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Cystic Fibrosis - An Ever Evolving Challenge

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Cystic Fibrosis - An Ever Evolving Challenge

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Abstract

Cystic fibrosis (CF) is a genetic disease that results from mutations in a large single gene located on chromosome 7. More than 2000 different mutations in the gene have been identified to have caused the disease. Most of these mutations are exceedingly rare and therefore not a part of CF screening or all testing panels. This case discusses an adult female with a history of asthma, bronchiectasis, pseudomonas colonization, and respiratory failure on chronic oxygen who presented to the ED with sudden onset shortness of breath, fever, chills, body aches, nonproductive cough, and headache. The patient's condition clinically improved with treatment and was discharged on day three. The patient had previously undergone a laboratory evaluation of bronchiectasis. Due to the patient's history of bronchiectasis and pseudomonas colonization, there was a decision to reconsider the possibility of CF. The patient underwent a routine cystic fibrosis genetic testing panel which subsequently confirmed a CFTR mutation. The discussion highlights the importance of remaining vigilant for signs of CF, to remain open to the possibility of CF or CFTR related disorders, when patients have had evaluations for such that predate current testing standards or capabilities.

Keywords

Cystic Fibrosis, CFTR mutations, Sweat Chloride Test, CFTR-Related Disorders

Conflict of Interest Statement

The authors have no conflicts of interest to declare

CASE REPORT

Cystic Fibrosis - An Ever Evolving Challenge

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Abstract

Cystic fibrosis (CF) is a genetic disease that results from mutations in a large single gene located on chromosome 7. More than 2000 different mutations in the gene have been identified to have caused the disease. Most of these mutations are exceedingly rare and therefore not a part of CF screening or all testing panels. This case discusses an adult female with a history of asthma, bronchiectasis, pseudomonas colonization, and respiratory failure on chronic oxygen who presented to the ED with sudden onset shortness of breath, fever, chills, body aches, nonproductive cough, and headache. The patient's condition clinically improved with treatment and was discharged on day three. The patient had previously undergone a laboratory evaluation of bronchiectasis. Due to the patient's history of bronchiectasis and pseudomonas colonization, there was a decision to reconsider the possibility of CF. The patient underwent a routine cystic fibrosis genetic testing panel which subsequently confirmed a CFTR mutation. The discussion highlights the importance of remaining vigilant for signs of CF, to remain open to the possibility of CF or CFTR related disorders, when patients have had evaluations for such that predate current testing standards or capabilities.

Keywords: Cystic fibrosis, CFTR mutations, Sweat chloride test, CFTR-Related disorders

1. Introduction

Cystic fibrosis is a genetic disease that results from the presence of pathogenic mutations in a single large gene located on chromosome 7. This gene encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein, and the expression and severity of the disease can vary depending on the specific mutations present.[1] Over 2000 different mutations in the CFTR gene have been identified as having the potential to cause the disease, with the most common being the F508del mutation, which involves the deletion of three DNA bases that code for the amino acid phenylalanine at position 508.[2] Due to the rarity of most individual mutations, a subset of the most frequent CFTR mutations is typically used for initial screening.[3]

2. Case presentation

We present a case of a 32-year-old female patient with a history of asthma, bronchiectasis, pseudomonas colonization and respiratory failure on chronic oxygen. The patient presented to our ED with sudden onset shortness of breath, fever, chills, body aches, nonproductive cough, and headache. On examination, the patient was in respiratory distress and auscultation revealed rales in right lower lobe along with wheezes throughout the lungs. Vitals included a blood pressure of 145/68 mmHg, 140 bpm pulse, temperature of 101.7 °F, and respiratory rate of 18 breaths per minute. The patient did not have any sick contacts recently and was reportedly compliant with medications. The patient was admitted to the inpatient department for further management and specialist care. Laboratory workup showed a

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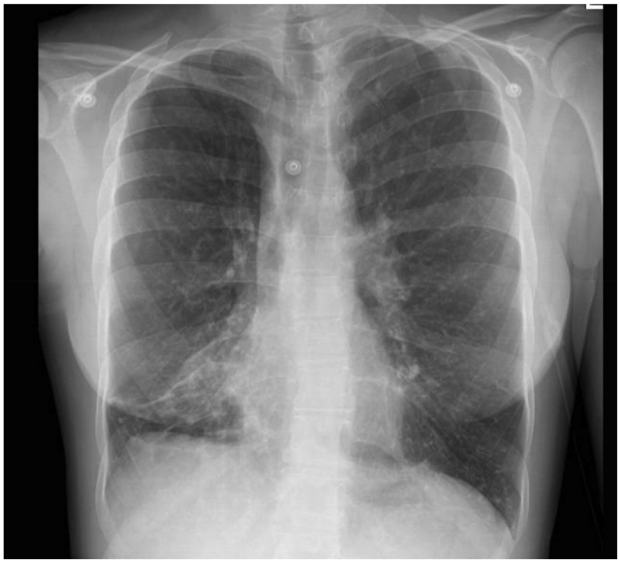

Fig. 1. Chest X-ray showing chronic right middle lobe cystic bronchiectasis and consolidation. Chronic bilateral reticulonodular opacities.

WBC count of 17,400 with 95% neutrophils. COVID, influenza and RSV were negative. Blood and respiratory cultures were sent. Troponin, creatinine, and lactic acid levels were normal. CXR showed chronic changes with no acute findings (Fig. 1).

The patient was started on intravenous Zosyn and also received a dose of intravenous methylprednisolone in the ED. Pulmonology was consulted and a five-day course of Prednisolone, chest physiotherapy, and a seven-day course of antibiotics was started. The patient responded well to the treatment.

Patient had prior evaluation for etiology of bronchiectasis, including (alpha-1 antitrypsin levels and immunoglobulins), which were unremarkable. She also had pulmonary function testing done, which showed an FRV 1/FVC of 61% and FEV1 of 25%. The CT scan of the chest with intravenous contrast was done previously, not in current admission, which showed extensive lower and right middle lobe bronchiectasis with air-fluid levels concerning infection in the clinical setting (Fig. 2). It also showed multiple tree-in-bud opacities with a lower lobe predominance, consistent with an infectious or inflammatory ideology.

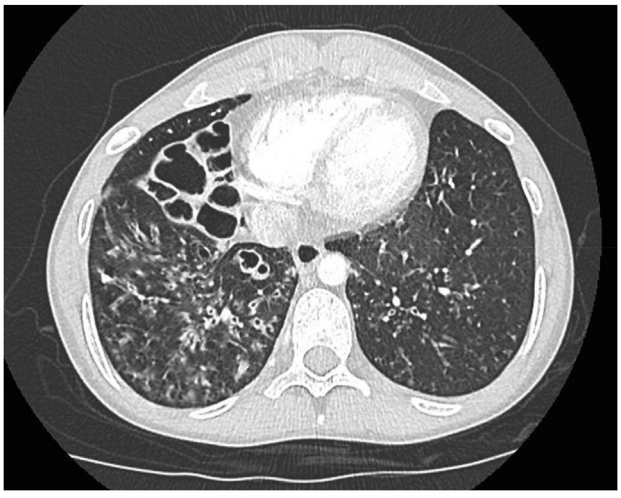

Fig. 2. Atelectasis and extensive cystic lower lobe predominant bronchiectasis with tree-in-bud nodularity. There are air-fluid levels within several dilated bronchi.

With bronchiectasis and multidrug-resistant pseudomonas colonization, and considering patient's age -group, cystic fibrosis was on the differential diagnosis. The patient's previous cystic fibrosis workup was negative, done 10 years ago in her home country (Venezuela), and hence a new cystic fibrosis panel was ordered by the Pulmonology team. The patient was discharged on day three after negative blood cultures, and sputum cultures growing Pseudomonas, which was chronic for her. The patient was counselled regarding genetic testing for cystic fibrosis and pulmonology follow-up.

The patient was ultimately found to be positive for one copy of a genetic mutation known to be responsible for CF and had an appropriate follow-up outpatient with the Pulmonology team.

3. Discussion

A CFTR-Related Disorders may be defined as "a clinical entity associated with CFTR dysfunction that does not fulfil diagnostic criteria for CF. Three main clinical entities illustrate these phenotypes: CBAVD (congenital bilateral absence of the vas deferens) with CFTR dysfunction, acute recurrent or chronic pancreatitis with CFTR dysfunction and disseminated bronchiectasis with CFTR dysfunction.[4]

Newborn screening for cystic fibrosis (CF) is now in place in all 50 US states and the District of Columbia, as well as many other countries around the world. While CF screening at birth is effective in identifying most cases of the disease, there are still factors within the screening process that can result in a missed diagnosis of CF. As such, healthcare providers should remain vigilant for signs of CF in patients with symptoms that are consistent with the disease, regardless of the newborn screening results. Identifying areas for quality improvement in specimen collection, laboratory analysis of immunoreactive trypsinogen (IRT), and CF mutation testing, communication, and sweat testing can help to address these factors that contribute to missed diagnoses in newborn screening programs for CF.

A study done by Henry et al. found four cases of negative cystic fibrosis workup in children.

Unfortunately, three of the children who were missed by the screening process experienced significant delays in their CF diagnosis. In all three cases, the clinical suspicion of CF was present, but a sweat test was delayed due to false reassurance from the normal CF screening results. In a fourth case, despite obtaining multiple elevated sweat electrolyte levels, the diagnosis of CF was not immediately made due to doubts arising from the normal IRT assay results. Therefore, it is essential to perform a sweat test on any child who is clinically suspected to have CF, regardless of the initial screening results.[5]

Another similar study done by Conde et al. found seven cases of false negative cystic fibrosis and hence suggested keeping a high clinical suspicion for the disease despite negative testing.[6]

Another study reported a case of a 65-year-old woman with a history of chronic cough and recurrent respiratory tract infections. Her sweat test was negative, but the genetic testing disclosed the presence of ΔF508 and R117H CF mutations.[7]

Similarly, another case report highlighted the challenges in the diagnosis of atypical CF, after a 57-year-old female was diagnosed with CF. The patient had a history of chronic bronchiectasis, recurrent Pseudomonas chest infection, latent TB and positive family history of CF, CF genetic testing revealed two separate mutations: a deletion in deltaF508 and Nt 3599 + 1 change from G → A[8].

Several other case studies have also come to a similar conclusion, that a clinician should keep in mind the possibility of the spectrum of CFTR-RD in suspected cases.[9,10]

This highlights the constant challenges faced by the Cystic Fibrosis Foundation, with consensus guidelines continuously being modified to clarify the diagnostic criteria and terminology, to address the diagnostic challenges that result from an evolving understanding of the CF genetics.[11]

In our case study, the patient had an extensive history of chest symptoms, coupled with extensive bronchiectasis and airway disease, resulting in the medical team revisiting the possibility of CF or a related disorder. The diagnosis of CF and CFTR related disorders have evolved, and a good clinician should be aware that there are patients with serious lung disease that share phenotypic presentations with CF, and those that have CFTR mutations, but do not meet the full genetic or functional definitions as CF disease causing mutations.

Over the last decade, new genes have been discovered that contribute to the development of cystic fibrosis. However, it is not common practice to test for all these genes, and currently only the most common CFTR mutations are being tested for worldwide. Clinicians should be aware that if a patient has a presentation typical of a CF patient, despite prior negative evaluation for CF, which can be genetic testing, or sweat testing, or nasal potential difference testing. It should be kept in mind that that there have been new developments in the recognition of CFTR mutations. The unusual CFTR mutations screening which are not performed routinely or as part of most screening panels, may result in real clinical disease (despite not meeting full genetic or functional criteria for CF). These cases are considered to represent a CFTR-related disorder (a definition which has replaced atypical CF or nonclassical CF) and can result in a spectrum of clinical phenotypes.

CF phenotype is a continuum of symptoms and organ involvement; disease expression depends on the severity of CFTR mutations genetic modifiers, lifestyle, and environmental factors. The relationship between these factors remains an enigma but suffice it to say that it is an area that has evolved and will likely continue to do so.

Conflict of interest

The authors have no conflicts of interest to declare.

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