

Autosomal Recessive Inheritance: Cystic Fibrosis

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289517715040>.

Keywords

pathology competencies, cystic fibrosis, developmental and functional abnormalities, disease mechanisms, genetic mechanisms, inheritance patterns

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Primary Objective

Objective GM1.2: Inheritance Patterns. Compare and contrast the inheritance patterns of different types of Mendelian disorders and give examples of each type of pattern.

Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.

Patient Presentation

A 22-year-old Caucasian male presents with a recurrent cough. He has had frequent respiratory illnesses and abdominal discomfort throughout his life. He has always been on the lower range of normal for height and significantly smaller than his siblings. His current primary care physician found his lung examination to be abnormal (wheezing and crackles) as well as an absence of the vas deferens on genitourinary examination.

Diagnostic Findings, Part I

What is Your Differential Diagnosis Based on the Clinical History?

The patient presents with signs and symptoms that are classical for cystic fibrosis (CF). Some similar findings (short stature

and chronic lung infections) may be seen in other disease states, such as primary ciliary dyskinesia (Kartagener syndrome) as well as asthma and should be excluded in this patient. In CF, progressive scarring ultimately leads to atrophy of the vasa deferentia.

Questions/Discussion Points, Part I

What Testing is Available for this Patient and Which is Recommended?

Cystic fibrosis results from loss of function of the CF transmembrane conductance regulator (CFTR) protein caused by mutations in the *CFTR* gene. The classic diagnostic test for CF is the measurement of sweat chloride levels. This would be the recommended test for a patient suspected of being affected with CF.

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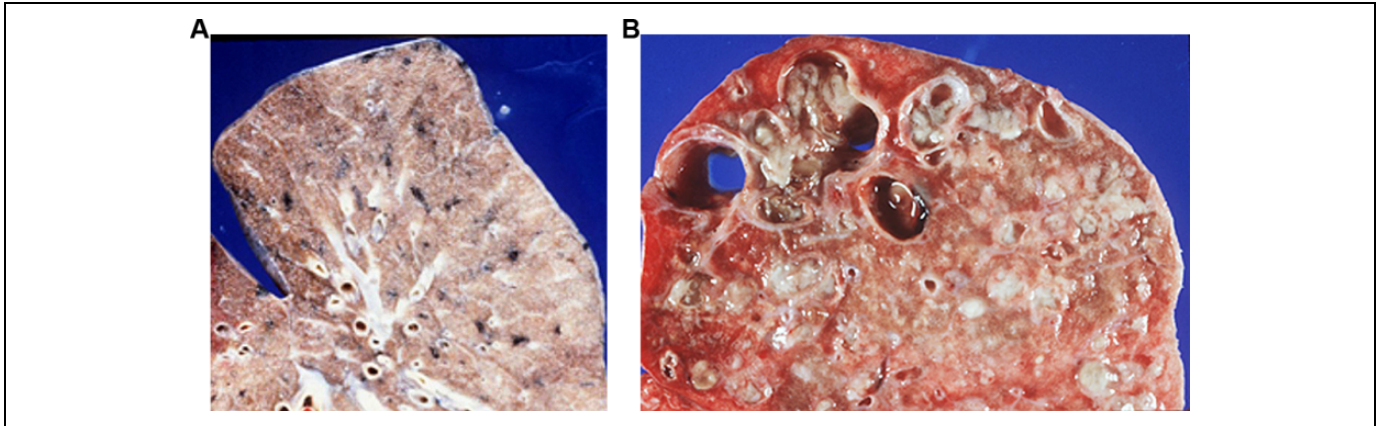


Figure 1. Autopsy findings. A, Normal lung. B, Lung affected by cystic fibrosis.

Biochemical screening tests for newborns typically measure plasma levels of immunoreactive trypsinogen (a proenzyme that builds up in the blood due to disease-related pancreatic duct dysfunction). These tests are advantageous for screening neonates as they demonstrate high sensitivity, can be run on dried blood spots, and proenzyme levels are altered regardless of the specific etiologic genetic alteration.

Genetic screening tests are useful for expectant parents to determine the “carrier status” of each parent and to assess the risk that a child born to them might be affected by CF. Since many genetic tests only evaluate a subset of all possible pathogenic mutations, patients must be counseled regarding the small residual possibility of having an affected child.³

Explain the Inheritance of CF and Show How It is Possible for an Individual to Inherit a Mutation in Each CFTR Allele and Present With No Disease, Mild Disease, or Severe CF

Cystic fibrosis is the most common, lethal, inherited disease in white populations. Approximately 1 in 2500 newborns in the United States is born with the disease.¹ It typically displays autosomal recessive inheritance requiring each parent to provide a pathogenic allele to their child for the disease to manifest. A single genetic mutation is responsible for 70% of cases and consists of a 3-base pair deletion leading to a loss of phenylalanine at codon 508 ($\Delta F508$ or $\text{del}508$). The $\Delta F508$ mutation displays classical Mendelian inheritance, whereby 2 carrier parents (each heterozygous for $\Delta F508$) would have an expected risk of having an affected child of 25% for each pregnancy (25% risk unaffected and 50% risk of carrier offspring). Not all parents will carry identical mutations and a child may therefore inherit different mutations from each parent, with differing impacts on the CFTR protein. This is one reason a spectrum of disease phenotypes may be observed. Additionally, some mutations may only demonstrate a partial effect, which may only create a CF phenotype when identified in concert with other specific mutations (R117 and poly[d]). This complexity and the current identification of over 1800 described mutations

in the *CFTR* gene produce wide variability in the effect that a given mutation will have on protein function and ultimately on the clinical phenotype.

Explain the Normal Physiologic Function of the CFTR Protein and Which Tissues are Affected by the Loss of CFTR Function

The CFTR protein is an ion channel protein regulating chloride concentrations across epithelial surfaces. In a healthy individual, negatively charged Cl^- ions are passively transported through the membrane via the CFTR. Water can then passively diffuse through the membrane to areas of high solute concentration producing typical mucus. The absence of a functional CFTR protein, either by a mutation that fails to transport it to the membrane or a mutation within a membrane-bound protein itself, leads to the inability of chloride to move outward and chloride becomes sequestered within the cell along with high concentrations of sodium. Since the movement of water passively follows solute concentration, secreted mucus in affected patients becomes viscous and tenacious leading to complications of transport.²

The CFTR also exists within the eccrine sweat glands of the skin to balance the reabsorption of sodium and chloride (salt) from initially excreted fluid. In the absence of a functional CFTR, the reabsorption of sodium chloride is ineffective and the amount of Na^+ and Cl^- in the excreted sweat remains high. The CFTR channel exists in many other tissues as well; however, the effects on the lungs and digestive tract become most clinically apparent in an affected patient.¹

Describe the Pathophysiologic Process that Occurs in the Lungs of Patients with Severe CF that Leads to Bronchiectasis and Chronic Pneumonia Including a Description of the Histopathology as the Disease Progresses

The more viscous secretions produced by failure of water to thin the mucus covering the lung epithelium inhibits

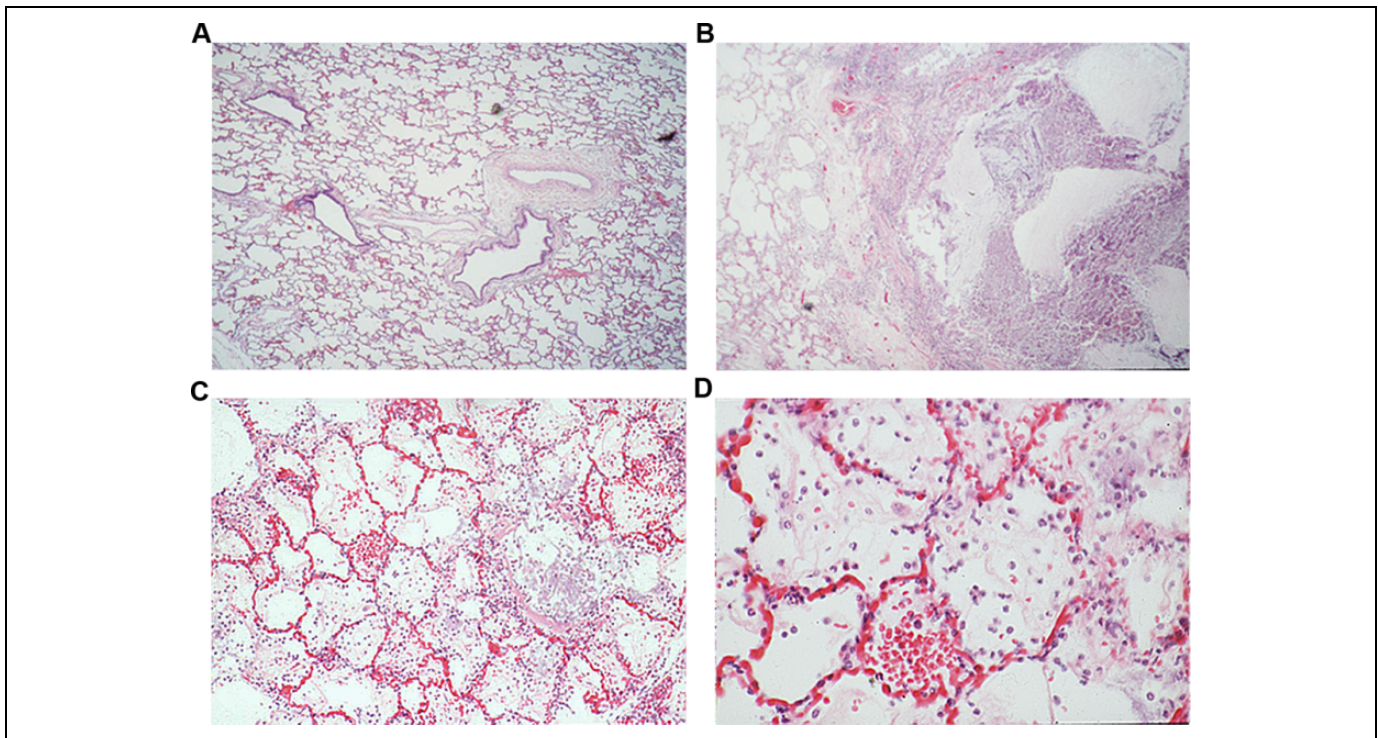


Figure 2. Histopathology. A, Normal Lung with patent airspaces. B, Extensive mucopurulent secretions in dilated airway. C, Alveolar lung parenchyma with mucus and acute and chronic inflammation. D, Higher power view of C demonstrating the mixed inflammatory infiltrate associated with cystic fibrosis.

mucociliary clearance and causes mucus plugging of the airways. This in effect seals off the terminal airspaces. Inhaled bacteria cannot be cleared effectively and chronic infections are the result. The body's attempts to contain these infections lead to an exuberant inflammatory response, progressive fibrosis, dilatation, and ultimately destruction of the airways.

Case continued—During the next year, the patient develops a severe pneumonia and is hospitalized. Respiratory cultures grew out *Pseudomonas aeruginosa* and the patient's oxygenation continued to decline. Antibiotics could not clear the patient's infection, and he was placed on ventilator support but ultimately progressed and died.

Diagnostic Findings, Part 2

Compare and Contrast the Gross Pathology in Figure 1A and B

- A. Normal Lung: Note the spongy appearance of the cut surface and gradual tapering of airways toward the periphery of the tissue. The surface has a “dry” appearance as it is actually made up of numerous tiny alveoli.
- B. Lung affected by CF: Bronchiectasis (airway space enlargement with associated wall thickening) with bronchi filled with excessive mucopurulent

secretions is seen. The secretions give a more “glossy” appearance to the cut surface. Note also the peripheral coalescence of airspaces with mucoid containing cyst-like spaces. These become continually infected and fibrotic over the course of the disease, hence, the given name of the disease, “cystic fibrosis”.

Compare and Contrast the Histopathology in Figure 2A-D

Panel A demonstrates a low power view of a slide from a healthy individual. The majority of airspaces are intact and lined by thin walled alveoli. The bronchioles present are patent and are typically composed of a low columnar to cuboidal epithelium. Panel B demonstrates a similar power view from an individual affected by cystic fibrosis with abundant mucopurulent material within an expanded airway. Panels C and D show higher power views of the mixed inflammatory infiltrate which is seen within the individual alveoli in patients affected with cystic fibrosis.

Questions/Discussion Points, Part 2

What Therapies May Minimize the Symptoms of CF?

There are a variety of biomechanical techniques that are aimed at clearing the thickened mucus from the airways and often involve some forms of percussion or vibration. Several

categories of medications are also available to aid in fighting infections, thinning mucus, and in some cases (given specific causative mutations) potentiating the CFTR channel to allow for increased chloride transport.

What are Some Possible Therapies that have a More Definitive Impact on the Disease?

The severe damage caused by the course of the disease leaves few medical options for improved pulmonary function; however, for some patients, lung transplantation can provide a much more definitive impact on lung function as well as the overall survival. Most importantly, however, lung transplantation is not a “cure” as it only alleviates the pulmonary symptoms of the patient. The other organs affected by the disease are not modulated by a transplant.

Recent investigations involving large-scale mathematical and chemical libraries have identified several possible drug molecules that target precise causes of the disease created by individual mutations. Given the diverse impacts the various CF mutations can have on protein production, processing, and regulation, it is not surprising that different drugs are necessary to provide differing corrective effects. Some drugs work by increasing shuttling of the CFTR to the membrane, while others act to improve chloride transport through the CFTR and even others attempt to overcome nonsense mutations by allowing the ribosome to “read through” premature stop codons during translation.⁴

Given that the disease is inherited in a patient’s DNA and many of the causative genetic mutations have been elucidated,

there is a possibility that in the future, site-directed gene editing may hold promise for a broader therapy unique to the patient’s own disease and impacting and improving all affected organ systems.

Teaching Points

- Cystic fibrosis is the most common inherited autosomal recessive disease in the Caucasian population.
- The disease affects multiple organ systems and can have a wide variety of clinical presentations.
- Genetic mutations of the CFTR gene lead to an ineffective chloride transporter that explains many of the clinical symptoms.
- There is hope that modern technological advancements could lead to not only symptomatic control but also possibly even cures for the disease in the future.

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