38-Year-Old Man With Asthma and Eosinophilia

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A 38-year-old man with a history of asthma, depression, and anxiety presented with a 3-year history of recurrent dyspnea and wheezing. He had previously been active with his local ice hockey team and had no respiratory symptoms. On presentation, he reported frequent nighttime waking, dyspnea on minimal exertion, and frequent (6-10 times daily) albuterol rescue inhaler use. He noted marked worsening of his symptoms over the preceding 9 months and had been taking continuous oral steroids for the preceding 6 months. He had been hospitalized once and had been to the emergency department on several occasions, owing to recurrent episodes of dyspnea. He denied symptoms of rhinitis, sinusitis, and gastroesophageal reflux disease. He was a lifelong nonsmoker, and results were normal on a recent allergy skin test. He reported exercise as his only trigger for dyspnea. He had no relevant travel history or other notable exposures.

Vital signs on presentation were all within normal limits. Physical examination was remarkable for bilateral expiratory wheezing. His medications included as-needed inhaled albuterol, fluticasone nasal spray, citalopram, propranolol, montelukast (10 mg/d), budesonide-formoterol (160-4.5 μg twice daily), and prednisone (10 mg/d). Initial baseline pulmonary function testing (PFT) revealed the following: forced expiratory volume in 1 second (FEV_1), 2.97 L (64% of predicted); forced vital capacity (FVC), 4.92 L (84% of predicted); FEV_1:FVC ratio, 60.3%; total lung capacity (TLC), 8.96 L (120% of predicted); residual volume, 4.19 L (261% of predicted); diffusing capacity of the lungs for carbon monoxide, 35.7 mmol carbon monoxide per minute per kPa (103% of predicted); and postbronchodilator FEV_1, 3.43 L (+15% change).

1. Which *one* of the following is the *most appropriate* conclusion to be drawn from the patient's PFT results?

a. The patient has airway obstruction that can be classified as severe
b. The degree of air trapping suggests that chronic obstructive pulmonary disease (COPD) is the most likely diagnosis
c. Propranolol is contributing substantially to the patient's symptoms
d. The PFT results show mixed obstruction and restriction
e. The bronchodilator response is notable and may be suggestive of asthma.

By standard classification, the patient has an obstructive pattern based on the low FEV_1:FVC ratio. The severity of obstruction is determined by the degree of FEV_1 reduction, with FEV_1 of 80% or more of the predicted value classified as borderline obstruction, 60% to 79% as mild, 40% to 59% as moderate, and less than 40% as severe. Even when considering the GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria for severity of obstruction in COPD, an FEV_1 of 64% of the predicted value would indicate moderate obstruction.[1] The substantially elevated residual volume and the elevated TLC are indicative of air trapping and hyperinflation, respectively. These symptoms are not specific to COPD, and little else in the presentation suggests a diagnosis of COPD. Although propranolol and nonselective β-blockers can worsen FEV_1 and diminish response to inhaled β_2-selective agonists, PFTs cannot provide definitive information as to whether propranolol is contributing to the patient's symptoms.[2] A diagnosis of restriction requires a low TLC and is thus ruled out in this case. A "positive" or "marked" bronchodilator response requires both a 12% relative increase and a 200-mL absolute increase in either the FEV_1 or FVC and is indicative of

See end of article for correct answers to questions.

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reversible airway obstruction. A positive bronchodilator response is one of many indicators of a diagnosis of asthma, but it is not diagnostic by itself. Patients may derive symptomatic benefit from bronchodilator therapy even in the absence of a positive bronchodilator response. Although PFT results are never diagnostic for any specific disease, the presence of an obstructive pattern with a preserved diffusing capacity is typically seen in airway-centric disorders such as asthma. By comparison, COPD affects the airways, and the alveoli and PFTs will reveal airway obstruction along with a reduced diffusing capacity, except in the COPD subgroup of chronic bronchitis, in which the diffusing capacity of the lungs for carbon monoxide may be normal. The diagnosis of asthma is a clinical diagnosis and requires consideration of several factors, including patient history, PFT results, medical history, family history, exhaled oral nitric oxide (NO) level, and response to oral and inhaled glucocorticoids.[3]

Although asthma was strongly suspected on the basis of the patient's history, examination findings, and PFT results, additional work-up was pursued because of the severity and refractory nature of the presentation. Further evaluation (reference ranges are provided parenthetically) was notable for a white blood cell count of 8.4 × 10^9/L (3.5-10.5 × 10^9/L) with an eosinophil count of 1.17 × 10^9/L (0.05-0.5 × 10^9/L), exhaled oral NO value of 173 parts per billion (<30 parts per billion), and IgE level of 1819 kU/L (≤214 kU/L). Computed tomography of the chest revealed a 5-mm pulmonary nodule in the right middle lobe, mild bronchial wall thickening, and evidence of expiratory air trapping.

2. Which *one* of the following is the *most appropriate next step* for pharmacologic management of this patient?

a. Increase dose of montelukast
b. Increase dose of oral prednisone
c. Add anti-IgE therapy
d. Add cyclosporine
e. Add levofloxacin

The patient is already at the peak effective dose for an oral leukotriene receptor antagonist (montelukast), so increasing the dose would not add to the efficacy of this agent. However, a transition from a leukotriene receptor antagonist to a 5-lipoxygenase inhibitor such as zileuton could be considered. Increasing oral corticosteroids temporarily is the most appropriate next step for severe, uncontrolled asthma in patients who are already receiving maximal therapy. Omalizumab is an anti-IgE monoclonal antibody used in the treatment of severe, persistent asthma that is refractory to oral corticosteroids. However, it is indicated only in patients with well-documented perennial allergies to environmental agents. Further, it is typically used only in patients with IgE levels between 30 and 700 kU/L, which is the only range in which the drug has been reported to have therapeutic effect.[3] Cyclosporine had glucocorticoid-sparing efficacy for severe asthma in small trials, but adverse effects are thought to outweigh benefits, and it is not a standard recommended treatment. Antibiotics can be given if an acute bacterial infection is suspected, but this is not the case in our patient. Long-term macrolide therapy is used in certain cases of COPD and bronchiectasis, owing to its known antibiotic and anti-inflammatory effects. However, its use for asthma has not been investigated with high-quality randomized trials.[3]

The decision was made to increase the patient's prednisone dose. He was instructed to take 30 mg/d for 1 week, followed by 20 mg/d for 1 week and then 10 mg/d. Once he had reached the dosage of 10 mg/d, a gradual corticosteroid tapering of 1 to 2 mg/wk was planned. In addition, he was given instruction in proper inhaler use technique, and an asthma action plan was established.

3. At this stage, with the increase of oral corticosteroid therapy, which *one* of the following management steps is *most appropriate*?

a. Start vitamin D and calcium supplementation
b. Initiate daily blood glucose monitoring
c. Begin inhaled pentamidine therapy
d. Prescribe a proton pump inhibitor
e. Obtain baseline dual-energy x-ray absorptiometry (DEXA)

Vitamin D and calcium supplementation are recommended for all patients receiving corticosteroids for 3 months or longer, as in our patient. Although oral glucocorticoids can affect serum

Mayo Clin Proc. ■ August 2017;92(8):e111-e115 ■ http://dx.doi.org/10.1016/j.mayocp.2016.11.018
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glucose levels, home blood glucose monitoring is not indicated in a patient without a history of diabetes. *Pneumocystis jiroveci* pneumonia (previously called *Pneumocystis carinii* pneumonia or PCP) prophylaxis is primarily indicated in patients receiving more than 20 mg of prednisone daily for 1 month or longer. Since the plan is to taper the dose of corticosteroids, PCP prophylaxis is not currently indicated. Inhaled pentamidine has substantially lower efficacy than trimethoprim-sulfamethoxazole for PCP prophylaxis and should be used with caution in patients with asthma, as it may induce bronchospasm.[4] Proton pump inhibitor therapy for stress ulcer prophylaxis is indicated only in critically ill patients taking an equivalent daily corticosteroid dose of 250 mg of hydrocortisone (~60 mg of prednisone) or more.[5] A baseline DEXA is not necessary in a male aged less than 40 years without a history of fragility fracture. Fractures are infrequent in this population, even with patients taking glucocorticoids, and fracture prediction models based on bone mineral density have not been validated in patients aged less than 40 years.[6] Some suggest that DEXA screening after 6 months of glucocorticoid therapy is warranted, but no strong evidence supports this claim.

The patient returned home and followed up with his local pulmonologist. He was seen again in the clinic 6 months after his initial presentation and reported that his symptoms had worsened. He remained on a maximal-dose inhaler regimen and was now taking 20 mg of prednisone daily. He reported having to take multiple days off work, owing to his symptoms. Worsening expiratory wheezing with a prolonged expiratory phase was noted on examination. Repeated laboratory testing yielded the following: white blood cell count, 11.7 × 10^9/L; eosinophils, 3.13 × 10^9/L; and IgE, 3722 kU/L. The repeated exhaled oral NO level was 226 parts per billion. Repeated PFTs revealed a further decrease in the FEV_1 to 2.72 L (57% of predicted).

4. Which *one* of the following clinical or laboratory findings *most likely* suggests an underlying etiology of this patient's lung disease?

a. An elevated and increasing exhaled oral NO value
b. An elevated and increasing IgE level
c. Expiratory wheezing with a prolonged expiratory phase
d. Decrease in FEV_1
e. An elevated and increasing eosinophil count

An increase in exhaled oral NO is indicative of increasing eosinophilic airway inflammation, consistent with the patient's worsening symptoms. However, this increase is a marker rather than a cause for his worsening eosinophilic inflammation. Elevation of IgE levels has been found to be correlated with asthma severity, but again, it is a marker rather than a cause of worsening asthma.[3] Wheezing and a prolonged expiratory phase are not specific findings. Further, the presence or absence of wheezing is a poor predictor of the severity of airflow obstruction. The decline in FEV_1 classifies the obstruction as moderate, in contrast to the mild obstruction noted earlier. Again, this marker provides objective evidence of his worsening symptoms but does not indicate why they are occurring. All 4 of these test results support a worsening clinical picture. However, the persistent and increasing eosinophilia (eosinophil count, >1.5 × 10^9/L on 2 separate occasions for at least 6 months) despite high-dose oral prednisone therapy is the only finding that is unexplained and necessitates further work-up.[7]

Results of an electrolyte panel, creatinine measurement, urinalysis, liver chemistries, and troponin test were unremarkable. A hematology consultation was obtained for input regarding appropriate work-up and management of the eosinophilia.

5. At this time, which *one* of the following diagnoses is *least likely*?

a. Human immunodeficiency virus (HIV) infection
b. Eosinophilic granulomatosis with polyangiitis (EGPA)
c. Myeloproliferative neoplasm
d. Fungal infection
e. Medication adverse effect

Human immunodeficiency virus infection is a known cause of peripheral eosinophilia. In addition to an appropriate history, HIV testing is needed before eliminating this possibility from the differential diagnosis.

Fourth-generation HIV assays are preferred to third-generation assays, owing to their higher sensitivity for revealing early infection as well as correctly classifying HIV-2 infection.[8] Eosinophilic granulomatosis with polyangiitis, previously known as Churg-Strauss syndrome, should be included in the differential diagnosis for any patient who has difficult to manage, refractory asthma and persistent eosinophilia. A test for antineutrophil cytoplasmic antibodies (ANCA) may yield positive results in 40% to 60% of EGPA cases and should be obtained. Although myeloproliferative neoplasms and other neoplastic diseases are included in the differential diagnosis for eosinophilia, these conditions typically present with eosinophil counts of 20×10^9/L or higher. Of the options listed, this is the least likely diagnosis. Although obtaining a peripheral blood smear could be considered, Janus kinase 2 testing is not typically performed during initial work-up of eosinophilia; it may, however, be considered at a later stage, especially if a clonal myeloproliferative disorder is suspected. Many fungal infections are known to be associated with eosinophilia, the most common being *Aspergillus* in the setting of bronchopulmonary aspergillosis. *Aspergillus* testing and fungal survey are indicated in the further work-up for this patient. Eosinophilia can be caused by many prescription and nonprescription medications, including herbal and dietary supplements. These medication-related adverse effects are a commonly overlooked cause of eosinophilia.

All of the following test results were unremarkable: HIV, an ANCA panel, parasite serologies, fungal antibody survey, peripheral blood smear, allergy skin testing, *Aspergillus* testing, and serum tryptase levels. A bone marrow biopsy was performed and revealed no abnormalities. Given these findings, the patient was diagnosed as having idiopathic hypereosinophilic syndrome, which is a diagnosis of exclusion. Treatment with hydroxyurea was initiated while he was continuing inhalers and tapering the prednisone down to 5 mg/d. Whether asthma was the cause or the effect of the patient's hypereosinophilic syndrome remained unclear. However, his symptoms improved within 3 weeks of starting hydroxyurea, and he was able to resume playing recreational ice hockey. After this response was observed, he was followed up by his primary care physician and local hematologist.

DISCUSSION

Asthma is a common medical condition affecting 20 million Americans and accounting for nearly 13 million medical visits per year.[9] The diagnosis of asthma is suggested by features of a patient's history and physical examination findings and can be confirmed by objective testing, such as PFT.

Asthma may be associated with mild peripheral eosinophilia. Eosinophilia is defined as an absolute eosinophil count of 0.5×10^9/L or higher. Although the degree of eosinophilia is not always correlated with symptoms or end-organ damage, eosinophilia severity can be classified as mild (eosinophil count of $0.5\text{-}1.499 \times 10^9$/L), moderate ($1.5\text{-}4.999 \times 10^9$/L), or severe ($\geq 5.0 \times 10^9$/L). The differential diagnosis for eosinophilia is wide and includes medication effects, atopic diseases, parasitic infections, fungal infections, hematologic malignancies, mastocytosis, and hypereosinophilic syndromes. Hypereosinophilic syndrome (HES) is defined by the finding of persistent peripheral eosinophilia (eosinophil count $>1.5 \times 10^9$/L on 2 separate occasions over a period of 6 months) along with tissue hypereosinophilia and associated end-organ damage.[7] Organs most commonly affected in HES include the skin, lungs, gastrointestinal tract, heart, and nervous system. Primary HES occurs in the setting of an underlying hematologic neoplasm, whereas secondary HES is seen in the setting of parasitic infection and tumors. Idiopathic HES is a diagnosis of exclusion and is defined by persistent marked eosinophilia without a clear explanation, as in our case.

In general, the decision to pursue further work-up of eosinophilia should be based on the degree of eosinophilia and suspicion for eosinophilia-related end-organ damage. Initial testing should be aimed at narrowing the differential diagnosis and should include HIV testing, serum chemistries, creatinine measurement, urinalysis, peripheral blood smear, liver chemistries, troponin measurement, chest imaging, and flow cytometry. Additional testing should be guided by clinical context and could include additional parasitic testing, ANCA

Mayo Clin Proc. ■ August 2017;92(8):e111-e115 ■ http://dx.doi.org/10.1016/j.mayocp.2016.11.018
www.mayoclinicproceedings.org

testing to identify EGPA, measurement of tryptase levels to identify mastocytosis, adrenal insufficiency work-up, fungal testing, and consideration of bone marrow biopsy. Complete evaluation of this population also includes specialized studies to identify underlying myeloproliferative and clonal lymphocytic variants of HES.

First-line treatment for HES involves treatment of the underlying etiology (if one is found). For those with idiopathic HES or those in need of accelerated resolution, first-line therapy is systemic glucocorticoids. Treatment with glucocorticoids usually requires long-term use at relatively high doses but is effective in inducing remission in most cases. For patients whose condition does not respond to glucocorticoids or those who require steroid-sparing agents, hydroxyurea is a mainstay of therapy. It can be used in combination with glucocorticoids or as monotherapy and is a preferred drug owing to its low cost and low adverse-effect profile.

In certain myeloproliferative variants of HES (eg, *FIP1L1-PDGFRα* tyrosine kinase mutation), imatinib has been reported to be an effective treatment option.[10] Other chemotherapeutic and immunosuppressive agents (eg, methotrexate, cyclophosphamide) also have promise in the treatment of corticosteroid-unresponsive HES and may be helpful in controlling end-organ damage rather than eradicating underlying eosinophilia.[11] Another option of particular interest is the recent US Food and Drug Administration approval of mepolizumab for severe eosinophilic asthma in patients 12 years of age and older. Mepolizumab is a humanized interleukin 5 monoclonal antibody that also has been found to be effective as a long-term corticosteroid-sparing agent for HES.[12]

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