

Cystic fibrosis diagnosed at age 45 based on symptoms of acute pancreatitis

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CASE PRESENTATION

A 45-year-old Caucasian woman was hospitalized because of progressively worsening midepigastic abdominal pain for 5 days. The pain, which was insidious in onset, was described as constant, nonradiating, nonpositional, and exacerbated by eating and drinking. She also had fever, chills, night sweats, nausea, and nonbilious vomiting for 1 day. She denied biliary colic, jaundice, scleral icterus, abdominal distention, hematemesis, melena, hematochezia, diarrhea, menorrhagia, or metromenorrhagia. She had had recurrent streptococcal and *Pseudomonas* sp. pneumonias since childhood. She was a nonsmoker, was diagnosed with bronchiectasis several years earlier, and had a chronic cough productive of yellow sputum. She had *Mycobacterium avium* pulmonary infection at age 40 and nasal polyps at age 42. She took minocycline for approximately 1 year for acne and levofloxacin orally for recent worsening of her chronic productive cough.

Both her mother and father had type II diabetes mellitus. She did not drink alcohol, smoke, or use illicit drugs. She had no tattoos and no history of sexually transmitted diseases or blood transfusions.

On admission, her temperature was 98.7°F; heart rate, 93 beats per minute; blood pressure, 129/77 mm Hg; respiratory rate, 18 breaths per minute; and arterial oxygen saturation, 98% on room air. Her body mass index was 29.4 kg/m². She was mildly distressed due to abdominal pain. She was not jaundiced. Her mucus membranes were dry and pink. The neck was supple, with no jugular venous distention, thyromegaly, or lymphadenopathy. Her abdomen was soft and nondistended, and bowel sounds were diminished. There was exquisite tenderness to palpation in the midepigastrium approximately 4 cm above the umbilicus, with no rebound or guarding. Murphy's, Cullen's, and Grey Turner's signs were not present. She had no hepatosplenomegaly, suprapubic tenderness, or palpable masses.

The patient's white blood cell count was 13,600 cells/mm³. Serum amylase and lipase levels were 477 and 512 units/L, respectively. Serum triglyceride and calcium levels were 46 and 8.9 mg/dL, respectively. Computed tomography of the abdomen/pelvis was significant for acute pancreatitis (Figure 1) without necrosis or abscess. No gallstones, strictures, or bile duct dilatation were visualized; bronchiectasis (Figure 2) was present in the lingula and right middle lobe. Endoscopic ultrasound

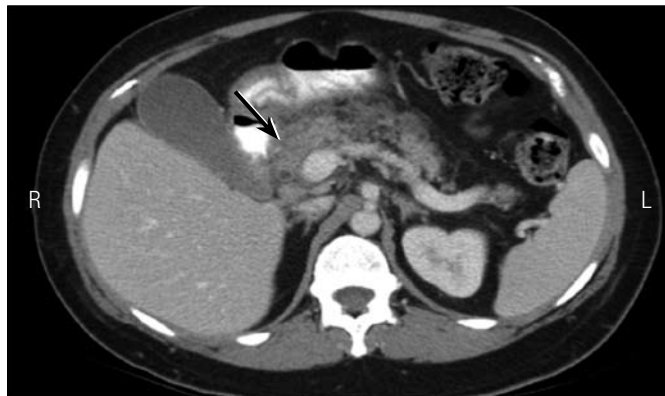


Figure 1. CT scan showing acute pancreatitis with surrounding inflammation.



Figure 2. CT scan showing bronchiectasis of the right middle lobe.

disclosed no abnormalities. The common bile duct was 5.8 mm in diameter. Sputum cultures were positive for *Pseudomonas aeruginosa*.

The patient was placed on bowel rest and given 0.9% normal saline at 200 cc/h and intravenous morphine as needed for pain. Her 10-day regimen of oral levofloxacin was continued. The patient's abdominal pain lessened within the first 48 hours of admission, and an oral diet was initiated on hospital day 3. Her amylase and lipase levels decreased to normal by hospital

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Table. Etiology of acute pancreatitis

Category	Specific causes	Statistical data	Details
Mechanical	Cholelithiasis, pancreas divisum, ductal tumors, ampullary stenosis	Most common cause: cholelithiasis causes 35% of AP; 3%–7% of patients with cholelithiasis develop AP (1)	Proposed mechanisms: obstruction of ampulla of Vater and reflux of pancreatic enzymes
Toxic	Ethanol, methanol, organophosphate poisoning, scorpion	Alcohol is second most common cause of AP; 10% of chronic alcoholics develop AP	Proposed mechanism: ethanol increases synthesis of lysosome and enzyme (2)
Metabolic	Hypertriglyceridemia, hypercalcemia	Incidence in hyperlipidemia: type I, 35%; type II, 15%; type V, 30%–40% (3, 4)	Triglyceride levels >1000 mg/dL (4, 5); hypercalcemia proposed mechanism: induction of trypsinogen (3)
Other	Drugs: tetracycline, minocycline, thiazides, furosemide, azathioprine, valproic acid, salicylates, didanosine, metronidazole, tamoxifen Trauma, post-ERCP, alpha-1-antitrypsin deficiency, infection	Drugs: 1.4% (6, 7)	Infectious agents: mumps, coxsackievirus, hepatitis B, <i>Mycoplasma</i> sp., <i>Legionella</i> sp., <i>Aspergillus</i> sp., <i>Toxoplasma</i> sp., <i>Cryptosporidium</i> sp., <i>Ascaris</i> sp.
Genetic	Cystic fibrosis transmembrane conductance regulator (<i>CFTR</i>); cationic trypsinogen gene; serine protease inhibitor, Kunitz type 1 (<i>SPINT1</i>)	Typically only patients <25 years are tested for a genetic etiology (8–12)	<i>CFTR</i> details: defective HCO ₃ /chloride exchanger in pancreatic ductal apical membrane

AP indicates acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography.

day 4. Her serum immunoglobulin-G level was normal at 1110. A cystic fibrosis transmembrane receptor (*CFTR*) genetic panel was ordered. The patient was eventually advanced to a regular oral diet without complications or recurrence of abdominal pain, and she was discharged home after 8 days.

DISCUSSION

This patient's diagnosis of acute pancreatitis was straightforward, but determining the etiology of the disease was somewhat elusive. The *Table* lists some possible etiologies (1–13). The history of recurrent *Pseudomonas* sp. and streptococcal pneumonias since childhood, bronchiectasis, *Mycobacterium avium* pulmonary infection, and nasal polyps suggested that the acute pancreatitis was secondary to previously undiagnosed cystic fibrosis. This hypothesis was confirmed by genetic tests, which revealed a compound heterozygous mutation: a $\Delta F508$ mutation (phenylalanine deletion) in exon 10 of the *CFTR* gene and a D1152H (aspartic acid to histidine) mutation in exon 18 of the *CFTR* gene. The combination of these mutations is consistent with cystic fibrosis when mutations are present on opposite chromosomes.

Cystic fibrosis is classically a pediatric disease. It is an autosomal recessive disease of the long arm of chromosome 7 on the *CFTR* gene. One in 22 to 25 Caucasians are heterozygotes; this mutation is the most common monogenic mutation among Caucasians. The average age at diagnosis is 2.9 years. The median survival is 32 years for males and 29 for females. Complications consist of recurrent *Pseudomonas* sp. pulmonary infections,

which are the most common cause of morbidity and mortality, as well as bronchiectasis, pancreatic exocrine and endocrine insufficiency, biliary cirrhosis, intestinal obstruction, nasal polyps, and, in men, congenital absence of bilateral vas deferens, causing infertility.

There are approximately 1250 known *CFTR* mutations, with homozygous $\Delta F508$ being the most common. Heterozygous $\Delta F508$ mutation in combination with a second heterozygous mutation, however, results in varying phenotypic expressions of the disease. These milder forms are typically compound heterozygotes, as seen here, with one other reported case being the same $\Delta F508/D1152H$ mutation—a 46-year-old nonsmoker presenting with bronchiectasis and recurrent acute respiratory tract infections (14). There are other case reports of adult-onset clinical disease presenting with chronic cough, recurrent childhood “bronchitis,” idiopathic acute pancreatitis, and pancreatic exocrine insufficiency. Sweat chloride levels

are normal in most of these cases (9). Furthermore, a strong association has been revealed between idiopathic pancreatitis and *CFTR* mutations. In a study by Cohn et al, patients with chronic idiopathic pancreatitis had single *CFTR* mutations 11 times the expected frequency and two abnormal *CFTR* alleles at a rate 80 times the expected frequency (8).

Clinical disease in cystic fibrosis results from defective or absent cyclic adenosine monophosphate (AMP)-dependent chloride secretion and sodium absorption. In the lungs, reduced chloride secretion reduces the salt and water content of bronchiolar mucus and periciliary liquid. As a result, mucus adheres to airway surfaces, leading to recurrent infection and bronchiectasis. Approximately 70% of adults have persistent *Pseudomonas aeruginosa* in their airways.

Pancreatitis in cystic fibrosis is thought to occur via a *CFTR*-mediated secretory abnormality as well. *CFTR* is present at higher levels in intralobular and proximal ductular epithelial cells and at lower levels in pancreatic acinar cells (12). *CFTR* at these sites regulates a chloride channel in the chloride/bicarbonate exchanger located in the apical membrane and mediates the secretion of a bicarbonate-rich alkaline fluid that, in turn, maintains the solubility of secreted enzymes. Loss of *CFTR* function, or its dysfunction, results in reduced intraluminal fluid and bicarbonate secretion. Scheele et al (10) have suggested that reduced luminal pH inhibits endocytosis of secretory granule proteins and reduces the solubility of secreted luminal proteins. Presumably, complete loss of *CFTR* function induces rapid pancreatic atrophy through

obstruction by secreted protein. In patients with pancreatic sufficiency, the presence of functional acinar cells is a prerequisite for pancreatitis; a change in ductal and acinar function must in some way be the precipitating event. Pancreatitis occurs in approximately 2% of patients with known cystic fibrosis.

CONCLUSION

Our patient had acute pancreatitis, most likely secondary to undiagnosed cystic fibrosis. Both drug-induced pancreatitis secondary to minocycline and idiopathic pancreatitis are less likely possibilities. Because cystic fibrosis is usually diagnosed in the pediatric population, milder forms manifesting during adulthood are probably underdiagnosed. When evaluating an adult patient with idiopathic pancreatitis—especially in the presence of common cystic fibrosis disease sequelae such as recurrent sinopulmonary infections, bronchiectasis, nasal polyps, intestinal obstruction, biliary cirrhosis, or male infertility—a diagnosis of cystic fibrosis should be considered. Sweat chloride tests may be normal in these patients. Genetic testing may be required to solidify the diagnosis (15).

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