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Case Series

Delays in Diagnosis of CF in Older Adults with Frequent Bronchiectasis Exacerbations: A Case Series

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Abstract

Objectives: The purpose of this case series is to provide valuable insights into the need to improve screening for cystic fibrosis (CF) with genetic testing among adult patients with bronchiectasis.

Case Series: Within one year, our bronchiectasis and CF specialty clinic had more than 4 cases of newly diagnosed CF among adults over the age of 60 with bronchiectasis. The first patient was a 66-year-old female with bronchiectasis diagnosed at age 30 and nasal polyps with history of normal sweat test. The second patient was a 75-year-old male with bronchiectasis diagnosed in his teenage years and *mycobacterium avium complex (MAC)* infection treated 10 years prior. The third patient is a 62-year-old male with Crohn's disease, nasal polyps, congenital bilateral absence of the vas deferens (CBAVD) and bronchiectasis. The fourth patient is a 65-year-old female with frequent pneumonias as a child and bronchiectasis diagnosed at age 57. All patients had daily cough and frequent pulmonary exacerbations. All were diagnosed with CF through commercial genetic testing and initiated on highly effective CFTR modulator therapy (HEMT). All patients remain exacerbation free >18 months since initiation of HEMT.

Conclusion: These cases show that there is a need to improve screening for CF among patients with bronchiectasis. All cases described here had at least one residual function mutation explaining the relatively later onset of symptoms. Sweat testing alone in these cases may be under the diagnostic threshold for CF. Availability of HEMT underscores the importance of genetic testing in many patients with unexplained bronchiectasis, even in those over age 60.

Keywords: Bronchiectasis; Cystic Fibrosis; Screening; CFTR; Elexacaftor/Tezacaftor/Ivacaftor.

Introduction

The incidence of bronchiectasis in the United States has increased over the past several decades, with prevalence increasing with age [1]. Currently, approximately 8-10% of new diagnoses of Cystic Fibrosis (CF) in the US are in individuals over the age of 18 years [2]. CF is a heterogenous disease and adult-diagnosed CF is associated with greater frequency of residual function mutations leading to milder phenotype with normal pancreatic function and onset of pulmonary symptoms at a later age –bronchiectasis being a characteristic pulmonary manifestation [3]. The rate of screening for CF among adults with bronchiectasis is likely very low. For example, the US Bronchiectasis Research Registry (BRR), a registry of over 3,000 patients with bronchiectasis nationwide, reports that sweat testing was performed in only 12% of patients [4]. Additionally, individuals presenting with CF in adulthood may have intermediate or even normal sweat chloride levels, therefore sweat testing alone is likely not sufficient to rule out CF among adults [5]. The prevalence of CF genetic testing among U.S. adults with bronchiectasis remains unknown and this case series highlights that there is a need to improve screening for CF among adults with bronchiectasis especially in the era of Highly Effective Modulator Therapy (HEMT) such as elexacaftor/tezacaftor/ivacaftor (ETI). These therapies have been shown to improve lung function, reduce pulmonary exacerbations and slow progression of lung disease [6].

Case Presentation

First Case: A 66-year-old Caucasian female was referred to our bronchiectasis clinic by her primary pulmonologist. Her medical history is notable for polycystic kidney disease with renal transplant at age 54, nasal polyps dating back to teenage years needing surgical removal on numerous occasions and bronchiectasis that was diagnosed at age 30. In her 40s she had hemoptysis and underwent bronchial artery embolization. She had chronic daily productive cough with intermittent hemoptysis and exacerbations requiring antibiotics 3-4 times a year. She had unlimited exercise capacity. She had no signs of pancreatic insufficiency. She had a sweat test in her 30s that was "negative" per patient report. She had no family history of bronchiectasis or CF. She is a former smoker with a 20-pack year history and quit at age 37. She had 1 biological child. Her physical exam was unremarkable with a body mass index (BMI) of 24.3. Her chest CT demonstrated bilateral diffuse bronchiectasis with mucus plugging. Serologic workup for etiology of bronchiectasis was unremarkable and included normal quantitative immunoglobulin profile, IgE, IgG subclasses, rheumatoid factor (RF) and a low-positive ANA. Sputum cultures isolated *methicillin-susceptible staphylococcus aureus (MSSA),* mucoid and non-mucoid *pseudomonas aeruginosa*. AFB cultures were negative. Her pulmonary function tests (PFTs) showed moderate obstructive ventilatory defect (OVD) with forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) 53 and FEV_1 1.68L (70%). She started on airway clearance regimen with nebulized hypertonic-saline and genetic testing for CF and Primary Ciliary Dyskinesia (PCD) was sent. Genetic testing revealed two disease-causing mutations F508/D1152H. She started on the HEMT elexacaftor/tezacaftor/ivacaftor (ETI) which resulted in marked improvement in lung function and resolution of cough. Her liver function tests (LFTs) remained normal throughout. She has not required antibiotics since initiation of therapy more than 18 months prior to this report. See Table 1.

Case	Age at symptom onset (years)	Age at diagnosis of CF (years)	Chest CT findings	Sputum pathogens	**Pre-ETI FEV_1 L(% predicted)**	**Post-ETI FEV_1 L(% predicted)**	**Change in FEV1 after ETI**	**Other organ involvement**	**Genetics**	**Exacerbations Pre-ETI à post-ETI**
1	30s	66	Bronchiectasis all lobes, mucus plugs	*P. aeruginosa*, MSSA*	1.68 (70%)	2.68 (120%)	50%	Nasal polyps	F508/ D1152H	3-4x/ year → 0 in 18+ months
2	17	75	Upper lobe predominant bronchiectasis, mucus plugging	*P. aeruginosa*, Chryseobacterium indologenes*, *Enterobacter cloacae* complex *Sphingobacterium multivorum MAC Mycobacterium mucogenicum*	1.56 (49%)	1.73 (54%)	5%	None	W1282X / D1152	2-4x/ year → 0 in 18+ months
3	47	62	Upper lobe predominant bronchiectasis, present all lobes	*P. Putida**, MSSA, Klebsiella*	1.97 (62%)	2.72 (86%)	12%	Nasal polyps, CBAVD, pancreatic insufficiency, diabetes	F508/p. L165S	1-2x/ year → 0 in 18+ months
4	Childhood	65	Mild cylindrical bronchiectasis all lobes, mucus plugging	*MSSA, P. aeruginosa*, Chryseobacterium indologenes, Haemophilus influenzae, Stenotrophomonas maltophilia*	2.29 (94%)	2.82 (105%)	11%	None	W1282X/ D1152H	3-4x/ year → 0 in 18+ months

Table 1: Clinical characteristics, imaging findings, and sputum microbiology and spirometry data before and after initiation of HEMT for all 4 patients. **P aeruginosa*: *Pseudomonas aeruginosa*; ***P putida*: *Pseudomonas putida*

Second Case: A 75-year-old Caucasian male presented to our bronchiectasis clinic as a self-referral. He grew up in Ukraine and was diagnosed with bronchiectasis around age 17 when he had daily cough. He only developed infections needing antibiotics in the last 10 years. Around 10 years ago, age 66, he completed treatment for pulmonary nontuberculous mycobacterium (NTM) infection with mycobacterium avium complex (MAC). He never had sweat chloride testing. He reported daily productive cough with intermittent hemoptysis and exacerbations needing antibiotics 2-4 times a year. He was maintained on airway percussive devices for airway clearance. He had unlimited exercise capacity. He had no signs of pancreatic insufficiency. He had no family history of CF. He was a former smoker and quit by age 50. He had no siblings or biological children. His physical exam was notable for scattered rhonchi but otherwise unremarkable with a BMI of 22.4. His chest CT showed bilateral diffuse bronchiectasis with mucus plugging. Serologic workup for etiology of bronchiectasis was notable for positive rheumatoid factor at 532 (ULN 14), positive PR-3 ANCA but otherwise unremarkable quantitative Ig profile, IgE, IgG subclasses, and negative ANA. Sputum cultures isolated mucoid and non-mucoid *Pseudomonas aeruginosa*, *Chryseobacterium indologenes*, *Enterobacter cloacae* complex and *Sphingobacterium multivorum*. AFB cultures grew MAC and *mycobacterium mucogenicum*. His PFTs showed severe OVD with FEV_1/FVC 68 with FEV_1 1.56L (49%). He was started on airway clearance regimen hypertonic-saline and genetic testing for CF and PCD was sent. His genetic testing revealed two disease-causing mutations W1282X/D1152H. He was started on ETI however, he developed a rash and temporarily stopped the drug with resolution of rash, with subsequent resumption of low dose ETI. He developed pruritus on low dose, which improved with a brief course of prednisone and was re-trialed on full dose ETI. He had recurrence of rash and needed another course of prednisone and brief interruption of ETI. He is currently maintained on reduced dose ETI. He had marked improvement in lung function and resolution of cough on ETI. His LFTs remained normal throughout. He has required one antibiotic course (while off modulator) over the 18 months prior to this report. See (Table 1).

Third Case: A 61-year-old Caucasian male was referred to our bronchiectasis clinic by his primary care physician. He was diagnosed with bronchiectasis at age 60. He had been diagnosed with Crohn's disease >10 years ago and had small bowel obstruction requiring surgery 5 years ago. He had nasal polyps requiring surgery around age 45. He reported daily productive cough and often required antibiotics 1-2 times a year. He denied history of pancreatitis however he had CT evidence of atrophic pancreas. He never had a sweat test in the past however he had infertility around age 35 and was diagnosed with CBAVD – genetic testing at that time revealed that he was a CF carrier. The rest of his medical history was notable for diabetes mellitus diagnosed at age 55. He had unlimited exercise capacity. He had minimal smoking history and quit around age 24. He had no family history of CF or bronchiectasis. He had no biological children. His physical exam was unremarkable with a BMI of 26.4. Chest CT showed bilateral cylindrical bronchiectasis more severe in the upper lobes. Serologic workup for etiology of bronchiectasis was notable for IgE 580 (ULN 114), otherwise normal quantitative Ig profile, IgG subclasses, ANCA and a low-positive ANA. Sputum cultures isolated *MSSA, Pseudomonas putida and Klebsiella*. Fecal elastase was <15 mcg/g (normal > 200 mcg/g). AFB cultures were negative. His PFTs showed moderate OVD with FEV_1/FVC 60 and FEV_1 2.09L (65%). He was started on airway clearance regimen, nebulized hypertonic saline and percussive therapies and genetic testing for CF and PCD were sent. His genetic testing revealed two disease-causing mutations F508/p.L165S. He started on ETI which resulted in marked improvement in lung function and resolution of cough. He had no significant LFT injury on ETI. He has not required antibiotics since initiation of ETI therapy more than 18 months prior to this report. See Table 1.

Fourth Case: A 65-year-old Caucasian female presented to our bronchiectasis clinic as a self-referral. She was diagnosed with bronchiectasis at age 57. She had history of frequent pneumonias as a child. She reported daily productive cough and required antibiotics at least 3 times a year. Her medical history was notable for uveitis believed to be from bisphosphonate use, osteoporosis, known CF carrier state and hyperparathyroidism s/p parathyroidectomy. She did not have a sweat test in the past. She was maintained on airway clearance nebulizers and percussive therapy. She had no signs of pancreatic insufficiency. She had unlimited exertional ability. She was a never smoker. She had a parakeet at home for 20 years and other exposures include a pet dog and hot tubs. She had 5 biological children. Her physical exam was unremarkable with a BMI of 33.8. Chest CT showed mild cylindrical bronchiectasis in all lobes with mucus plugging more notable in the upper lobes. Serologic workup for etiology of bronchiectasis was unremarkable and included a normal IgE, quantitative Ig profile, IgG subclasses, RF, A1AT and a low-positive ANA. Sputum cultures isolated *MSSA, Pseudomonas aeruginosa, Chryseobacterium indologenes, Haemophilus influenzae* and *Stenotrophomonas maltophilia*. AFB cultures were no growth. Her PFTs were normal with FEV_1/FVC 78 with FEV_1 2.29L (94%). Genetic testing for CF revealed two disease-causing mutations W1282X/D1152H. She was started on ETI which resulted in marked improvement of her symptoms with near resolution of cough. She had no LFT injury on ETI. She has still not required antibiotics since initiation of HEMT more than 18 months prior to this report. See Table 1.

Discussion

We describe a new diagnosis of CF in four individuals over 60 years old with longstanding bronchiectasis and pulmonary

symptoms for more than 10 years. All 4 patients described above were followed by pulmonologists, highlighting the need to define and improve recognition of the adult CF phenotype. There is also a need to better understand whether all adults with unexplained bronchiectasis should undergo genetic testing for CF or whether there is a specific phenotype that should be targeted. The prevalence of CF genetic testing among U.S. adults with bronchiectasis remains unknown but is likely to be quite low. This case series highlights that there is a need to improve screening for CF among adults with bronchiectasis, especially in the era of highly effective treatment with HEMT.

Class I, II and III CFTR mutations are associated with no functional CFTR protein in the cell membrane or defective channel regulation and are associated with a severe lung disease phenotype with pancreatic insufficiency, often presenting within the first two years of life. Class IV and V mutations are residual function mutations with some CFTR function and are associated with a milder disease phenotype, which often presents after childhood and pancreatic sufficiency [7]. It is noteworthy that 3 of the 4 patients had the D1152H mutation. The D1152H mutation is class IV mutation, which is a residual function mutation, which impairs chloride conductance through reduced gating of the CFTR channel, but is associated with some preserved CFTR function. This mutation is associated with a highly variable phenotype, including borderline or mildly elevated sweat chloride, preserved pancreatic function and later onset pulmonary disease [8]. There is a higher frequency of Class IV and V mutations among patients diagnosed with CF as adults [3, 5].

Sweat testing to screen for CF may not be as reliable in the adult population. A study of patients in the US CF registry showed that nearly 25% of adults diagnosed with CF > age 18 had normal or indeterminate sweat test results highlighting the fact that a normal sweat test in adults does not rule out CF [5]. Studies have also demonstrated that the number of positive sweat chloride tests and prevalence of ΔF508 mutation, the most common CFTR mutation in the US, decrease significantly with older age at diagnosis [5]. This limitation of sweat chloride testing among adults is likely secondary to residual function CFTR mutations which is seen with greater frequency with older age at diagnosis of CF [3,5]. Though sweat testing is often performed as the initial diagnostic test for CF, it was not performed for any of the patients described here since genetics are more easily accessible at our institution and are ultimately needed to determine modulator eligibility. The fact that two of the four patients were known to be CF "carriers" highlights the need for more comprehensive genotyping to identify less common mutations especially if an older and likely more abbreviated genetic panel was non diagnostic.

Approval of elexacaftor/tezacaftor/ivacaftor (ETI) in October 2019 has made a highly effective modulator therapy (HEMT) available for nearly 200 CFTR mutations, encompassing >90% of individuals with CF[6]. HEMT leads to a mean 14% predicted improvement in FEV_1, 65% reduction in pulmonary exacerbations and slower disease progression, highlighting the importance of not missing the diagnosis [6, 9]. The patients described in this case series had a mean FEV_1 improvement of 19.5%, marked improvement in daily cough and all remain exacerbation free since initiation of HEMT.

We anticipate finding more cases of CF carrier states in the coming years especially owing to increased availability of CFTR genotyping and increased awareness of CF disease heterogeneity. Two small prospective studies suggest a high prevalence of CFTR mutations among adults with unknown etiology of bronchiectasis, with a range 30-50% [10, 11]. One was a smaller cohort study (n=50) that prospectively examined patients with unknown etiology of bronchiectasis and/or NTM and found that 50% had at least one CFTR pathogenic mutation [10]. A similar study out of France (n=122) prospectively examined patients with diffuse bronchiectasis of unknown etiology and a normal sweat chloride test and found that 30.3% had at least one mutation [11]. Of note, some studies have shown that CF carriers with bronchiectasis appear to have a more severe disease phenotype compared to non-carriers – with 2.4 times greater odds of hospitalization, 2 times greater odds of needing antibiotic courses, 4.2 and 5.4-times greater odds of Pseudomonas and NTM respectively, as well as increased risk of developing cystic fibrosis related conditions [12, 13]. Cystic fibrosis related disorder (CF-RD) has been defined as a clinical condition caused by dysfunction of the CFTR protein, without meeting full diagnostic criteria for CF. These disorders are typically associated with CFTR variants that result in residual CFTR function, often leading to milder disease, indeterminate or normal sweat test, or single organ phenotypes. The individuals described here each fulfill criteria for CF as they have multi-organ involvement including bronchiectasis, and two disease-causing mutations. The role, if any, of HEMT among CF carriers with bronchiectasis with one HEMT-eligible mutation is an active area research. Case series and retrospective cohort analysis have shown improved lung function, symptoms and a significant reduction in annual pulmonary exacerbations however, both studies had limited sample size [14, 15]. Currently there is an open label phase 4 trial underway [16].

Conclusion

The descriptions of these four cases show that CF should be considered regardless of age, especially when encountering patients with bronchiectasis of unknown cause or with chronic infection with typical CF pathogens such as *P aeruginosa, S aureus* and/or MAC. When CF is suspected, the work-up typically requires both a sweat chloride test and CFTR genotyping; however, it is important to note some key limitations of sweat chloride testing.

There is likely significant under-screening and underdiagnosis of CF among adult patients with bronchiectasis. Availability of HEMT underscores the importance of genetic testing in many patients with unexplained bronchiectasis, even in those over age 60. Future research is needed to shed light on more directed CF genetic testing in the older population with bronchiectasis to best identify those more likely to have CF.

Declarations

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