Extremely delayed diagnosis of cystic fibrosis in an elderly female presenting with IgG subclass deficiency

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BACKGROUND

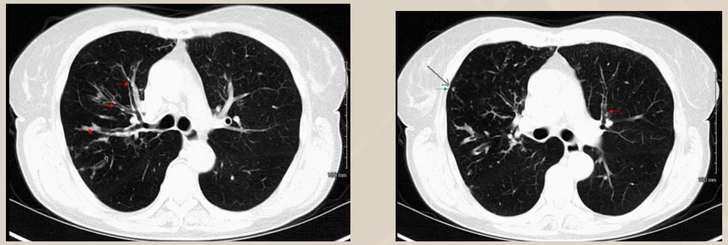
Cystic fibrosis (CF) is a life-limiting genetic disorder caused by mutations in the CFTR gene, leading to defective ion transport and multisystem complications. While CF is typically diagnosed in infancy or early childhood due to severe respiratory and gastrointestinal manifestations, atypical presentations can result in delayed diagnoses.In adults, CF often mimics immunodeficiency, manifesting as recurrent respiratory infections or bronchiectasis. Advances in genetic testing have increased recognition of late-onset or atypical CF cases, with adult diagnosis most commonly occurring by a median age of 38 years (Padoan et al., 2021). Early identification remains crucial to optimize management and improve long-term outcomes, even in non-traditional cases.

CASE

This is a 65 year old female initially referred for evaluation of suspected primary immunodeficiency. Prior to this, she has been extensively followed by various specialists including Pulmonology, Gastroenterology and Infectious disease. Her clinical history was significant for recurrent bronchial and ear infections which started in childhood. Around age 13, she had her first pneumonia and by her mid twenties, she had experienced significant illness associated with weight loss and malabsorption subsequently managed as celiac disease. Further workup revealed positive fecal elastase concerning for exocrine pancreatic insufficiency which improved with enzymatic replacement. She would continue having mild infections during the interim. When she entered her mid fifties, she was diagnosed with Hansen's disease after developing a large plaque on her back, which was treated with dapsone and rifampin. During this period, she also developed complicated pneumonia with parapneumonic effusions and was found to have multiple pulmonary nodules and bronchiectasis on CT imaging (Fig. 1) and subsequently was followed by Pulmonology. She was diagnosed with non-tuberculous mycobacteria (NTM) and initially treated with triple mycobacterial therapy. However due to intolerance and medication side effects, this was later changed to inhaled amikacin. She was then referred to Infectious Disease due to difficulty in treatment of NTM. Upon further infectious workup, her sputum cultures remained persistently positive for *Mycobacterium abscessus* and later on grew *Mycobacterium avium complex* as well. Despite appropriate therapy, she developed colonization with Pseudomonas and was found to have Aspergillus growth on sputum. On top of treatment for NTM and superimposed Pseudomonal infection, she was treated with voriconazole and steroids for suspected Allergic Bronchopulmonary Aspergillosis. Given her multiple atypical infections, an immunodeficiency work-up was pursued which revealed mildly low levels of IgG1 subclass and an inappropriate response to pneumococcal vaccine for which she was referred to an Immunologist. The consideration at that time was IgG subclass deficiency vs. IL-12 receptor defect. However upon further in-depth clinical history, aside from multiple history of sinopulmonary infections, chronic bronchiectasis and pancreatic insufficiency, it was revealed that she has been suspiciously infertile and of Ashkenazi Jew ancestry which raised the suspicion for cystic fibrosis. An initial carrier screening for cystic fibrosis was positive for heterozygous delta F508 pathogenic variant. Further genetic consultation revealed family history of intestinal obstruction and pulmonary fibrosis in her maternal side and an older sibling with pancreatitis increasing the suspicion of cystic fibrosis. Confirmatory CFTR gene testing was positive for two pathogenic variants consistent with an autosomal recessive cystic fibrosis. She was referred to a cystic fibrosis center and a sweat chloride iontophoresis test revealed intermediate results, but at this time she was already started on elexacaftor/tezacaftor/ivacaftor with marked improvement in sputum clearance. Upon continued follow-up, her IgG1 subclass continued to be persistently low but she has remained free of clinically significant infections.

Figure 1

Red arrows showing bilateral bronchiectatic changes. Green arrow showing pulmonary nodule



DISCUSSION

This case of an elderly female with delayed cystic fibrosis (CF) diagnosis underscores the challenge of recognizing atypical adult CF presentations and possible diagnostic bias. Misattributed symptoms led to years of ineffective treatments until genetic testing confirmed CF with delta F508 mutations. Recurrent infections, chronic bronchiectasis, pancreatic insufficiency, and IgG subclass deficiency compounded her respiratory issues, with difficult to treat non-tuberculous mycobacteria, and Pseudomonas and Aspergillus colonization further complicating care. Treatment with CFTR modulators markedly improved her outcomes. This case highlights the importance of having a high index of suspicion for CF, even in adults, particularly with features including persistent sinopulmonary infections, bronchiectasis, pancreatic insufficiency and infertility.

References
Padoan R, Quattrucci S, Amato A, Carnovale V, Salvatore D, Salvatore M, Campagna G. The Diagnosis of Cystic Fibrosis in Adult Age. Data from the Italian Registry. Diagnostics (Basel). 2021 Feb 16;11(2):321. doi: 10.3390/diagnostics11020321. PMID: 33669477; PMCID: PMC7920411.