Adult-onset cystic fibrosis in an African-American male

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This report describes a case of adult-onset cystic fibrosis (CF) in an African-American male. Although CF is a common autosomal recessive disorder in populations of European descent, it is relatively rare in the African-American population (1 in 17,000), with only Asian population ancestries being less affected than African blacks. We present our patient's disease course in order to elucidate the manifestations of CF in this particular ethnic population. More specifically, this patient had a form of CF with late-onset features, which may represent a new clinical phenotype of CF. We seek to improve clinician awareness of CF disease subtypes. We also show the radiographic intra- and extra-thoracic manifestations of CF and the peculiar clinical scenario that brought forth this condition.

Case report

Our patient's history began 9 years ago, when he was 21. He presented to his primary care doctor for a regular checkup, with no complaints but with a past medical history of ambylopia. Throughout this entire history, the patient denied smoking as well as living with a smoker or illicit drug use. He was occupied as a student, with no known environmental hazards at work or home. On physical examination he was found to have left-sided abdominal fullness, suspicious of a mass. A hepatic function panel showed mildly elevated liver enzymes, suggestive of hepatitis. A workup for the hepatitides came back negative. His primary medical doctor (PMD) recommended that he have an abdominal sonogram, the results of which were interpreted as diffuse hepatic fatty infiltration (Fig. 1).

A few months later, the patient returned to the clinic for followup of elevated liver enzymes, again with no com-
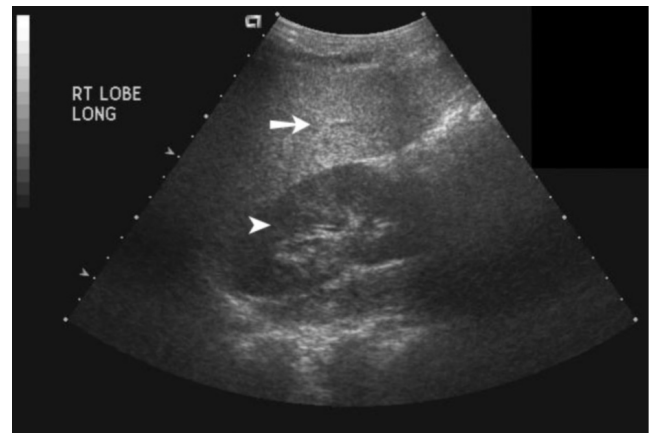

Figure 1. 27-year-old African-American male with late-onset cystic fibrosis. Transabdominal ultrasound scan shows a highly echogenic liver (arrow) in comparison to adjacent right kidney (arrowhead).

plaints. On physical examination he was found to have digital clubbing. He did not return to the clinic for one year, after which time he returned complaining of vague epigastric pain. A chest x-ray was read as normal. A Holter monitor and echocardiogram showed an ejection fraction of 69%. He had persistently elevated liver enzymes and underwent computed tomography (CT)-guided liver biopsy. It revealed micro- and macro-vesicular steatosis, few fibrotic portal tracts, and focal bridging fibrosis, suggesting nonal-

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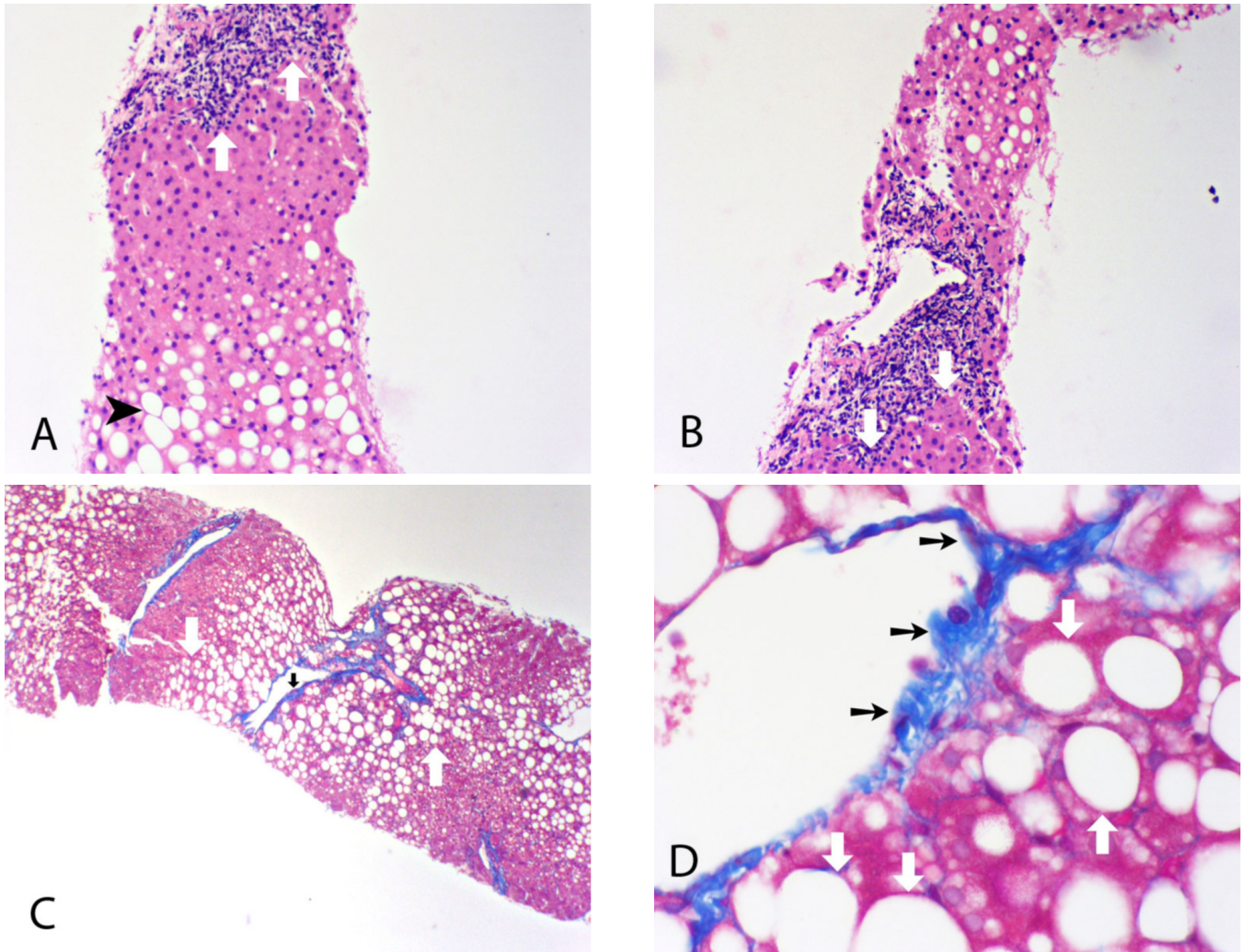
Figure 2. 27-year-old African-American male with late-onset cystic fibrosis. High-powered light microscopy of the liver obtained from CT-guided biopsy (H+E stain). A) 10x view, macrovesicular fatty infiltrate (lipocytes, black arrowhead) and chronic portal inflammation (inflammatory cells, white arrows), characteristic of nonalcoholic steatohepatitis. B) 10x image shows portal inflammation again noted, with spill into liver parenchyma (interface of inflammation, arrows), also characteristic of hepatitis. C) and D) 10x and 40x views, respectively, of trichrome stain highlighting perivenular fibrosis (black arrows) and steatosis (white arrows).

coholic steatohepatitis (NASH), stage II (Fig. 2). He was started on ursodiol. At that time he also tested negative for antimitochondrial, smooth muscle, microsomal, and nuclear antibodies.

Later that year, he presented to his PMD with nasal discharge, mild cough, and greenish sputum production. He was prescribed antibiotics and did not return to the clinic for almost two years, after which he returned with the same symptoms, in addition to frontal headaches. During this time he had undergone nasal endoscopy and polypectomy at an outside hospital. On his return, he received a head CT and was diagnosed with significant paranasal sinus disease and was prescribed prednisone. When his symptoms did not resolve after two months, maxillofacial CT was performed (Fig. 3). Pansinusitis was observed, and fiberoptic endoscopic sinus surgery was recommended and completed.

At this time, the patient was referred for a sweat chloride test, which revealed a chloride level of 106 mmol/L, diagnostic for CF. He went for followup genetic testing, which was sent out to Quest Diagnostics. The test was performed using a polymerase chain reaction, followed by oligonucleotide ligation assay. Their panel included 23 allele mutations, as recommended by the American College of Medical Genetics. The patient tested negative for all allele mutations. He was referred for larger panel testing at an outside location but did not follow up. After normal spirometry testing
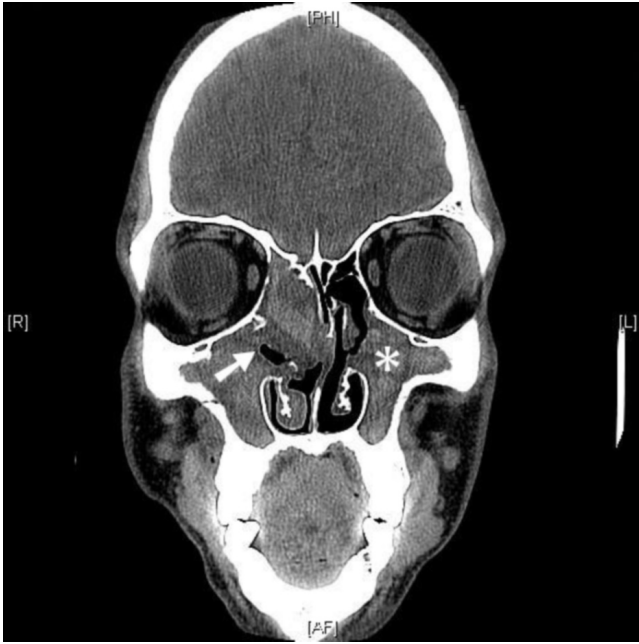
Figure 3. 27-year-old African-American male with late-onset cystic fibrosis. Coronal view of reformatted maxillofacial CT, performed one year after endoscopic polypectomy. Image shows complete occlusion of the ostiomeatal complex (white arrow) and opacification of the sinuses. Heterogeneous attenuation of secretions within the maxillary sinus suggests trapped fluid centrally (asterisk). The ostia are markedly widened, with mucoid material extending into the nasal sinuses.

and chest x-ray, the patient was given a diagnosis of chronic cough secondary to postnasal drip.

The following year, now at 24 years of age, the patient returned with a worsening cough, producing gray sputum and nasal discharge. He was prescribed antibiotics. Also, with persistently abnormal liver cemistries, and a new development of hypoalbuminemia, a liver ultrasound revealed normal liver with cholelithasis. He was continued on ursodiol. During the next three years, the patient repeated this cycle, with numerous serumchemistries performed, another ultrasound showing fatty liver, a biopsy demonstrating steatosis involving 55% of lobules, and pericellular fibrosis in perivenular areas. He also underwent workups for several syndromes including hypothyroidism, vasculitides, angiotensin-converting enzyme (ACE) deficiency, human immunodeficiency virus (HIV), syphilis, iron and copper metabolism abnormalities, and amyloidosis, all of which returned negative.

This year, the 27-year-old patient returned again with the same upper respiratory symptoms, and was found to have decreased oxygen saturation. A chest x-ray revealed diffuse reticular opacities. A chest CT revealed predominantly upper-lobe bronchiectasis, with diffuse tree-in-bud opacities (Fig. 4). Although the patient did not have gastrointestinal complaints, transient intussusception of the small bowel

was noted as well as dilation and severe fecal impaction within the large bowel (Fig. 5A). The pancreas was diffusely atrophic and showed marked fatty replacement (Fig. 5B). With continued abnormal liver lab results, he received subsequent testing for alpha-1 antitrypsin deficiency and sputum for tuberculosis, both of which were negative.
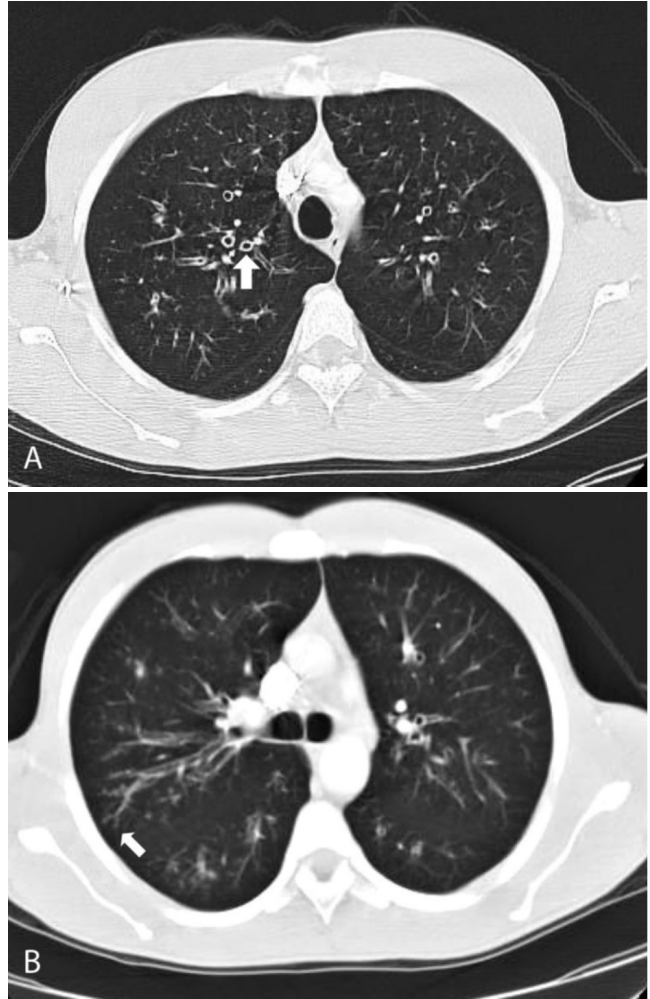

Figure 4. 27-year-old African-American male with late-onset cystic fibrosis. Axial views of contrast-enhanced reformatted chest CT. A) Localized dilation of the bronchi reveals upper-lobe bronchiectasis (arrow). Peribronchial cuffing demonstrates extent of inflammation and mucous impaction. B) Tree-in-bud opacities appear within the lungs (arrow). Note the narrowed mediastinum.

In worsening condition, our patient recently provided sputum for gram stain and culture. The gram stain showed gram-positive cocci in pairs, chains, and clusters, as well as gram-negative bacilli. The culture grew Pseudomonas fluorescens, a rare bacterium documented in immunosuppressed individuals (1). Immunofixation analyses also
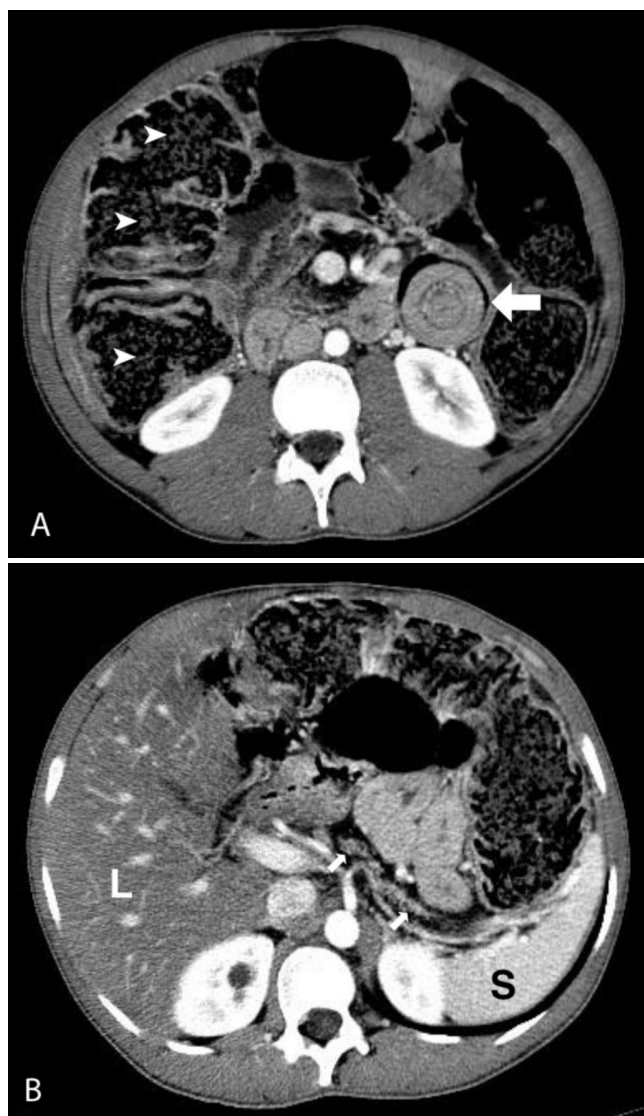
Figure 5. 27-year-old African-American male with late-onset cystic fibrosis. Axial views of the abdomen from contrast-enhanced chest CT. A) The target sign is seen within the small bowel, indicating transient intussusception (arrow). The large bowel is dilated with severe fecal impaction (arrowheads). B) Diffusely atrophic pancreas (arrows) is noted anterior to the left kidney demonstrating hyperattenuation secondary to fatty replacement. Also note decreased liver attenuation (L) as compared to the spleen (S).

showed increased levels of immunoglobulin G, sometimes associated with chronic infection.

It is clear that our patient suffers from an adult-onset form of CF, with elevated sweat chloride level and no known CFTR mutation. To this day, our patient's condition deteriorates, and he remains with no documented diagnosis of CF. Insurance coverage for diagnostic testing generally follows nationally established health guidelines, which are designed to identify the disease in the vast majority of cases. However this strategy excludes coverage for new clinical profiles such as atypical CF, late-onset CF, and CF not testing positive against standard mutation and sweat chloride analyses.

Discussion

History and evolution of CF

CF is a disease whose emerging new phenotypes have important implications for clinicians. After its first description in 1938, CF became known as an autosomal recessive illness, with an incidence of approximately 1 in 3,000 North Americans of Caucasian origin (2). Soon thereafter, it was revealed that elevated sweat chloride levels were a prominent feature of the disease. This finding led to the development and implementation of the diagnostic sweat chloride test for CF. Until the late 1980s, CF was associated with the classic clinical picture of elevated sweat chloride levels, perinatal meconium ileus, early and recurrent lung infection, defective pancreatic secretion (leading to malabsorption, malnutrition, and pancreatic insufficiency), and absence of the vas deferens in males. Predictably, these variable but progressive symptoms were found to lead to a shortened lifespan in CF patients (3). Later, with the discovery of the ΔF508 mutation on the cystic fibrosis transmembrane regulator (CFTR) gene, prenatal and postnatal screening was established, with the ΔF508 allele being the most frequent abnormal genotype. As more allele mutations within the CFTR gene segments were discovered, screening panels were revised accordingly.

Therapy improved for patients, namely pancreatic enzyme supplementation, more effective antibiotics specific for CF-related infections, and (more recently) gene therapy (4). Improved treatment regimens have considerably improved morbidity and mortality for those suffering from CF, and have subsequently allowed a greater population of CF to be studied (both in terms of age range and clinical phenotype). The last decade of research has suggested that the disease is widely varied in both genetic and phenotypic profiles, with a now-documented broad spectrum of disease symptoms. Atypical CF, subacute disease, late-onset disease, and single-organ involvement have all been described (5). Over 1,700 allele mutations, polymorphisms, or unclassified variations of the CFTR gene have been reported (6). Furthermore, clusters of groups other than Caucasians with CF-like symptoms are being examined for the presence of the disease, mostly African Americans and Hispanics in the United States. In this regard, allele mutations specific to clusters of human populations have now been documented with the aim of improving diagnostic efficacy within these population groups (7).

Current practice

Screening and diagnostic devices have been broadened over time to include these new disease subtypes. Intestinal current measurement, nasal potential difference, and immunoreactive trypsinogen (IRT) are examples of tests used to predict CF in varied age groups, racial groups, and clinical spectra. These new developments, however, have made

even more apparent the complexity of CF and the difficulties of approaching it. For example, while IRT has been the primary newborn screening tool in the past decade, it was recently shown to lead to a significantly disproportionate number of false positives in the African-American population (8). This illustrates the need for developing better diagnostic and assessment tools that can be applied to minority groups.

The gold standard for diagnosis remains a positive sweat chloride(Cl) test on two separate occasions, as defined by sweat Cl >60mmol/L. Despite this, the literature cites several examples of CF patients with borderline or normal sweat-chloride values (9). The finding of two mutations in the CFTR gene is also diagnostic of CF, though patients not testing positive for known mutations have been documented as well. Not all documented allele mutations are included in these testing panels; rather, each laboratory tests for frequently occurring mutations in the specific local population being served. In light of the recent discoveries in CF, patients with undiagnosed symptoms, especially those with alternative symptomatology, or those of non-Caucasian origin, may want to pursue further testing beyond the routine tests being offered. Other testing used for detection and monitoring of disease progression are stool assays, sputum analysis, pulmonary function, and imaging techniques such as ultrasound, x-ray, and CT scan.

Imaging

CF has several classic radiologic findings that have been studied over the years (10). Since CF is a progressive disease, imaging features are expected to change over a lifetime. For instance, the lungs are affected by abnormally viscous secretions that prevent proper clearance and promote bacterial growth. A chest x-ray in a baby or young child may be normal, but with age the typical findings of hyperaeration, peribronchial cuffing, increased linear opacities, and bronchiectasis become visibly apparent (11). Similarly, longstanding disease progression can result in the appearance of a flattened diaphragm, mediastinal narrowing, thoracic kyphosis, and sternal bowing. Finally, CT chest findings in children often reveal bronchiectasis, peribronchial wall thickening, mosaic perfusion, and mucous plugging. Pan-sinus disease is also characteristic of CF, due to thickened mucous, and nasal polyps are almost always present in the classic form of the disease. Maxillofacial CT shows mucoceles, opacification of the sinuses, and inflammatory changes as well (12.13).

Hepatobiliary manifestations of CF are typically less common than those of the respiratory system, but with increased patient survival many clinicians have postulated that this will change. Imaging findings associated with hepatic, biliary, and pancreatic involvement have been investigated more recently; although significant conclusions about the appearance of long-term disease are less common. In almost 50% of all cases, abdominal ultrasound of children with CF shows increased echogenicity of the liver related to fatty infiltration, specifically in centrilobular and periportal regions. In abdominal CT, the liver may appear normal or show decreased attenuation, and many patients develop focal biliary cirrhosis, which can also be visualized. CT and magnetic resonance (MR) classically demonstrate progressive fatty replacement, dilated ducts, and eventual fibrosis and atrophy of the pancreas (14). Gallbladder cholesterol stones are common and are best visualized on MR cholangiopancreatography (MRCP); microgallbladder has also been often noted (15). Bowel dysfunction leads to sequela manifesting on CT and MR as fecal impaction, colonic wall thickening, mural striation, mesenteric soft tissue infiltration, and increased pericolonic fat, predominantly in the right colon.

Atypical CF

We have presented a unique case of CF found in an African-American male with adult-onset features. While CF is common in North Americans of European origin, the estimated incidence of it is much lower in other ethnic groups, with African Americans representing 1 in 17,000 new cases (2). Furthermore, the diagnosis of CF has traditionally been made at birth or during early childhood. Our patient, however, presented with his first symptom of CF at the age of 21. In the past several years, the clinical spectrum has widened with respect to age at presentation, ethnic background, severity of disease, and extent of organ involvement. Our patient's CF exhibits two of these newly emerging characteristics and thus provides a forum for discussing the need to expand our diagnosis and assessment approaches to this disease.

Although the medical records do not indicate a formal diagnosis of CF in our patient, most likely due to his negative genetic testing, his slew of imaging findings, symptomatology, laboratory results, and negative testing that excluded other diseases confirms and supports our current diagnosis. Regarding imaging findings, our patient had signs of CF well before he complained of any symptoms. At the age of 19, ultrasound tests found him to have idiopathic fatty liver, which has been cited as the most common hepatobiliary manifestation of the disease (16). A later liver biopsy showed NASH; ultrasounds showed cholelithiasis and microgallbladder. Subsequent imaging after the onset of symptoms were also highly suggestive of CF, with classic manifestations such as pansinusitis on maxillofacial CT, and predominantly upper-lobe bronchiectasis, pancreatic atrophy, and severe fecal impaction on chest CT.

In addition to the patient's appearance on imaging, his unexplained signs and symptoms also indicate CF, despite the fact that the age at presentation was later than usual. These included: difficulty breathing, nasal discharge, diffuse nasal polyps requiring surgery, recurrent cough with sputum production, and frontal headaches. His physical exam findings were also characteristic of CF: digital clubbing and decreased oxygen saturation. Although the patient's imaging reflected some gastrointestinal involvement, the patient did not have clear symptomatology related to this. This is in concert with recent evidence that cases of adult-onset CF are milder and are largely associated with predominantly respiratory symptoms (17). These adult cases were further

shown to be associated with allele mutations other than the classic ΔF508, for which our patient also tested negative.

Positive and negative laboratory testing also supports a diagnosis of CF in this patient. The most striking element of his positive testing is the elevated sweat chloride level. Although this test was not repeated, his levels were well above normal and in the diagnostic range for CF. Furthermore, he underwent workup for other illnesses that could cause elevated sweat chloride, such as hypothyroidism, nephrogenic diabetes insipidus, and Addison's disease, the results of which were all negative. His persistently elevated hepatic enzymes reflect liver involvement and have been shown to be common in CF (18). Similarly, this patient's gram stain showed Staphylococcus aureus and Pseudomonas aeruginosa, organisms that have traditionally infected the lungs of CF patients (19, 20). Sputum culture grew Pseudomonas fluorescens, a rare organism that has not been typically associated with CF, but documented to colonize lungs of immunosuppressed individuals with HIV (21). P. fluorescens colonization most likely represents our patient's decreased immune function within the lungs, and may demonstrate a feature of one or more emerging clinical spectra of CF. Negative laboratory tests performed in our patient include those for sickle cell disease, autoimmune disease, vasculitides, hepatitides, iron and copper metabolism abnormalities, tuberculosis, HIV, syphilis, drug abuse, ACE-, alph-1 antitrypsin-, and complement deficiencies and amyloidosis. He was also tested extensively for liver disease and anemia, to no further avail.

His negative genetic testing for CF does not rule out the disease. The test of 23 disease-causing CFTR mutations performed on our patient had a 69% likelihood of diagnosing CF in the African-American population (22). It has been reported that only 50% of CFTR mutations causing disease in African-Americans have been discovered. ΔF508 is the most commonly occurring known allele mutation regardless of race (with the exception of the Ashkenazi population), but it is predicted that this only accounts for 48% of African-American allele mutations (23). Molecular data regarding allele mutations in African Americans is more extensive than that in African populations, with more than double the number of disease-causing mutations discovered. Research has demonstrated that in the United States it is difficult to identify CF mutations that are population-specific, which may be attributable to ethnic diversity, racial admixture, and the wide range of genetic profiles. A 2001 study, which genotyped 202 African-Americans with CF, found that the standard mutation panel would have missed 1 in 7 subjects (24), and proposed expanded mutation panels. In the case of our patient, his insurance plan did not cover further genetic testing with a larger mutation panel outside our institution. His lack of genetic evidence for CF seems to have prevented him from being diagnosed with and treated for CF.

Conclusion

The confusion in assessing a proper diagnosis in our patient over the years was likely due to his rare CF "profile."

Despite the fact that his constellation of signs and symptoms were classic for CF, he is of African-American background and presented at a much later age than usual. Underdiagnosis in non-Caucasian patients leads to difficulty in determining the impact of CF on this particular population group. Additionally, further characterization of the broad spectrum of clinical appearances now associated with CF is required, such as that related to CF with pancreatic sparing, single organ involvement, and late-onset disease. Education of health personnel about the emerging clinical profiles and ethnic backgrounds of CF patients can lead to improved detection of symptoms and referral for proper testing.

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