Scientific Research Publishing

Case Reports in Clinical Medicine, 2026, 15(8), 315-322
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

CFTR-Related Disorder in a Patient with Sjögren-Associated Bronchiolitis and Recurrent Pulmonary Infections: A Diagnostic Challenge

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How to cite this paper: McCoach, T., Wright, E. and Kenyon, J. (2026) CFTR-Related Disorder in a Patient with Sjögren-Associated Bronchiolitis and Recurrent Pulmonary Infections: A Diagnostic Challenge. *Case Reports in Clinical Medicine*, **15**, 315-322.
https://doi.org/10.4236/crcm.2026.158041

Received: June 29, 2026
Accepted: August 7, 2026
Published: August 10, 2026

Abstract

Cystic fibrosis (CF) is an autosomal recessive disorder caused by an inherited defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It classically manifests with chronic sinopulmonary disease, pancreatic insufficiency, and infertility/subfertility. However, there are many patients whose symptoms do not align well with classic CF presentations, leading to a separate classification of many CFTR-related disorders which may have variable genotypic and phenotypic expression. This is the case of a 42-year-old female with recurrent sinopulmonary infections, autoimmune disorders, asthma, and progressive respiratory failure who had been admitted to the hospital multiple times over the course of months. Ultimately, an intermediate sweat chloride test led to further investigation which resulted in a diagnosis of a CFTR-related disorder caused by an F508del mutation. This diagnosis led to the initiation of CFTR modulator therapy, which was incorporated into a broader multidisciplinary treatment strategy that also included antimicrobial therapy, immunosuppression for Sjögren-associated bronchiolitis, and airway-clearance measures. Although the patient experienced transient clinical stabilization, the relative contribution of each intervention could not be determined, and the patient was ultimately referred for bilateral lung transplant.

Keywords

CFTR, CFTR-Related Disorder, Bronchiectasis, Sjögren-Associated Bronchiolitis

1. Introduction

Cystic fibrosis (CF) is an inherited defect in the cystic fibrosis transmembrane

conductance regulator (CFTR) channel that affects over 30,000 children and adults in the United States [1] [2]. In 2010, the cystic fibrosis screening test was implemented across all 50 states, ensuring this devastating disease can be caught early in its course [3]. However, individuals born outside of hospital settings and many adults born before the implementation of universal newborn screening in 2010 may not have undergone CF screening, and it has been estimated that up to 35% of people living with CF remain undiagnosed [4]. While classic cystic fibrosis is characterized by multisystemic organ dysfunction including chronic sinopulmonary disease, pancreatic insufficiency, infertility in males, and subfertility in females, a growing number of patients are recognized to have CFTR-related disorders that do not meet diagnostic criteria for classic CF [5] [6]. CFTR-related syndromes encompass a spectrum of clinical conditions associated with impaired CFTR function and variable phenotypic expression limited to only one organ system [6] [7]. These patients may present with recurrent respiratory infections, chronic sinus disease, pancreatitis, bronchiectasis, male infertility, or other manifestations in conjunction with inconclusive genetic testing or borderline diagnostic studies [6] [8]. The diagnosis of a CFTR-related disorder can be challenging due to its atypical presentation and overlapping symptoms with other common pulmonary, gastrointestinal, and infectious diagnoses [9]. Additionally, the degree of CFTR dysfunction can vary greatly between patients, further complicating the diagnosis [10] [11]. As understanding of CFTR-related disorders continues to evolve, recognition of atypical presentations has become increasingly important to facilitate appropriate evaluation, management, and consideration of targeted therapies [6] [12]. We present the case of a patient with a CFTR-related disorder whose clinical course highlights the diagnostic complexity and multidisciplinary management considerations associated with this uncommon condition.

2. Case Presentation

A 42-year-old female with a past medical history of asthma, stage III chronic kidney disease, hypertension, hypothyroidism, a history of a cerebrovascular accident (CVA) and an undefined autoimmune disorder labeled as systemic lupus erythematosus (SLE) vs. rheumatoid arthritis presented with progressive respiratory symptoms over the course of several months. In early 2024, pulmonary function testing showed severe airflow obstruction with an FEV1 of 29% predicted and an FEV1/FVC ratio of 27%, without significant bronchodilator response. A CT scan performed at that time demonstrated diffuse ground-glass opacities without substantial bronchiectasis or cavitary disease. She was treated for presumed severe asthma throughout 2024.

The patient originally presented to a community hospital emergency department due to worsening cough and shortness of breath after being diagnosed with pneumonia in an outpatient setting one week prior. The patient then underwent a CT scan, which revealed multiple nodules/focal consolidations in bilateral lungs; the largest being 3.8 cm in the left lower lobe (**Figure 1**, **Figure 2**). She was admit-

ted for continuous monitoring, empiric antibiotics, and further diagnostic workup including bronchoalveolar lavage (BAL). The patient was discharged home two days later and prescribed amoxicillin-clavulanate pending results from the BAL.

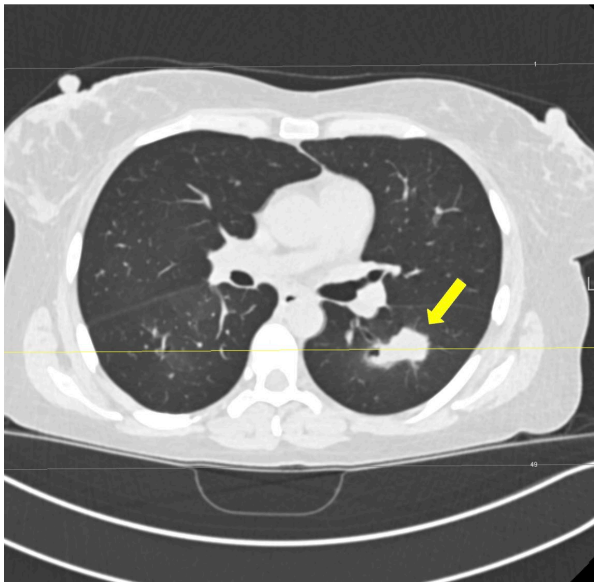

Figure 1. CT Chest: Transverse view of 3.8 cm nodule.

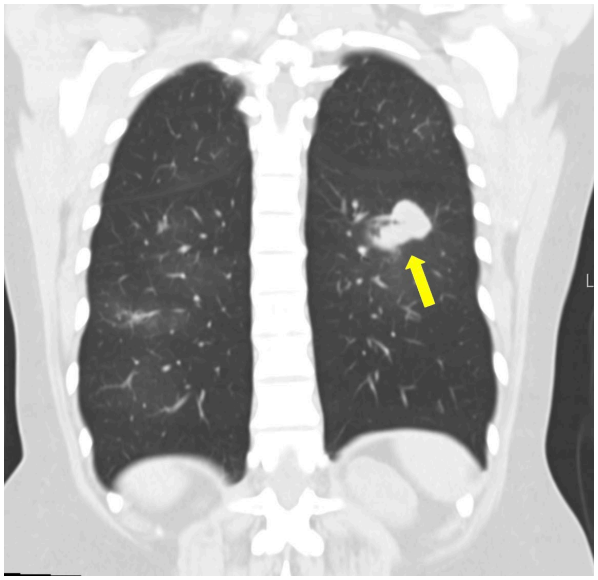

Figure 2. CT Chest: Coronal view of 3.8 cm nodule.

Nineteen days after discharge, the patient was readmitted to the community hospital from urgent care due to hypoxia and shortness of breath and tested positive for Influenza A in the emergency department. During this hospitalization, BAL culture results returned positive for mycobacterium avium-intracellulare and the patient was started on piperacillin/tazobactam. The patient was discharged

seven days post admission on amoxicillin-clavulanate.

Approximately one month later, the patient returned with massive hemoptysis complicated by syncope and acute respiratory failure requiring intubation for airway protection. Sputum cultures grew methicillin-resistant Staphylococcus aureus (MRSA), and repeat acid-fast cultures remained positive for MAC. Following stabilization, she was discharged but presented again two weeks later with worsening dyspnea, fatigue, and hypercapnic respiratory failure requiring ventilation and admission to the intensive care unit (ICU).

During each of these admissions, the patient experienced multiple episodes of acute on chronic respiratory failure requiring admission to the ICU. Despite treatment, the patient's hypercapnia persisted. Additional evaluation demonstrated sicca symptoms and positive antinuclear antibodies. Minor salivary gland biopsy of the left lower lip ultimately confirmed the previously unidentified autoimmune disorder as seronegative Sjögren's syndrome.

Investigations

Serial chest imaging demonstrated progressive multifocal nodular and cavitary pulmonary infiltrates. Initial CT imaging from early 2024 showed diffuse ground-glass opacities without significant bronchiectasis or cavitary lesions. Repeat imaging in December 2024 demonstrated multiple bilateral nodules and focal consolidations. Subsequent imaging through early 2025 showed progression to bilateral cavitary disease involving both upper and lower lobes with bronchial wall thickening.

Bronchoscopy with transbronchial biopsy performed in December 2024 showed necrotizing granulomatous inflammation consistent with nontuberculous mycobacterial infection. Multiple sputum and tracheal aspirate cultures subsequently grew Mycobacterium avium complex (MAC). Additional respiratory cultures throughout her hospitalization grew MRSA and later Pseudomonas aeruginosa.

Arterial blood gas analysis repeatedly demonstrated severe hypercapnic respiratory failure with pCO2 values exceeding 80 mmHg during episodes of decompensation. Additionally, pulmonary function testing revealed severe fixed airflow obstruction predating the development of cavitary infection. Because the degree of hypercapnia and recurrent nontuberculous mycobacterial infection appeared disproportionate to imaging findings, further investigation for underlying causes of pulmonary disease was pursued. A sweat chloride test was ordered and performed on two separate occasions, yielding intermediate values of 44 mmol/L and 50 mmol/L (<29 mmol/L). Subsequent CFTR genetic testing identified one copy of the F508del mutation.

Autoimmune evaluation demonstrated an antinuclear antibody titer of 1:640 with speckled pattern, while extractable nuclear antigen antibodies, rheumatoid factor, cyclic citrullinated peptide antibodies, and multiple additional serologies were negative. Minor salivary gland biopsy showed findings consistent with

Sjögren's syndrome. Based on pulmonary function testing, imaging findings, and multidisciplinary evaluation, the patient was diagnosed with Sjögren-associated obliterative bronchiolitis. However, the patient's symptoms and clinical progression were considered disproportionate to the diagnosis of Sjögren-associated bronchiolitis alone due to continued progression of disease and worsening hypercapnia despite medical intervention with corticosteroids and rituximab. Additionally, the patient's seronegative status and absence of additional symptoms to suggest uncontrolled connective tissue disease made connective tissue disease-associated interstitial lung disease (CTD-ILD) less likely. Cystic fibrosis specialists were consulted for evaluation of this patient's phenotype given the known presence of a CFTR mutation. Given the diagnosis of seronegative Sjögren's disease, the presence of recurrent nontuberculous mycobacterial infection, severity of pulmonary symptoms out of proportion with her imaging findings, a diagnosis of coexisting CFTR-related disorders was supported by intermediate sweat chloride values < 60 mmol/L, and lack of other typical CFTR-related diseases, including pancreatic insufficiency, pancreatitis and malnutrition.

3. Outcome and Follow-Up

The patient was treated for cavitary MAC infection consisting of azithromycin, ethambutol, clofazimine, and inhaled amikacin. Additional antibiotic courses were administered for MRSA and multidrug-resistant Pseudomonas pneumonia. Because Sjögren-associated bronchiolitis was believed to be the major driver of her respiratory decline, high-dose corticosteroids and rituximab were initiated. The patient's respiratory symptoms demonstrated significant improvement following immunosuppressive therapy, supporting the contribution of an autoimmune component to her disease. Following the identification of the F508del mutation and the possibility that impaired CFTR function contributed to chronic airway disease and recurrent infections, treatment was escalated with chest vest therapy, dornase alfa (Pulmozyme), and andelexacaftor/tezacaftor/ivacaftor (Trikafta). CFTR-modulating therapy was specifically initiated due to the frequency and severity of the patient's pulmonary exacerbations, failure of prior treatments to resolve the issue, and patient's desire for aggressive intervention to improve or sustain lung function. This was a multi-disciplinary clinical decision with input from infectious disease, rheumatology, pulmonology/critical care, bedside nursing staff, and the patient and her family.

Despite transient stabilization with the combination of antimicrobial therapy, immunosuppression, airway-clearance interventions, and CFTR modulation, the patient continued to experience multiple recurrent hospitalizations for acute on chronic respiratory failure. The patient's progressive decline in pulmonary function ultimately led to referral for lung transplantation. She subsequently required extracorporeal membrane oxygenation as a bridge to transplantation, and due to concomitant CKD, the patient underwent a successful combined double lung-kidney transplant. Following transplantation, she experienced gradual recovery and

was discharged home with stable graft function and ongoing follow-up with transplant pulmonology, infectious disease, and rheumatology.

Discussion

This case highlights the complexity of diagnosing a CFTR-related disorder in the presence of multiple coexisting pulmonary processes. The patient's disease process initially appeared to be explained by severe asthma and later pulmonary MAC infection, complicated by bacterial pneumonia. Following diagnosis of Sjögren's syndrome and evidence of severe airflow obstruction predating infectious complications, Sjögren-associated obliterative bronchiolitis emerged as the predominant explanation for her respiratory decline. The patient's marked clinical improvement following initiation of corticosteroids and rituximab strongly supported Sjögren-associated obliterative bronchiolitis as a major contributor to her respiratory decline. However, several features of the patient's presentation suggested that additional pathology might be present. Specifically, recurrent nontuberculous mycobacterial infection, progressive changes consistent with bronchiectasis, and persistent respiratory morbidity prompted further evaluation. Upon ordering a sweat chloride test, the values were repeatedly intermediate rather than normal, and genetic testing demonstrated a F508del CFTR mutation.

Classic cystic fibrosis was considered unlikely because the patient lacked many of the typical manifestations of the disease. She had no pancreatic abnormalities, no childhood diagnosis, and initially had minimal bronchiectasis on imaging. Despite all of this, increasing evidence suggests that partial CFTR dysfunction can have an entirely different clinical manifestation from classic cystic fibrosis [6] [7]. Patients with a CFTR-related disorder may present later in life with chronic respiratory infections, bronchiectasis, recurrent sinus disease, or nontuberculous mycobacterial infection, despite not fulfilling the classic diagnostic criteria for cystic fibrosis [6] [8].

The patient's hypercapnic respiratory failure appeared to be driven by severe Sjögren-associated bronchiolitis. Importantly, the existing airflow obstruction prior to development of cavitations supported this conclusion. It is plausible the presence of CFTR dysfunction contributed to chronic airway infection and impaired clearance of bacterial and viral pathogens; however, the magnitude of its contribution relative to Sjögren-associated bronchiolitis cannot be determined. Once the underlying CFTR dysfunction was identified, it expanded the available treatment options to improve clearance of these pathogens, namely through initiation of CFTR modulator therapy in addition to ongoing antimicrobial therapy and immunosuppression.

This case study highlights the importance of maintaining a broad differential diagnosis and revisiting prior diagnoses throughout a patient's disease course. Given the patient's medical history and imaging findings, it would have been reasonable to attribute all pulmonary manifestations to autoimmune bronchiolitis or recurrent infections. However, through reevaluation of persistent clinical symp-

toms, an additional disease process was uncovered that was likely contributing to the patient's morbidity.

Although the extent to which CFTR dysfunction contributed to this patient's disease course cannot be quantified, recognition of a CFTR-related disorder altered clinical management by prompting consideration of additional airway-clearance strategies and CFTR-directed therapy. This case underscores both the phenotypic spectrum of CFTR-related disorders and the importance of avoiding attribution of clinical outcomes to any single intervention in patients receiving complex multidisciplinary care. Further investigation into the efficacy of targeted therapies in patients with intermediate sweat chloride values and single CFTR mutations is warranted.

4. Conclusion

This case report emphasizes the importance of considering alternate diagnoses when faced with a challenging clinical picture that includes numerous concurrent diagnoses. For individuals who were born prior to the implementation of universal newborn screening for CF, this is especially true. This patient with recurrent pulmonary infections, asthma, autoimmune disorders, and other conditions was ultimately diagnosed with CFTR dysfunction syndrome after two different intermediate sweat chloride tests. This diagnosis ultimately changed the clinical management of this patient's condition. CFTR-related disorders can present in a wide variety of ways and should be considered in patients with recurrent pulmonary infections for which no underlying cause has been determined.

Consent

Informed consent was obtained from the patient to report this case.

Author Contributions

J.K. was involved in the direct clinical care of the patient and conceived the report. T.M. performed the literature review and drafted the initial manuscript. T.M. And E.W. reviewed and interpreted the patient's medical records and imaging and contributed to the diagnostic reasoning outlined in the text. J.K. provided critical feedback on the manuscript and assisted with revision of the final text. All authors approved the final version of this text.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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