Scenario cont.:
Her studies return and are notable for the following: absolute eosinophil count of 1200, IgE 482, *A. fumigatus*-specific IgE ≤ 0.35 kU/L, negative serum *A. fumigatus* IgG. She has not yet had her CT scan due to insurance pre-authorization issues.

Question 8: Does she have ABPA?

No – the IgE is lower than the typical threshold, and she has negative serum A. fumigatus antibodies.

Question 9: She does have eosinophilia. What conditions should you consider that cause eosinophilia and pulmonary disease?

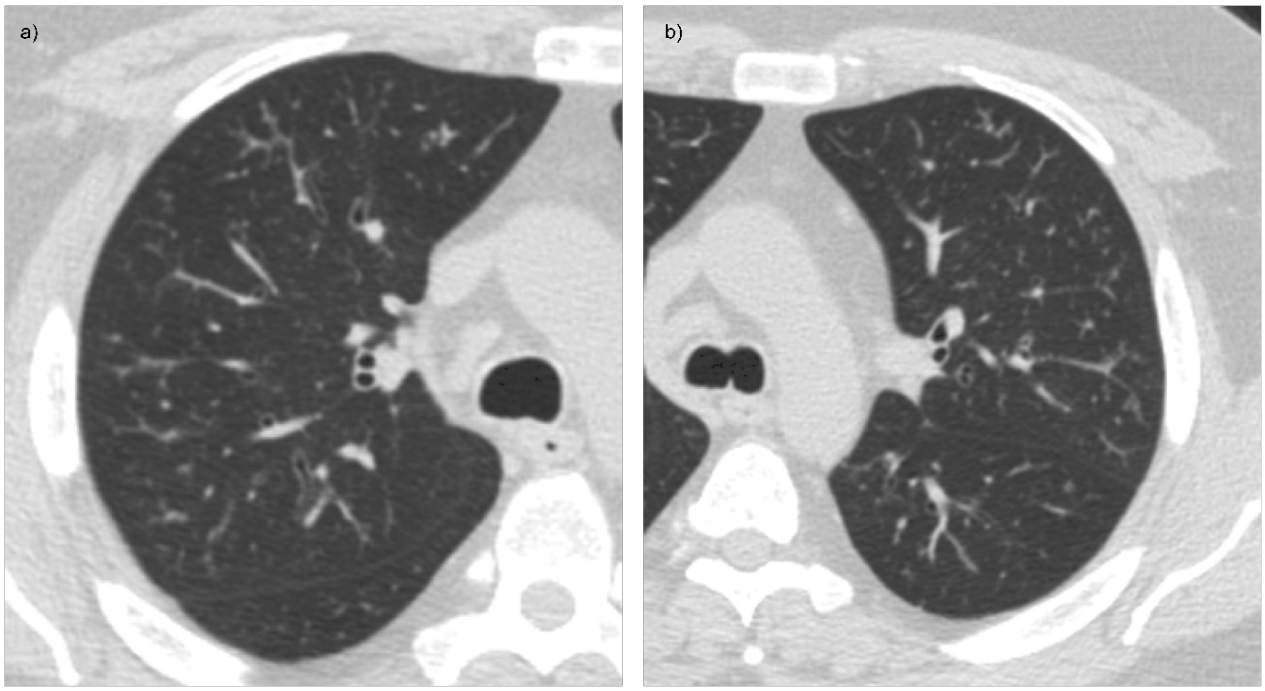
The differential diagnosis of eosinophilia is reviewed in Table 2.

Table 2. Differential Diagnosis of Eosinophilia

Disorders Causing Eosinophilia	**Additional Diagnostic Testing to Consider**
Inflammatory Conditions	
Eosinophilic granulomatosis with polyangiitis	Anti-neutrophil cytoplasmic antibodies
ABPA	Aspergillus skin testing, IgE, antibodies
Idiopathic acute eosinophilic pneumonia	Bronchoalveolar lavage (BAL)
Chronic eosinophilic pneumonia	BAL, transbronchial biopsies, surgical lung biopsy
Hypereosinophilic bronchiolitis	Surgical lung biopsy
Infections	
Loffler's syndrome: Ascaris, Hookworm, Strongyloides	Antibody Enzyme-linked Immunosorbent Assay (ELISA) testing Fleeting imaging abnormalities
Parenchymal invasion: Paragonimiasis	Antibody ELISA testing
Hematogenous seeding: includes Schistosomiasis, disseminated Strongyloides	Antibody ELISA testing
Endemic mycoses: histoplasmosis, blastomycosis, coccidiomycosis	Antigen and antibody testing, BAL cultures
Drugs and toxins	
Can range between asymptomatic pulmonary infiltration with eosinophils to drug reaction with eosinophilia and systemic symptoms; NSAIDs and some antibiotics including: nitrofurantoin, minocycline, daptomycin	
Inhalation of cocaine, marijuana, or heroin Significant exposure to dust and smoke	

Scenario cont.:
Her CT scan in Figure 3 demonstrates some areas of air trapping with tiny, peripheral-predominant nodules.

Figure 3. CT Chest Showing Tree in Bud Pattern and Centrilobular Nodules



CT chest showing tree in bud pattern and centrilobular nodules in the a) right and b) left lungs
Images reproduced from Cordier et al[7]

Question 10: Which uncommon diagnosis should you consider?

Hypereosinophilic obliterative bronchiolitis (eosinophilic bronchiolitis) is a rare condition with the following diagnostic characteristics[7]:

- Peripheral eosinophilia with AEC > 1000 and/or BAL eosinophilia > 25%
- Airflow obstruction not improved by a prolonged course of high dose inhaled bronchodilator and corticosteroid therapy
- Characteristic signs of bronchiolitis on HRCT imaging and/or lung biopsy

Case series descriptions note improvement with prolonged courses of systemic corticosteroids. There are also case reports of effective treatment with benralizumab.[8]

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Asthma Mimics

Post-Test Case Related Questions

1. To diagnose a patient with ABPA (allergic bronchopulmonary aspergillosis), which of the following MUST be present?
    a. Absolute eosinophil count >500
    b. Central bronchiectasis on CT chest
    c. IgG Ab to A. fumigatus
    d. Positive A. fumigatus-specific IgE

2. A 35-year-old female presents to your office for evaluation of dyspnea and wheezing. She has normal chest imaging and reports a previously negative bronchoprovocation study. She is a never-smoker and thus, you are clinically concerned based on her story for possible vocal cord dysfunction. Which of the following is NOT a characteristic finding of vocal cord dysfunction?
    a. Flat inspiratory limb of the flow volume loop on PFTs
    b. Partial bronchodilator responsiveness on PFTs
    c. Adduction of vocal cords on direct laryngoscopy
    d. Intermittent episodes of stridor or upper airway wheeze

3. A 60-year-old male with HIV (CD4 100, intermittently adherent to HAART therapy) presents to evaluate possible asthma and eosinophilia. He also notes some ongoing issues with abdominal pain and diarrhea. He is originally from Guatemala and is a never smoker. You are concerned about possible hematogenous seeding from a helminth infection with Strongyloides and decide the next best course for diagnostic testing should be:
    a. Transbronchial lung biopsy
    b. Surgical lung biopsy
    c. Serial imaging and PFTs
    d. Antibody ELISA testing

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Post-Test Case Related Questions with Answer Key

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