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Case Report

A case of severe pulmonary exacerbation in a young patient with cystic fibrosis in the era of CFTR modulators

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ABSTRACT

The introduction of CFTR modulator drugs like elexacaftor-tezacaftor-ivacaftor (ETI) has transformed the management of cystic fibrosis (CF), significantly improving symptoms, lung function, and quality of life, while reducing reliance on intravenous antibiotics. However, respiratory exacerbations in the CFTR modulators era remain poorly understood from both pathophysiological and clinical perspectives.

We present the case of a 20-year-old Caucasian woman with CF (F508del/L1077P) who, after three years of ETI treatment, experienced a severe episode of hemoptysis, despite being almost asymptomatic in the weeks leading up to admission, requiring bronchial artery embolization. Following ETI treatment, auscultatory findings and FEV_1 changes may be less significant, making the detection of respiratory exacerbation more challenging. This highlights the need for heightened vigilance in managing such cases and underscores the challenge of diagnosing and managing exacerbations in the era of modulators. Long term real-world studies are essential to comprehend the evolving course of the disease during ETI treatment.

1. Introduction

Treatment of cystic fibrosis (CF) has primarily focused on managing symptoms. In the last ten years, the introduction of highly effective CFTR modulators, particularly elexacaftor-tezacaftor-ivacaftor (ETI) therapy has dramatically transformed the landscape of CF care [1,2].

Multiple clinical trials and real-world observational studies have consistently highlighted the clinical benefits of ETI therapy. These benefits include improved nutritional status, reduced sweat chloride concentration (SwCl) and respiratory exacerbations rate, and an overall enhancement in health-related quality of life [3,4].

The improvement in pulmonary function, assessed through forced expiratory volume in one second (FEV1), ranges from 8 to 14 percentage points [5,6]. Patients treated with ETI show enhanced lung ventilation, reduced mucus plugging and airway wall thickening, and improved morphology and perfusion scores. Computed tomography (CT) is the method of choice for CF imaging, due to its widespread availability and expertise [7]. However, magnetic resonance imaging (MRI) can also assess efficacy, offering significant advantages in functional imaging and allowing frequent monitoring without exposing patients to radiation [8,9].

Before the introduction of highly effective modulators, CF exacerbations typically presented with increased sputum production, decline in respiratory function tests, dyspnoea, and weight loss. Hemoptysis may also occur, indicating a severe complication associated with chronic bronchial ischemia and inflammation [10].

Despite the proven efficacy of ETI, some patients, especially those who had already developed lung damage before the start of the treatment, may still experience respiratory exacerbations [5]. These episodes may present with symptoms different from the pre-modulator era. We present the case of a young woman with CF who, after three years of ETI treatment, experienced haemoptysis during an episode of pulmonary exacerbation, without any other distinctive symptoms.

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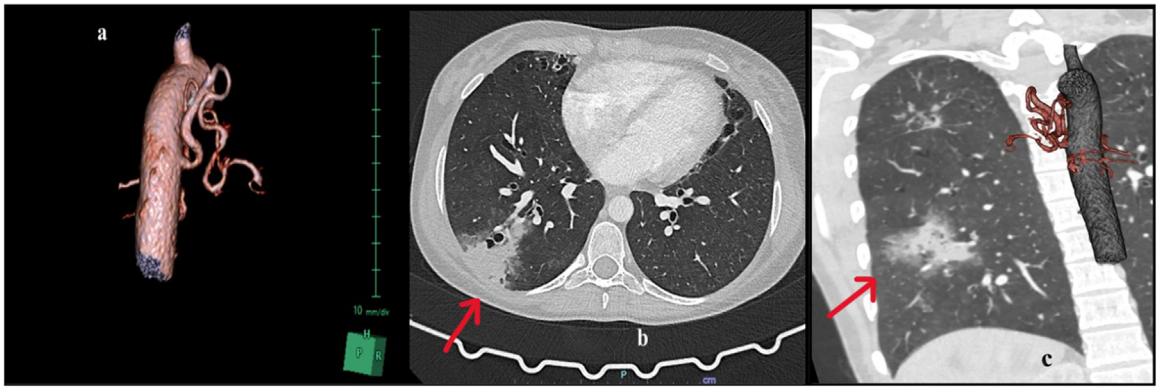

Figure 1. (a) 3D angio CT reconstruction of the right hypertrophic bronchial artery emerging from the descending aorta; (b) Axial CT image of parenchymal consolidation in the superior segment of the right lower lobe; (c) 3D angio CT reconstruction of the right hypertrophic bronchial artery and coronal CT section of the right lower lobe parenchymal consolidation.

2. Case report

On September 18, 2023, a 20-year-old woman with CF, treated with ETI for the past three years, was admitted to our hospital due to a severe episode of hemoptysis. The patient was a carrier of the deltaF508 mutation, the most common pathogenetic variant worldwide, and the milder L1077P mutation, which together can cause typical cystic fibrosis symptoms with varying severity [11].

She was pancreatic insufficient and presented a moderate-severe lung disease, and a chronic pulmonary colonization by *Pseudomonas aeruginosa* (PsA) and *Achromobacter xylosoxidans*. She successfully completed treatment for *Mycobacterium abscessus* infection in February 2022.

The patient suffered also of multiple documented allergic reactions to antibiotics, including beta-lactams, aminoglycosides, fosfomycin, and colistin, and of a documented peripheral sensory neuropathy, likely induced by linezolid.

The response to ETI therapy was remarkable, with a significant improvement in FEV_1 (from 2.02 to 2.98 L after 6 months of therapy), and a reduction in sweat chloride concentrations (from 117 mEq/L before treatment to 54 mEq/L after 12 months). During the three years of ETI therapy, there was no further need for antibiotic treatment.

In early July 2023, she experienced her first episode of mild hemoptysis, occurring approximately one week before her menstrual cycle, without any other symptoms. The patient was assessed at the CF center and found to be in good general condition with stable weight, a normal BMI (24.6 kg/m^2), and normal vital signs (oxygen saturation of 100% in room air, heart rate of 87/min, and blood pressure of 117/84 mmHg). Her respiratory examination showed no significant abnormalities, but there was a notable decrease in forced expiratory flow (FEF 25-75) to 2.68 L/s, a reduction of 640 mL from the previous spirometry. There were no significant changes in FEV1 (3.16 L) and forced vital capacity (4.04 L).

No other symptoms have been reported since mid-September 2023, when a second episode of moderate hemoptysis was followed by a more concerning third episode a few hours later, during which she expectorated 150 mL of blood and experienced chest pain without any other typical symptoms of pulmonary exacerbation. Interestingly, the patient had been entirely asymptomatic in the weeks leading up to admission.

Upon admission, her blood tests showed an increase in inflammatory markers (C-reactive protein: 8.26 mg/dL, White blood cells: 12.050/mmc), supporting the diagnosis of acute pulmonary exacerbation. The coagulation indices were normal. Aspergillus infection was ruled out, with total IgE measuring 85 kUA/L and specific IgE and IgG for Aspergillus showing no reactivity. Serum galactomannan and beta-D-glucan assays also produced negative findings.

Considering her multi-allergic status, and her recent sputum culture positive for PsA, intravenous therapy with a single antibiotic, levofloxacin, along with tranexamic acid was started. A contrast-enhanced chest CT-scan showed multiple bronchial arteries originating from the proximal descending thoracic aorta, with diameters ranging from 3 to 5 millimeters and with a tortuous course towards the right pulmonary hilum (Figure 1a). Furthermore, the imaging identified a parenchymal consolidation in the posterior part of the right lower lobe, characterized by a denser central area, air bronchogram, and peripheral ground-glass attenuation (Figure 1b and c). Another smaller area of parenchymal consolidation was visible at the right upper lobe. Above the right diaphragm, there were small areas of micronodular ground-glass attenuation suspected as interstitial inflammation. Given the worsening of the radiological findings, trimethoprim/sulfamethoxazole was added to the ongoing intravenous antibiotic therapy. Ten days later, a chest MRI was performed, revealing a partial reduction in the size of the right posterior lower lobe consolidation, with a maximum diameter of approximately 4 cm.

In early October, bronchial arteries embolization procedure was performed in local anesthesia with selective catheterization of the right bronchial branch, which was found to be ectasic with multiple peripheral pathological vascularization (Figure 2a and b). Super-selective catheterization was performed using a 2.7 Fr microcatheter to prevent non-target embolization, followed by embolization using 500-700-micron polyvinyl alcohol particles mixed with iodine contrast. The procedure concluded upon achieving flow reduction, without any procedural complications.

Unfortunately, following the initiation of ETI treatment, the patient was unable to produce sputum, and given the recent episode of hemoptysis, an induced sputum test to rule out Mycobacterial infection was not performed. The patient was discharged after 23 days in good conditions. One month later, MRI was conducted and revealed a remarkable reduction in the parenchymal right lower lobe consolidation, with no further parenchymal consolidations observed at this time (Figure 3). Spirometry also indicated notable improvements in FEF 25-75% (+400 mL) and FEV1 (+100 mL) compared to the spirometry performed in July.

3. Discussion

Numerous clinical studies and real-world observations have confirmed the remarkable efficacy of ETI in individuals with CF carrying the F508del CFTR mutation [5,12]. The clinical benefits

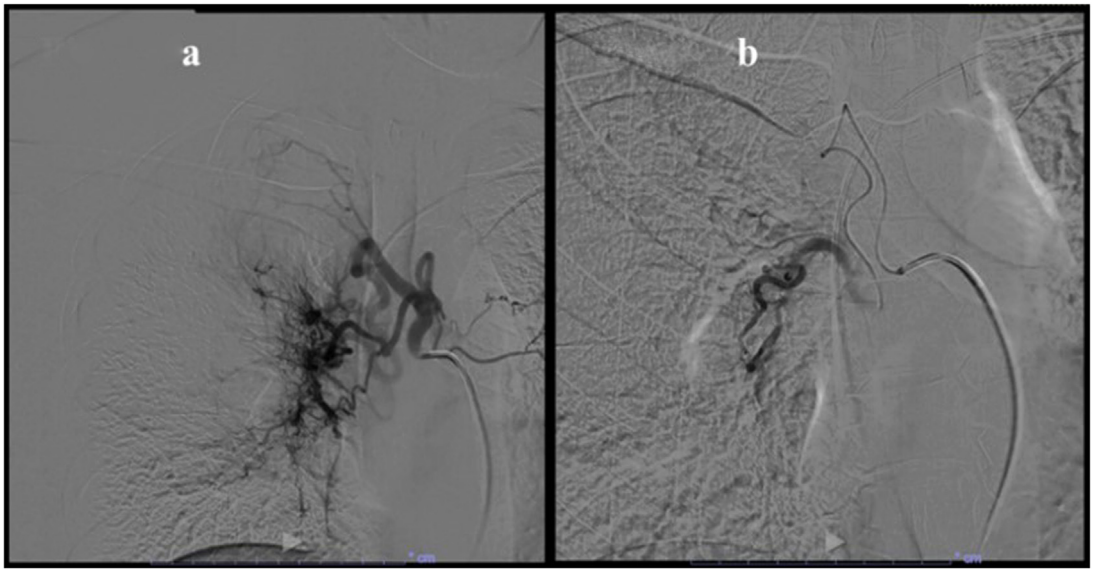

Figure 2. (a) Angiography of the right bronchial artery with ectatic vessels and pathological vascularization; (b) Angiography after embolization with occlusion of distal bronchial branches.

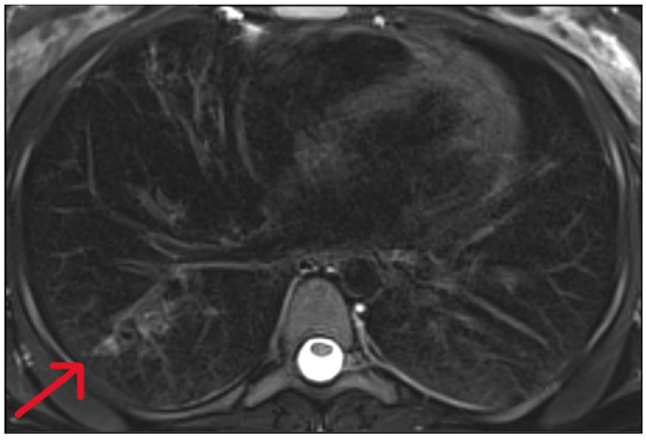

Figure 3. MRI T2 weighted axial image of thorax showing a significant reduction in the previous consolidation.

were observed in both patients previously exposed to modulator therapies and those who are modulator-naïve, with minimal documented adverse events [5,12].

Our patient experienced an unexpected, severe pulmonary exacerbation, marked by an episode of severe hemoptysis, without other symptoms, despite three years of ETI therapy. Notably, she had been entirely asymptomatic in the weeks preceding admission. As far as we know, there are currently no reports in the literature describing the clinical manifestations of respiratory exacerbations in patients treated with ETI. In the era of modulators, the diagnosis of respiratory infections becomes more challenging, as most patients experience a reduction and sometimes even the disappearance of both cough and sputum.

Respiratory exacerbations in CF patients undergoing ETI treatment may occur not only less frequently but also manifest with different and more subtle symptoms than previously observed. Auscultatory findings may also be misleading, and FEV_1 may exhibit limited significant changes. Furthermore the

heterogeneity of phenotypic manifestations in CF can vary not only based on patient-specific mutations but also on the severity of the underlying lung disease at the onset of modulator treatment. Therefore, caution is necessary in managing these cases. Physicians specializing in CF care must learn to recognize symptoms that differ from those observed in the past to promptly identify potentially critical situations. Deterioration in FEF 25-75% and multiple breath washout could serve as early markers of pulmonary exacerbation. However, large studies are needed to better define recommendations for managing these patients, including subgroup analysis based on the severity of pre-existing disease.

In conclusion, our case underscores the importance of vigilance in managing CF patients undergoing ETI therapy. Additionally, there is an urgent need for new non-invasive methods beyond surveillance to enable the identification of potentially responsible pathogens for pulmonary exacerbations.

Declarations of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Author contributions

Chiara Lanfranchi: Writing – review and editing. **Carmela Rizza:** Writing–review. **Maria Chiara Russo:** Writing–review. **Irene Borzani:** Writing–review. **Salvatore Alessio Angileri:** Writing – review. **Erica Nazzari:** Writing – review. **Gianfranco Alicandro:** Writing review and editing. **Francesco Blasi:** Writing–review. **Valeria Daccò:** Conceptualization; writing review and editing.

References

[1] Flume PA, Harris RS, Paz-Diaz H, et al. Long-term tezacaftor/ivacaftor safety and efficacy in people with cystic fibrosis and an F508del-CFTR mutation: 96-week, open-label extension of the EXTEND trial. *J Cystic Fibrosis* 2023;**22**(3):464–70.

[2] Bacalhau M, Camargo M, Magalhães-Ghiotto GAV, et al. Elexacaftor-tezacaftor-ivacaftor: a life-changing triple combination of CFTR modulator drugs for cystic fibrosis. *Pharmaceuticals* 2023;**16**(3):1–42.

[3] Kapouni N, Moustaki M, Douros K, Loukou I.. Efficacy and safety of elexacaftor-tezacaftor-ivacaftor in the treatment of cystic fibrosis: a systematic review. *Children* 2023;**10**(3):1–23.

[4] Gifford AH, Taylor-Cousar JL, Davies JC. McNally P. Update on clinical outcomes of highly effective modulator therapy. *Clin Chest Med* 2022;**43**(4):677–95.

[5] Bower JK, Volkova N, Ahluwalia N, et al. Real-world safety and effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: interim results of a long-term registry-based study. *J Cystic Fibrosis* 2023;**22**(4):730–7.

[6] Nichols DP, Paynter AC, Heltshe SL, et al. Clinical effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis—a clinical trial. *Am J Respir Crit Care Med* 2022;**205**(5):529–39.

[7] Joyce S, Carey BW, Moore N, et al. Computed tomography in cystic fibrosis lung disease: a focus on radiation exposure. *Pediatr Radiol* 2021;**51**(4):544–53. doi:10.1007/s00247-020-04706-0.

[8] Bec R, Reynaud-Gaubert M, Arnaud F, et al. Chest computed tomography improvement in patients with cystic fibrosis treated with elexacaftor-tezacaftor-ivacaftor: early report. *Eur J Radiol* 2022;**154**:110421.

[9] Graeber SY, Renz DM, Stahl M, et al. Effects of elexacaftor/tezacaftor/ivacaftor therapy on lung clearance index and magnetic resonance imaging in patients with cystic fibrosis and one or two F508del alleles. *Am J Respir Crit Care Med* 2022;**206**(3):311–20.

[10] Roussel A, Sage E, Roux A, et al. Bronchial artery embolization for hemoptysis in adult patients with cystic fibrosis: a single-center retrospective study. *Acta radiol* 2023;**64**(4):1381–9.

[11] Bozon D, Zielenski J, Rininsland F, et al. Identification of four new mutations in the cystic, 3. *Hum Mutat* 1994;**3**(3):330.

[12] Taylor-Cousar JL, Robinson PD, Shteinberg M, Downey DG. CFTR modulator therapy: transforming the landscape of clinical care in cystic fibrosis. *Lancet* 2023;**402**(10408):1171–84.