42-Year-Old Man With Asthma Symptoms and Recurrent Bronchitis

Benjamin R. Griffin, MD; Christopher R. Stephenson, MD; and Mark E. Wylam, MD

A 42-year-old man from southern Iowa presented to our institution for evaluation of symptoms of asthma and recurrent bronchitis. The patient's body mass index was 17.0, and he had never smoked. Since high school, he had had a persistent, productive cough. Asthma had been diagnosed years previously, and over the years, multiple medications were prescribed including fluticasone/salmeterol HFA, montelukast, albuterol, other inhaled glucocorticoids, and ipratropium/albuterol nebulization. The medications were minimally effective at controlling respiratory symptoms.

In addition, he reported frequent (several per year) pneumonias (frequently afebrile), which occurred in various lung lobes. Each episode responded symptomatically to antibiotics. He noted that over the years, respiratory secretions had become progressively more difficult to clear and that the frequency of respiratory exacerbations was increasing. A recent trial of guaifenesin had been useful.

In 2000, he was treated for acute pancreatitis ascribed to gallstones. Further evaluation by computed tomography (CT) revealed an atrophic pancreas. He continued to have periodic "abdominal pain attacks," which he described as epigastric pain. He reported chronic bloating with foul-smelling, floating stool exacerbated by fatty or greasy foods. He had tried to limit his intake of these foods and also took probiotics. He was currently having one normal stool per day and experienced abdominal pain attacks once or twice per month.

During the past year, he had noted increasing fatigue and weight loss of 4.5 to 6.75 kg. He became exhausted early in the day and frequently slept through much of the weekend before returning to work on Monday. He had also begun to have drenching night sweats.

The patient had no history of excesive alcohol consumption and had been abstinent since his episode of pancreatitis in 2000. He reported no intravenous (IV) drug use and had no other risk factors for human immunodeficiency virus (HIV) or sexually transmitted diseases. He was sexually active with his wife of many years and had no children despite not using contraception. Infertility was ascribed to his wife's polycystic ovary syndrome, although no formal infertility evaluation had been pursued. No one in the patient's immediate family had chronic respiratory disease.

Physical examination revealed a tall, thin (180.1 cm, 55.3 kg; body mass index, 17.0) man with soft crackles predominantly in the upper lung fields. Mild digital clubbing was noted in his extremities. Examination of the heart, abdomen, and other systems yielded unremarkable findings.

1. Which *one* of the following is the *most likely* cause of this patient's recurrent respiratory symptoms?

a. Autosomal recessive chloride channel abnormality
b. Airway inflammation, intermittent airflow obstruction, and airway hyperresponsiveness
c. Autosomal codominant deficiency of elastase inhibitor
d. Retrovirus infection targeting CD4 cells
e. Autosomal recessive defect in ciliary function

The patient's constellation of symptoms including chronic bronchitis, pancreatic insufficiency, and infertility in a man suggests cystic fibrosis (CF), an autosomal recessive disease caused by mutation of the CF transmembrane conductance regulator (CFTR) protein. The CFTR transports chloride across epithelial cell membranes. Although airway inflammation, intermittent airflow obstruction, and airway hyperresponsiveness are features of asthma, our patient's response to asthma medications was limited. Moreover, asthma is not likely to explain his gastrointestinal (GI) symptoms. α_1-Antitrypsin (A1AT) deficiency caused by mutations in the *SERPINA1* gene

See end of article for correct answers to questions.

Resident in Internal Medicine, Mayo School of Graduate Medical Education, Rochester, MN (B.R.G., C.R.S.); Advisor to residents and Consultant in Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN (M.E.W).

elicits panacinar emphysema due to diminished elastin cleavage by neutrophil elastase. Neutrophil elastase is normally inhibited by the A1AT protein. α_1-Antitrypsin deficiency may cause biliary cirrhosis and portal hypertension but is unlikely to cause pancreatic disease. In A1AT deficiency, the hepatocellular disease is due to intrahepatocyte accumulation of misfolded A1AT molecules. Although there are cases of latent HIV/AIDS caused by a retrovirus targeting CD4 cells, it would not explain our patient's symptoms dating back to high school. Primary ciliary dyskinesia, also known as immotile cilia syndrome, is a rare autosomal recessive defect in ciliary function that causes bronchiectasis and infertility. When associated with situs inversus primary ciliary dyskinesia, it is called Kartagener syndrome. Chronic recurrent respiratory infections, including sinusitis, bronchitis, pneumonia, and otitis media, lead to progressive damage to the respiratory system beginning in early childhood. Primary ciliary dyskinesia does not have GI manifestations.

Initial blood work included a complete blood cell count, electrolyte panel, and thyrotropin, HIV, and fat-soluble vitamin testing. The test results revealed deficiencies in vitamins A and E but were otherwise unremarkable.

2. At this point, which *one* of the following is the *best* test to confirm the suspected diagnosis?

a. CT scan of the chest and abdomen
b. Pulmonary function test
c. Sweat chloride testing
d. Genetic testing for CF mutation
e. Fecal fat testing

A CT scan may reveal findings suggestive of CF such as upper lobe–predominant bronchiectasis or fatty atrophy of the pancreas, but these findings are not diagnostic. Similarly, pulmonary function tests may reveal an obstructive pattern with hyperinflation, but these results are not specific for a diagnosis of CF. Sweat chloride testing remains the criterion standard as the primary test for diagnosis of CF because it measures a functional effect of CFTR. Sweat is induced by pilocarpine iontophoresis, and 2 specimens, each with a minimum volume of 100 μL, must be collected for the test to be considered valid. For a person older than 6 months of age, normal concentrations of chloride in sweat are less than 40 mmol/L. Values greater than 60 mmol/L are consistent with a diagnosis of CF. Values between 40 and 60 mmol/L are considered indeterminate. Detection of 2 disease-causing mutations on DNA analysis can also establish the diagnosis and is often used as a confirmatory test after positive or indeterminate results are obtained on the sweat chloride test. It is not the initial test of choice because of its substantially increased cost over sweat chloride testing. In adults, quantitative fecal fat testing, or measurement of the fecal elastase-1 level, may suggest pancreatic insufficiency but cannot diagnose CF.

Pulmonary function testing revealed severe airway obstruction without bronchodilator response. The ratio of forced expiratory volume in the first second of expiration (FEV_1) to forced vital capacity ratio was 54%. The FEV_1 was 29% of predicted. Diffusing capacity was at 56% of predicted. A CT scan of the chest illustrated bilateral bronchial wall thickening and upper lung–predominant cylindrical and cystic bronchiectasis.

Sweat chloride testing was positive for CF with a value of 90 mmol/L. Confirmatory genetic testing by multimutation method (106-mutation panel) revealed 2 copies of the most common disease-causing mutation in whites, the F508del mutation (c.1521_1523delCTT by Human Genome Variation Society nomenclature).

When the patient was informed of the results, he was surprised that he had a "childhood" disease. He wondered if there would be any difference in his clinical course compared with those diagnosed at a young age.

3. Which *one* of the following is *true* regarding this patient's prognosis compared with that for a patient diagnosed during childhood?

a. He is at higher risk for *Pseudomonas aeruginosa* infection
b. He is at higher risk for severe lung disease
c. He is at higher risk for pancreatic insufficiency
d. He is at higher risk for pancreatitis
e. He is at higher risk for the F508del mutation

Clinical manifestations of CF diagnosed in adults range widely from subclinical disease in a single organ system to the full classic

Mayo Clin Proc. ■ April 2015;90(4):527-531 ■ http://dx.doi.org/10.1016/j.mayocp.2014.09.012
www.mayoclinicproceedings.org