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Case Report

Cystic Fibrosis – Alternative Therapies

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Abstract

Cystic Fibrosis (CF) is a chronic disease with progressive and irreversible degradation of lung function, being a common indication for lung transplantation. At the stage of inclusion in the transplant list, the risk of death is already extremely high.

We are presenting a clinical case of a 17-year-old adolescent with CF, severe mixed chronic respiratory failure, and chronic infection by methicillin-resistant *Staphylococcus aureus*, in the awaiting list for lung transplantation. Despite the use of non-invasive ventilation for long periods and continuous oxygen therapy, presented more frequent respiratory exacerbations, with an increased number of cycles of intravenous antibiotics. There were a clinical improvement and reduction in the number of hospitalizations after initiation of treatment with inhaled vancomycin. However, he presented progressive worsening of dyspnea in activities of daily living. After the introduction of high flow nasal cannula oxygen therapy, there was an evident improvement in signs of breathing difficulty and quality of life.

In this case report, inhaled vancomycin and high flow nasal cannula had a significant role in pre-transplant supportive treatment.

Keywords: Cystic Fibrosis; Chronic Respiratory Failure; Lung Transplant; MRSA; Inhaled Vancomycin; High Flow Nasal Cannula

Abbreviations

BiPAP: Bilevel Positive Airway Pressure; CF: Cystic Fibrosis; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator; CT: Computerized Tomography; EPAP: Expiratory Positive Airway Pressure; FEV1: Forced Expiratory Volume in One Second; FiO_2: Fraction of Inspired Oxygen; HFNC: High Flow Nasal Cannula; IPAP: Inspiratory Positive Airway Pressure; LT: Lung Transplant; MRSA: Methicillin-Resistant *Staphylococcus aureus;* NIV: Non-invasive Ventilation; O_2: Oxygen; S/T mode: Spontaneous/timed Mode; Iv: Intravenous; pCO_2: Partial Pressure of Carbon Dioxide.

Introduction

Cystic fibrosis (CF) is the most common autosomal recessive disorder in Caucasian populations that leads to chronic lung infections and recurrent respiratory exacerbations. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Over time, there have been substantial improvements in the survival of people with CF. One consequence of improving survival is the emergence of pulmonary infections with resistant pathogens, such as Methicillin-resistant *Staphylococcus Aureus* (MRSA). The chronic infection with MRSA seems to be associated with worsening of the pulmonary disease, with an accelerated decline in lung function and/or a prolonged recovery period after clinical exacerbations [1,3].

Nevertheless, progressive respiratory insufficiency remains the major cause of mortality in CF patients, and lung transplant (LT) is eventually required. Timing of listing for LT is critical, because up to 25 to 41% of CF patients have died while awaiting LT [3].

We present a case report in which inhaled vancomycin and high flow nasal cannula (HFNC) oxygen therapy were used in pre-transplant supportive treatment.

Case Presentation

We present a case of a 17-year-old male with CF (homozygous for ΔF508), with meconium ileus as the first manifestation of the disease. At this stage of disease progression, he presented with severe mixed chronic respiratory failure: forced expiratory volume in one second (FEV1) 29%, requiring continuous oxygen therapy - FiO_2 0,26 and non-invasive ventilation (NIV) - Bilevel positive airway pressure (BiPAP) around 18 hours/day. He has been on the waiting list for lung transplantation since he was 16 years old. The chest CT scan shows a decrease in the pulmonary volume of the lower lobes bilaterally conditioned by the presence of cystic bronchiectasis and diffuse ground glass opacities. These findings are also present in the chest radiograph (Figure 1). He had a chronic infection by MRSA since age 16 and intermittent infection by *Stenotrophomonas maltophilia* and *Candida parapsilosis*. For MRSA eradication therapy, he had several courses of oral rifampicin plus fusidic acid or trimethoprim/sulfamethoxazole and intravenous (iv) vancomycin, without success. Although severe exocrine pancreatic insufficiency, the body mass index was 20 kg/m^2 (P15-50). At the time he was referred to the pulmonary transplant team, the echocardiography showed adequate left ventricular function, without pulmonary hypertension.

Figure 1: Chest radiograph (anteroposterior view) showing hyperinflation, presence of linear marking due to prominence of bronchi, and bronchiectasis.

After being placed on the transplantation list, he had several hospitalizations due to respiratory exacerbations - MRSA infection and two pneumothoraxes. Given the frequent exacerbations with the isolation of MRSA and gradual worsening of respiratory difficulty, it was decided to start treatment with inhaled vancomycin. We used iv vancomycin formulation, 250 mg three times daily in the PARI eFlow® rapid nebulizer associated with oral antibiotics previously mentioned. No side effects were recorded during treatment, including bronchospasm. Within 3 months of starting this treatment, there was no further isolation of MRSA from sputum respiratory secretions.

During a new respiratory exacerbation with the isolation of *Candida Parapsilosis* and *Proteus mirabilis*, there was an increase in O_2 requirements and worsening dyspnea for small efforts. The NIV with FiO_2 0.5 was used almost continuously, limiting simple activities like personal hygiene, and feeding. As an alternative therapy, he started HFNC oxygen therapy in these periods (AIRVO™ 2 Humidification System – Flow 35 L/min; FiO_2 0,35). The respiratory rate, work of breathing, dyspnea, and consequently, quality of life immediately improved. O_2 requirements and pCO_2 remained stable (pCO_2: 40.2 mmHg before HFNC and 45.8 mmHg after starting HFNC). He maintained this ventilatory modality (BiPAP: S/T mode; IPAP 20 cmH_2O; EPAP 5 cmH_2O; rate 24 bpm; FiO_2 0,4, and HFNC: Flow 35 L/min; FiO_2 0,35) until the day he was called for lung transplantation (total 12 days).

Discussion

For most CF patients, lung disease is the most important problem in terms of symptoms and the treatment required and the fact that it is the most likely cause of death [4]. The prevalence of MRSA respiratory infection in CF has increased dramatically over the last years. A cohort study [1], shows that the presence of MRSA in the respiratory tract of CF patients was associated with a more rapid decline in lung function as measured by FEV1 percent predicted and consequently worse survival. The population of CF individuals with stringently defined persistent MRSA infection, eradication of MRSA is difficult to achieve despite an aggressive treatment regimen. The notion of inhaled antibiotics producing high concentrations at the site of infection while reducing systemic levels and effects is an attractive concept.

Some studies [5-7] use inhaled vancomycin in their MRSA eradication protocol together with oral and/or topical antibiotics. They have demonstrated it to be well-tolerated, safe, and reduces or may

even eliminate MRSA from the sputum of CF patients. (eradication success 56-86%). Results from a phase 2 study (NCT01746095) showed that participants who received vancomycin inhalation powder (AeroVanc™) experienced a significant reduction in MRSA density in their sputum compared with those given a placebo. A phase 3 study to test AeroVanc™ in adults and children over 6 years old with CF is underway (NCT03181932). In Portugal, we still don't have AeroVanc™, so we had to use the IV formulation, with a very good result. In our patient, the treatment with inhaled vancomycin played an important role in MRSA eradication and consequently reduced respiratory exacerbations.

Given to this clinical complexity, it was necessary to start a different ventilatory modality for patient comfort. HFNC oxygen therapy is a promising technique that is changing the management of patients with acute and chronic respiratory failure. The delivery of heated and humidified oxygen at high-flow rates has several positive effects on the airways and respiratory function. In addition, the device, using a comfortable nasal cannula, is exceptionally well tolerated by most patients [8,9].

A randomized clinical trial in adult CF patients [10] showed no difference is observed in HFNC compared to NIV with respect to the diaphragmatic work per breath in CF patients stabilized after a clinical indication for ventilatory support but significantly reduces the respiratory rate and the work per minute. These preliminary data suggest that HFNC may confer physiological benefits by decreasing ventilation needs and may constitute an interesting alternative or supplement to NIV. Randomized pediatric studies are needed to verify the effects of HFNC oxygen therapy in CF patients. In our patient, HFNC in complementarity with NIV improved dyspnea and, consequently, quality of life. It is important to emphasize that at the time this clinical case occurred, CFTR modulator therapies were not available in our country.

Conclusion

In CF patients with severe clinical symptoms, particularly those on the lung transplant list, alternative/supportive therapies should be considered. Inhaled vancomycin therapy reduced MRSA exacerbations and was well tolerated by our patient. Although there are few data in the literature regarding the application of HFNC therapy in chronic pathology (including CF), this can be a therapy to consider in such cases. Inhaled vancomycin and HFNC play a significant role in pre-transplant supportive treatment in our patient.

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