Whistling in the Dark

Daniel A. Solomon, M.D., Christopher H. Fanta, M.D., Bruce D. Levy, M.D., and Joseph Loscalzo, M.D., Ph.D.

In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors’ commentary follows.

A 38-year-old woman living in Florida presented to her primary care physician with shortness of breath, fever, and cough productive of yellow sputum soon after the birth of her third child. She received a course of antibiotics for a presumed respiratory tract infection, and her symptoms resolved. Soon thereafter, however, she returned to her physician with an intermittent, nonproductive cough, wheezing, and shortness of breath. She was unable to identify any specific exposures that might have provoked these symptoms, although she noted that her symptoms tended to worsen at night. She reported no fever, orthopnea, leg swelling, or aspiration with swallowing, but she had a history of episodic retrosternal burning that was consistent with gastroesophageal reflux.

Recurrent episodes of shortness of breath, cough, and wheezing suggest a diagnosis of asthma. Nocturnal worsening of symptoms is consistent with this diagnosis. Atypical features, opening the possibility of alternative diagnoses, are the relatively late age at onset and the absence of identifiable triggers for the symptoms. Other potential causes of her symptoms include recurrent respiratory tract infections (due to being the mother of young children), gastroesophageal reflux with microaspiration of gastric contents, and congestive heart failure, including that resulting from valvular heart disease or diastolic dysfunction, which may cause “cardiac asthma.”

The patient’s other active medical problems included depression and seasonal allergic rhinitis. She had smoked cigarettes for approximately 10 years and quit 10 years before presentation. She was not employed and lived at home with three children and two golden retrievers. She had no history of aspirin intolerance or recurrent sinusitis. Her examination was notable for her body-mass index (BMI, the weight in kilograms divided by the square of the height in meters), which was 45.4, and loud, diffuse expiratory wheezing in both lungs.

The wheezing supports a possible diagnosis of asthma. Risk factors for adult-onset asthma include a history of cigarette smoking, atopy (suggested by her seasonal allergic rhinitis), and obesity. Aspirin-exacerbated respiratory disease is also a possibility because it often presents in adulthood with a characteristic sequence of recurrent sinusitis, followed by the development of asthma and then the recognition of exacerbations of asthma precipitated by ingestion of aspirin or any other cyclooxygenase-1 inhibitor. Her young age and limited smoking history (less than 20 pack-years) diminish the likelihood of a diagnosis of chronic obstructive pulmonary disease (COPD) in the absence of alpha-1-antitrypsin deficiency.
Given her history and the findings on physical examination, the patient received an empirical diagnosis of asthma and was started on controller therapy with an inhaled glucocorticoid and a long-acting beta-agonist bronchodilator, together with a short-acting beta-agonist bronchodilator for the relief of acute symptoms. On skin tests for allergies, she reacted only to antigens from the house-dust mite.

A presumptive diagnosis of asthma was made on the basis of the patient’s symptoms, the findings on physical examination, and the initial improvement in her condition with antiasthma therapy. However, confirmatory evidence was lacking; specifically, the presence of airflow obstruction on pulmonary-function testing that abates over time or in response to the use of a quick-acting bronchodilator.

During the ensuing 5 years, the patient remained active but required hospitalization as often as once yearly for episodes of severe shortness of breath and wheezing, typically provoked by respiratory tract infections. The leukotriene-receptor antagonist montelukast was added to her treatment regimen but had little effect on her symptoms.

After a move from Florida to New Hampshire, her symptoms worsened. During the next 3 years, she required hospitalization every 3 to 4 months for respiratory distress, and on one occasion she required a brief period of mechanical ventilation for respiratory failure.

The patient now has severe disease that is refractory to seemingly appropriate treatment. At this point, the treating physician must make a systematic assessment of the possible reasons for the failure of treatment that is highly effective in most patients with asthma. Are there inciting factors, such as allergens or cigarette smoke, in the patient’s home (or work or school) environment that are intensifying the underlying inflammation in the airways? Could the lack of responsiveness to treatment be due to aggravating coexisting conditions (gastroesophageal reflux, uncontrolled rhinosinusitis, allergic bronchopulmonary aspergillosis, or Churg–Strauss syndrome) or aggravating agents (beta-blocker medications or illicit inhaled drugs)? Is the patient adhering to the treatment regimen, or is a lack of comprehension of the regimen, a lack of access to medications, fear of medication side effects, or an unconventional view of health care contributing to nonadherence? Is the diagnosis of asthma correct, or is an alternative disease mimicking asthma?

In an effort to reduce the frequency of disease flares, anti-IgE monoclonal antibody therapy was initiated and evoked a modest response. In addition, the patient was treated with multiple courses of oral glucocorticoids and ultimately with 15 mg of prednisone daily. Intermittent attempts to reduce the dose of prednisone resulted in symptomatic worsening. Despite treatment with daily systemic glucocorticoids, she received little relief, reporting a persistent barklike cough, wheezing on an almost daily basis, and severe exertional dyspnea. She was admitted to our hospital for further evaluation.

Despite maximal therapy, the patient’s symptoms have progressively worsened to the point that she takes oral glucocorticoids daily for symptom control. However, the worsening of symptoms when steroid doses are tapered does not necessarily indicate increased airway inflammation and obstruction. A range of symptoms can be associated with a dose reduction in patients who have undergone long-term treatment with systemic glucocorticoids, including weakness, lethargy, depression, decreased appetite, myalgias, and arthralgias, and such symptoms might have contributed to the difficulty in changing her treatment regimen. Objective measurement of lung function can help to distinguish the increased airflow obstruction characteristic of worsened asthma from the side effects of the withdrawal of glucocorticoids. Spirometry is preferable to peak-flow measurement in this circumstance because the patient’s effort is more readily assessed in the graphic display of the test results and because it is possible to distinguish a low peak flow that is caused by restriction (i.e., something other than asthma) from a low peak flow that is caused by obstruction. An objective assessment of airflow is warranted before the initiation of additional therapy, with its attendant costs and possible harms.

On admission to the hospital, the patient’s weight was approximately 128 kg (282 lb) and her height approximately 168 cm (66 in.); her blood pressure was 148/89 mm Hg, and her pulse 103 beats per minute and regular. She was afebrile. Her oxygen saturation was 96% at rest while breathing ambient air. Her breathing appeared uncomfortable,
but she was in no acute respiratory distress. Notable physical findings were a prolonged expiratory phase during respiration and diffuse expiratory wheezes that were audible with and without a stethoscope, with the loudest wheezing heard over the trachea and upper chest. The remainder of her examination was normal; she had no nasal polyps, jugular venous distention, heart murmurs, or peripheral edema.

The cause of the patient’s loud expiratory wheezing, which can be heard easily without a stethoscope, may be diffuse intrathoracic airway obstruction, such as occurs during a severe asthma attack, or obstruction of the upper or central airways, from which the sounds are transmitted throughout all lung fields. The source of the obstruction can be determined with the use of pulmonary-function testing, in which the characteristic patterns produced in flow-volume curves serve to distinguish upper-airway obstruction from diffuse intrathoracic airway obstruction.

The intermittent nature of her symptoms also raises the possibility of vocal-cord dysfunction (i.e., the occurrence of a functional abnormality in a structurally normal larynx). Wheezing results when air flows through the narrow residual glottic opening made when the vocal cords inappropriately adduct during breathing. This condition may occur as an abnormal response to stress or be a manifestation of various psychiatric disorders. Symptoms may also be triggered by laryngeal irritants, such as laryngopharyngeal reflux and postnasal drip. When it is inspiratory, the wheezing of vocal-cord dysfunction mimics stridor; when expiratory, it is often mistaken for asthma. Direct inspection of the vocal cords at a time when the patient is actively wheezing can establish or rule out the diagnosis.

The patient had a normal complete blood count and normal findings on chest radiography. Pulmonary-function testing showed a forced vital capacity (FVC) of 3.62 liters (91% of the predicted value) and a forced expiratory volume in 1 second (FEV$_1$) of 2.67 liters (83% of the predicted value), with a normal FEV$_1$/FVC ratio of 0.73. Total lung capacity was measured at 6.03 liters (102% of the predicted value), with a residual volume of 2.41 liters (122% of the predicted value). The flow-volume loop was normal (Fig. 1). Computed tomography (CT) of the chest showed clear lungs without evidence of airway or parenchymal abnormalities. Direct fiber-optic laryngoscopy revealed normal vocal-cord movement and no structural abnormalities in the upper airway.

It is surprising to observe unobstructed airflow on spirometry and normal vocal-cord movement in a patient with loud, nonfocal expiratory wheezing. These findings suggest that the source of wheezing may be the intrathoracic trachea. Further investigation should include CT with dynamic imaging of the trachea or fiberoptic bronchoscopy with direct tracheal inspection. Potential causes of airflow obstruction in the central airways, particularly in the trachea, include endobronchial tumors, aspirated foreign bodies, extrinsic compression, strictures, and malacia.

The findings on subsequent fiberoptic bronchoscopy were abnormal. The trachea narrowed dramatically during exhalation, particularly when the patient coughed, leaving only a thin crescentic lucent for airflow. Anterior bulging of the posterior membranous sheath extended throughout the length of the trachea, and there was expiratory narrowing of both main-stem bronchi (Fig. 2).
Normally, the posterior membranous sheath (pars membranacea) of the intrathoracic trachea bows slightly inward on exhalation and to a greater degree with cough, the result of positive pleural (and mediastinal) pressure that is greater than intrathoracic pressure. Healthy persons may have a wheezy cough or may wheeze on forced exhalation as the anterior bulging of the posterior membranous sheath narrows the tracheal lumen to a thin crescent. In tracheomalacia and other conditions in which there is excessive airway collapse on exhalation, the exaggerated dynamic movement of the posterior membrane can compromise the airway lumen on exhalation, even during tidal breathing.

A diagnosis of excessive dynamic airway collapse, presumably resulting from tracheomalacia, ties together many aspects of the patient’s presentation: dyspnea and a barklike cough that is unresponsive to conventional asthma therapy, diffuse expiratory wheezes heard most easily over the neck and upper chest, and normal results on chest imaging and pulmonary-function tests. Unlike our patient, many patients with tracheomalacia have airflow obstruction that can be detected on spirometry; typically, there is reduced peak expiratory flow and notching or repeated oscillations along the expiratory limb of the flow-volume curve.

A Y-shaped silicone stent was placed in the trachea and main bronchi by means of rigid bronchoscopy. However, the patient had difficulty clearing secretions through the stented segment of the airway (as documented on bronchoscopy) and asked for the stent to be removed. At a subsequent visit, a metal tracheobronchial stent was placed. She noted initial improvement in her breathing, but 3 weeks later, when respiratory difficulty developed during a respiratory tract infection, the stent was removed. Thereafter, she elected to proceed with surgical tracheoplasty. At a follow-up visit 6 months after surgery, the patient’s condition was much improved. She noted minimal wheezing, had begun to taper the dose of systemic glucocorticoids, and was starting to pursue an active lifestyle.

**Commentary**

In this 38-year-old woman who presented with recurrent wheezing, coughing, and shortness of breath, a diagnosis of asthma initially seemed reasonable. The early abatement of symptoms and the improvement in physical findings with the use of bronchodilators and inhaled and oral glucocorticoids were consistent with this presumptive diagnosis. However, there was no confirmatory evidence on pulmonary-function testing that airflow obstruction had abated over time or in response to the use of bronchodilators. This case illustrates how the absence of appropriate diagnostic testing can lead to a long delay in reaching the correct diagnosis, and in this instance, to an extended course of costly and potentially harmful treatment. The management of severe, refractory asthma calls for a systematic approach that includes assessment of the accuracy of the diagnosis, with consideration of other conditions that can mimic asthma, including tracheomalacia.

Although in our patient the diagnosis of tracheomalacia was made with the use of fiberoptic bronchoscopy, the speed of image collection on modern multidetector CT equipment makes chest CT a useful alternative means of diagnosis. Images should be obtained during inspiration and expiration and then compared (Fig. 3). For images collected during expiration, the goal is to maximize the abnormal movement of the posterior tracheal wall (or any other malacic portion of the wall). The best time to obtain the image is...
near but not at the end of exhalation (i.e., there should still be expiratory airflow), when the pleural pressure is still positive, rather than during the period when exhalation is complete and inhalation has yet to begin. At this point in respiration pleural pressure returns to a level just below the atmospheric pressure. Precise criteria for radiographic diagnosis of tracheomalacia have not yet been defined, but many radiologists use a luminal narrowing of 50% on exhalation as a benchmark.²

In adults, the most common cause of tracheomalacia is prolonged mechanical ventilation; high pressures in the endotracheal tube cuff may cause localized ischemic injury to the tracheal wall (the cartilage and the membranous sheath). Other causes of segmental tracheomalacia include prolonged external pressure on the tracheal wall, such as may be caused by a large substernal goiter or a congenital vascular sling (e.g., a right-sided aortic arch with an aberrant subclavian artery). More diffuse tracheomalacia is encountered in patients with the rare conditions of tracheobronchomegaly (Mounier–Kuhn syndrome)³ and relapsing polychondritis.⁴ In patients with advanced COPD, there may be development of a distinctive form of tracheomalacia in which distortion of the cartilaginous rings leads to a lateral narrowing of the trachea, known as saber-sheath trachea, which becomes exaggerated on exhalation.⁵ In other patients, similar to ours, diffuse anterior bulging of the posterior tracheal wall develops, leading to a crescent shape on cross-sectional imaging or direct endobronchial inspection.⁶ The pathogenesis is uncertain, although limited autopsy data suggest that the atrophy of longitudinal elastic fibers is a contributing factor.⁷ Reported risk factors include cigarette smoking and long-term use of glucocorticoids.⁸

In some patients with less severe disease, symptoms related to tracheomalacia appear only

---

**Figure 3. Radiographic Imaging of Tracheomalacia.**

CT images captured at 5-mm intervals above, at, and below the main carina on inspiration (left panels) and exhalation (right panels) reveal dramatic expiratory airway narrowing (arrows). (These images are not from the case patient.)
in the context of an acute infection of the lower respiratory tract. During a bout of tracheobronchitis, intraluminal secretions cannot be effectively cleared past the involved segment and cause critical obstruction at this site. Supportive care during acute respiratory infections is often sufficient, but continuous positive airway pressure, administered through a nasal or full-face mask, may be used to provide a pneumatic stent for the central airways during exhalation.

For more severe tracheomalacia, treatment options supported by evidence from case series include the surgical repair of areas of localized disease (tracheal resection and reconstruction), the placement of tracheal stents, and surgical tracheoplasty. The use of a tracheal stent for extensive tracheomalacia is for the most part a short-term solution. Complications include stent migration, the development of granulation tissue in response to the rubbing of the tips of the stent against the mucosa during respiration, and the accumulation of airway secretions inside the stent (which lacks normal mucociliary clearance mechanisms). Tracheoplasty is currently performed through a right thoracotomy. Polyethylene mesh is sewn to the outside of the posterior membrane, reducing its mobility while at the same time reducing the compliance of the trachea by shortening the distance between the tips of the cartilaginous rings. This surgical procedure does not provide access to the subglottic trachea (which requires a separate cervical approach) or address malacia in the distal bronchi.

The present case underscores the need to consider a broad differential diagnosis for wheezing, especially when findings are atypical for asthma or when symptoms fail to subside as expected in response to conventional therapy. This case also highlights the importance of measuring lung function both when attempting to confirm (or rule out) a diagnosis of asthma if it is suspected and when adjusting medications in patients with established asthma. In our patient, pulmonary-function testing (performed after a prolonged course of illness attributed to “refractory asthma”) failed to confirm the diagnosis. Further testing led to the identification of tracheomalacia as the cause of symptoms and, with appropriate therapy, to clinical improvement.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES


Copyright © 2012 Massachusetts Medical Society.