MAYO CLINIC

52-Year-Old Man With Hyposmia, Rhinorrhea, and Wheezing

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See end of article for correct answers to questions.

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A 52-year-old man presents for evaluation of persistent nasal congestion, hyposmia, rhinorrhea, and wheezing. He had a medical history of gout and gastroesophageal reflux disease. His symptoms initially developed 7 years earlier when he experienced anosmia associated with rhinorrhea and a constant sense of fullness behind the eyebrows. He was diagnosed with nasal polyposis and chronic sinusitis following a computed tomography (CT) of the paranasal sinuses. Over the course of 3 years he underwent multiple surgical procedures including nasal polypectomy and functional endoscopic sinus surgery with clinical improvement. He subsequently developed persistent wheezing associated with a morning cough. He was diagnosed with mild intermittent asthma and prescribed an albuterol inhaler with minimal improvement to his cough and wheezing. Since then he has required a course of prednisone 30 mg by mouth daily for about a week almost every 3 months because of exacerbations of wheezing associated with exertional dyspnea. Two weeks before consultation he went to the emergency department because of persistent wheezing associated with rhinorrhea after taking ibuprofen 200 mg by mouth for lower back pain. Symptoms occurred within 20 minutes of taking the medication. Pertinent physical examination findings included anterior rhinorrhea with nasal mucosal erythema as well as diffuse polyphonic expiratory wheezes on lung auscultation. He was treated with oxygen and nebulized albuterol. The patient was discharged home on 5 days of oral prednisone 40 mg daily. On questioning, he denied any history of allergies and said he never smoked. His other medications included fluticasone/salmeterol 250-50 μg 1 puff inhaled twice daily, albuterol 90 μg/actuated hydrofluoroalkane aerosol 1 to 2 puffs by inhalation twice daily as needed, allopurinol 100 mg oral once daily, and omeprazole 40 mg oral once daily.

On presentation the patient had a respiratory rate of 16 breaths per minute saturating 99% oxygen on room air. He had a pulse rate of 96 beats per minute with a blood pressure reading of 136/82 mm Hg and oral temperature being 36.8°C. His lungs revealed sparse polyphonic expiratory wheezing over the left upper and right middle lung zones on auscultation. Cardiovascular and abdominal examinations were unremarkable. No focal motor or sensory deficits were identified on neurologic examination. Left lumbar paraspinal tenderness was elicited on palpation when performing musculoskeletal examination. However, there was full range of movement of the spine and 4 limbs. Laboratory studies revealed the following: hemoglobin, 15.4 g/dL (12.0-15.5 g/dL); white blood cell count, 10.3 × 10^9/L (3.5-10.5 × 10^9/L); eosinophil count, 0.5 × 10^9/L (0.05-0.5 × 10^9/L); platelet count, 226 × 10^9/L (150-450 × 10^9/L); and fasting serum glucose, 132 mmol/L (70-100 mmol/L). Other values for a metabolic panel were within reference range. Serum IgE level was within normal limits and the patient had negative skin prick testing for common aeroallergens. A sinus CT showed mucoperiosteal thickening in the ethmoid, sphenoid, and maxillary sinuses (Supplemental Figure, available online at http://www.mayoclinicproceedings.org).

1. What *one* of the following is the *most specific* diagnosis in this patient?

a. Allergic rhinitis
b. Aspirin-exacerbated respiratory disease (AERD)
c. Asthma
d. Chronic obstructive pulmonary disease (COPD)
e. Chronic rhinosinusitis

The patient's history does not identify any specific allergen that exacerbated his symptoms. In allergic rhinitis, patients would report symptom exacerbation either indoors or

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outdoors or at the workplace in relation to specific allergen exposure. Allergy skin testing or measurement of serum specific IgE may identify culprit allergens. The patient meets criteria for diagnosis of AERD given his tetrad of chronic rhinosinusitis, nasal polyposis, asthma symptoms, and a positive oral aspirin challenge test result.[1,2] The patient has a diagnosis of asthma; however, the additional aforementioned sinonasal symptoms would suggest a specific diagnosis of AERD. Spirometry should be performed when asthma is suspected. An exhaled nitric oxide test may also be helpful to measure underlying airway inflammation. A methacholine challenge would not be recommended in this patient given that his presentation is classical for asthma and a methacholine challenge could cause a severe drop in FEV_1. The test should be reserved for patients in whom the diagnosis of asthma is unclear.[3] Chronic obstructive pulmonary disease is an obstructive airway disease with minimal reversibility of airway obstruction characterized by chronic bronchitis and emphysema. For this reason, a pulmonary function test would be expected to show airway obstruction.[3] The patient meets criteria for diagnosis of chronic rhinosinusitis, which requires at least 2 of the following 4 cardinal symptoms: mucopurulent nasal discharge, nasal congestion, facial fullness or pain, and reduction in sense of smell.[4] However, chronic sinusitis on its own does not explain his symptoms of wheezing and exacerbation with ibuprofen.

The patient's diagnosis is established. He is counseled on strict avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin.

2. Which *one* of the following tests is *most likely* to confirm the underlying diagnosis?

a. Arterial blood gas
b. Chest radiograph
c. Oral aspirin challenge
d. Peak expiratory flow rate
e. Spirometry testing

An arterial blood gas analysis is indicated in acute respiratory distress to assess the degree of hypoxemia and acid-base status. It is useful in acute asthma to identify patients requiring ventilator support. Hypercapnia in acute asthma is suggestive of respiratory muscle exhaustion. An arterial blood gas is not indicated in this setting because the patient has a normal respiratory rate and oxygen concentration. A chest radiograph in this patient with wheezing may show bronchial thickening, lung hyperinflation, and focal atelectasis suggestive of obstructive airway disease. Obstructive airway diseases include asthma, bronchiectasis, and chronic obstructive pulmonary disease (COPD); thus, it would not definitively establish an underlying diagnosis. The diagnosis of AERD includes the presence of chronic rhinosinusitis with nasal polyposis, asthma, and sensitivity to aspirin or cyclooxygenase-1–inhibiting NSAIDs. A positive oral aspirin challenge helps confirm the diagnosis of AERD provided that the patient has the aforementioned respiratory symptoms.[5] However, oral aspirin challenge is not always necessary when the medical history is convincing of AERD. Peak expiratory flow rate (PEFR) is a bedside test measuring bronchial airflow and helps identify the degree of airway obstruction by comparing the value obtained to an expected value for age, sex, and height. Spirometry is a noninvasive pulmonary test that measures lung air flow and volumes with inhalation and exhalation maneuvers. It may suggest obstructive or restrictive lung disease. However, both PEFR and spirometry cannot pinpoint the underlying etiology contributing to lung pathophysiology.

A chest radiograph showed mild lung hyperinflation while pulmonary function testing showed a forced vital capacity (FVC) of 4.89 L (101% predicted), FEV_1 of 4.08 L (106% predicted), and FEV_1/FVC of 83.5%. The patient underwent an oral aspirin challenge with sequential dose escalation (oral aspirin 20 mg followed by 40 mg and 60 mg, respectively). He developed moderate dyspnea and wheezing with 60 mg oral aspirin. Repeat FEV_1 decreased by 22% to 3.18 L. The patient was treated with nebulized albuterol and his symptoms resolved.

3. What is the *most appropriate* next step aimed at treating his underlying condition?

a. Anti–IL-5 mAbs
b. Aspirin desensitization
c. High-dose oral corticosteroids
d. Prescribe nonsedating antihistamine
e. Repeat sinus surgery

Mepolizumab is an anti—IL-5 mAb that may have a role in treating severe nasal polyposis refractory to glucocorticoid therapy as shown in a small randomized controlled trial.[6] IL-5 stimulates eosinophil production, and thus mepolizumab may have a role in the treatment of eosinophilic nasal polyposis. Mepolizumab and reslizumab (both anti—IL-5 mAbs) are approved by the Food and Drug Administration (FDA) for the treatment of eosinophilic asthma. However, they are not approved by the FDA for the treatment of nasal polyps or sinus disease.[6] Aspirin desensitization is indicated in AERD with nasal polyposis that is refractory to intranasal glucocorticoids, leukotriene-receptor antagonists, and sinus surgery. Oral aspirin desensitization follows a protocol of administering aspirin doses over given time intervals. Various desensitization protocols have been developed. These include a 3-day oral desensitization, a combined ketorolac 2-day desensitization, and most recently a 1-day oral desensitization.[7] Following a successful desensitization the patient would continue taking high-dose aspirin (typically 325 mg oral aspirin twice daily or greater) to maintain a desensitized state. This therapy can reduce upper and lower airway symptoms in AERD.[8] Utility of high-dose oral corticosteroids is to afford symptomatic improvement of flares with sinonasal or asthma symptoms. Although a nonsedating antihistamine may help rhinitis symptoms earlier in the disease course, they would not be expected to significantly improve the patient's conditions given that his symptoms have been refractory to standard therapy for AERD. Repeat sinus surgery is not a definite treatment. However, it can help debulk polyps; thus, patients may have greater tolerance for aspirin desensitization.

The patient undergoes successful aspirin desensitization and is prescribed oral aspirin 650 mg twice daily. He asks whether any other medication would be helpful for his symptoms.

4. Which *one* of the following pharmacologic interventions will target a known *specific* pathophysiologic abnormality in this disease?

a. Leukotriene-receptor antagonists
b. Long-acting inhaled B_2-agonists
c. Oral corticosteroids
d. Short-acting inhaled B_2-agonists
e. Subcutaneous allergen immunotherapy

Elevated leukotrienes are one of the key mediators for symptoms in AERD. Leukotriene C_4 is thought to be the main leukotriene causing bronchoconstriction in AERD.[5] Leukotriene-receptor antagonists such as montelukast and zafirlukast selectively antagonize cysteinyl leukotriene receptor 1 with preferential inhibition of leukotrienes C_4 and D_4. Zileuton is an oral inhibitor of 5-lipoxygenase, which has a global inhibition on leukotriene synthesis.[9] B2-agonists are effective airway bronchodilators in obstructive airway disease. Long-acting and short-acting inhaled B_2-agonists have a role as preventative and rescue medication, respectively. However, they do not specifically target mediators responsible for the patient's clinical symptoms. Corticosteroids are effective at decreasing the level of anti-inflammatory mediators; however, they are not specific to inhibiting the leukotriene pathway. Subcutaneous immunotherapy is indicated for desensitization to a specific allergen mediating the patient's symptoms. In this case, this is not indicated because the patient tested negative on allergen skin prick testing.

He presents 2 years later before a scheduled total knee replacement. He has not had an asthma exacerbation since aspirin desensitization. Moreover, he reports decreased nasal congestion and improved sense of smell. The patient's orthopedic surgeon recommended stopping aspirin 1 week before the procedure. At present he takes oral aspirin 325 mg twice daily. He asks about your opinion on restarting aspirin postoperatively.

5. How should aspirin be reintroduced following the surgical procedure?

a. No need to restart aspirin
b. Oral aspirin 325 mg twice daily
c. Oral aspirin 650 mg twice daily
d. Repeat oral aspirin challenge and desensitization
e. Start low-dose oral aspirin 81 mg daily

Patients who undergo aspirin desensitization must continue taking aspirin daily to maintain a desensitized state, thus slowing regrowth of nasal polyps and improving asthma symptoms. Patients who omit aspirin for 2 to 3 days may restart aspirin at their previous dose with a small risk of experiencing

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exacerbation of AERD symptoms. However, in patients who omit taking aspirin beyond 3 days, a full aspirin challenge and desensitization process must be repeated. After 1 week of omission, restarting oral aspirin at doses of 325 mg or 650 mg twice daily may produce severe wheezing and dyspnea. Low-dose oral aspirin at 81 mg daily would not be effective at suppressing AERD symptoms.[2,8]

The patient undergoes repeat aspirin oral challenge and is desensitized to oral aspirin 325 mg twice daily.

DISCUSSION

Aspirin-exacerbated respiratory disease is characterized by asthma, chronic rhinosinusitis with nasal polyposis, and respiratory reactions to aspirin or other NSAIDs; the triad of asthma, nasal polyps, and aspirin sensitivity was previously termed Samter triad.[10] The disorder is thought to have a prevalence of 7% in adults having asthma and 14% of patients with severe asthma. Ingestion of aspirin or NSAIDs typically produces rhinorrhea, nasal congestion, conjunctivitis, and bronchoconstriction with symptom severity being largely dose-dependent.[1,5]

Although the pathophysiology of AERD is not fully understood, there is substantial evidence of dysregulated 5-lipoxygenase and prostaglandin pathways. This leads mast cells to overproduce cysteinyl leukotrienes that are potent airway bronchoconstrictors.[5] Prostaglandin D_2 is a potent bronchoconstrictor and appears to be elevated in AERD, whereas the levels of the bronchodilator prostaglandin E_2 are reduced.[9] Together with mast cells, eosinophils are thought to play a role in the pathophysiology of AERD.[11] Around half of the patients with AERD may have peripheral blood eosinophilia, which correlates with the severity of chronic rhinosinusitis.[11] Anti-IgE and anti–IL-5 mAbs have been shown to produce symptomatic improvement and reduction in nasal polpys, respectively, in patients with AERD.[5,6]

The diagnosis of AERD is established with a positive provocative oral or intranasal challenge with aspirin or another NSAID.[2] Aspirin-exacerbated respiratory disease may be widely undiagnosed given that double-blinded oral aspirin challenges have revealed positive test results for aspirin sensitivity in patients with asthma who were previously unaware of this syndrome.[5] Asthma typically occurs in the third or fourth decade; however, aspirin sensitivity may develop at any stage during the disease course.[12]

Aspirin and NSAID avoidance, H1 antihistamines, intranasal corticosteroids, and leukotriene-receptor antagonists all have a role in the treatment of AERD. Although not curative, sinus surgery is helpful for patients with symptoms of nasal fullness, rhinorrhea, or hyposmia secondary to chronic rhinosinusitis and nasal polyposis. Aspirin desensitization is indicated for patients with AERD who require daily NSAIDs or aspirin for another medical condition or as another treatment option in patients who have recalcitrant AERD. Aspirin desensitization and continued daily aspirin thereafter leads to decreased sinus infections and decreased nasal polyp formation, and lowers the need for systemic corticosteroids. It is a cost-effective treatment approach that may improve daily symptoms and overall quality of life.[5] However, only a few randomized, placebo-controlled studies of aspirin desensitization have been performed to date and symptomatic benefits may be modest.[12] The aspirin desensitization protocol is typically performed by an allergist who is equipped to handle the potentially severe respiratory reactions that may occur. Patients who omit taking daily aspirin for more than 3 days would generally require a repeat aspirin challenge and desensitization given that resensitization to aspirin and oral NSAIDs would occur within a 1-week time frame.[2]

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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

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