Case Report

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Decades of cough: delayed recognition of atypical cystic fibrosis in an adult patient

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Lesson

We present a case of a 30-year-old male diagnosed with atypical cystic fibrosis. This report demonstrates the heterogeneity of the presentation of this common genetic disease.

Keywords

clinical, cystic fibrosis, diagnostics, general practice/family medicine, radiology and imaging, respiratory medicine

Case presentation

A 30-year-old Caucasian male active duty service member in the United States Army with a history of recurrent sinusitis and multiple childhood pneumonias presented to the pulmonary sub-specialty clinic with a chief complaint of chronic cough since childhood. The patient reported the cough to be productive of yellow-green sputum and worse in the morning. He denied shortness of breath, chest pain, gastrointestinal symptoms or post-nasal drip. His only medication was albuterol which he utilised on average once every 48 h. The patient denied any functional limitations and he noted he was able to perform and pass his biennial military mandated physical fitness assessment, including a two-mile run, without difficulty. The patient had never smoked and denied recreational drug use. There were no significant occupational exposures in his history. He has no family history of cystic fibrosis (CF) or other pulmonary disease. He has a sister who is alive and well with one non-biologic child. The patient was previously married and divorced and he did not have children of his own. Vital signs were normal and his body mass index was 25.8 kg/m^2. His clinical exam was unremarkable with no evidence of sinus disease and clear lung sounds amidst frequent coughing.

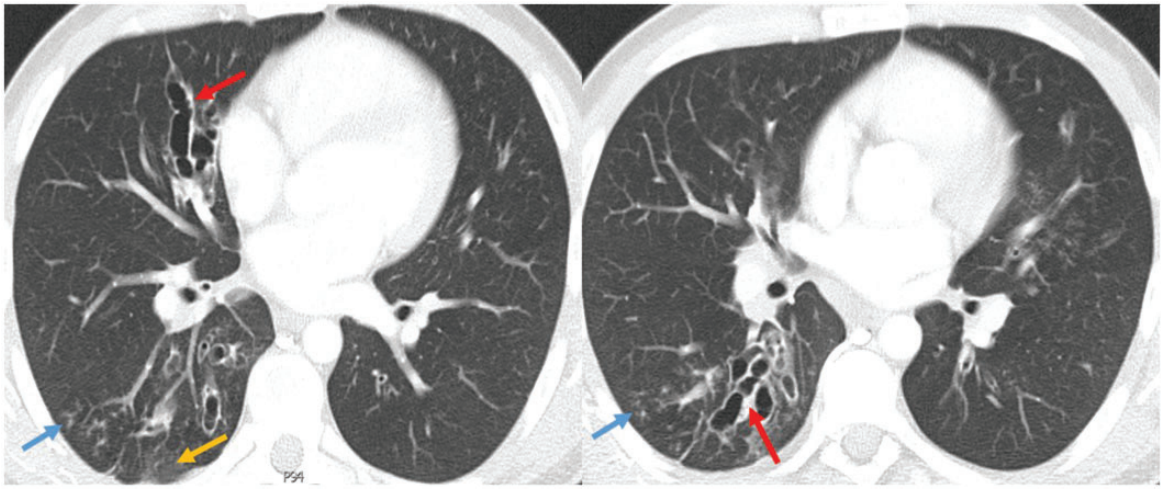
Over a period of decades, the patient had been evaluated by multiple providers and had been empirically treated for conditions including seasonal allergies, upper airway cough syndrome, reactive airway disease and gastroesophageal reflux without any significant improvement of his cough. He described occasionally disjointed care that often resulted in trials of similar medications with limited effect. The patient noted frustration with his medical care to date and described periods of time where he was lost to follow-up related to his frustration.

Additionally, he had been diagnosed and treated for bacterial pneumonia four times in the past. Of the four episodes, the most severe occurred when he was a teenager. During this illness, he underwent bronchoscopy with bronchoalveolar lavage. Bronchoalveolar lavage culture grew *Staphylococcus aureus*. During a subsequent case of pneumonia seven years prior to the current presentation, he had reported haemoptysis. This presentation prompted a chest CT which demonstrated bilateral varicose bronchiectasis (Figure 1). The patient completed a course of antibiotics for community-acquired pneumonia at that time with overall improvement and resolution of his haemoptysis. However, no additional evaluation for his chronic cough and bronchiectasis was pursued.

Differential diagnosis

The list of differential diagnoses for chronic cough is broad, but the focus can be significantly narrowed in this case by the presence of bronchiectasis. Bronchiectasis is characterised by the permanent dilatation of medium-sized bronchi that occurs in the setting of recurrent infection and inflammation.[1] Recurrent pulmonary infections and their associated inflammation typically occur due to dysregulation of the immune system. Immune dysregulation from hypo-immunity can result from either defective native clearance such as in primary ciliary dyskinesia or defective adaptive immunity as seen in immunodeficiency syndromes. Immune dysregulation from hyper-immunity results from autoimmune diseases.[2] The recurrent pulmonary infections that patients experience initiates the well-described 'vicious cycle

Figure 1. Chest CT from seven years prior to current presentation. Imaging demonstrated varicose bronchiectasis with peribronchial thickening (red arrows), regions of ground glass (yellow arrow) and tree-and-bud opacities (blue arrows). These findings were present bilaterally but are best represented in the right lung.



hypothesis' of bronchiectasis.[3] Frequent pulmonary infections damage the airways through persistent inflammation, leading to airway dilatation. The abnormal distortion of the airways allows mucus stasis to develop and places the patient at further risk for chronic infections and subsequent damage to the airways.[2]

Bronchiectasis is categorised as CF bronchiectasis or non-CF bronchiectasis. Non-CF bronchiectasis can be secondary to remodelling from severe infection; immunodeficiency; cilia abnormalities such as in primary ciliary dyskinesia; autoimmune diseases such as rheumatoid arthritis, Sjögren's syndrome, inflammatory bowel disease or connective tissue diseases; allergic bronchopulmonary aspergillosis; HIV; Alpha-1 antitrypsin deficiency and airway obstructions from tumours, foreign bodies or lymphadenopathy.[1]

Investigations

Pulmonary function testing was performed which revealed mild obstruction without a significant response to inhaled bronchodilators and a subsequent negative methacholine challenge test. A repeat chest CT at the time of his presentation to sub-specialty clinic revealed interval worsening of his bilateral varicose bronchiectasis. His complete blood count revealed a mild leukocytosis of 11,500/mcL with a neutrophil predominance and 3.2% eosinophils. His haemoglobin, platelet count, serum electrolytes, liver-function tests and inflammatory markers were normal. Antinuclear antibody testing was negative and total immunoglobulins were also within normal limits. *Aspergillus* species antibody was non-reactive and bacterial and mycobacterial sputum cultures were significant for growth of methicillin-resistant *S. aureus*.

The patient subsequently underwent sweat chloride testing which was positive. His initial chloride level was 68.5 mmol/L (normal range 0–30 mmol/L) and repeat level was 66.0 mmol/L. A cystic fibrosis transmembrane conductance regulator (CFTR) genetic analysis was performed at the time of diagnosis. This testing revealed the patient to be a compound heterozygote for the 3849+10Kb C>T and the R117H mutation. Additional testing was performed that demonstrated the R117H mutation occurred in conjunction with the 5T allele (the patient is 5T/7T).

Treatment

Based on the sweat chloride testing and results of genetic testing, a multi-disciplinary CF team convened to discuss a new diagnosis of CF with the patient and to outline a management strategy. The patient was started on standard CF therapy with an emphasis on airway clearance and frequent exercise to maintain pulmonary function. In addition to using his albuterol inhaler twice daily, he was started on nebulised 7% hypertonic saline and nebulised dornase alpha. He was also counselled on the use of oscillating positive expiratory pressure therapy and chest wall oscillatory therapy. Faecal pancreatic elastase testing was performed and was within normal

limits. Pneumococcal vaccination was provided and the patient was educated on common infection control measures. Given the presence of the CFTR residual function mutation 3849+10Kb C>T, the patient was started on combination CFTR modulator therapy with tezacaftor–ivacaftor.

Outcome and follow-up

After starting treatment, the patient continued to follow-up with the CF multi-disciplinary clinic. The patient's presenting cough has resolved with airway clearance therapies. He remains able to exercise and complete his physical fitness requirements without limitations or difficulties. Interestingly, given his minimal functional impairment, the patient will likely be allowed to remain on active military status with efforts to allow him to remain in close proximity to a military treatment facility that has significant cystic fibrosis treatment experience.

Discussion

CF is an autosomal recessive genetic disorder, which is the most common genetic disorder in the Caucasian population and is caused by mutations of the CFTR gene.[4,5] This gene codes for a transmembrane protein responsible for secreting chloride ions to epithelial surfaces of varying tissues throughout the body. It is by this mechanism that the human airway is both protected and functionally unimpeded at the cellular level. The defective chloride transport protein leads to excessive mucus stasis in the airways, which if not cleared, will predispose the airways to infection and inflammation.[4]

CF exhibits significant genetic variation and clinical heterogeneity.[6] The most common genetic factor identified is the mutation F508del, which accounts for about 70% of patients with CF. However, in addition to the F508del mutation, there are nearly 2000 other mutations of the *CFTR* gene. These other 'non-F508del' mutations lead to varying *CFTR* function, which results in variable phenotypic expression and different degrees of clinical severity.[4,6] Interestingly, patients with the same *CFTR* genotype demonstrate clinical heterogeneity which implies that there are other non-CFTR mutations that can contribute to CF.[6] One clinical method devised in order to help simplify the organisation of the substantial genetic and phenotypic variations in CF is categorising CF into either classical or atypical CF. Classical CF is frequently a disease of childhood and represents the more severe form of the disease. This type of CF is usually diagnosed by either newborn screening or by early childhood CF symptoms.[7] Classical CF typically affects more than one organ system; the most common organ systems involved include the respiratory, gastrointestinal, endocrine and genitourinary systems.[4,7] Alternatively, atypical CF is the milder form of the disease.[7] It is often diagnosed in adulthood and tends to involve only the respiratory system; however, up to 10% of patients can be asymptomatic at the time of diagnosis.[7,8] Homozygosity for the F508del mutation accounts for less than 5% of these adult-diagnosed individuals.[8] As in our patient's described history, the isolation of *S. aureus* from the sputum of adult patients with bronchiectasis strongly increases the likelihood of a subsequent diagnosis of atypical cystic fibrosis.[9]

Patients with atypical CF are frequently misdiagnosed or experience significant delay in time to diagnosis. Although most primary care physicians are familiar with the clinical presentation of patients with typical CF, the presentation of atypical CF can be subtle and symptoms may not be thought to be severe enough to warrant further diagnostic considerations. Although atypical CF is not as severe as classical CF, it is not a benign diagnosis and the natural history of the disease can include all of the complications of typical CF and bronchiectasis.[7] As such, if suspected, steps to establish the diagnosis and subsequent treatment should never be delayed.

Based on his history, clinical exam and sweat chloride testing, our patient was diagnosed with atypical CF. His symptoms were consistent with a mild form of CF limited to one organ system. Genetic testing confirmed that he had two non-F508del mutations, which included one residual function CFTR mutation. Unfortunately, similar to other patients with atypical CF and given his subtle symptoms and excellent overall functional status, his diagnosis and treatment with both airway clearance therapies and CFTR modulators were delayed despite a number of clinical clues.

Sixty years ago, CF was primarily a childhood disease with only 6% of patients in the Cystic Fibrosis Foundation Patient Registry (CFFPR) being over the age of 18. Over the last 30 years, there has been a gradual increase in the number of adults with CF, and in 2014 adults represented almost 50% of all patients with CF listed in the CFFPR.[5] Based on this trajectory, adult patients with CF may soon exceed the paediatric population with CF. Advances in CF management undoubtedly have contributed to this increase in total prevalence of disease. Given these treatment advances, primary care familiarity and recognition of atypical signs and symptoms is of ever expanding importance.

In conclusion, in a patient with newly diagnosed bronchiectasis, a complete diagnostic evaluation to

attempt to identify the aetiology of the bronchiectasis should be performed. Atypical CF should be considered in adult patients with bronchiectasis even if they have mild symptoms and lack of other organ system involvement. Sweat chloride testing should be performed in these patients. Other potential diagnostic testing for CF, including nasal potential difference and intestinal current measurements are less commonly utilised and not widely available in the United States outside of research settings. These tools may play a future role in aiding diagnosis at centres with standardised protocols for this testing. If the diagnosis of CF is established, the mainstay of treatment is airway clearance, which includes inhaled therapy, oscillatory therapy and exercise. All patients diagnosed with CF should be screened at the time of diagnosis for pancreatic insufficiency. Pneumonia vaccination is recommended as well. CFTR modulator therapy should be considered and implemented based on genetic analysis. Given that CF is a multi-systemic, life-changing and potentially lethal disease, multidisciplinary care is essential in the care of these patients.[10]

Declarations

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