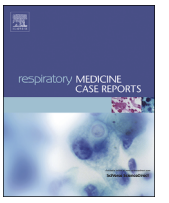
Respiratory Medicine Case Reports 34 (2021) 101545

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Delayed HIV diagnosis in a cystic fibrosis patient: Not just another exacerbation

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ARTICLE INFO

Keywords:
Cystic fibrosis
HIV
Pneumocystis pneumonia

ABSTRACT

Patients with cystic fibrosis (CF) are living longer due to advancements in treatment. We present a patient with CF in whom diagnoses of Human Immunodeficiency Virus (HIV) and severe pneumocystis pneumonia were delayed due to anchor bias. Our case highlights the importance of routine age-appropriate health screenings in patients with CF. In addition, we discuss the number of management challenges that may arise in patients with a dual diagnosis of CF and HIV.

1. Introduction

Patients with cystic fibrosis (CF) are living longer due to advances in care, with an average life expectancy of approximately 44 years [1]. Thus, it is important for CF providers not only to prevent disease progression and treat CF exacerbations, but also to consider age-appropriate health screening recommended for the general population. In patients with chronic illnesses, new or co-existing diagnoses may be missed due to anchor bias. Anchoring is a cognitive bias that may cause clinicians to focus too heavily on previously known information when making clinical decisions. We describe a case in which anchor bias (known CF diagnosis) delayed diagnosis and treatment of pneumocystis pneumonia (PCP) in a patient with undiagnosed HIV, resulting in adverse outcomes.

1.1. Case description

A 39-year-old man diagnosed in childhood with cystic fibrosis (genotype 3849 + 10 kb leading to a C to-T change, homozygous) had been followed at a CF specialty clinic but had significant gaps between visits. The patient presented with a three-day history of dyspnea, productive cough, fevers, and hypoxia. Prior to hospitalization patient was on as needed oxygen at night, but had increased to 2.5 lpm at home over the past three days. Chest radiograph showed new bilateral perihilar infiltrates and laboratory evaluation showed leukocytosis (14×10^3 cells/μL). The patient had a history of colonization with methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa,* chronic sinusitis, obesity, and gastric reflux disease. Patient did not have history of pancreatic insufficiency prior to hospitalization. Three months prior to hospitalization, pulmonary function tests were FVC 3.60L/76% predicted, FEV1 2.18L/57% predicted, FEV1/FVC 60/75% predicted, FEV 25–75 30% predicted; oxygen saturation was 93% on room air. At that time patient was also diagnosed with thrush and tinea cruris. Prior to that visit there was a 3-year gap in care. At the time of hospitalization home medications included albuterol/ipratropium inhalation solution, azithromycin, docusate, dornase alfa, ergocalciferol, fluticasone/salmeterol inhalation powder, multivitamin, pantoprazole and tobramycin inhalation solution. The patient denied tobacco, alco-

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https://doi.org/10.1016/j.rmcr.2021.101545
Received 18 June 2021; Received in revised form 5 October 2021; Accepted 7 November 2021
Available online 9 November 2021

hol, or recreational/injection drug use. He was in a monogamous relationship with a female partner. The patient denied history of having sexual contact with men. The patient also had no history of blood transfusions. Patient did report that a former female partner died of an unknown illness several years prior to his hospitalization.

The patient was admitted to the hospital with a presumed diagnosis of CF exacerbation. Initially the patient received 5 lpm of oxygen and oxygen saturation was 94%. Intravenous cefepime, tobramycin, vancomycin and standard CF therapies were initiated. Infectious Diseases and Pulmonary services were consulted. Evaluations for causes of acute hypoxic respiratory failure included bacterial, fungal, and mycobacterial sputum cultures, mycoplasma and coccidioides serologies, screening for connective tissue disease, urine legionella antigen, urine pneumococcal antigen, and respiratory viral panel, all of which were unrevealing. An echocardiogram showed normal left ventricular systolic function (LEVF) with pulmonary artery pressure of 37 mmHg. The patient's pulmonary condition worsened; on hospital day 4 he developed respiratory distress and sudden increase in oxygen requirement. A computed tomography (CT) scan of the chest with contrast showed extensive bilateral parenchymal ground glass opacities with peribronchial consolidation, read as more consistent with atypical pneumonia than with CF exacerbation, though pre-existing bronchiectasis made interpretation difficult. The patient was transferred to the intensive care unit (ICU) (see Fig. 1). On hospital day 5 a consultant suggested HIV testing, as well as a bronchoscopy, but the patient was initially unstable and the procedure was deferred. On hospital day 8, an HIV screen was positive and confirmed with Western blot; $CD4^+$ cell count was 56 cells/μL and HIV viral load was 947,000 copies/mL. On hospital day 9, the patient underwent bronchoscopy; pneumocystis was identified by calcofluor stain from bronchoalveolar lavage. The patient was treated with sulfamethoxazole/trimethoprim 15mg/kg/day (based on trimethoprim component), prednisone taper, and antiretroviral therapy. The patient responded to treatment and did not require intubation; however, he developed a spontaneous pneumothorax, requiring multiple thoracostomy tubes (one with a Heimlich valve) and eventually was transferred to a specialty hospital for chemical pleurodesis. Screening tests for sexually transmitted diseases, tuberculosis, hepatitis, and toxoplasmosis were negative.

The patient is now followed by both the HIV and CF specialty clinics at our institution and he has remained stable with chronic oxygen requirement (2–3 LPM), improved CD4 cell count and an undetectable HIV viral load. No evidence of prior HIV screening was documented prior to hospitalization. His current female partner is not infected with HIV.

2. Discussion and conclusions

To our knowledge there are only two cases reported in the literature describing HIV infection in patients with CF [2,3]. Hoyer et al. [2] described a 39-year-old man with long-standing HIV, well controlled on ART, who was diagnosed with CF after being hospitalized several times for recurrent pneumonias, initially presumed to be due to his underlying immunocompromise. When BAL culture yielded non-mucoid and mucoid phenotypes of *P. aeruginosa*, a subsequent diagnosis of CF was made. Anchor bias in the case presented by Hoyer et al. delayed the diagnosis and treatment of CF. The authors concluded that the prevalence of CF in people with HIV (PWH) may be underestimated and should be suspected in a diagnosis of *P. aeruginosa* pneumonia.

Our case illustrates anchor bias in the reverse, where expert specialty providers presumed the patient's condition was caused by CF, leading to delayed diagnosis and treatment of PCP and HIV. Because CF is a serious chronic condition that historically has had a short lifespan and where symptoms dominate patients' health, CF patients like ours may not receive usual health screening, such as HIV testing. HIV screening had not been performed in this patient case prior to hospitalization, despite the United States Centers for Disease Control recommendation that all patients aged 13–64 years be screened [4]. Additionally, the patient would have been considered low-risk, not meeting criteria for indicator condition-guided HIV testing as outlined by European Centre for Disease Prevention and Control [5].

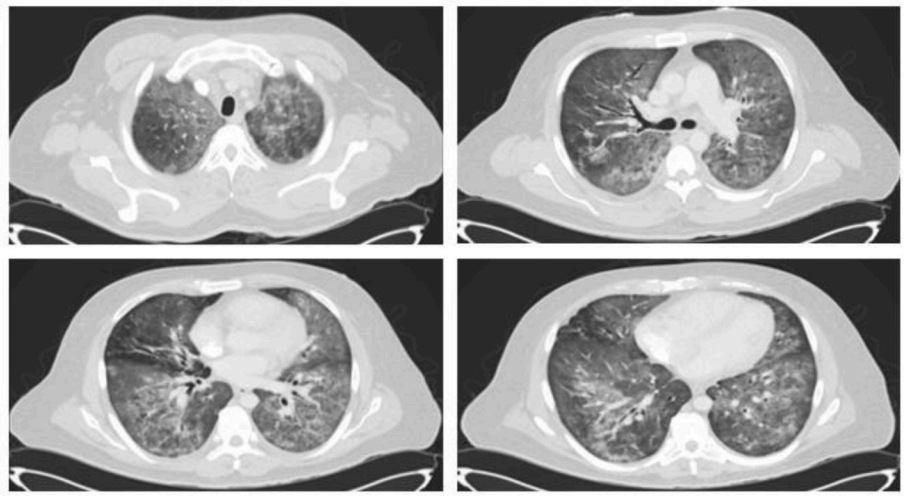

Fig. 1. CT scan showing extensive bilateral parenchymal ground glass opacities with peribronchial consolidation.

Table 1
Potential drug interactions to consider in patients with CF and HIV [24,25].

Medications commonly used in patients with CF	Drug interaction with HIV antiretroviral medication
Vitamins containing divalent cations (e.g., iron, magnesium)	May decrease absorption of integrase strand transfer inhibitors (e.g., dolutegravir, raltegravir)
Corticosteroids, including inhaled formulations (e.g., fluticasone)	Antiretrovirals and antiretroviral boosting agents (e.g., ritonavir, cobicistat) may increase corticosteroid concentrations
Acid suppressant therapy (e.g., ompeprazole)	May decrease concentrations of rilpivirine and atazanavir
Triazole antifungals (e.g., voriconazole)	Triazole concentrations may be increased or decreased and antivirals concentrations may be increased.
CFTR modulators (e.g. lumacaftor)	CFTR modulators may decrease concentrations of non-nucleoside reverse transcriptase inhibitors (e.g., rilpivirine and doravirine), pharmacokinetic enhancers (i.e., ritonavir, cobicistat), and some integrase strand transfer inhibitors (i.e., elvitegravir, bictegravir) Protease inhibitors (e.g., atazanavir) and cobicistat may increase concentrations of CFTR modulators. Efavirenz may decrease concentrations of CFTR modulators.
Azithromycin	Supratherapeutic doses of rilpivirine are associated with prolongation of Qtc, but this is unlikely to occur with coadministration with azithromycin.
Inhaled beta-2 adrenergic receptor agonists	No interaction expected
Inhaled anticholinergics (e.g., ipratropium, tiotropium)	No interaction expected
Theophylline	Ritonavir may decrease theophylline levels

The importance of early diagnosis and treatment of HIV has been demonstrated, resulting in improved patient outcomes [6,7]. The patient's hospitalization, totaling over 3 months, may have been averted or ameliorated by earlier HIV screening. As advances in care and treatment continue to extend life expectancy in both CF and HIV, providers may see more patients with this dual diagnosis. Clinicians providing care for CF patients should screen for not only CF-related co-morbidities (e.g. diabetes, bone, liver disease, anxiety and depression) [8–11], but also for conditions, such as HIV, found in the general population.

The outcomes for patients with this dual diagnosis are unknown, but each condition is likely to impact the disease course of the other. HIV suppresses CFTR biogenesis and function and bronchial epithelial cell differentiation [12,13]. This may partly explain why PWH are at increased risk of lung infections, fibrosis and other pulmonary comorbidities [14,15]. Increased HIV viral loads have been associated with fibrotic changes in the lung [16]. However, even in patients with controlled HIV, increased risk of pulmonary comorbidities remains [17].

A dual diagnosis of CF and HIV presents a number of management challenges, which may include drug interactions (shown in Table 1), altered drug absorption and pharmacokinetics [18–20], medication adherence, and potential macrolide resistance in mycobacterial infection. Rates of depression are higher in both patient populations [21–23] and may negatively impact outcomes. In addition, CF patients may require lung transplantation. In most transplant centers HIV infection is still considered a contraindication to lung transplantation. However, a successful double lung transplant in a patient with CF and HIV was reported by Bertani et al. [3]. In 2013 the HIV Organ Policy Equity act was passed, which allows for transplantation of organs from donors with HIV to PWH as part of a clinical trial. Lung transplantation may be considered routinely in the future for this population. Additional care will need to be taken to evaluate the complications posed by drug interactions between CF, HIV and transplant mediations.

In conclusion, our case involving a patient with known CF and a new diagnosis of advanced HIV illustrates that: 1) providers caring for patients with one serious chronic medical condition may be susceptible to anchor bias, attributing new findings to the known condition before considering alternative explanations, resulting delayed diagnoses; and 2) patients with CF are living longer and HIV screening should be incorporated into their routine care.

Author contributions

All authors meet the four ICMJE criteria for authorship.

Declarations

- Written informed consent was obtained from the patient for publication of this case report and is available from the corresponding author;
- This research did not receive any grant funding support from public, commercial, or not-for profit sectors;
- This manuscript has not been published previously, nor is it under consideration for publication elsewhere.
- The manuscript has been approved by all authors

Declaration of competing interest

Bernadette Jakeman, PharmD, serves as a consultant for Wolters-Kluwer. Keenan Ryan PharmD, serves as a speaker for Surgent Pharmcon. The other authors of this manuscript have no conflicts of interest to declare, including employment, consultancies, stock ownership and options, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding received or pending.

Acknowledgements

None.

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