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Multiple life-threatening complications in a patient who received lung transplantation due to cystic fibrosis and their management

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Abstract

Cystic fibrosis patients may be considered for lung transplantation. Although these patients may experience more successful outcomes and survival rates compared to others, various complications can arise. In particular, infectious complications and septic deaths may be more prevalent in cystic fibrosis patients compared to other lung transplant indications. Considering all these factors, recognizing and managing complications that may arise during the postoperative period in this patient group are of critical importance. In this article, multiple life-threatening complications occurring in the post-transplant period in a patient who underwent lung transplantation due to cystic fibrosis are chronologically presented, and their management is discussed.

Keywords: Lung transplantation, cystic fibrosis, complications

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Introduction

When cystic fibrosis involves the lungs, recurrent respiratory tract infections due to bronchiectasis and progressive airway inflammation can lead to chronic respiratory failure.[1] Progressive respiratory failure is a major cause of mortality in these patients. If deemed suitable, lung transplantation may be considered as a final treatment approach. Although lung transplantation for cystic fibrosis tends to yield more successful outcomes and longer survival times compared to other indications, various complications can arise post-transplantation.[2]

The majority of these complications, particularly in patients monitored under immunosuppressive therapy, are opportunistic infections. This article presents a case of lung transplantation due to cystic fibrosis, detailing postoperative psychiatric complications, paralytic ileus secondary to *Clostridium difficile* infection, infections secondary to multidrug-resistant microorganisms, and significant infectious complications such as *Cytomegalovirus* (CMV) and COVID-19 pneumonia, along with gastrointestinal complications, and their management.

Methods

The reporting of this study conforms to the CARE checklist (Supplemental Material).[3]

Case report

Despite complaints since childhood, the 41-year-old patient was diagnosed with cystic fibrosis in 2012 and was being followed for lung involvement and chronic pancreatitis (Figure 1). Additionally, he had a history of depression as a comorbidity. The patient who had undergone cystic fibrosis genetic mutation testing was not receiving modulator treatment because the mutation result was not suitable for the use of CFTR modulator. Patient, who had *Pseudomonas aeruginosa* colonization for 9 years and finally both *P. aeruginosa* and *Staphylococcus aureus* colonization, was receiving appropriate inhaled antibiotic treatment according to the sensitivity of the agent in the preoperative period (colistin/tobramycin/amikacin) (inhaled treatment appropriate to the agent was continued in the early postoperative period). He had also been using long-term oxygen therapy at home for 3 years due to chronic respiratory failure. There was no respiratory function test during this period

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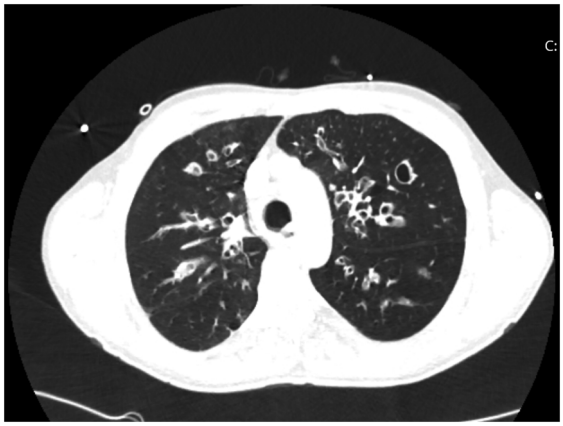

Figure 1. Preoperative chest CT.

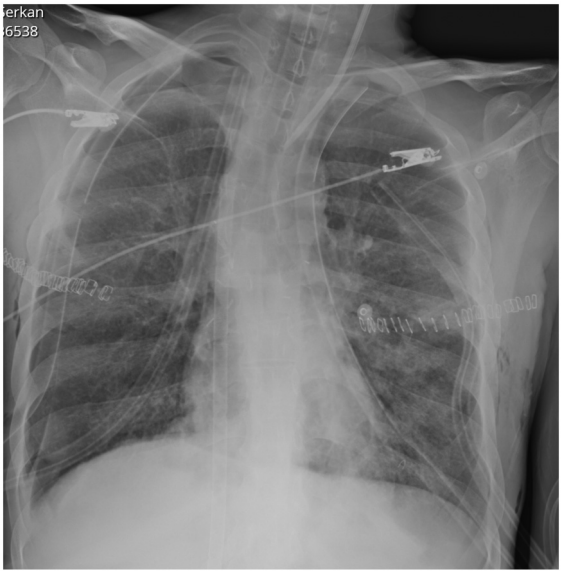

Figure 2. Postoperative chest X-ray.

because the patient was oxygen-dependent and could not provide sufficient effort in respiratory function tests.

As the patient's overall condition deteriorated during this period, with increasing exacerbations requiring hospitalization, preparations were made for lung transplantation, and the patient underwent bilateral lung transplantation (Figure 2). The procedure was started from the right hemithorax. When the right pulmonary artery and veins were clamped by rotation, desaturation and hypotension were observed and the patient was applied femoral A-V extracorporeal membrane oxygenation (ECMO). Following bilateral lung transplantation, the patient was taken to the intensive care unit under ECMO support. The patient, whose saturation and blood pressure were stable on the first postoperative day, was separated from ECMO, and extubation was performed on the second day. Due to the absence of problems other than psychiatric symptoms such as insomnia and anxiety during intensive care monitoring, the patient was transferred to the ward on the tenth postoperative day. Intermittent noninvasive mechanical ventilation support was applied in the ward.

To facilitate the transfer of information, the complications that arose in the postoperative period will be described chronologically, divided into time intervals.

Days 5 to 25

During this period, psychiatric complications were prominent in the patient. On the fifth postoperative day, symptoms such as fear of death, anxiety, and insomnia emerged. The patient was evaluated by a psychiatric specialist, and lorazepam was initiated. However, following the commencement of the medication, carbon dioxide retention occurred. Consequently, the patient, re-evaluated by the psychiatric specialist, had lorazepam discontinued, and mirtazapine was initiated. On the 13th postoperative day, delirium developed during ward follow-up, and haloperidol was added to the treatment.

Days 25 to 40

During this period, the patient exhibited gastrointestinal symptoms. On the 26th postoperative day, the patient developed symptoms of fever, abdominal pain, and diarrhea. Culture of stool did not show any growth, but *C. difficile* was detected as positive through polymerase chain reaction (PCR) method. In response, the patient was initiated on metronidazole and vancomycin treatment. A few days after the onset of diarrhea, the patient developed a fever. Treatment for *extensively drug-resistant (XDR) Klebsiella pneumoniae*, previously found in the patient's urine but not considered as the causative agent, was expanded to include ceftazidime/avibactam. In the following days, as the patient developed abdominal distension and fecal incontinence, the diagnosis of paralytic ileus led to the addition of pyridostigmine to the treatment plan. Meanwhile, due to the

patient's diarrhea and nutritional issues, lymphatic leakage developed at the site of ECMO entry in the right inguinal area. Surgical revisions were performed 3 times. By the 40th postoperative day, the patient's symptoms came to an end.

Days 40 to 60

During this period, there was a progression in the patient's psychiatric symptoms. In addition to the fear of death and insomnia, the onset of eating disorders led to a reorganization of the psychiatric treatment. The patient's psychiatric symptoms were also impacting overall treatment compliance. On the 60th postoperative day, despite the application of bi-level positive airway pressure, hypercapnia deepened. With the onset of a tendency towards sleep, the patient was readmitted to intensive care.

Days 60 to 90

During this period, infectious complications were prominent in the patient. One of the samples taken due to the fever was a swab for COVID-19. On the 63rd postoperative day, the patient's COVID-19 PCR test resulted positive (Figure 3). With increasing dyspnea, tachypnea, and oxygen requirements, the patient was intubated, and invasive mechanical ventilation was initiated. They were placed in the prone position after sedation and paralysis. Meanwhile, the steroid dose used for lung transplantation was increased, and a total of 90 g of intravenous immunoglobulin (IVIG) was administered over a 5-day period. The microbiological samples were initially assessed, and considering the patient's risk factors, empirical treatment with meropenem, ertapenem, daptomycin, and inhaled colistin was initiated. The body temperature dropped to 33 °C, and the heart rate decreased to 40 beats per minute, leading to sinus bradycardia. During this period, the patient underwent protective mechanical ventilation and supportive therapies. In the respiratory sample of the patient, *panresistant P. aeruginosa* and *XDR K. pneumonia*, along with *multidrug-resistant (MDR) K. pneumonia* in the urine, were cultured. Fosfomycin was added to the ongoing antibiotic therapy. Anticipating prolonged intubation, a tracheostomy was performed on the fifth day of intubation. On the 73rd postoperative day, the patient, who also experienced melena-like stool passage, was evaluated by the gastroenterology clinic and was recommended for conservative monitoring. On the 75th postoperative day, the patient developed septic shock, and vasopressor treatment was initiated. During this period, with decreasing urine output and a positive fluid balance, the patient responded well to diuretic infusion. In the following days, a peripheral blood and catheter blood microbiological examination, prompted by hyperthermia, reported only fosfomycin-sensitive *K. pneumoniae*. In deep tracheal aspirate samples, cultures of *Achromobacter xylosoxidans* were reported. As a result, the patient's antibiotic therapy was reorganized (fosfomycin and cubistin were discontinued, colistin was added parenterally, and high-dose meropenem was initiated with a prolonged infusion). Additionally, yeast and *Pseudomonas fluorescens* cultures were reported in the deep tracheal aspirate sample. Considering clinical, radiological, and laboratory findings, these were also considered as causative agents, leading to a revision of the patient's antimicrobial therapy with the inclusion of antifungal treatment. On the 90th postoperative day, the patient's COVID-19 PCR test resulted negative.

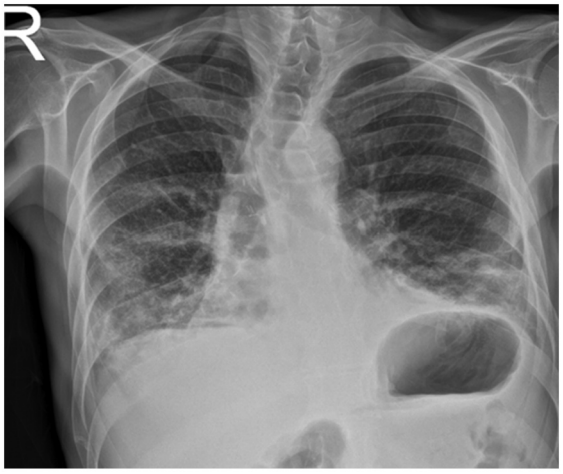

Figure 3. Chest X-ray after COVID-19 positivity.

Days 90 to 100

During this period, the patient continued to experience gastrointestinal symptoms and psychiatric issues. The patient, experiencing delirium and anxiety, had challenges with treatment adherence. One of the most significant issues among these challenges was inadequate nutrition. Evaluated daily by psychiatry, the decision was made to address the ongoing nutrition issues by performing a percutaneous endoscopic gastrostomy (PEG).

The patient, who experienced bleeding around the PEG site and subsequently developed hematochezia, underwent endoscopy. The endoscopic examination revealed fresh blood and clots in the stomach, along with an ulcerated area at the PEG exit site. Despite attempts to control the bleeding through endoscopic interventions, the patient underwent surgery to achieve hemostasis. The previous PEG site was closed, and a new PEG was applied.

Days 100 to 128

The patient's infection with multidrug-resistant microorganisms persisted. During intensive care monitoring, cultures at different times reported the growth of *Corynebacterium striatum*, *Acinetobacter baumannii*, *K. pneumoniae*, and *P. aeruginosa*. If considered as causative agents, appropriate antibiotic therapy was administered. With radiological and clinical infectious signs regressing, the patient, conscious, oriented, and cooperative, was readmitted to the ward on the 128th postoperative day. In the ward, the patient was monitored with home ventilation.

Days 128 to 150

During ward follow-up, consolidation development was observed in the lung X-ray of the patient, and CMV DNA testing resulted positive. Since the patient was already under valganciclovir prophylaxis, an increase in valganciclovir treatment dose was initiated upon the emergence of CMV pneumonia. Pneumonia symptoms regressed under treatment. Within the framework of a pulmonary rehabilitation program, the patient's mobilization was achieved with the assistance of a physiotherapist. The patient was nourished orally and through PEG. With a stable overall condition, arterial blood gas results, and vital signs during follow-up, the patient, whose need for in-hospital care ceased, was discharged with home ventilation in the fifth month postoperatively.

After the conclusion of the hospital process, the patient's outpatient follow-ups were continued. With no further need for home ventilation during follow-up, the patient was decannulated 4 months after discharge.

Discussion

In our article, the complications developed during the postoperative period of our case, who underwent lung transplantation due to cystic fibrosis, respiratory failure, and frequent resistant infections leading to frequent hospitalizations, are shared chronologically. The importance of collaboration between the patient, their relatives, and healthcare professionals, as well as the multidisciplinary approach, is once again emphasized through this process.

Patients with cystic fibrosis have a longer survival period after lung transplantation compared to other indications. A report published by the International Society for Heart and Lung Transplantation in 2019 stated a median survival of 9.9 years.[4] Infections are a leading cause of death in the post-transplantation period. The causes of septic death in cystic fibrosis patients are higher compared to other indications such as interstitial lung disease, emphysema, and pulmonary hypertension.[5] Due to the high incidence of chronic suppurative lung infections in these patients, post-lung transplant infections can be serious and life-threatening. In the pre-transplant period, the most common microorganism colonizing the sinuses and airways in cystic fibrosis patients is *P. aeruginosa*.[6] This microorganism continues to be the most common cause of bronchopulmonary or sinus infections in the post-lung transplantation period.[7] Additionally, Vos et al[8] have emphasized that airway colonization with *P. aeruginosa* after lung transplantation may increase the risk of developing bronchiolitis obliterans syndrome (BOS). Our patient had been colonized with *P. aeruginosa* for 9 years during the pre-transplant period, and in the last few years, *S. aureus* was also detected as another colonizing agent. Despite starting antibiotic prophylaxis covering these agents in the early postoperative period, we encountered another gram-negative bacterium as the causative agent for the initial infection. It is considered that the likelihood of encountering *P. aeruginosa* in the later stages of hospitalization is higher due to prolonged hospital stay, antibiotic use, and the severity of the disease.

During the ongoing pandemic, COVID-19 pneumonia has emerged as a significant risk for lung transplant recipients undergoing immunosuppressive therapy in the postoperative period. Various studies from different countries have reported varying mortality rates associated with COVID-19 in lung transplant patients. In a study conducted in Spain, examining 44 lung

transplant recipients, the mortality rate was reported as 39%. Another study from the United States, which included 30 patients, reported a mortality rate of 33%.[9,10] In a study published by Kamp et al[11] from Germany, data from 31 lung transplant recipients were analyzed. It was reported that 84% of patients were hospitalized, with dyspnea being the most common symptom. More than 50% of those hospitalized required intensive care, and approximately one-third of them died due to disease. The overall mortality rate in this study was 46%. In a series encompassing all French lung transplant centers, 35 patients were evaluated.[12] In this series, 71% of patients were hospitalized, and 37% required intensive care. Among the patients monitored in the intensive care unit, 53.8% received mechanical ventilation. In 34.3% of patients, a lung superinfection of bacterial or fungal origin was added to the existing clinical picture. The mortality rate among the critically ill patients in this series was 30.7%, and the overall mortality rate was 14.3%. There are also studies in the literature investigating the effects of COVID-19 on patients who have undergone lung transplantation due to cystic fibrosis. A study investigating the factors that lead to serious outcomes following COVID-19 infection in patients with cystic fibrosis reported an increased risk of death in those who underwent lung transplantation.[13] In line with this, another study stated that lung transplantation and moderate-severe lung disease were independent risk factors for serious outcomes after COVID-19.[14] In our case, prior to admission, intermittent noninvasive mechanical ventilation support was provided in the ward. With the onset of COVID-19 pneumonia, respiratory support was intensified, eventually leading to endotracheal intubation. Additionally, anticipating prolonged intubation needs in the patient, a tracheostomy was performed on the fifth day of intubation. Despite ongoing treatment for secondary bacterial and fungal infections during the extended intensive care period, the patient's COVID-19 PCR test yielded a negative result on the 30th day of intensive care admission. In a consensus approach derived from guidelines of the transplantation society, reducing immunosuppression has been suggested as a moderate recommendation.[15] Before testing positive for COVID-19, our patient was on a triple immunosuppressive treatment consisting of a calcineurin inhibitor, corticosteroid, and antimetabolite therapy. We increased the steroid dose used for COVID-19 treatment. The patient's platelet and leukocyte counts were too low during this period to allow for the use of antimetabolites. Additionally, IVIG therapy was administered for 5 days. In this vulnerable patient group, especially due to their high risk of morbidity, high-dose immunosuppressive regimens, limited respiratory reserves, and significant allograft dysfunction rates, increased mortality and morbidity associated with COVID-19 have been observed. Therefore, caution should be exercised in managing these patients.

CMV is the most common opportunistic infection following human lung transplantation.[16] In a study involving 231 lung transplant recipients, Snyder et al[17] demonstrated that post-transplant CMV pneumonia led to an increased risk of BOS (hazard ratio [HR] = 2.19, $P = .001$) and shorter post-transplant survival (HR = 1.89, $P = .02$). Currently, antiviral prophylaxis with ganciclovir or valganciclovir has become standard in lung transplant centers to limit CMV and graft dysfunction.[18] In our clinic, we routinely apply prophylaxis to post-transplant patients with IV ganciclovir until oral intake is initiated, and afterward, we switch to valganciclovir. Additionally, CMV immunoglobulin is used in serologically high-risk patients (donor-positive, recipient-negative). Our patient was also receiving prophylaxis with valganciclovir. Despite this, in the event of CMV pneumonia development, the patient's antiviral treatment was adjusted by escalating from the prophylactic dose to the therapeutic dose, resulting in regression of pneumonia symptoms under treatment.

C. difficile colitis is a rare but potentially serious complication following lung transplantation. Clinical symptoms can range from mild diarrhea to severe fulminant colitis with septic shock.[19] Treatment with metronidazole or vancomycin should be initiated promptly. Surgical intervention is mandatory in cases of perforation and may be necessary in severe cases where medical treatment is insufficient or improvement is not observed.[20] Risk factors for the development of *C. difficile* colitis include antimicrobial use, prolonged hospitalization, advanced age, recent surgery, and immunosuppression.[21,22] In a study investigating the development of *C. difficile* infection in solid organ transplant recipients,

Stelzmueller and colleagues[23] reported the highest incidence rates in liver and pancreas transplant recipients, while the most severe cases requiring surgical intervention were observed in heart and lung transplant recipients. In a study by Lee and colleagues,[21] which included 151 patients who underwent lung transplantation, they reported that 22.5% of the patients developed *C. difficile* infection, and one of them underwent colectomy due to fulminant colitis. Furthermore, the development of *C. difficile* was associated with an increased death rate, although it did not reach statistical significance. When compared to other patients in the same hospital during the same time period, this study showed that the rate of developing *C. difficile* infection in lung transplant recipients was 2.5 times higher. This situation can arise in lung transplant recipients due to factors such as a history of frequent pulmonary infections requiring antibiotic use, recurrent hospitalizations before transplantation, and the need for high doses of immunosuppressive therapy in the postoperative period. Dallal and colleagues,[22] in their study examining patients who developed *C. difficile* colitis while hospitalized, reported that 31% of lung transplant recipients had proven *C. difficile* colitis, and 13% of them developed fulminant colitis. The overall mortality rate was 50%. The likelihood of having *C. difficile* colitis in lung transplant recipients is 46 times higher compared to others. When compared to other patients, lung transplant recipients were also shown to have a higher probability of having fulminant symptoms (13% vs 1.6%, $P < .001$). However, the mortality rate was found to be similar. Additionally, in this study, it was revealed that 32% of patients who underwent colectomy and 65% of patients in the autopsy group were immunocompromised individuals. Our patient was investigated for fever, abdominal pain, and diarrhea symptoms in the postoperative period. In the bacteriological examination of stool, no leukocytes or erythrocytes were observed, and there was no growth; however, *C. difficile* toxin was detected. Following the initiation of antibiotic treatment, the patient developed paralytic ileus as a complication. Issues such as impaired wound healing due to diarrhea were encountered. The patient's symptoms resolved under medical treatment, 14 days after the diagnosis of colitis. In potential lung recipients with cystic fibrosis, especially those with a history of previously developed pseudomembranous colitis, it should be known that there may be persistent *C. difficile* carriage in the intestines. Considering the intensity of existing risk factors, vigilance should be exercised for the development of post-transplant colitis in patients.

Candidates for lung transplantation often experience psychiatric disorders, particularly in the context of end-stage lung disease. One study has shown that lower FEV1, recent occurrence of hemoptysis/pneumothorax, and listing status for lung transplantation were associated with more symptoms of depression in patients with cystic fibrosis.[24] In a study involving 30 patients who underwent lung transplantation, Woodman et al[25] reported that major depressive disorder and generalized anxiety disorder were the most commonly observed psychiatric conditions, and some patients received multiple psychiatric diagnoses. Moreover, this study indicated no significant differences in outcomes such as organ rejection, bronchiolitis obliterans development, or treatment noncompliance between recipients with a psychiatric history and those without. This might be attributed to the fact that all patients included in the study underwent psychiatric evaluations before transplantation, and if necessary, received appropriate treatments. In another study conducted by Smith et al,[26] involving 251 lung transplant patients, pre-existing depressive symptoms before transplantation did not predict the risk of death. However, depressive symptoms identified immediately after hospital discharge ($P = .012$) or after completion of rehabilitation ($P = .013$) were associated with an increased risk of death. Depressive symptoms detected 3 months after transplantation were shown to be associated with mortality ($P = .021$) and lower exercise capacity ($P = .039$). Additionally, in secondary analyses, depressive symptoms independently predicted chronic lung allograft dysfunction (CLAD) (HR = 1.29 [1.01, 1.65], $P = .045$) and the composite outcome of CLAD and mortality (HR = 1.30 [1.09, 1.56], $P = .005$).

Our patient also experienced psychiatric symptoms in the post-transplant period, including fear of death, anxiety, insomnia, resistance to treatment approaches other than medication, and nutritional disorders. This situation complicated the patient's adherence to treatment and negatively affected the recovery process. The patient being fed through a PEG tube due to nutritional disorders also led to gastrointestinal complications

such as bleeding. Therefore, it is crucial to conduct thorough screenings for lung transplant candidates before transplantation and optimize their psychiatric conditions. This is of utmost importance for improving post-transplant outcomes.

Conclusion

Given the high incidence of chronic suppurative lung infections in cystic fibrosis patients and the effects of postoperative immunosuppressive therapy, serious and life-threatening infections, as well as various complications, can occur after lung transplantation. However, with appropriate treatment strategies and a multidisciplinary approach, these complications can be controlled. Despite the emergence of serious complications after lung transplantation, this case has successfully returned to daily life with clinical improvement through proper treatment and intensive care follow-up. We believe that sharing this case and its management process will contribute to the literature.

Declarations

Ethical approval and consent to participate

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki. Written informed consent was obtained from patients included in the study.

Consent for publication

Written consent was obtained from the patient for the use of his medical data and radiological images in the case report.

Author contribution(s)

Gizem Kececi Ozgur: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft.
Ali Ozdil: Conceptualization; Methodology; Supervision; Validation; Visualization; Writing – review & editing.
Pervin Korkmaz: Conceptualization; Investigation; Methodology; Supervision; Validation; Writing – review & editing.
Tevfik İlker Akcam: Conceptualization; Methodology; Supervision; Writing – review & editing.

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Declaration of conflicting interests

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Availability of data and materials

The dataset of the research presented in this article is under record. The corresponding author can be contacted to reach the required data network.

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Supplemental material

Supplemental material for this article is available online.

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