Cystic Fibrosis in the 21st Century : What Every Radiologist Should Know

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Disclosures

- The authors have nothing to disclose.

Goals and Objectives

- Review the pathophysiology, genetics, demographics, diagnosis, and treatment of cystic fibrosis (CF)
- Demonstrate the role of imaging (radiograph, CT, MR, ultrasound) in the diagnosis and management of patients with CF
- Learn the appropriate imaging follow-up for these patients
- Help improve radiology reports for patients with CF
- Educate about recent advances in research

Target Audience

Medical students, residents, radiologists

Introduction

- Multisystemic disease
- **Chloride transport dysfunction** across secretory epithelia:
 - Results in thick and viscous secretions
 - Affects the lungs, digestive system, sweat glands, and the reproductive tract
- **Lung disease** continues to be the major cause of morbidity and mortality:
 - Failure to expectorate mucus → recurrent infections → airway destruction
 - Death from respiratory failure, *cor pulmonale*, hemoptysis
 - Current life expectancy in the USA: 37 years
 - **More and more patients survive into 5th decade and beyond**

Genetics

- Autosomal recessive disorder
- Mutations of *CFTR* gene (chromosome 7):
 - Encodes the cystic fibrosis transmembrane conductance regulator protein
 - Functions as a regulated chloride channel
- > 2000 mutations, most common F508del (90%)
- Phenotypic variation in age of onset and severity of disease, with numerous nonclassic cases:
 - Nonclassic CF: disease manifestations are unusually mild or limited to one organ system
 - Different classes of mutations (5)
 - Presence of gene modifiers

Genetics

Class	Type of defect
Class I	Defective protein production
Class II	Defective protein processing
Class III	Defective regulation
Class IV	Defective conduction
Class V	Reduced amounts of functional CFTR protein

CFTR Gene Mutations

Percentage of cystic fibrosis transmembrane conductance regulator (CFTR) activity correlates with disease manifestations.

Demographics

- **Most lethal** autosomal recessive disease in the **white population**
 - Northern European origine - **1:3,200-3,500**
 - Hispanics - 1:9,200-9,500
 - African Americans - 1:15,000-17,000
 - Asian Americans - 1 : 31,000
- Currently 30,000 cases in the USA (70,000 worldwide)

Diagnosis

- Most diagnosed by **3 years**
 - Occasional mild cases not diagnosed until adulthood (7%)
- USA: newborn screening in all 50 states
 - Serum immunoreactive trypsinogen (IRT)
 - DNA analysis for mutations in CFTR
- **Sweat test:** reference standard for CF diagnosis
- Nasal potential difference : for patients with inconclusive results of sweat test and DNA testing

Pathogenesis and Imaging : Lungs

- Chronic bronchitis with typical organisms: mostly *S. aureus*, *P. aeruginosa*
- Ongoing inflammation → damage to the bronchial walls → bronchiectasis
 - Upper lobes less effective in clearing secretions (upper right lobe often more affected)
 - Permanent loss of lung function over time

Radiographic Findings

- Chest X-ray:
 - Less sensitive than CT regarding structural lung disease
 - Still routinely used for follow-up (less radiation exposure)
 - Evaluation of acute complications (pneumonia, pneumothorax, effusion)
- Angiography: may be used for planning embolization of bronchial arteries for hemoptysis

Radiographic Findings

PA chest radiograph in a 21-year old man shows bilateral bronchial wall thickening (**yellow arrows**) and cystic lucencies consistent with bronchiectasis (**blue arrows**).

Radiographic Findings

PA chest radiograph with corresponding unenhanced CT image in a 24-year old man with more severe disease shows right multicystic lesions with surrounding pleural thickening and effusion.

Radiographic Findings

Angiographic images in a 24-year old woman undergoing bilateral bronchial arterial embolization for hemoptysis. There is bilateral bronchial arterial hypertrophy.

CT Findings

- **Airways:**
 - Bronchial wall thickening is the earliest finding
 - Bronchiectasis:
 - Cylindrical, varicoid, and saccular
 - Most severe in upper lobes (right > left)
 - Mucous plugging: centrilobular nodules
 - Atelectasis
- **Lungs:**
 - Air-trapping: hyperinflation, mosaic attenuation
 - Recurrent consolidation: pneumonia, atelectasis, hemorrhage
 - Cystic changes: blebs and bullae, typically upper lobe and subpleural → may rupture and cause a pneumothorax

CT Findings

Coronal unenhanced chest CT image in a 24-year old man shows varicoid and cystic bronchiectasis (**yellow arrows**), mucous plugging (**blue arrow**), mosaic attenuation (white arrow), and atelectasis (*).

CT Findings

Axial unenhanced CT images of the chest in patients of about the same age (20 to 25 years old) show the wide spectrum of disease, ranging from mild cylindrical bronchiectasis (left) to diffuse varicoid and saccular bronchiectasis with mucous plugging and consolidation (middle) to mucoid impactions in dilated bronchi (finger in glove sign) with centrilobular nodules (right) consistent with allergic bronchopulmonary aspergillosis (ABPA).

CT Findings

- Associated chest findings:
 - Increase in right heart size (*cor pulmonale*)
 - Bronchial arterial enlargement (pulmonary hypertension)
 - Reactive lymphadenopathy
 - Parapneumonic effusion
 - Esophageal varices secondary to portal hypertension

CT Findings

Axial enhanced chest CT image in a 24-year old man shows esophageal varices related to portal hypertension (**yellow arrow**).

CT Scoring

- Some **scoring systems** have been developed to describe the degree of **disease involvement**:
 - Based on the subjective assessment of airway and parenchymal involvement (bronchiectasis, bronchial wall thickening, mucous plugging, and air-trapping)
 - Points are added to produce a total score
- Could be a more sensitive method to track progression of CF lung disease compared to spirometry
- **Bhalla score** routinely used in Europe

MR Findings

- There is an increase in **radiation exposure** in CF patients who may accumulate significant doses during their lifetime
- MR is more and more used for follow-up due to lack of ionizing radiation
 - Could potentially be used to visualize earlier signs of disease
- **Structural imaging**
 - Bronchial wall edema: hyperintense signal on T2-weighted images
 - Inflamed airways: post-gadolinium enhancement
- **Functional imaging**
 - Ventilation and perfusion imaging sequences have been developed
 - MR angiography: to better visualize bronchial arteries

Beyond the Lungs: Gastrointestinal Findings

PANCREAS	LIVER & BILE DUCTS	ESOPHAGUS	BOWEL
Inspissated secretions leading to ductal obstruction	Thick secretions leading to ductal obstruction and chronic inflammation		Thickened intestinal secretions, delayed transit
<ul style="list-style-type: none"> - Fatty replacement - Cystic changes: multiple small cysts (1-3 mm) or cystosis (replace entire parenchyma) - Recurrent episodes of pancreatitis → signs of chronic pancreatitis (dilated and irregular ducts, calcifications) 	<ul style="list-style-type: none"> - Hepatic steatosis ± hepatomegaly - Focal biliary cirrhosis is pathognomonic: periductal thickening and fibrosis - Multinodular cirrhosis ± portal hypertension → increased risk of hepatocellular carcinoma - Gallstones - Sclerosing cholangitis 	<ul style="list-style-type: none"> - Gastroesophageal reflux (up to 39%): may aggravate respiratory symptoms - Esophageal dysmotility - Peptic ulcer disease 	<ul style="list-style-type: none"> - Chronic constipation - Obstruction <u>Infants</u>: meconium ileus (pathognomonic for CF) <u>Adults</u>: distal intestinal obstruction syndrome (DIOS) - increased risk after lung transplantation - Intussusception (most often ileocolic) - Chronically distended appendix - Colonic wall thickening - Pneumatosis intestinalis

Spectrum of Gastrointestinal Findings

Coronal contrast-enhanced abdominal CT image in a 25-year old woman shows pancreatic fatty replacement and cystic changes (yellow arrow). (Of note, there is also splenomegaly and varices.)

Axial contrast-enhanced abdominal CT image in a 30-year old man shows dilated pancreatic duct (blue arrow).

Spectrum of Gastrointestinal Findings

Coronal contrast-enhanced abdominal CT image in a 18-year old woman shows nodular cirrhosis (**yellow arrow**), splenomegaly with varices (**blue arrows**), and pancreatic calcifications (white arrow).

Spectrum of Gastrointestinal Findings

Coronal and axial unenhanced CT images in a 19-year old man show mildly dilated loops of small bowel with fecalized contents, consistent with distal intestinal obstruction syndrome (DIOS).

Spectrum of Gastrointestinal Findings

Abdominal radiograph in a 20 year-old man shows a mottled mass in the stomach representing undigested food secondary to impaired digestion and decreased gastric motility (bezoar) (blue arrows).

Beyond the Lungs: Other Findings

SINUS	BONE	REPRODUCTION	URINARY TRACT
<ul style="list-style-type: none"> - Pansinusitis in 100% of patients <ul style="list-style-type: none"> - <i>S. aureus</i>, <i>P. aeruginosa</i>, <i>Aspergillus</i> - Sinus obstruction, polyposis, mucocele, bony sclerosis - Hypoplastic frontal sinuses are pathognomonic 	<p>Bone demineralization secondary to poor nutritional status, inflammatory state, glucocorticoid therapy, inactivity</p>	<p>Women: Thickened cervical mucus.</p> <p>Men:</p> <ul style="list-style-type: none"> - Congenital bilateral absence of the vas deferens - Tubular ectasia in the epididymal head - Dilation of the rete testis 	<ul style="list-style-type: none"> - Nephrolithiasis: secondary to low urine volume, antibiotics - Interstitial nephritis: secondary to IgA nephropathy, secondary amyloidosis (chronic infection resulting in nephrotic syndrome), antibiotics, diabetes

Sinonasal Disease

Axial and coronal unenhanced CT images of the sinus in a 25-year old woman show sinus obstruction and osseous thickening (yellow arrows) secondary to chronic inflammation.

Frontal and sphenoid sinuses are hypoplastic (blue arrows).

CF-related Bone Disease

Résumé des résultats:

Région	Surface [cm²]	CMO [(g)]	DMO [g/cm²]	T-score	PR (Pic de référence)	Z-score	MA (Même Age)
L1	9.78	5.83	0.597	-4.3	56	-4.3	56
L2	10.72	7.30	0.681	-3.8	62	-3.8	62
L3	11.23	8.64	0.770	-3.0	70	-3.0	70
L4	12.18	8.53	0.701	-3.5	64	-3.5	64
L1 - L2	20.49	13.13	0.641	-3.7	61	-3.7	61
L1, L3	21.00	14.47	0.689	-3.4	65	-3.4	65
L1, L4	21.95	14.37	0.655	-3.9	60	-3.9	60
L2 - L3	21.94	15.93	0.726	-3.4	66	-3.4	66
L2, L4	22.89	15.83	0.692	-3.9	62	-3.9	62
L3 - L4	23.40	17.17	0.734	-3.5	65	-3.5	65
L1 - L3	31.72	21.77	0.686	-3.5	64	-3.5	64
L1-L2, L4	32.67	21.66	0.663	-3.9	61	-3.9	61
L1, L3-L4	33.18	23.01	0.693	-3.6	64	-3.6	64
L2 - L4	34.12	24.47	0.717	-3.6	64	-3.6	64
L1 - L4	43.89	30.30	0.690	-3.6	63	-3.6	64

CV TOTALE DMO 1.0%, ACF = 1.038, BCF = 1.013, TH = 7.376

Risque fracturaire : Elevé; Classification OMS : Ostéoporose

Dual x-ray absorptiometry (DEXA) scan in a 24-year old man shows marked osteoporosis. Bisphosphonate therapy is indicated with a Z-score of less than -2 on DEXA scan.

CF-related Bone Disease

Sagittal unenhanced CT image in a 25-year old woman shows osteoporotic compression fractures (**yellow arrow**) with **kyphosis** of the thoracic spine.

Obstetric Imaging

- **Echogenic bowel** in 2nd trimester due to inspissated mucus → bowel dilation in 3rd trimester
 - 11% of fetuses with CF have echogenic bowel
- **Meconium ileus:**
 - Dilated, echogenic small bowel (indistinguishable from ileal atresia)
 - May lead to perforation with meconium peritonitis
 - 8% of fetuses with meconium peritonitis have CF
- Normal US exam **does not** rule out CF

Recommended Follow-up

- **Imaging:**

- It is recommended to perform chest X-rays on an annual basis, and at times of clinical deterioration*
- High resolution chest CT scanning should be available depending on the clinical picture*
- Appropriate imaging should be available to evaluate liver and pancreatic complications (e.g. ultrasonography, CT, or MRI)*
- Bone densitometry (DEXA) should begin at the age of 18 years or earlier if substantial risk factors for bone disease*

- **Others:**

- Colorectal cancer screening should begin at age 40 in individuals with continued re-screening every five years*

* Based on the European Cystic Fibrosis Society (ECFS) best practice guidelines (2018)

* Recommended by the Cystic Fibrosis Foundation

Treatment

- Nutrition and physiotherapy programs
- Antimicrobial and mucolytics
- Pancreatic enzyme supplementation
- Lung transplantation:
 - Most frequent complications: DIOS, post-transplant lymphoproliferative disease
 - Represent 2nd cause of death (after cardiorespiratory failure)

What the Clinician Wants to Know

- **Severity of the disease:**
 - Profusion and evolution: bronchiectasis, peribronchial thickening, mucus plugging, centrilobular nodules, mosaic perfusion
 - Distribution of atelectasis
- **Complications:**
 - Signs of infection with unusual pathogens
 - Air-fluid levels in bronchiectatic cavities: related to acute exacerbations
 - Requiring immediate intervention: pneumothorax, massive effusion
- Mapping of the bronchial arteries in the case of hemoptysis
- **Beyond the lungs:**
 - Signs of invasive sinusitis, mucocoele
 - Signs of portal hypertension

Future Directions

- **Functional MRI** of the CF lung is increasingly used for routine imaging in young patients and may better depict early disease.
- **Low-dose CT protocols** are also being developed for follow-up.
- **New molecules** are appearing on the market and may change the imaging manifestations of the disease:
 - Orkambi®, Symdeko®: help increase the number of CFTR proteins that are trafficked to the cell surface
- Literature have shown that there is an **increased risk of cancer** in CF patients, particularly following transplantation:
 - Mostly: digestive tract cancer, lymphoid leukemia, testicular cancer
 - May affect cancer screening recommendations in this population

Conclusion

- CF is a common genetic disease with which modern radiologists should be familiar, especially those working in endemic regions.
- With the advances in treatment, there has been an important improvement in life expectancy, with patients surviving beyond the 5th decade.
- Some complications will likely become more common as patients live longer.
- Appropriate imaging follow-up is an integral part of patient care.
- The radiologist has an important role in documenting the disease manifestations and in recognizing its complications to guide the clinician.

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Thank you!

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