



Multi-System Consequences of Cystic Fibrosis

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Objectives

- Index Patient
- Review Cystic Fibrosis (CF)
 - Epidemiology
 - Genetics and Pathogenesis
 - Diagnosis
 - Clinical Manifestations
 - Radiologic Findings
 - Prognosis and Treatment



Index Patient: History and Clinical Presentation

- MT is a 13 year old girl with CF, pancreatic insufficiency, allergic bronchopulmonary aspergillosis, difficulty gaining weight, cystic fibrosis liver disease, and low bone density.
- She presents to pulmonary clinic with complaints of nighttime cough and decreased exercise tolerance. She also endorses post-nasal drip, clear nasal discharge, and left lumbar back pain and swelling.



Index Patient: Physical Exam

- Gen: alert, oriented x3, cooperative, NAD
- VS: afebrile, HR 103, RR 20, BP 91/72, O2 sat 97% on room air, weight 36.3 kg, height 144.8 cm, BMI 17.3 (23rd percentile)
- HEENT: + rhinorrhea
- Lungs: symmetric, no increased work of breathing, clear to auscultation
- Cardiac, Abd, Derm, Neuro: all within normal limits
- Extremities: warm, well perfused, + clubbing
- MSK: mild swelling over L lumbar area



Index Patient: Lab Values

- Spirometry: FEV1 54%, FVC 67%
(compared to her current year's best of FEV1 82%, FVC 97%)
- Flow Volume Curve shows obstructive pattern
- TLC 107%, RV 219%, RV/TLC 53%
(indicates air trapping)



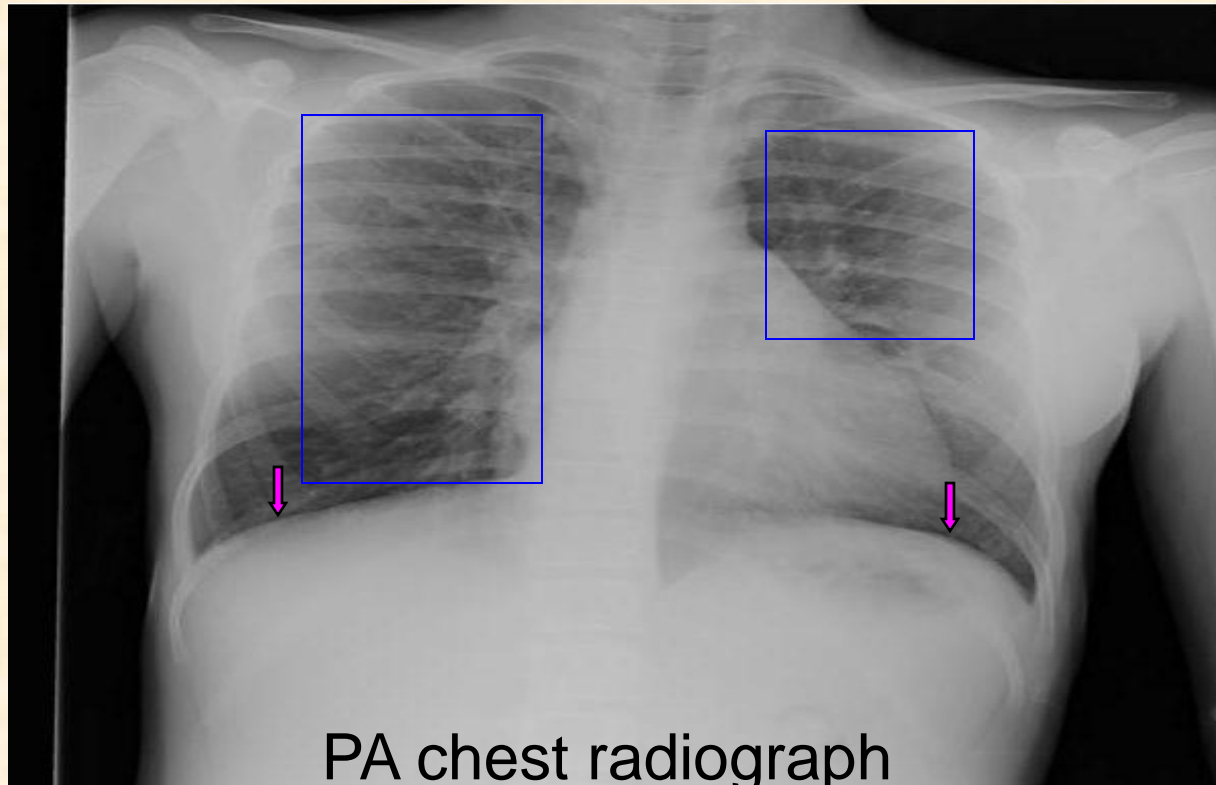
Pertinent images taken upon the patient's presentation will be shown on the following slides.



Index Patient: Frontal CXR

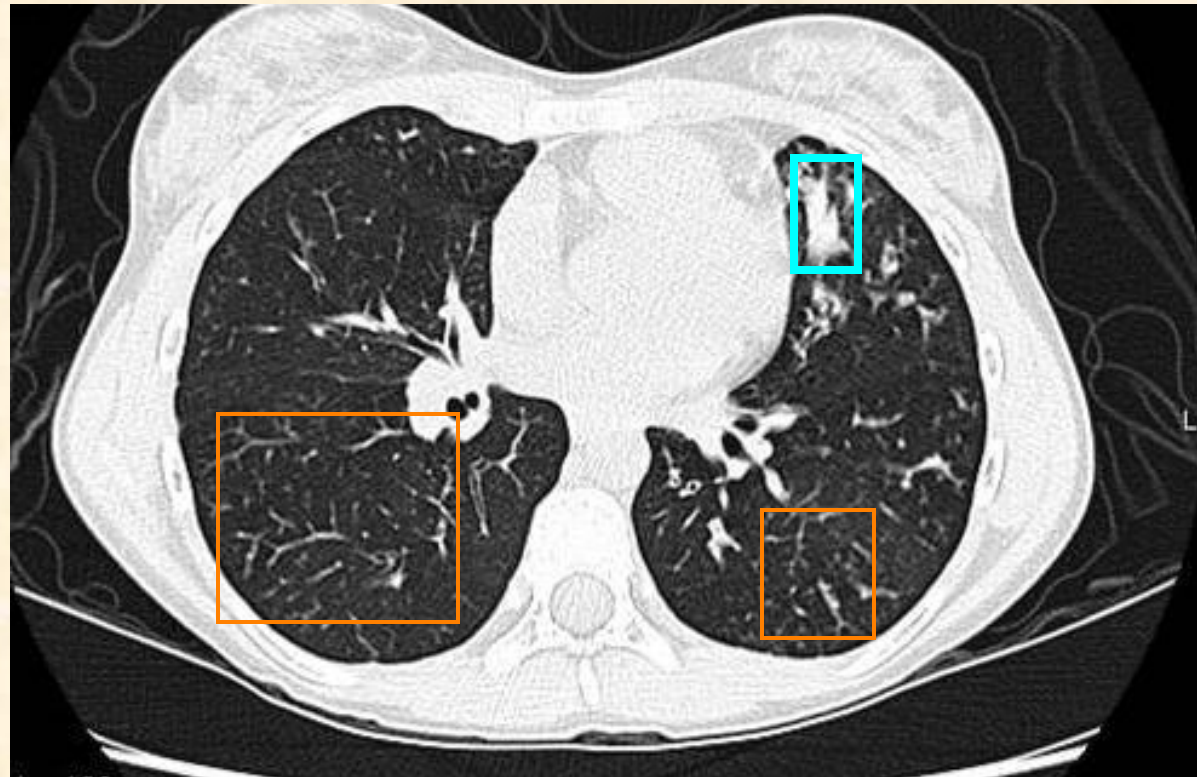
areas of
increased
bronchovascular
markings
indicate
thickened
bronchial walls
seen in
bronchiectasis

flattened
diaphragm is
a sign of
hyperinflation
due to air
trapping





Index Patient: Tree in Bud Sign on Chest CT



area of
consolidation

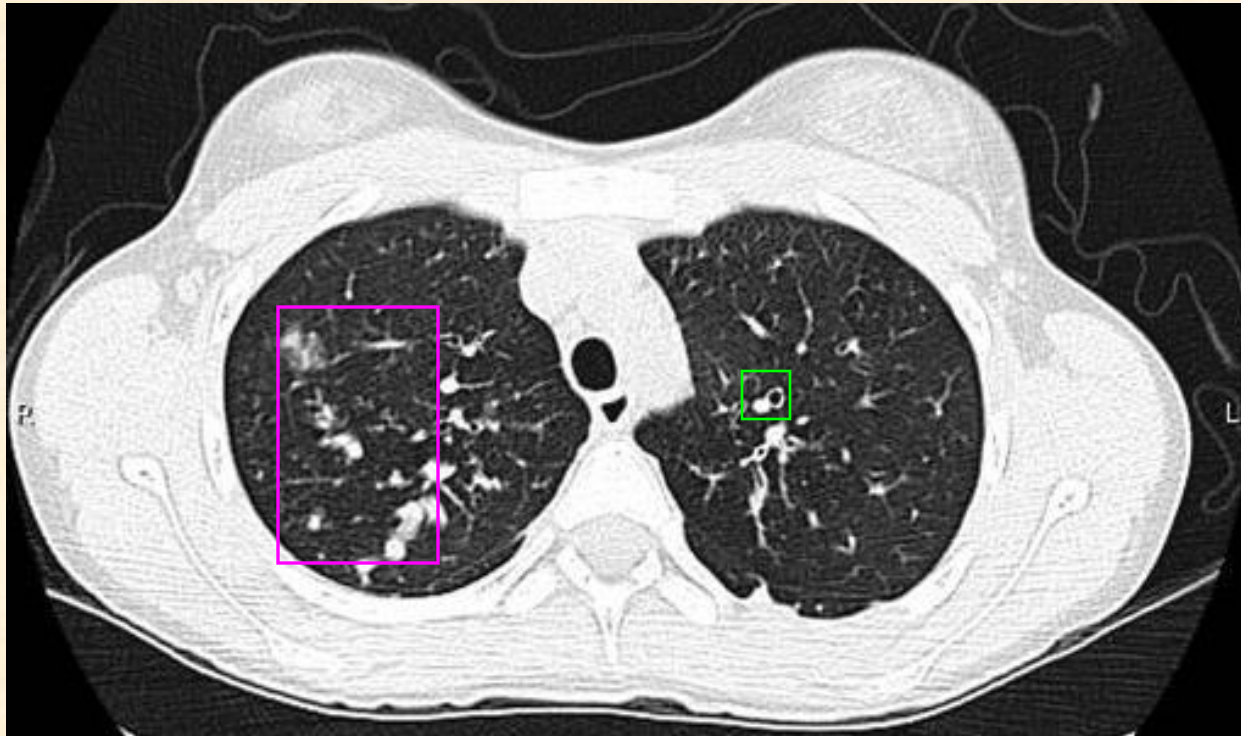
“tree in
bud” sign
represents
secretions
in distal
airways

CT Chest with contrast



Index Patient: Atelectasis and Signet Ring Sign on Chest CT

scattered
areas of
atelectasis
resulting
from
mucus
plugging



signet ring
sign
indicates
dilated
bronchus in
association
with its
adjacent
artery

CT Chest with contrast

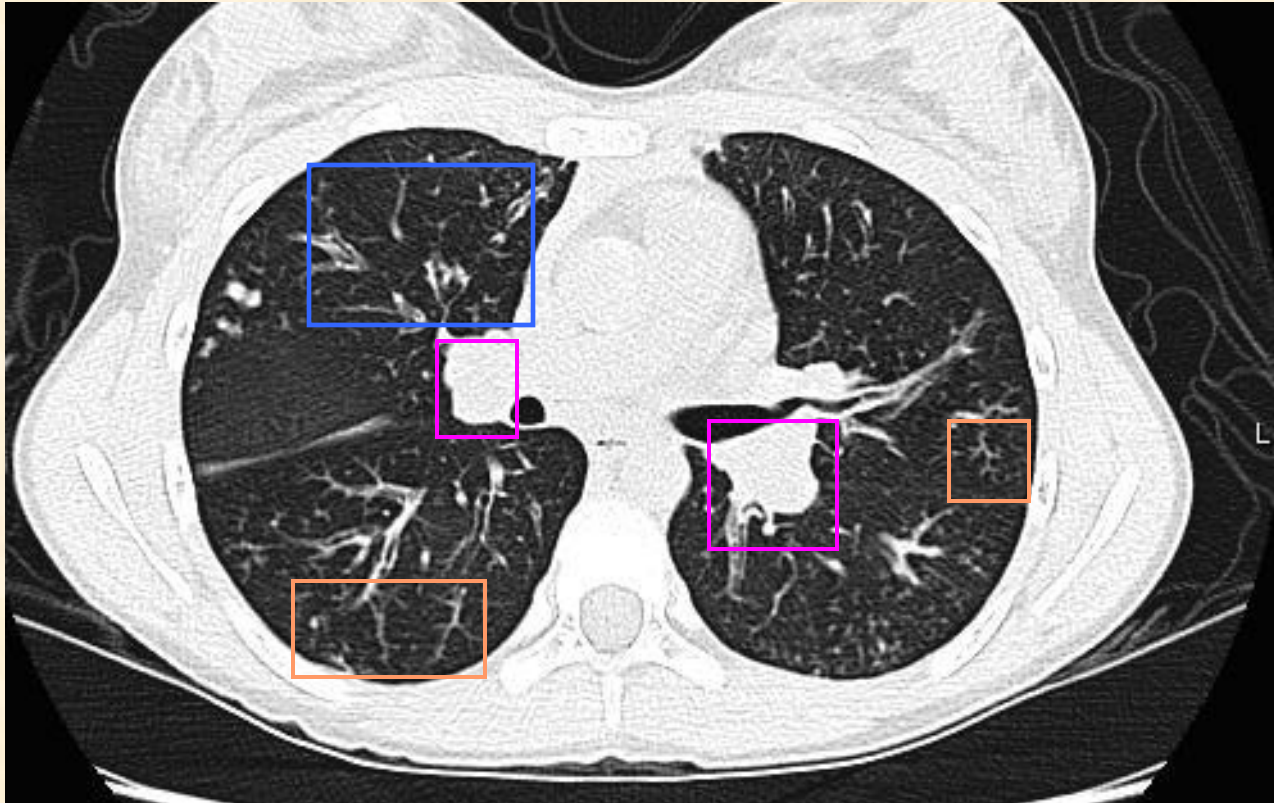


Index Patient: Bronchiectasis and Mucus Plugging on Chest CT

bronchiectasis:
dilated airway
surrounded by
thickened walls

Mucus
plugging

“tree in
bud” sign
represents
secretions
in distal
airways

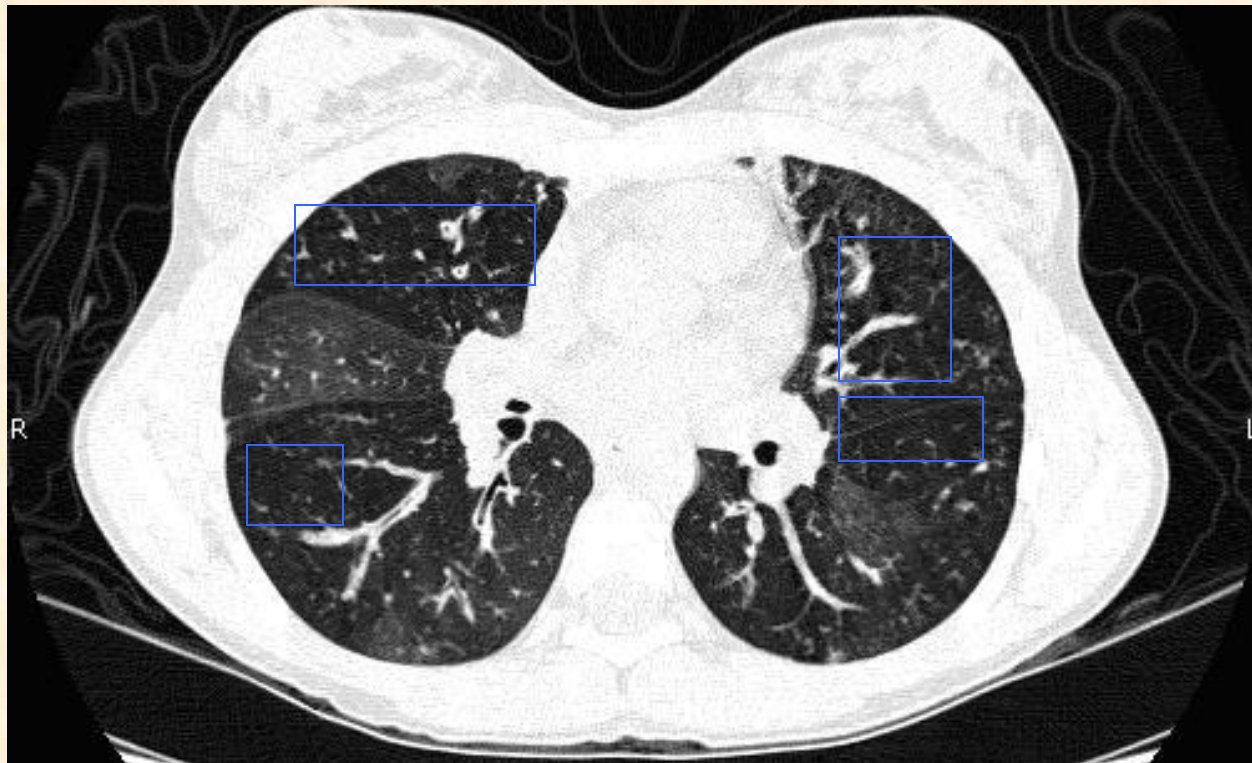


CT Chest with contrast



Index Patient: Air Trapping on Chest CT

areas of
increased
lucency
represent
regions of
air trapping



CT Chest with contrast



Now that our index patient has been introduced, the following slides will introduce the general topic of cystic fibrosis.



Cystic Fibrosis: Definition and Features

- A hereditary disease that appears usually in early childhood
- Dysfunction of exocrine glands
- Notable features
 - Excessive loss of salt in sweat
 - Mucus accumulation in airways
 - Impaired digestion due to deficiency of pancreatic enzymes



Cystic Fibrosis: Epidemiology

- Most common fatal Autosomal Recessive (AR) disease in Caucasian populations
- 1/2500-1/3500 live Caucasian births
- 1/17000 in African Americans
- 1/31000 in Asian Americans
- Prevalence estimates likely to rise due to newborn screening



Cystic Fibrosis: Genetics

- AR inheritance
- Mutations in gene that encodes CFTR protein (chloride channel found in exocrine tissues) on chromosome 7q31.2
- Over 1000 mutations identified
- Most common: delta F508
- Mutations alter the production, structure, or stability of the chloride channel



Cystic Fibrosis: Pathogenesis

- Abnormal chloride transport >
- Thick, viscous mucus produced by cells that line passageways of lungs, pancreas, and other organs >
- Secretions can't be cleared from airways and ducts >
 - Airways: secondary infections > Persistent infections destroy airways
 - Ducts: obstructed > organ dysfunction



Cystic Fibrosis: Pathology

- Thickened bronchial walls
 - Chronic inflammation
 - Granulation tissue and fibrosis
- Bronchial wall weakness
- Parenchymal loss and distortion
- Colonization with pseudomonas, etc.



Cystic Fibrosis: Diagnosis

- Clinically:
 - clinical symptoms AND
 - one of the following
 - a) +chloride sweat test ($>60\text{mmol/L}$) twice
 - b) 2 disease-causing mutation in CFTR
 - c) abnormal nasal potential difference (more negative baseline)
- DNA testing
- Newborn screening



Newborn Screening

- All 50 states include CF in newborn screening panel
- Elevated immunoreactive trypsin (IRT) is a positive screen
- DNA analysis to identify mutations in CFTR gene



At this point the effects of CF on various organ systems will be elucidated.



CF: Manifestations in Respiratory System

- Persistent, productive cough
- Hemoptysis
- Chronic bronchitis +/- bronchiectasis
- PFTs consistent with obstructive airway disease
- Acute exacerbations: increased cough, tachypnea, dyspnea, increased sputum production



CF: Radiologic Findings in Respiratory System

- Modalities
 - Chest Radiographs: best for long-term follow-up and acute exacerbations
 - Chest CT: more sensitive for mild disease detection and best for detecting bronchial wall thickening and dilation
- Findings
 - Hyperinflation (air trapping)
 - Atelectasis
 - Bronchiectasis (usually upper lobe)
 - Mucus plugging



CF: Radiologic Signs Related to Respiratory System

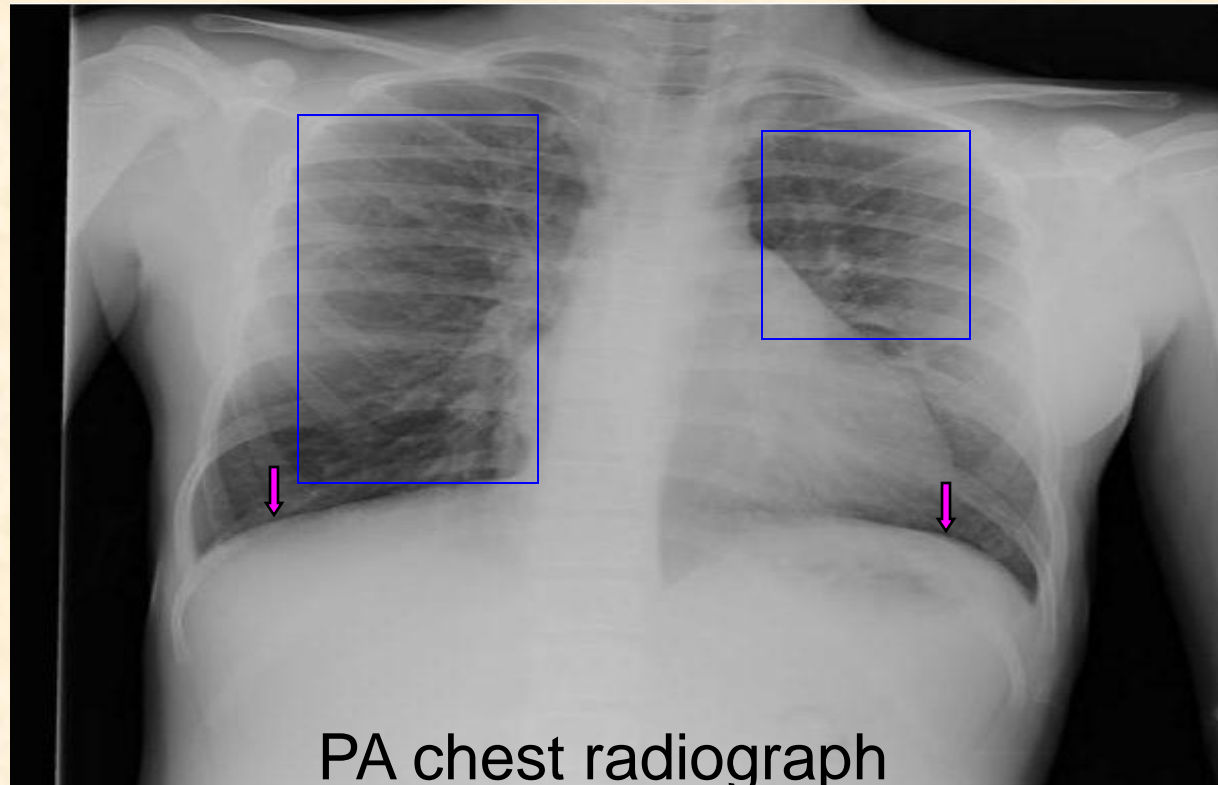
- Signs:
 - Signet ring sign = dilated bronchus in association with adjacent artery on axial CT images
 - Tree in bud sign = secretions within peripheral small centrilobular bronchioles can give Y or V shaped opacities



As many of the radiologic findings and signs that reflect the effects of CF on the respiratory system were evident in our index patient's images, some of these images are reproduced in the following slides to allow for further review.



Index Patient: Frontal CXR



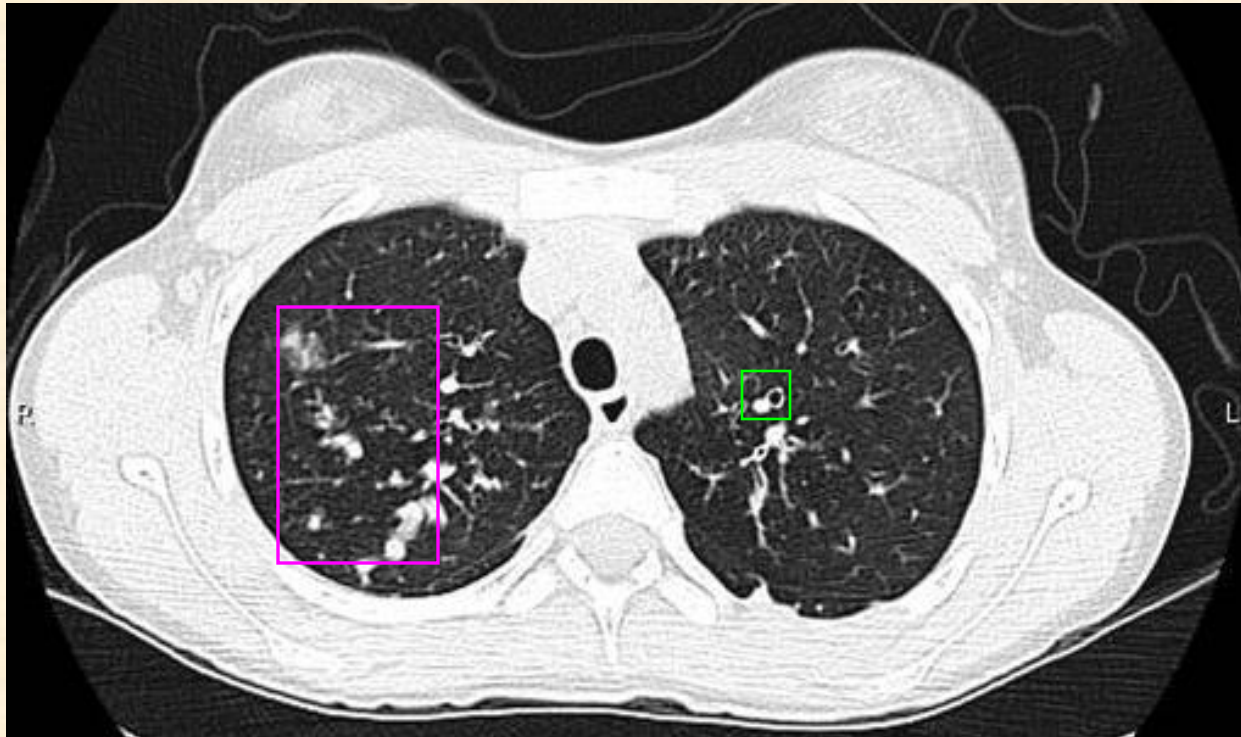
areas of increased bronchovascular markings indicate thickened bronchial walls seen in bronchiectasis

flattened diaphragm is a sign of hyperinflation due to air trapping



Index Patient: Atelectasis and Signet Ring Sign on Chest CT

scattered
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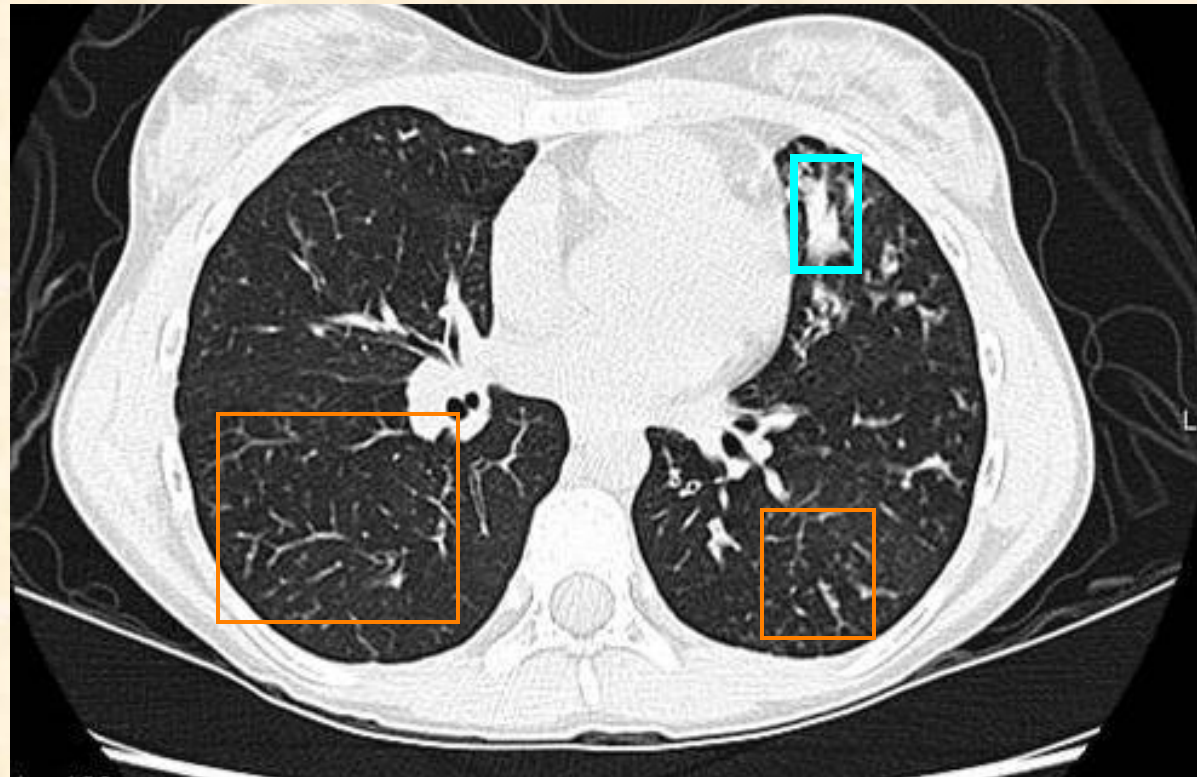


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CT Chest with contrast



Index Patient: Tree in Bud Sign on Chest CT



area of
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Although our index patient is known to have CF, it is important to consider other possible diagnoses based on symptoms of respiratory distress, recurrent pneumonias, and certain radiologic findings on CXR and Chest CT as shown. Note that close clinical follow-up is necessary to differentiate among the following diagnoses.



Differential Diagnosis

- Recurrent aspiration
- Asthma
- Primary ciliary dyskinesia
- Primary Immunodeficiency



It is also important to consider complications of CF as this is a chronic illness with various downstream consequences. One such complication, to be discussed in the following slides, may be responsible for acute worsening of lung function and certain corresponding findings on imaging.



Complication of CF: ABPA

- Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction in the lung that occurs when bronchi become colonized by *Aspergillus* species, usually *A. fumigatus*.
 - Susceptible patients: CF (7-9%) , asthma (1-2%)
 - Repeated episodes of bronchial obstruction, inflammation, and mucoid impaction can lead to bronchiectasis, fibrosis, and respiratory compromise.
- Pathogenesis: Inflammatory response characterized by Th2 responses to *Aspergillus* allergens, increased serum IgE, and eosinophilia.
 - This response may result in airway damage and bronchiectasis.



Diagnosis of ABPA

- Diagnosis: based on clinical symptoms and immunologic reactivity to *A. fumigatus*.
- Minimal criteria required for diagnosis:
 - (1) asthma or cystic fibrosis with deterioration of lung function
 - (2) immediate *Aspergillus* skin test reactivity
 - (3) total serum IgE ≥ 1000 IU/mL
 - (4) elevated *Aspergillus* specific IgE and IgG antibodies
 - (5) chest radiographic infiltrates
- Additional criteria may include
 - peripheral blood eosinophilia
 - *Aspergillus* serum precipitating antibodies
 - central bronchiectasis
 - *Aspergillus*-containing mucus plug production



Radiologic Findings in ABPA

- parenchymal infiltrates (usually involving the upper lobes)
- atelectasis due to mucoid impaction
- bronchiectasis
- “gloved finger shadows” due to intrabronchial exudates with bronchial wall thickening: these appear as branched tubular radiodensities that extend from the hilus.



Our index patient held the diagnosis of ABPA as a complication of CF. Some of her images will again be reproduced in the following slides in order to demonstrate findings consistent with ABPA. Note the difficulty one would have in attempting to identify, based on imaging alone, the cause of the radiologic findings in this patient as they may be due to chronic damage from CF or may be due to her ABPA complication.

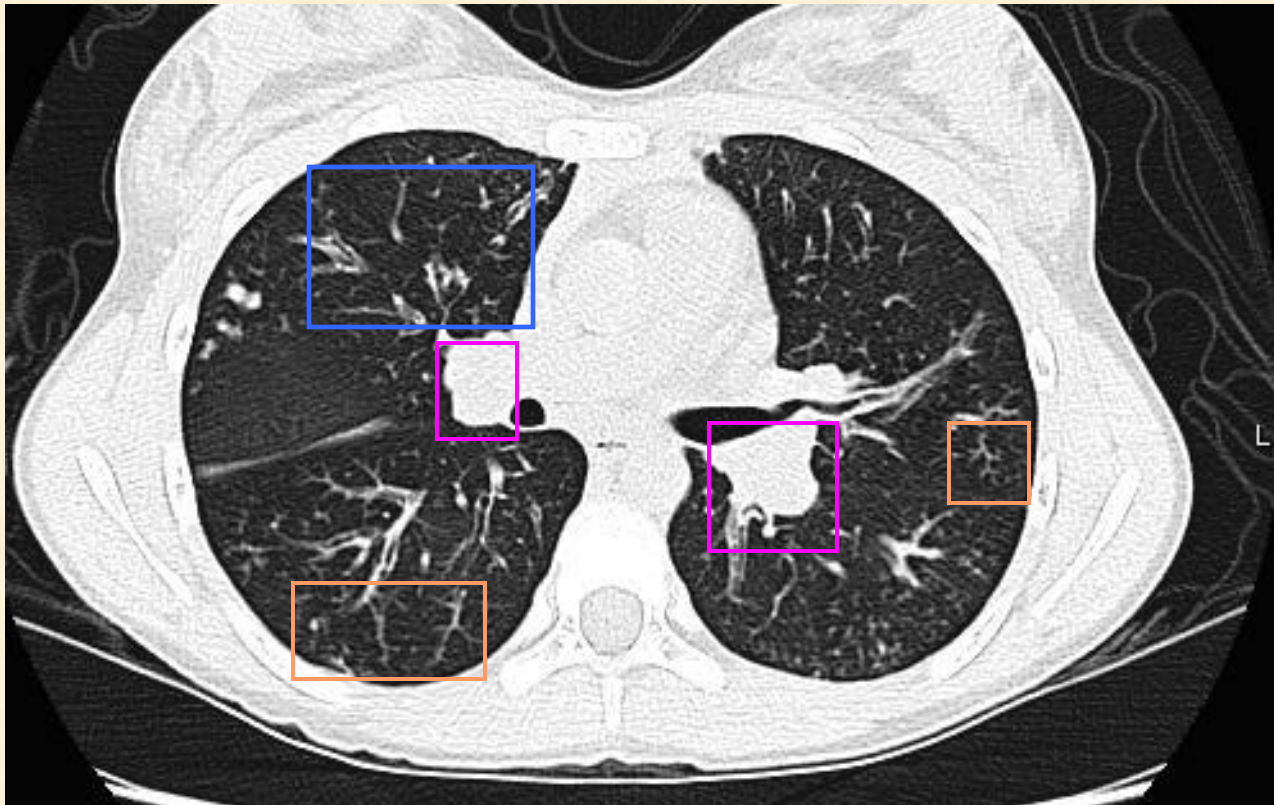


Index Patient: Bronchiectasis and Mucus Plugging on Chest CT

bronchiectasis:
dilated airway
surrounded by
thickened walls

Mucus
plugging

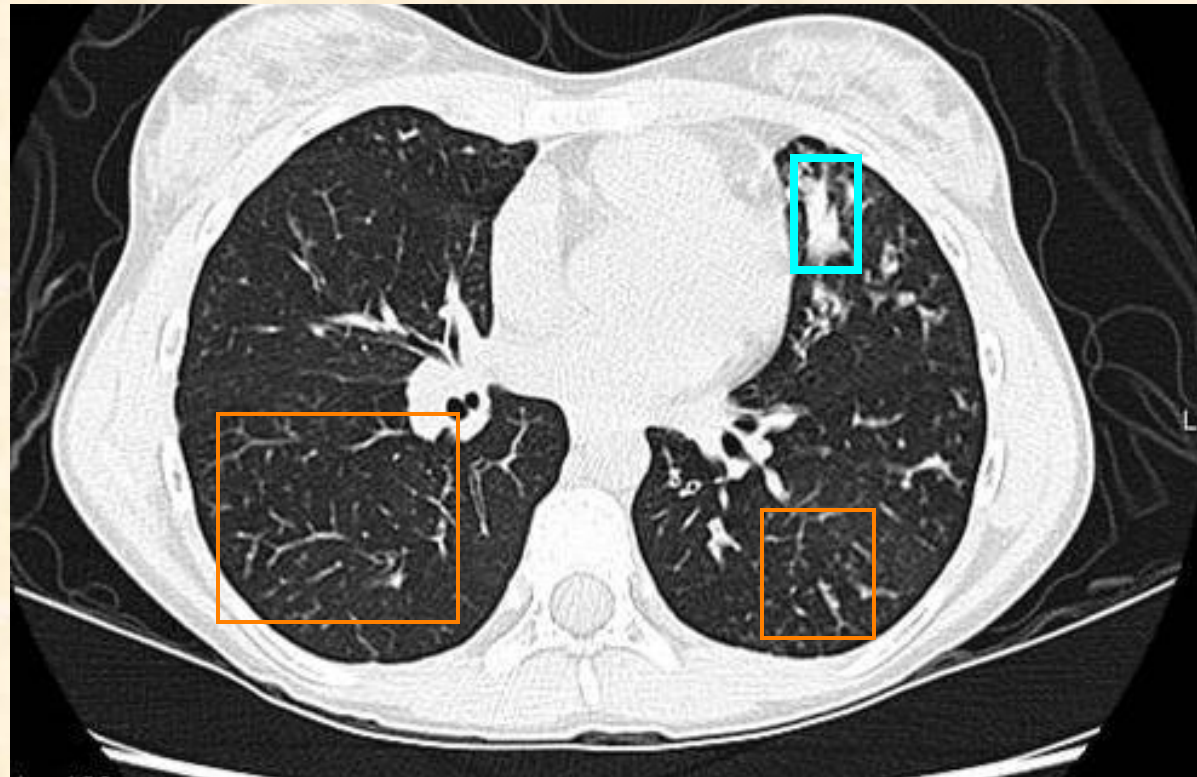
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CT Chest with contrast



Although our patient is known to have ABPA, again it is important to consider other diagnoses in patients who present similarly.



Differential Diagnosis

The differential diagnosis for transitory lung infiltrates associated with peripheral blood eosinophilia:

- Non-ABPA CF exacerbation
- Chronic eosinophilic pneumonia
- Hypereosinophilic syndromes
- Churg-Strauss syndrome
- Autoimmune diseases such as sarcoidosis
- Crack-cocaine abuse



Thus far the effects of CF on the respiratory system have been thoroughly addressed since our index patient's acute presentation was due to pulmonary complications. Note that complications such as these are often the most pervasive etiology of morbidity and mortality in patients in CF.

Now attention will be turned to the various other organ systems that may be impacted by CF; in fact, many of these systems were impacted in our index patient.



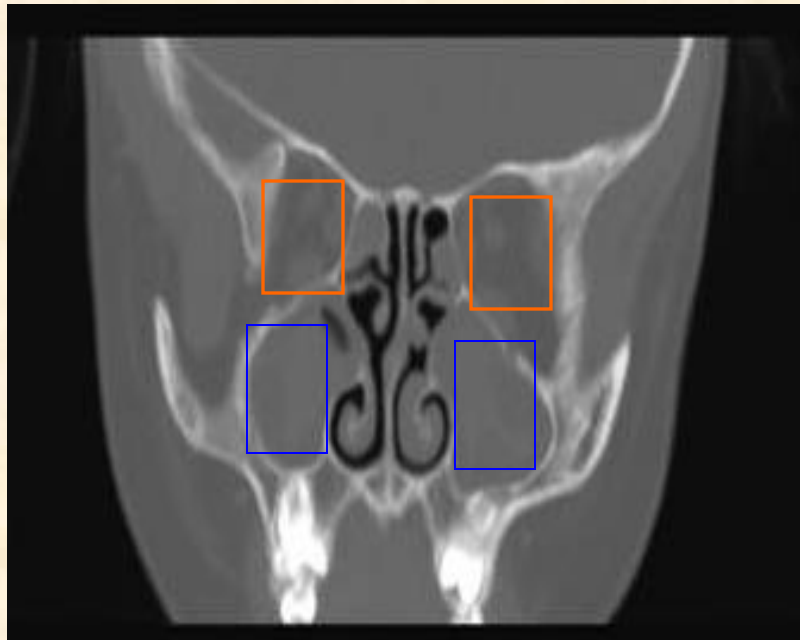
CF: Manifestations in Sinuses

- Chronic sinusitis
- Nasal polyps



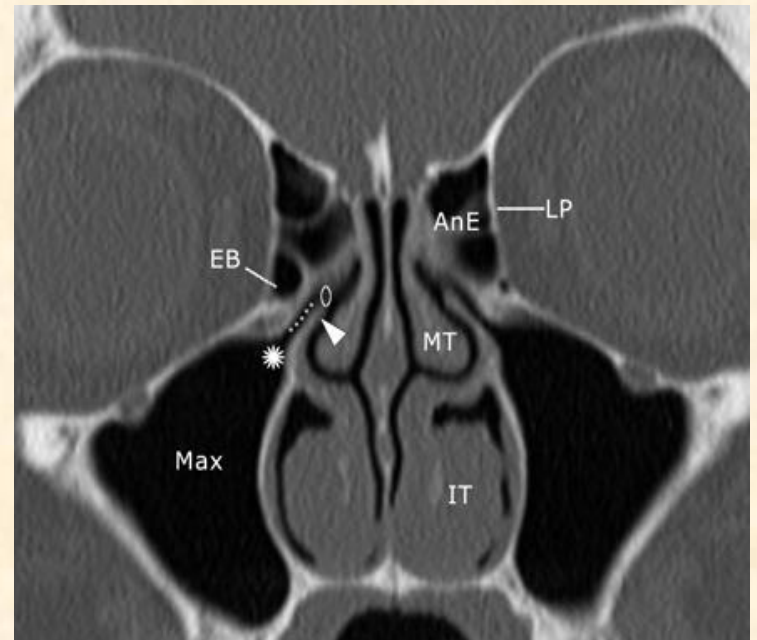
CF: Radiologic Findings in Sinuses

Index Patient



coronal sinus CT
opacified **maxillary** and **ethmoid** sinuses

Companion Patient 1: Normal



coronal sinus CT
normal sinuses

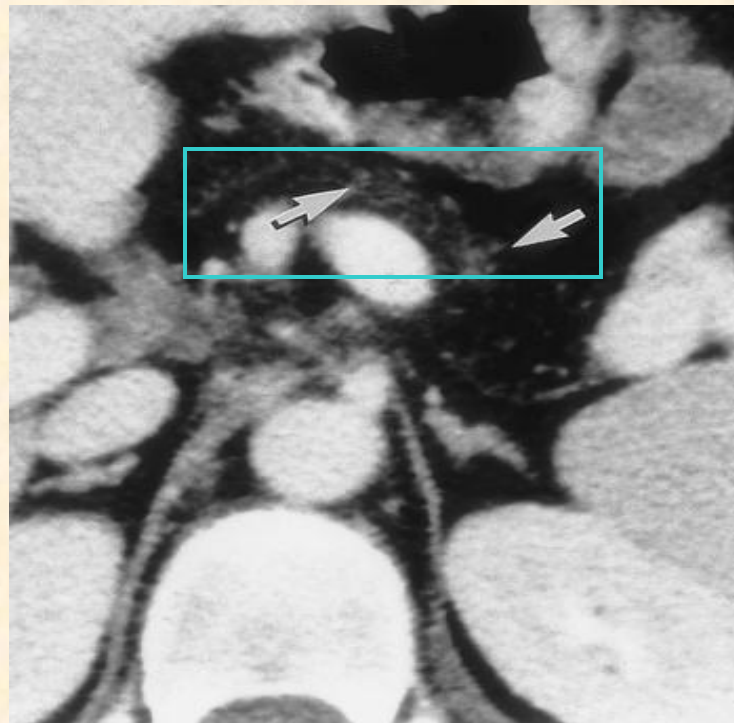


CF: Manifestations in GI Tract

- Pancreatic insufficiency (90%)
- Malabsorption; vitamin deficiencies
- Dysfunction of endocrine pancreas > glucose intolerance, CF-related diabetes
- Meconium ileus (10-20% of newborns with CF)
- Liver disease: periportal fibrosis, cirrhosis, portal HTN, variceal bleeds



Companion Patient #2: Fatty Replacement of the Pancreas on CT



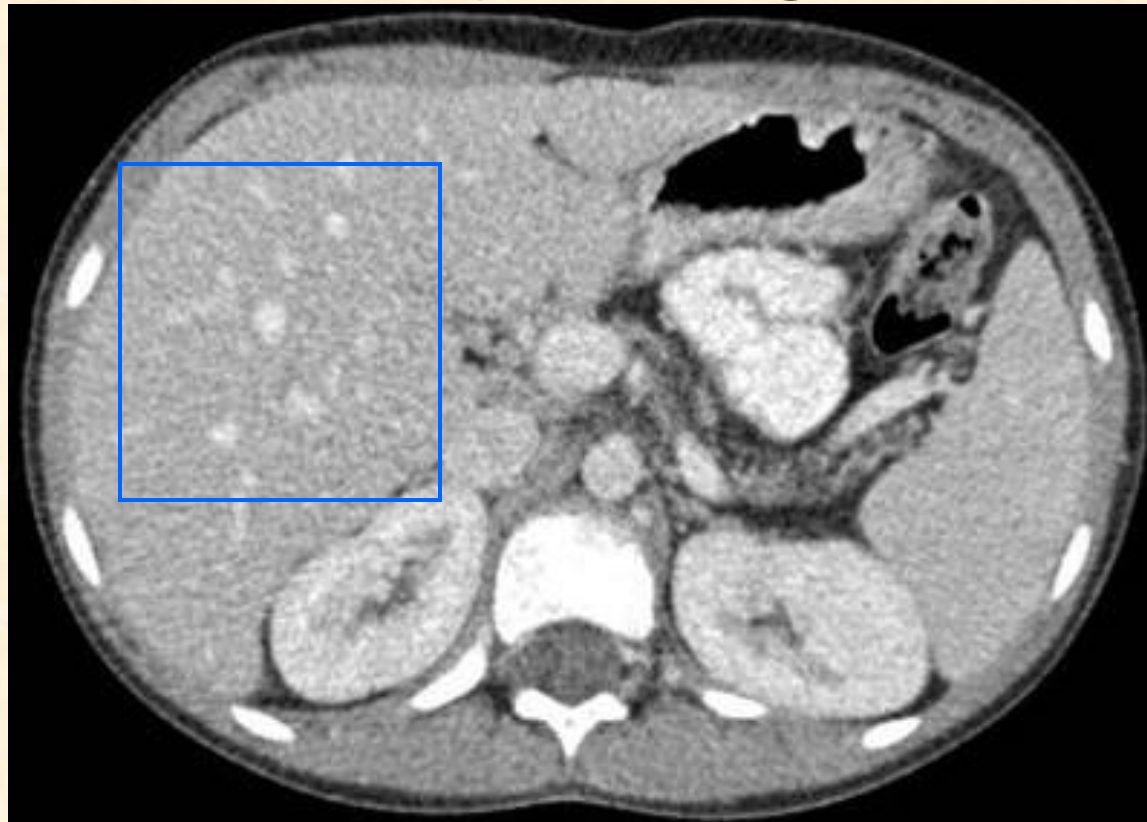
fatty replacement
of the pancreas

CT Abdomen with contrast



Index Patient: Heterogeneous Liver on CT

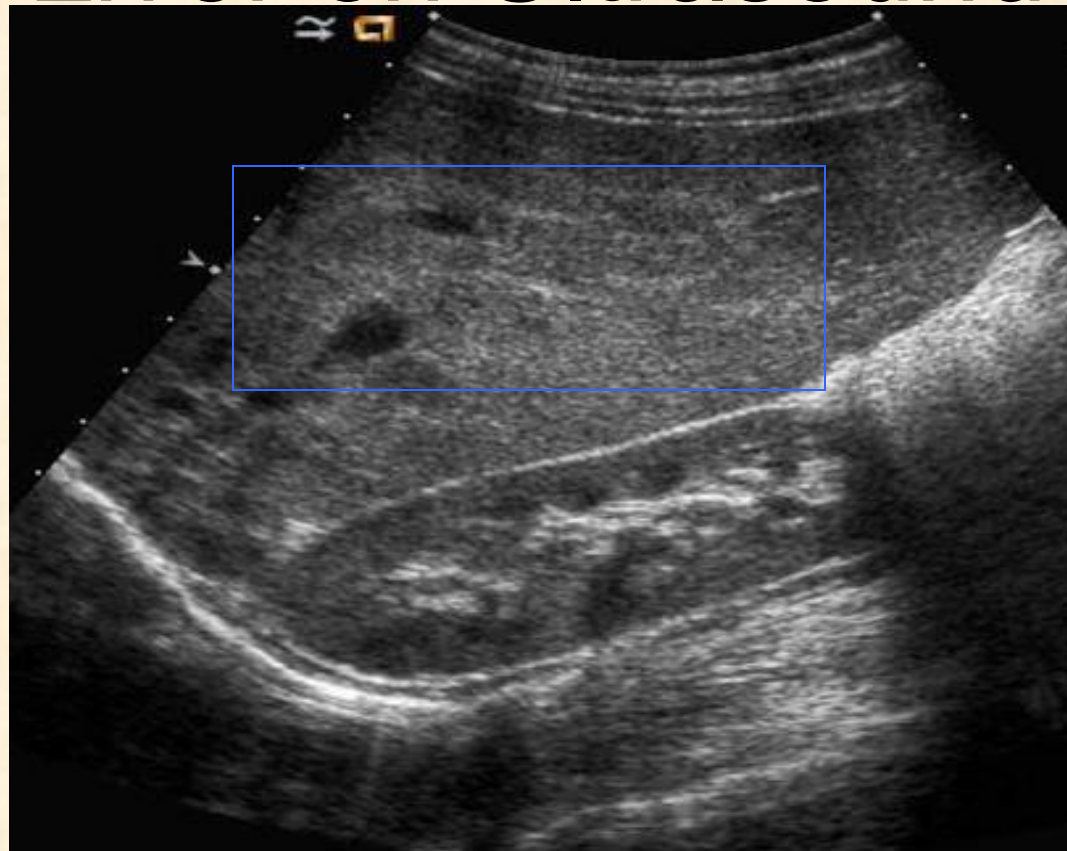
heterogeneous
liver



CT Abdomen with contrast



Index Patient: Heterogeneous Liver on Ultrasound



heterogeneous
liver: note areas
of coarsened
echotexture

Abdominal Ultrasound



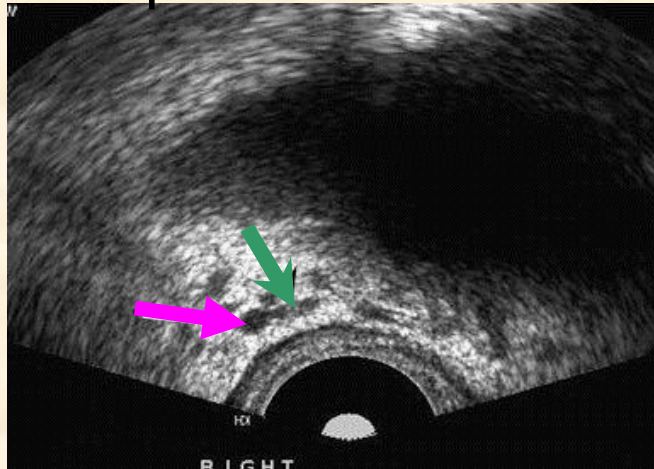
CF: Manifestations in GU Tract

- Male infertility (95% of men with CF)
 - Absent vas deferens
- Female infertility (up to 20% of women with CF)
 - Secondary to amenorrhea caused by malnutrition
 - Abnormal cervical mucus



Companion Patient #3: Congenital Absence of Bilateral Vas Deferens on Transrectal Ultrasound

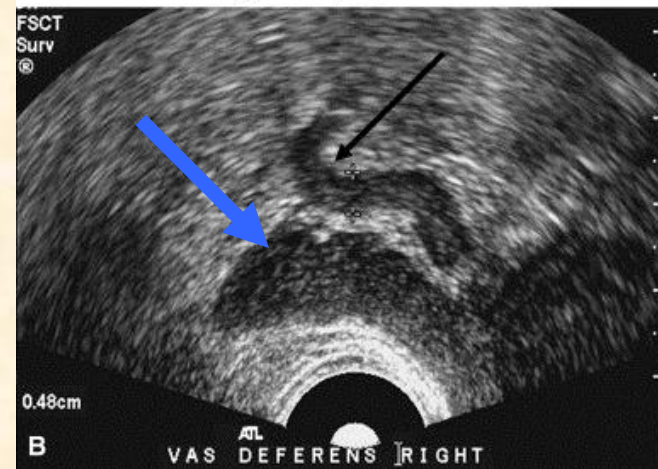
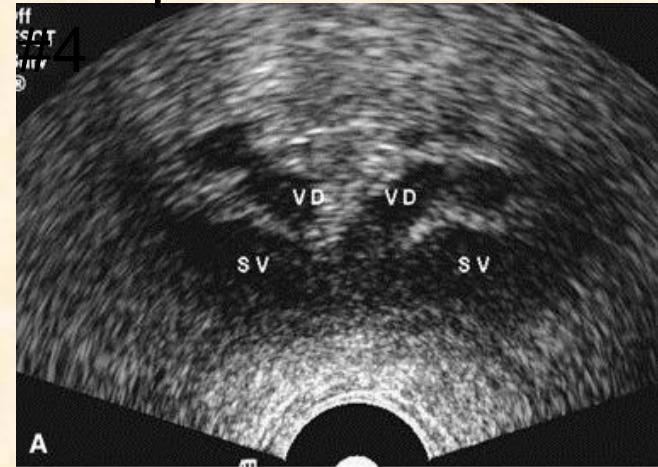
Companion Patient #3



Transrectal Ultrasound

Atrophied **Seminal Vesicles** and **Vas Deferens** in a patient with congenital absence of bilateral VDs

Companion Patient



Normal **Seminal Vesicles** and **Vas Deferens**

Transrectal Ultrasound



CF: Manifestations in Musculoskeletal System

- Up to 30% of patients with CF have reduced bone mineral content
 - Reduced bone production
 - Accelerated rates of bone loss
- Clubbing of fingers/toes
- Hypertrophic osteoarthropathy (5%)
- Arthropathy (2-9%)
 - Episodes of painful and swollen joints



Now that the multi-system detrimental effects of CF have been explored, symptom management and patient prognosis shall be addressed.



Cystic Fibrosis: Treatment

- Chest Physiotherapy
- Antibiotics
- Bronchodilators
- Glucocorticoids
- Vaccinations
 - Influenza, pneumococcus, palivizumab (RSV)
- Pancreatic enzymes



Cystic Fibrosis: Prognosis

- Life expectancy of ~35 years
- Clinical picture eventually may warrant a lung transplant
 - FEV1 below 30% predicted
 - Rapid decline in FEV1
 - Increasing frequency of exacerbations requiring antibiotic therapy
 - Refractory and/or recurrent pneumothorax
 - Recurrent hemoptysis not controlled by embolization



Lung Transplantation in Cystic Fibrosis

- United Network for Organ Sharing lung allocation score
- Both lungs transplanted (because of possibility of cross-infection from retained original lung)
- Patients with CF who undergo lung transplantation have better survival rates compared with patients who are transplanted for other indications
- Contraindication: colonization with *Burkholderia cenocepacia*



Take-Home Points

- Cystic Fibrosis is a chronic and fatal autosomal recessive hereditary illness that has detrimental effects on multiple organ systems, most notably the respiratory system and those involving exocrine glands such as the GI tract.
- Radiologic findings, such as those on Chest CT, may indicate effects of the chronic illness itself or complicating diagnoses such as ABPA.
- Management is not curative, but prognosis continues to improve over time.



References

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