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

phenotype.[1] In general, patients who have late presentation of CF are more likely to have lower incidences of *P aeruginosa* infection, less severe lung disease, and higher rates of pancreatic sufficiency.[2,3] Because these patients have functioning pancreases, they are more likely to have development of pancreatitis. In fact, idiopathic pancreatitis can be the presenting symptom of late presentation CF. Although homozygous F508del mutation is still seen in most patients with CF diagnosed in adulthood, the percentage appears to be significantly less than the 86.7% having at least one copy in the CF population at large.[4,5]

A sputum culture grew *Escherichia coli*, *P aeruginosa*, and methicillin-sensitive *Staphylococcus aureus*. The organisms isolated were widely susceptible to antimicrobial agents.

4. Which *one* of the following is the *most appropriate* antibiotic regimen?

a. IV vancomycin, IV cefepime, and IV tobramycin
b. IV cefepime and IV tobramycin
c. IV cefepime
d. IV cefepime and IV colistin
e. IV cefepime and inhaled tobramycin

Given that the patient's culture isolated methicillin-sensitive *S aureus* rather than methicillin-resistant *S aureus*, vancomycin is unnecessary. *Pseudomonas* should be "double covered" with 2 agents of different classes to which it is susceptible. There is insufficient evidence to recommend the use of a single antibiotic as being equivalent to the use of more than one antibiotic class for treatment of *Pseudomonas* infection during an acute exacerbation of pulmonary disease. A β-lactam and an aminoglycoside is the best option for this patient. Cefepime as a single agent would be inappropriate because it would not double cover *Pseudomonas*. Intravenous colistin is associated with serious adverse effects including renal toxicity and should not be used if there is an aminoglycoside available for which there is no resistance. Inhaled tobramycin is generally thought to be less effective than the IV form because of inhomogeneous distribution of absorption within the lung, although it is sometimes used in addition to IV tobramycin in severe cases. Inhaled tobramycin and aztreonam are US Food and Drug Administration–approved to reduce CF respiratory exacerbations.

Airway clearance therapy should be increased as part of the treatment of an acute exacerbation of pulmonary disease. The Cystic Fibrosis Foundation recommends against delivery of IV antibiotics for the treatment of an acute exacerbation of pulmonary disease in a nonhospital setting unless resources and support equivalent to the hospital setting can be assured.[6] The volume of distribution of aminoglycosides is considerably higher in patients with CF, who typically require larger doses. The Cystic Fibrosis Foundation recommends that once daily dosing of aminoglycosides is preferable to 3 times daily dosing for treatment of an acute exacerbation of pulmonary disease.[6] The optimal duration of antibiotic treatment of an acute exacerbation of pulmonary disease is not certain, but 2 to 3 weeks is most often seen in practice.

The patient was admitted to the chest service for an inpatient "tune-up," and treatment with IV cefepime and IV tobramycin was initiated.

5. In addition to antibiotics, which one of the following is the next *most appropriate* treatment?

a. Ivacaftor
b. Lung transplant
c. Systemic glucocorticoids
d. Ibuprofen
e. Inhaled DNase

Mutations in the CFTR gene can be categorized into 5 classes according to the mechanism by which they disrupt the production, conduction, regulation, or processing of CFTR. Ivacaftor is a drug that is specifically designed to increase the open probability of the chloride channel in patients who have 1 of 9 class IV mutations (such as G551D) that abolish adenosine triphosphate–dependent gating of the channel. It is not approved for patients with the F508del mutation; however, this group is being studied. Lung transplant is an option in CF but is usually reserved for patients with an FEV_1 of less than 30%, increasingly frequent exacerbations requiring hospitalization, and refractory or recurrent pneumothorax. Our patient has not had any of these events so would not be treated

immediately with transplant. Systemic glucocorticoids have not been found to be effective either in long-term management or in acute exacerbations of CF. Ibuprofen use in CF began in 1995 with publication of the results of a Cystic Fibrosis Foundation—supported 4-year, double-blind, placebo-controlled trial of ibuprofen in patients with CF who were 5 to 39 years of age.[7] The study found that ibuprofen slowed the rate of pulmonary decline over a 4-year period. However, the drug has diminished in use because of GI and renal toxicity. Inhaled DNase promotes secretion clearance by degrading the long strands of DNA primarily from polymorphonuclear cells that increase the viscosity of mucus and is the best option in this case.

The patient returned home after hospital dismissal. In the 6 months since, he has done well and has not had any CF exacerbations requiring emergency care or inpatient management.

DISCUSSION

Cystic fibrosis is the most common lethal inherited disease among white populations.[8] It is autosomal recessive, affecting the CFTR protein, and has an incidence of 1 in 3500 live births in the United States.[9] Although CF was once routinely fatal in childhood, patients with CF now have a predicted median survival of 40.7 years according to data from the Cystic Fibrosis Foundation 2013 report.[9,10]

Most new cases of CF in the United States are diagnosed via newborn screening. Most states currently begin with a measurement of immunoreactive trypsinogen from a heel stick blood specimen, and if the result is high, a gene mutation test is performed. Routine statewide testing was first initiated in Colorado and Wyoming in 1989. Not until 2009, however, did all 50 states have a routine screening program. Minnesota, for instance, did not adopt screening until 2006. It is not surprising then that 7% of patients with CF are adults at the time of diagnosis,[11] with the oldest patient with a new diagnosis in 2012 being 76 years of age.

Because of the more than 1400 different gene mutations or polymorphisms noted so far in CF clinical manifestations, clinical presentations in CF diagnosed in adults vary significantly.[1] In general, patients with late presentation of CF tend to have less severe disease and to live longer than age-matched peers.[2,3] Clinical features that should prompt consideration of CF in the adult population include allergic bronchopulmonary aspergillosis, chronic parasinusitis or nasal polyposis, bronchiectasis, hemoptysis, portal hypertension, delayed puberty, and azoospermia due to bilateral absence of the vas deferens.[12]

Newborn screening can also identify patients with CFTR-related metabolic syndrome, defined as having intermediate sweat chloride test results on 2 occasions and fewer than 2 CF-causing mutations or a normal sweat chloride test result and 2 CFTR mutations, at least 1 of which is not clearly categorized as causing CF.[13] These patients will have variable symptoms ranging from asymptomatic to mild CF and can present with atypical symptoms such as isolated pancreatitis or recurrent sinusitis. Because this condition is increasingly identified by newborn screening, physicians who treat adults will need to be able to identify and treat these patients appropriately using Cystic Fibrosis Foundation guidelines.[13]

Although a variety of diagnostic guidelines exist, in general patients are required to manifest clinical symptoms consistent with CF in at least one organ system and have evidence of CFTR dysfunction by sweat chloride testing, positive genetic test results, or abnormal nasal transepithelial potential difference.[14] Nasal transepithelial potential difference is the direct measurement of voltage across the nasal epithelium that results from transepithelial ion transport, and it reflects in part CFTR chloride transport.

Diagnosis of CF can be challenging in the adult patient because results of sweat chloride testing can be normal.[11] Multiple studies have shown that sweat chloride values tend to be lower in this group and can be normal in up to a third of patients.[11] In patients with highly suspicious features, genetic or nasal impedance testing should be pursued despite a normal sweat chloride test result.[9] Conversely, a small subset of patients with highly suggestive phenotypic features will have novel mutations and/or mutations of undetermined significance and thereby do not meet classic diagnostic criteria.[15] Nasal transepithelial potential difference may be useful in this population, although its effort-intensive nature and low availability can be barriers.

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

CONCLUSION

Although CF is rightly considered a disease of childhood, diagnoses in adult patients are not uncommon. Because newborn screening was not universally adopted in the United States until 2009, CF should be considered in adult patients with suspicious pulmonary or GI findings.

Correspondence: Address to Mark E. Wylam, MD, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55904 (wylam.mark@mayo.edu).

REFERENCES

1. Burke W, Aitken ML, Chen SH, Scott CR. Variable severity of pulmonary disease in adults with identical cystic fibrosis mutations. *Chest*. 1992;102(2):506-509.
2. Gan KH, Geus WP, Bakker W, Lamers CB, Heijerman HG. Genetic and clinical features of patients with cystic fibrosis diagnosed after the age of 16 years. *Thorax*. 1995;50(12):1301-1304.
3. Modolell I, Alvarez A, Guarner L, De Gracia J, Malagelada JR. Gastrointestinal, liver, and pancreatic involvement in adult patients with cystic fibrosis. *Pancreas*. 2001;22(4):395-399.
4. Rodman DM, Polis JM, Heltshe SL, et al. Late diagnosis defines a unique population of long-term survivors of cystic fibrosis. *Am J Respir Crit Care Med*. 2005;171(6):621-626.
5. Widerman E, Millner L, Sexauer W, Fiel S. Health status and sociodemographic characteristics of adults receiving a cystic fibrosis diagnosis after age 18 years. *Chest*. 2000;118(2):427-433.
6. Flume PA, Mogayzel PJ Jr, Robinson KA, et al; Clinical Practice Guidelines for Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med*. 2009;180(9):802-808.
7. Konstan MW, Byard PJ, Hoppel CL, Davis PB. Effect of high-dose ibuprofen in patients with cytstic fibrosis. *N Engl J Med*. 1995;332(13):848-854.
8. Davis PB, Drumm M, Konstan MW. Cystic fibrosis. *Am J Respir Crit Care Med*. 1996;154(5):1229-1256.
9. Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. 2008;153(2):S4-S14.
10. Cystic Fibrosis Foundation Patient Registry. Annual Data Report to the Center Directors. Bethesda, MD: Cystic Fibrosis Foundation; 2013.
11. Gilljam M, Ellis L, Corey M, Zielenski J, Durie P, Tullis DE. Clinical manifestations of cystic fibrosis among patients with diagnosis in adulthood. *Chest*. 2004;126(4):1215-1224.
12. O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet*. 2009;373(9678):1891-1904.
13. Borowitz D, Parad RB, Sharp JK, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. *J Pediatr*. 2009;155(6, suppl):S106-S116.
14. Rowe SM, Clancy JP, Wilschanski M. Nasal potential difference measurements to assess CFTR ion channel activity. *Methods Mol Biol*. 2011;741:69-86.
15. Groman JD, Karczeski B, Sheridan M, Robinson TE, Fallin MD, Cutting GR. Phenotypic and genetic characterization of patients with features of "nonclassic" forms of cystic fibrosis. *J Pediatr*. 2005;146(5):675-680.

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