CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 40-2018: A 47-Year-Old Woman with Recurrent Sinusitis, Cough, and Bronchiectasis

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PRESENTATION OF CASE

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Dr. Christopher J. Richards: A 47-year-old woman was evaluated at the outpatient pulmonary clinic of this hospital because of recurrent sinusitis with progressive cough and bronchiectasis.

Since her mid-20s, the patient had had recurrent episodes of sinus congestion, with two or three sinus infections annually, which had prompted treatment with multiple courses of antibiotics. When she was approximately 30 years of age, she was evaluated by an otorhinologist at another hospital, who suggested the possibility of an allergic trigger. Skin testing revealed environmental allergies, to dust, grass, and cats. Blood testing revealed allergies to multiple foods, including milk, yeast, wheat, gluten, rye, and egg white. Elimination of milk, grains, and eggs from her diet resulted in a reduction in sinus symptoms for approximately 5 years. However, sinus congestion and sinus infections recurred in subsequent years. Three years before the current evaluation, a persistent cough developed. The patient was evaluated at a second hospital; she received a diagnosis of bacterial pneumonia and was treated. Thereafter, she was referred to a third hospital for sinus surgery with turbinectomy.

Approximately 6 months before the current evaluation, the patient noted the onset of daily production of yellowish-white sputum. The amount of sputum increased, and the sputum occasionally appeared green. Two months later, the patient was evaluated by her primary care physician at the second hospital. Chest radiography was notable for bronchiectasis, predominantly in the upper and middle lung zones.

A sputum culture reportedly grew *Enterobacter cloacae*, *Serratia marcescens*, and *Mycobacterium abscessus*. A complete blood count and results of kidney- and liver-function tests were normal. The blood level of IgE was normal (5 IU per milliliter; reference range, 0 to 158), as was the alpha$_1$-antitrypsin level (146 mg per deciliter; reference range, 100 to 190). A test for antineutrophil cytoplasmic antibody was negative, as was radioallergosorbent testing for environmental allergens that are common in the northeastern United States. Pulmonary-function testing report-

edly revealed a forced expiratory volume in 1 second (FEV_1) of 2.22 liters (80% of the predicted value), a forced vital capacity (FVC) of 2.72 liters (81% of the predicted value), and a ratio of FEV_1 to FVC of 82%. The total lung capacity was normal, but the ratio of residual volume to total lung capacity was elevated, at 45% (predicted value, 35%). The diffusion capacity for carbon monoxide was normal. Inhaled fluticasone propionate–salmeterol and levofloxacin were administered, and the cough diminished temporarily. Additional courses of levofloxacin were prescribed for recurrent cough and sputum production during the next 4 months, until the patient was evaluated in the pulmonary clinic of this hospital.

During her evaluation in the pulmonary clinic, the patient reported mild but increasing dyspnea on exertion and progressive fatigue. She had persistent sinus congestion and occasional headaches. She had no history of asthma, heart-failure symptoms, hemoptysis, fevers, chills, night sweats, weight loss, myalgias, arthralgias, rash, or gastrointestinal symptoms. She reported no sick contacts and had no known exposure to tuberculosis.

The patient had a history of migraines. She had undergone tonsillectomy in the remote past, uterine polypectomy 3 years earlier, bilateral laser-assisted in situ keratomileusis 4 years earlier, and removal of a benign breast mass 8 years earlier. Her medications included inhaled fluticasone propionate–salmeterol and over-the-counter guaifenesin–phenylephrine. She had no known allergies to medications. She had never smoked and did not drink alcohol or use illicit drugs. She was engaged to be married and had no children. She lived in Massachusetts, and her travel history included trips to Canada and the Caribbean. She worked in an office and had no known occupational or inhalational exposures; she had no animal exposures, although she enjoyed gardening. Her father had had prostate cancer, coronary artery disease, and a stroke, and her mother had had coronary artery disease and had undergone a thyroidectomy for a benign nodule. Her brother had allergic rhinitis, and her sister was healthy.

The patient appeared to be well and comfortable. The respiratory rate was 14 breaths per minute, and the oxygen saturation 99% while she was breathing ambient air. The height was 165 cm, the weight 64 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 23.5. There was no tenderness on sinus percussion. Crackles were present at the right apex on lung auscultation. There was no clubbing, and the remainder of the examination was normal. Laboratory test results are shown in Table 1. Imaging studies were obtained.

Dr. Jad S. Husseini: Posteroanterior and lateral radiographs of the chest showed "tram track"

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Initial Evaluation, This Hospital
Hemoglobin (g/dl)	12.0–16.0	13.3
Hematocrit (%)	36.0–46.0	38.3
White-cell count (per mm^3)	4500–11,000	10,800
Differential count (%)		
Neutrophils	40–70	81
Lymphocytes	22–44	10
Monocytes	4–11	6
Eosinophils	0–8	3
Basophils	0–3	0
Platelet count (per mm^3)	150,000–350,000	272,000
Sodium (mmol/liter)	135–145	140
Potassium (mmol/liter)	3.4–4.8	4.3
Chloride (mmol/liter)	100–108	96
Carbon dioxide (mmol/liter)	23.0–31.9	26
Urea nitrogen (mg/dl)	8–25	8
Creatinine (mg/dl)	0.60–1.50	0.7
Glucose (mg/dl)	70–110	87
Calcium (mg/dl)	8.5–10.5	9.3
Total protein (g/dl)	6.0–8.3	7.4
Albumin (g/dl)	3.3–5.0	4.1
Globulin (g/dl)	2.6–4.1	3.3
Alanine aminotransferase (U/liter)	7–30	19
Aspartate aminotransferase (U/liter)	9–32	21
Alkaline phosphatase (U/liter)	30–100	71
Total bilirubin (mg/dl)	0.0–1.0	0.4
Erythrocyte sedimentation rate (mm/hr)	1–25	28

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

opacities that involved both upper lung zones and the left lower lung zone, a finding consistent with bronchiectasis. The lung volumes were normal. There was no consolidative opacity or evidence of pulmonary edema, pleural effusion, or mediastinal or hilar lymphadenopathy (Fig. 1).

Computed tomography (CT) of the chest, performed after the administration of intravenous contrast material, revealed bronchiectasis that involved all lobes of the lung but was most severe in the right upper lobe. Areas of mucous plugging were present in airways in the upper lobes. There were scattered "tree in bud" opacities, as well as multiple scattered solid pulmonary nodules, measuring up to 1.5 cm in diameter. There was no evidence of pulmonary edema, pleural effusion, or mediastinal or hilar lymphadenopathy (Fig. 2).

Dr. Richards: Examination of a sputum sample revealed 3+ to 4+ acid-fast bacilli, along with occasional polymorphonuclear leukocytes and a few gram-positive bacteria.

Diagnostic tests were performed.

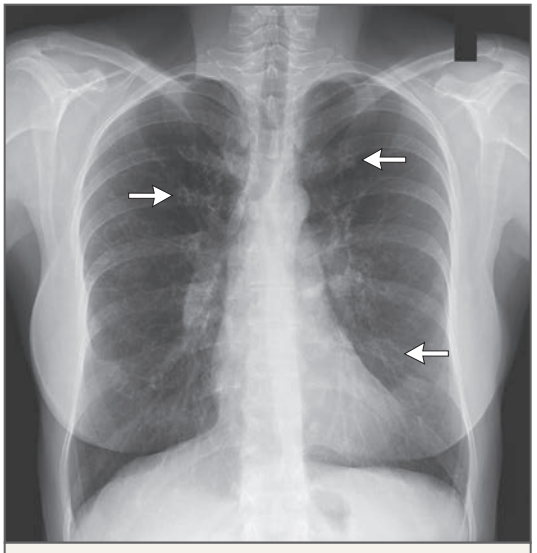

Figure 1. Radiograph of the Chest.

A posteroanterior radiograph of the chest shows "tram track" opacities involving both upper lung zones and the left lower lung zone (arrows), a finding consistent with bronchiectasis. No other abnormalities are visible.

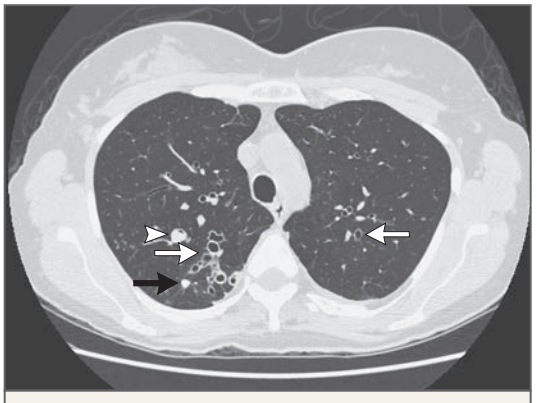

Figure 2. CT Scan of the Chest.

A CT scan of the chest, obtained after the administration of intravenous contrast material, shows bronchiectasis that involves all lobes of the lung but is most pronounced in the right upper lobe (white arrows), mucous plugging in dilated airways in the right upper lobe (arrowhead), and scattered pulmonary nodules, measuring up to 1.5 cm in diameter (black arrow).

DIFFERENTIAL DIAGNOSIS

Dr. James E. Mojica: This 47-year-old woman presented with recurrent sinus infections and chronic cough despite multiple courses of antibacterial therapy and treatment with inhaled glucocorticoids. It is notable that she had had sinus symptoms for most of her adult life and that her symptoms had persisted and progressively worsened despite identification of environmental allergies, management of sinus symptoms, and restriction of her diet. Chronic cough, sputum production, and recurrent respiratory infections are suggestive of bronchiectasis, which was confirmed on chest CT.

BRONCHIECTASIS

What is bronchiectasis and why did this patient have it? Bronchiectasis is characterized by irreversible damage of the airways that results in dilatation. The pathophysiological event that occurs in all patients with bronchiectasis is chronic inflammation. Although some patients have idiopathic bronchiectasis, which does not have a clear cause, I will focus my differential diagnosis on disorders that cause chronic inflammation of the lung and bronchiectasis, including pulmonary infections, immunodeficiency syndromes, allergies, and disorders that cause impaired airway clearance.

Pulmonary Infections

Many lung infections can result in the development of bronchiectasis, and several are worth

considering in this case. Infection with *M. tuberculosis* may cause chronic infection and inflammation that results in bronchiectasis. However, this patient had no known exposure to tuberculosis and reported no fever, weight loss, night sweats, or other history suggestive of *M. tuberculosis* infection. Although examination of a sputum sample was notable for the presence of 3+ to 4+ acid-fast bacilli, I suspect that this finding was associated with nontuberculous mycobacteria, such as *M. abscessus*, which had been isolated in an earlier sputum culture. Isolation of nontuberculous mycobacteria is typically a result of bronchiectasis rather than its cause. Furthermore, this patient had no evidence of remote tuberculous disease, such as calcified granulomas.

Infection with *Bordetella pertussis* has also been associated with the development of bronchiectasis. Patients with pertussis often have a severe cough of several months' duration. For this reason, pertussis has classically been called the "100-day cough." Although this patient may have had pertussis as a child, she had probably been vaccinated against the pathogen. Immunity to pertussis may wane, but she did not report a history of infection consistent with this diagnosis.

Bronchiectasis may develop in patients with a history of recurrent pneumonia, particularly those with chronic aspiration. Although this patient was treated with multiple courses of antibiotics, only one episode of pneumonia was described. Furthermore, nothing mentioned in the case history would make us think that she had chronic aspiration.

Immunodeficiency Syndromes

Patients with immunodeficiency syndromes are at high risk for the development of bronchiectasis. Primary immunodeficiency syndromes, such as X-linked agammaglobulinemia and common variable immunodeficiency, are disorders that disrupt normal antibody production, leading to defective humoral immunity and recurrent infections. In X-linked agammaglobulinemia, an autosomal recessive disruption of B-cell development prevents the production of serum antibodies. In common variable immunodeficiency, which is the most common primary immunodeficiency syndrome in adults, levels of circulating immunoglobulins are reduced. When a patient has a low IgG level, further evaluation is warranted. Levels of IgG subclasses, IgA, IgM, and IgE may be obtained, and testing for responsiveness to immunization may be performed. In addition, tests may be performed to rule out secondary causes of immunodeficiency, such as human immunodeficiency virus infection.

Allergies

Another consideration in this case is an allergic response to fungal spores. In some people, inhalation of *Aspergillus fumigatus* provokes a brisk allergic response that is characterized by eosinophilia and a high level of IgE antibodies. A hypersensitivity response, known as allergic bronchopulmonary aspergillosis, may ensue, leading to a cycle of bronchial inflammation, mucoid impaction, and bronchial obstruction that results in bronchiectasis.

Exposure to nontuberculous mycobacteria in soil and water (e.g., in showers and pools) is common. Since these organisms are less pathogenic than tuberculosis, they generally affect people who have impaired immunity or chronic lung disease. I suspect that this patient's positive stain for acid-fast bacilli in the sputum was indicative of a secondary nontuberculous mycobacterial infection that was related to underlying lung disease and was not the primary driver of bronchiectasis.

Disorders That Cause Impaired Airway Clearance

This patient had a history of recurrent sinus symptoms. Rhinosinusitis is characterized by inflammation of the nose and paranasal sinuses, which can result in nasal congestion, nasal obstruction, rhinorrhea, loss of smell (anosmia), and facial pressure. Given the patient's long history of chronic rhinosinusitis, the differential diagnosis can be further narrowed to disorders that cause impaired airway clearance.

Cystic fibrosis is a recessive genetic disease that is caused by mutations in both alleles of the *CFTR* gene, which encodes the cystic fibrosis transmembrane conductance regulator (CFTR).[1] The CFTR protein forms a chloride channel that is critical to efficient mucus transport. Mutations in *CFTR* disrupt sodium absorption, chloride secretion, and water transport, leading to the development of viscous mucus that adheres to the airway and impairs bacterial clearance.

The diagnosis of cystic fibrosis is based on the presence of clinical signs or symptoms that are consistent with the disease, along with objec-

tive evidence of CFTR dysfunction. Guidelines aimed at standardizing the diagnosis were recently updated.[2] The results of sweat chloride testing can be used to confirm the diagnosis, rule out the diagnosis, or prompt further testing, such as genetic testing to identify *CFTR* mutations. Given the presence of chronic rhinosinusitis, purulent cough, and bronchiectasis, the diagnosis of cystic fibrosis must be considered in this case.

If cystic fibrosis is not the diagnosis, the next most likely diagnosis would be a disorder of ciliary motility. Cilia are hairlike attachments that are found on epithelial surfaces of several cell types. In the respiratory tract, cilia are capable of movement because of nine longitudinal microtubules that are arranged around a central microtubule pair (known as a 9+2 arrangement). The peripheral microtubules have dynein arms, powered by ATP, that slide to produce motion. Ciliary dysfunction is related to short or absent dynein arms on the peripheral microtubules.[3]

Primary ciliary dyskinesia is a congenital, autosomal recessive disorder that is characterized by immotile or dyskinetic cilia. Ciliary dysfunction can result in recurrent infections, including otitis media, rhinosinusitis, and pneumonia. In addition to impaired airway clearance, fertility problems can arise in males as a result of impaired spermatozoa motility and in females as a result of impaired ciliary function in the oviduct. It is worth noting that this 47-year-old woman did not have children. This may have been a personal decision, unrelated to her diagnosis. Women with either cystic fibrosis or primary ciliary dyskinesia are typically fertile but may have difficulty becoming pregnant. Ultimately, her nulliparous state does not help to narrow the differential diagnosis.

Primary ciliary dyskinesia can also cause left–right asymmetry. In the primitive streak of an embryo, in a region called the node, cilia on cells create "nodal flow" that controls developmental symmetry. Nodal ciliary dysfunction can produce dextrocardia, situs inversus totalis, and situs ambiguus. However, the classic triad of primary ciliary dyskinesia — bronchiectasis, chronic sinusitis, and situs inversus — was not present in this patient.[4]

This patient's clinical history of chronic rhinosinusitis and bronchiectasis has allowed us to narrow the differential diagnosis, but further testing would be needed to establish the diagnosis. For example, airway cilia, obtained by means of brushing or scraping of the inferior turbinate, can be examined under light and electron microscopes. In specialized centers, a nasal nitric oxide level can be measured as a noninvasive surrogate assessment of ciliary dysfunction. Nasal nitric oxide is produced by the paranasal sinus epithelium and is present at a high level throughout the upper airway.[5] Low levels have been reported in patients with sinus and lung disease, and extremely low levels have been seen in patients with ciliary dyskinesia.[6] However, genetic testing may become the most reliable means of establishing these diagnoses. Disease-specific sequencing is available to find a genetic basis for pulmonary diseases such as cystic lung disease, pulmonary fibrosis, and bronchiectasis.

In summary, this patient is a normal-weight, nulliparous woman with recurrent sinopulmonary infections who presented with bronchiectasis that was complicated by productive cough, exertional dyspnea, fatigue, and rapid growth of nontuberculous mycobacteria in the sputum. On the basis of her history of chronic sinusitis and recent lower respiratory infections, I suspect her bronchiectasis was caused by impaired airway clearance. Therefore, cystic fibrosis and primary ciliary dyskinesia are highest on my differential diagnosis. I would try to establish the diagnosis with the use of a sweat chloride test to evaluate for cystic fibrosis, given the predominant involvement of the upper lobe. However, in adults with certain types of *CTFR* mutations, the results of a sweat chloride test may not be abnormal (i.e., the test may be false negative). The patient's food allergies are possible gastrointestinal manifestations of a *CFTR* mutation and could help to distinguish cystic fibrosis from primary ciliary dyskinesia. Ultimately, it may be best to proceed with genetic testing for pulmonary disorders.

DR. JAMES E. MOJICA'S DIAGNOSIS

Cystic fibrosis (nonclassic) or primary ciliary dyskinesia.

GENETIC TESTING

Dr. Richards: The patient had a long history of progressive pulmonary disease associated with recurrent infections involving the upper and lower respiratory tracts and with severe bronchiectasis on chest CT; these findings are consis-

tent with a diagnosis of cystic fibrosis. Although the onset of cystic fibrosis usually occurs early in life, there are nearly 2000 recognized *CFTR* mutations, and each one confers a different degree of diminished chloride ion transport. Sweat chloride testing is often used in establishing the diagnosis; a chloride level of more than 60 mmol per liter is highly suggestive of cystic fibrosis. In this patient, sweat chloride testing revealed a chloride level of 40 to 45 mmol per liter, a result that is consistent with partial CFTR function and cannot be used to confirm the diagnosis.[7] The next step in establishing the diagnosis of cystic fibrosis is to identify a *CFTR* mutation. Although full sequencing of *CFTR* is available, there are multiple commercially available genetic tests that differ with regard to the number of *CFTR* mutations that they can detect. It is therefore possible to perform testing for the most common *CFTR* mutations and not establish a diagnosis. In this patient, genetic testing revealed a deletion of phenylalanine at amino acid position 508 (Phe508del) and a substitution of aspartic acid for histidine at position 1152 (D1152H). The identification of these mutations confirms the diagnosis of cystic fibrosis in this patient. In the CFTR2 database, there are 358 patients who are heterozygous for these mutations, which are associated with a relatively mild variant of cystic fibrosis.[8]

There are approximately 29,000 patients with cystic fibrosis in the United States, with 1000 new cases occurring annually.[9] Management of cystic fibrosis is focused on a combination of airway clearance by means of mechanical and pharmacologic methods (chest physiotherapy, inhaled human recombinant dornase alfa therapy, and the administration of inhaled hypertonic saline), pancreatic-enzyme replacement in patients with a pancreatic insufficiency, nutritional supplementation, suppressive antibiotic therapy (e.g., inhaled tobramycin), and early recognition of pulmonary exacerbations.[10-12] With the administration of these treatments at cystic fibrosis–specific treatment centers, median survival has increased from 33.3 years (interquartile range, 31.0 to 35.1) in 2000 to 41.7 years (interquartile range, 38.5 to 44.0) in 2015.[13] Despite this patient's strict adherence to such therapies since the time of her diagnosis, she had a steady decline in lung function, as measured by the percent of predicted FEV_1.

A clinically significant contributor to the decline in lung function was the persistence of *M. abscessus* infection. After the patient received the diagnosis of cystic fibrosis, she was treated for *M. abscessus* infection at this hospital. She completed a 6-month course of antibiotics, including linezolid, amikacin, and clarithromycin. Treatment was complicated by the development of tinnitus and severe peripheral neuropathy. After she completed this course of therapy, she did well for several months but then presented to the third hospital with fever, cough, and new airspace opacities on chest radiography. Empirical therapy with vancomycin and piperacillin–tazobactam was administered; the cough diminished, but fever persisted. Because of unrelenting fever, video-assisted thoracoscopic biopsy was performed at the third hospital.

Dr. Lida P. Hariri: Examination of the histologic slides from the third hospital (Fig. 3) reveals multifocal abscesses with associated granulomatous inflammation and purulent necrosis. There was multifocal cystic bronchiectasis with dense chronic and acute inflammation, reactive squamous metaplasia, and intraluminal mucopurulent debris. Regions of dense fibrosis with lymphoid aggregates and granulomas were seen in association with bronchiectasis. Overall, the histologic features are most consistent with cystic bronchiectasis complicated by atypical mycobacterial infection. These histologic features are highly consistent with the diagnosis of cystic fibrosis. *M. abscessus* was again isolated in culture.

Dr. Richards: On the basis of the results of the biopsy and the persistence of *M. abscessus* in culture, the patient was again treated for nontuberculous mycobacterial infection with antibiotics, including amikacin, clarithromycin, and cefpodoxime. Fortunately, she had a good response to this regimen and has not needed additional therapy for *M. abscessus* infection.

More recently, the patient has begun treatment for cystic fibrosis on the basis of the detected *CFTR* mutations. The primary defect that is caused by the Phe508del mutation is that the CFTR protein is synthesized but misfolded, which keeps it from reaching the cell surface. This is the target of action of the drugs lumacaftor and tezacaftor. In addition to the Phe508del mutation, the patient had a D1152H mutation, which is considered to be a partial-function mutation that results in diminished ion transport. This type of mutation is the target of the drug ivacaftor, which partially restores ion transport. In the initial trial of ivacaftor, which involved patients

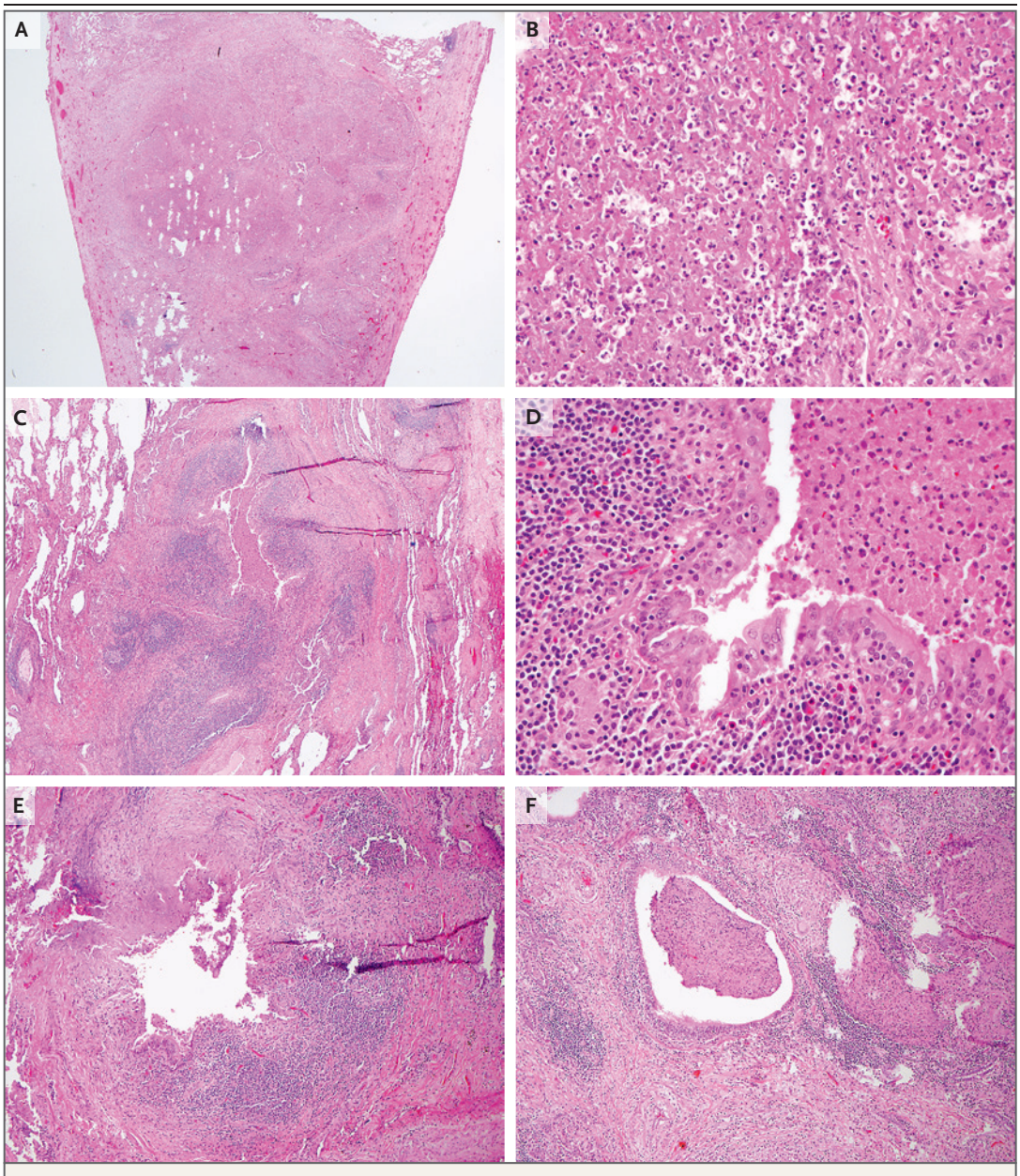

Figure 3. Lung-Biopsy Specimen.

Hematoxylin and eosin staining was performed on wedge-resection specimens of the right middle, upper, and lower lobes. Panel A shows multifocal abscess formation. Panel B shows purulent necrosis. Panel C shows multiple foci of cystic bronchiectasis with dense chronic inflammation. Panel D shows reactive squamous metaplasia and mucopurulent debris. Panel E shows regions of dense fibrosis in association with bronchiectasis, with areas of airway obliteration. Panel F shows associated granulomatous inflammation. These features are most consistent with cystic bronchiectasis complicated by atypical mycobacterial infection in a patient with features consistent with cystic fibrosis.

with at least one G551D mutation, the average increase in the percent of predicted FEV_1 was 10.6 percentage points greater with ivacaftor than with placebo, and patients who received ivacaftor were 55% less likely to have a pulmonary exacerbation in the first 48 weeks than those who received placebo.[14] In 2017, the qualifying mutations for the administration of ivacaftor were

expanded to include D1152H, and among patients with such mutations, the average increase in the percent of predicted FEV_1 was 2.4 percentage points greater with ivacaftor than with placebo. In 2017, the EXPAND trial showed that treatment with tezacaftor–ivacaftor was associated with greater improvement than treatment with ivacaftor monotherapy among patients who are heterozygous for one Phe508del mutation and one minimal-function mutation (e.g., D1152H), with an average increase in the percent of predicted FEV_1 of 6.8 percentage points as compared with 4.7 percentage points.[15] Very recently, phase 2 studies showed that treatment with either VX-659–tezacaftor–ivacaftor or VX-445–tezacaftor–ivacaftor was associated with even greater improvement, with an additional increase of 13 percentage points among patients with one Phe508del mutation and one minimal-function mutation and of 10 percentage points among patients with Phe508del–Phe508del mutations who were already receiving tezacaftor–ivacaftor.[16,17]

This patient has received treatment with ivacaftor since 2017, and the sputum volume has decreased and the percent of predicted FEV_1 has stabilized. She remains dependent on oxygen supplementation but has noted a qualitative decrease in dyspnea on exertion. With her meticulous approach to airway clearance and the dedication of her husband, who performs manual percussive therapy twice daily, she has not had an inpatient admission for treatment with intravenous antibiotics for more than 2 years. Since her treatment for *M. abscessus*, the organisms have not regrown, but she has had persistent growth of *M. avium* complex, for which she is under continued surveillance. Her course has been further complicated by the development of cystic fibrosis–related diabetes mellitus, the antiphospholipid syndrome, pulmonary embolism, and pulmonary hypertension. She continues to have episodes of hemoptysis. However, in the presence of anticoagulation, nontuberculous mycobacterial infection, and bronchiectasis exacerbation, the cause of hemoptysis is difficult to distinguish.

ANATOMICAL DIAGNOSIS

Cystic fibrosis due to compound heterozygous *CFTR* Phe508del and D1152H mutations.

This case was presented at the Medical Case Conference.

Dr. Hariri reports receiving consulting fees from Biogen, Pliant Therapeutics, Indalo Therapeutics, and Boehringer Ingelheim and consulting fees and advisory board fees from LX Medical. No other 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.

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