THE ANTONIO J. AND JANET PALUMBO CYSTIC FIBROSIS CENTER

A center dedicated to providing state-of-the-art care to patients and families with cystic fibrosis (CF)

The Antonio J. and Janet Palumbo Cystic Fibrosis Center (CF Center), directed by David Orenstein, MD, MA, and Daniel Weiner, MD, was established in 1959 and treats more than 500 pediatric and adult patients annually.

The mission of the CF Center is three-fold:

• To provide state-of-the-art clinical care to children and adults with CF and their families.
• To participate in cutting-edge research that will contribute to the development of new therapies.
• To train the next generation of CF care providers.

Research

The CF Center is a leader in research and has a robust basic science program led by Raymond Frizzell, PhD. As a long-standing site for the Cystic Fibrosis Foundation’s Therapeutic Development Network, the CF Center participates in trials of CFTR potentiators and correctors, inhaled antibiotics, vitamins, and patient-reported outcomes.

Dr. Frizzell, a distinguished scientist who studies ion transport in CF, is the principal investigator of an NIH P-30 Center Core Grant award for the University of Pittsburgh Cystic Fibrosis Research Center. The CF Center garners nearly $10 million in external grants and contracts to support its CF research efforts.

Notable research efforts by the CF Center include:

• Timothy Corcoran, PhD, is developing new nuclear imaging methods for measuring mucus clearance and liquid absorption in the lungs of pediatric and adult CF patients, which will provide a way to rapidly screen new therapies being developed.
• Jay Kolls, MD, directs the Richard King Mellon Research Foundation Institute for Pediatric Research and is an international leader in studies of pulmonary immunity.
• David Orenstein, MD, MA, is spearheading a multicenter study of the effects of aerobic exercise on lung function, quality of life, and mucociliary clearance.
• Joe Pilewski, MD, is studying the effects of inhaled bicarbonate on mucus clearance, lung function, and pulmonary exacerbations.
• Daniel Weiner, MD, is studying whether children with CF are able to perceive changes in their own lung function and whether children with CF differ from those with asthma.

About 1,000 new cases of cystic fibrosis are diagnosed each year in the United States. More than 75 percent of patients are diagnosed by age 2.
A 13-year-old girl with cystic fibrosis (CF) (homozygous F508del) presented to our clinic after moving to the region. She denied any chronic respiratory symptoms, but complained of steatorrhea. She had one isolated episode of “coughing out blood” two months prior. She had not received antibiotics in several years, and was being treated with inhaled hypertonic saline, pancreatic enzymes, multivitamins, and manual chest physiotherapy. She had only one prior hospitalization, at the age of 6 months.

Her physical exam demonstrated splenomegaly and digital clubbing but was otherwise normal. Her chest radiograph and pulmonary function tests (PFTs) were also normal (FEV1 108% predicted). Her laboratory analyses demonstrated elevated transaminases, low fat-soluble vitamin levels, thrombocytopenia, and coagulopathy. An esophagogastroduodenoscopy (EGD) demonstrated grade III esophageal varices (Figure 1) and portal hypertensive gastropathy. A flexible bronchoscopy showed minimal secretions, and her bronchoalveolar lavage (BAL) was negative for hemosiderin-laden macrophages. Cultures of BAL grew P. aeruginosa. She was treated with inhaled tobramycin, ursodeoxycholic acid, and vitamin K. She received antibiotics in several years, and was being treated with airway clearance and systemic antibiotics.

Four months after her initial visit, she coughed out approximately 35 ml of bright red blood. She was evaluated in our Emergency Department. An EGD demonstrated no signs of recent or active bleeding. A flexible bronchoscopy showed dried blood in the posterior segment of the right upper lobe. She was admitted to the hospital and treated with airway clearance and systemic antibiotics for a suspected pulmonary exacerbation. Nevertheless, her physical exam, laboratory analyses, PFTs, and CXR were unchanged during the admission.

The patient had a similar episode one week later. Again, an EGD failed to demonstrate evidence of recent or active bleeding, and her physical exam, laboratory analyses, and PFTs were normal. A PPD and an echocardiogram were also normal. Her CXR was unchanged, but a chest CT demonstrated minimal bronchiectasis in the right upper lobe, right middle lobe, and lingula (Figure 2). She was admitted to the hospital and her symptoms improved with airway clearance and systemic antibiotics.

Differentiating between hemoptysis and hematemesis in a patient with CF-related lung and liver disease with a chief complaint of “blood from mouth” can be very challenging. Hemoptysis is a common complication of CF, occurring in approximately 9% of patients, and it is usually thought to occur in the setting of a pulmonary exacerbation. The management of isolated hemoptysis without other features of a pulmonary exacerbation, as in this case, is controversial. The current recommendation is admission to the hospital for hemoptysis of more than 5 ml and treatment with antibiotics, even with no other evident features of exacerbation.1

CF-related liver disease (CFLD) is an important non-respiratory complication of the disease. The majority of CF patients will have evidence of minor hepatic abnormalities such as transaminitis at some point, but only about 5% to 10% will progress to clinically significant cirrhosis or portal hypertension.2 The reason certain patients progress to severe disease while others do not is not well understood, but is an area of intense research.3 While CFLD occurs almost exclusively in patients with severe class I-III mutations, there is currently no evidence of a phenotypic relationship with specific CFTR mutations.4 However, other genes leading to the development of significant CFLD have been identified (i.e., the SERPINA1Z allele).5 Risk factors associated with the development of CFLD include: pancreatic insufficiency, class I-III CFTR genotype, gender (male), history of meconium ileus, and older age at diagnosis of CF.6 Our patient had some of these risk factors, including pancreatic insufficiency and the CFTR genotype, but not others.

Most patients who develop CFLD do so during or after puberty. Evidence of CFLD is often subclinical until pathologic changes are diffuse. Patients are usually asymptomatic, and thus clinicians rely heavily on physical exam and annual labwork (liver enzymes). However, abnormalities in transaminases have low sensitivity and specificity and do not correlate well with liver histology or predict CFLD severity. Liver ultrasoundography is abnormal at baseline in 35% to 50% of CF patients, but most of these patients will not develop clinically significant portal hypertension. Liver biopsy, which serves as the gold standard for diagnosis of many chronic liver diseases, is invasive and also may underrepresent CFLD due to sampling error from the patchy distribution of lesions.4

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Management of CFLD is supportive. Ursodeoxycholic acid is believed to improve bile flow by removing toxic hydrophobic bile acids and offer possible cytoprotection through stimulation of biliary chloride and bicarbonate secretion. However, CFLD may still progress on ursodeoxycholic acid. Once overt liver disease occurs, treatment relies on the management of the complications of portal hypertension, including ligation of the esophageal varices that lead to hematemesis. Liver transplantation is an option for end-stage CFLD, but patient selection and timing remain controversial. Poorer lung function prior to surgery has been associated with increased early mortality; thus, transplant relatively early in the disease course may be warranted before lung function worsens, and may ultimately lead to stabilized or improved pulmonary function postoperatively. However, one-year mortality rates after liver transplantation in children with CF are historically between 10% to 25%, so many suggest that transplant should be reserved for more severe CFLD disease. Under UNOS scoring, the typical CFLD patient will not garner a high enough score for transplant until very late in the disease course, by which time it may be too late to find an appropriate organ. Clear guidelines for liver transplantation in CFLD are lacking. Furthermore, the role of multivisceral transplant has yet to be determined.

In the patient with both lung and liver manifestations of CF, as in this case, identifying the source of bleeding can be difficult. In addition to bronchoscopy and/or endoscopy, it is important to rely on historic clues, such as associated symptoms of nausea and vomiting, and the appearance of the blood. If a sample is available, pH testing can be useful, as hematemesis is usually acidic and hemoptysis alkaline. An elevated diffusing capacity of the lung for carbon monoxide (DLCO) has been associated with hemoptysis and, thus, may provide noninvasive supporting evidence for diagnosis.

Because of the diagnostic and therapeutic complexity of CFLD and its complications, the Antonio J. and Janet Palumbo Cystic Fibrosis Center at Children’s Hospital of Pittsburgh of UPMC has partnered with the Division of Pediatric Gastroenterology to establish multidisciplinary care for our CF patients with hepatobiliary complaints.

References

ABOUT CHILDREN'S HOSPITAL OF PITTSBURGH OF UPMC

Children's Hospital of Pittsburgh of UPMC is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists.

Children’s is consistently recognized for its research and clinical achievements, including ranking seventh among children’s hospitals and schools of medicine (FY13) in NIH funding for pediatric research, and being named to the 2014-15 U.S. News & World Report Honor Roll of America’s Best Children’s Hospitals.

RECENT RECOGNITIONS, HONORS, AND AWARDS

David Orenstein, MD, MA, was recently recognized by the division for his 30th year of service as the CF Center director.

The CF Center providers serve as leaders at the national level within the Cystic Fibrosis Foundation and the Therapeutic Development Network (TDN). Joe Pilewski, MD, is chair of the TDN Steering Committee. David Orenstein, MD, MA, is chair of the TDN Publications Committee. Daniel Weiner, MD, serves on the CFF Care Center Committee.

Jonathan Finder, MD, raised nearly $7,000 for the Cystic Fibrosis Foundation in the 2014 Cycle for Life, during which he cycled 100 miles. In addition to providing care for many patients with CF, he raised more funds than any other single cyclist at the event.

Connie Richless, CNS, recently received the first Mary Kontos Care Champion Award, presented by the Cystic Fibrosis Foundation, for her hard work, leadership, and dedication in the adult CF program.

A BRIEF HISTORY OF THE CYSTIC FIBROSIS CENTER

The Antonio J. and Janet Palumbo Cystic Fibrosis Center was founded in 1959 by Joan Rodnan, MD, in collaboration with Bertram Girdany, MD. By 1968 the center had added a social worker, nutritionist, and child life specialist. In 1982, under the direction of Joel Weinberg, MD, the CF Center began providing specialized care to adults. Shortly after that the CF Center made two notable recruitments: in 1983 it welcomed its first pediatric pulmonology trainee, and in 1984 David Orenstein, MD, MA, current center co-director, joined the program.

In 2000, the CF Center was endowed by a generous grant from Antonio J. and Janet Palumbo. In 2009 and 2011, the CF Center was recognized with the Care Center Chapter Partnership Award and the Cystic Fibrosis Foundation’s Quality Care Award for Outstanding QI Processes and Accomplishments.