

Management of Chronic *Pseudomonas aeruginosa* Infection and Ventilatory Failure in Kartagener's Syndrome: Case Report

Kartagener Sendromunda Kronik Solunum Yetmezliği ve *Pseudomonas aeruginosa* Enfeksiyonunun Tedavisi

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ABSTRACT The management of chronic respiratory failure and *Pseudomonas aeruginosa* infections may be difficult in patients with Kartagener's syndrome (KS), characterized by the clinical triad of chronic sinusitis, bronchiectasis, and situs inversus. We reported an adult patient with KS suffering from a severe disease course complicated with chronic respiratory failure and frequent acute infectious exacerbations due to *P. aeruginosa* and treated with inhaled tobramycin and home mechanical ventilation. These patients are difficult to treat and to follow-up and the treatment strategies are not evidence based. Long-term ventilatory assistance at home (non-invasive mechanical ventilation, positive pressure ventilation via tracheostomy) is required for end-stage patients and inhaled antibiotics can be an alternative option for controlling acute infectious exacerbations due to resistant microorganisms without systemic toxicities. In this case report, the possible treatment alternatives for severe KS patients were discussed mainly based on the literature of cystic fibrosis experiences.

Key Words: Kartagener syndrome; tobramycin

ÖZET Kronik sinüzit, bronşektazi ve situs inversus klinik triadı ile karakterli Kartagener Sendromlu hastalarda kronik solunum yetmezliği ve *Pseudomonas aeruginosa* enfeksiyonlarının tedavisi güç olabilmektedir. Bu çalışmada, kronik solunum yetmezliği ve *P. aeruginosa*'ya bağlı sık akut enfeksiyöz ataklar nedeni ile komplike bir seyir izleyen, inhale tobramisinin ve evde mekanik ventilatör tedavisi alan Kartagener sendromlu erişkin yaşta bir olgu sunuldu. Bu olguların takip ve tedavisi güçtür ve tedavi yaklaşımları kanıt dayalı değildir. Evde uzun süreli solunum desteği (noninvaziv mekanik ventilasyon, trakeostomiyle pozitif basınçlı ventilasyon) son dönem olgular için gerekmektedir ve inhale antibiyotikler sistemik toksisite olmaksızın akut enfeksiyöz atakları kontrol etmede alternatif olabilirler. Bu olgu sunumunda daha çok kistik fibrozis deneyimlerine dayanan literatür bilgileriyle ağır seyir gösteren Kartagener sendromlu olgular için olası tedavi yaklaşımları tartışılmıştır.

Anahtar Kelimeler: Kartagener sendromu; tobramisinin

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Kartagener's syndrome (KS) is a rare condition characterized by the clinical triad of chronic sinusitis, bronchiectasis, and situs inversus described in 1933.¹ It is inherited by an autosomal recessive pattern, and this syndrome is a part of the larger group of disorders referred to as primary ciliary dyskinesia (PCD). KS occurs in 50% of patients with PCD. Clinical manifestations include chronic upper and lower respiratory tract disease resulting from ineffective mucociliary clearance and recurrent or pro-

longed pulmonary infections, which may ultimately lead to bronchiectasis. The clinical phenotype in PCD is broad and overlaps with other chronic airway diseases. Bronchiectasis tends to be age dependent and develops with the decline in lung function of PCD patients. Although PCD is considered a milder disease than cystic fibrosis (CF), a significant portion of PCD patients has severe disease with respiratory failure.² Treatment is not evidence based and recommendations are largely extrapolated from CF and other suppurative lung diseases.³ Treatment includes rigorous lung physiotherapy, prophylactic and organism-specific antibiotics and immunization against common pulmonary pathogens. Late stages of the disease may require surgical intervention for bronchiectasis or lung transplant for end-stage lung disease.⁴ In this report, we described an adult patient with KS who had a very severe disease complicated with chronic respiratory failure and frequent acute infectious exacerbations. This case report demonstrates that multidimensional treatment and follow-up approaches are required for KS patients in terms of long-term ventilatory assistance strategies and management of infectious exacerbations due to *Pseudomonas aeruginosa*, none of which are well defined in the literature.

CASE REPORT

A 34-year-old woman was hospitalized with increasing dyspnea, cough, and purulent sputum, and developed severe respiratory failure. She was transferred to the respiratory intensive care unit (RICU). She had a history of frequent sinopulmonary infections throughout her childhood and had received the diagnosis of complete triad of KS with situs inversus totalis, bronchiectasis and sinusitis when she was 9 years old. She had several hospital admissions requiring hospitalization within the previous year with infectious exacerbations mostly related to bronchial infection with *P. aeruginosa* confirmed by sputum cultures and acute respiratory failure episodes. Her pulmonary function testing results were as follows; Forced Expiratory Volume in the first second (FEV_1) 0.73 L, with FEV_1 30% predicted, forced vital capacity (FVC)

0.87 L, with FVC 30% predicted, and FEV_1/FVC 83.9%. She was regularly using bronchodilators and receiving home oxygen therapy. On physical examination, her respiratory rate was 40 breaths/min, pulse rate was 140 beats/min, blood pressure was 100/60 mmHg, and temperature was 37.2°C. Respiratory crackles were heard over the basal fields of both lungs. Cardiac auscultation revealed that the maximal impulse of the heart was at the fifth right interspace on the midclavicular line along with a loud second heart sound and a pansystolic murmur at the apex. The liver was palpable three fingerbreadths below the left costal margin. In addition, she had jugular venous distention, grade II bipedal pitting edema, and digital clubbing. A chest X-ray obtained on admission revealed dextrocardia, bilateral bronchiectasis confirmed by computed tomography (CT) of thorax (Figure 1, 2), and arterial blood gas (ABG) analysis on ambient air showed severe hypoxemia and hypercapnia (pH: 7.43, PaO₂: 41.2 mmHg, and PaCO₂: 72.8 mmHg). The results of laboratory tests revealed a high leukocyte count (15.700 cells/ μ L) and a C-reactive protein (CRP) level of 60 mg/L. Non-invasive mechanical ventilation (NIMV) with nasal



FIGURE 1: Chest X-ray revealed dextrocardia, bilateral bronchiectasis.

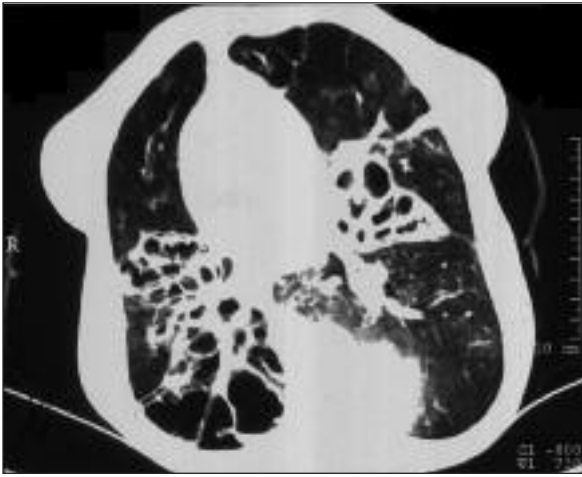


FIGURE 2: Computerized tomography of thorax: bronchiectatic changes predominantly involve the middle and lower lobes of the lungs, and dextrocardia.

mask was initiated and was switched to mechanical ventilation because of clinical deterioration after reevaluation. At day 4, weaning from mechanical ventilation was achieved and NIMV support was reinstated. Microbiological examination of bronchial lavage was positive for *P. aeruginosa* and she received a course of antipseudomonal antibiotic therapy. Chest physiotherapy, nutritional and psychiatric support were also provided during her first hospital stay in our institution. She was discharged with home NIMV therapy after 3 months of hospitalization. Oral azithromycin (250 mg/day, 3 days/week) was added for chronic *P. aeruginosa* infection treatment. One month after hospital discharge, the patient was re-hospitalized because of rapidly progressive respiratory failure requiring mechanical ventilation. Sputum culture was positive for *P. aeruginosa* sensitive to aminoglycosides including tobramycin and sputum *P. aeruginosa* density confirmed by quantitative assessment did not change. She was extubated at day 15 and NIMV support provided the stabilization of ABGs with no significant decrease in hypercapnia. Since acute exacerbations of chronic *P. aeruginosa* infection were responsible for her clinical deterioration resulting with frequent hospital admissions, inhaled tobramycin (TOBI, Chiron, Canada) was introduced for the treatment of *P. aeruginosa* infection. She received inhaled tobramycin 300 mg bid and completed three treatment cycles (28 days of drug

therapy and 28 days off drug). During inhaled tobramycin course, she did not experience any non-respiratory adverse events and sometimes had coughs and transient bronchospasm, well controlled with pretreatment bronchodilator administration. Sputum *P. aeruginosa* density decreased from 100.000 cfu/mL to 30.000 cfu/mL in the follow-up and *P. aeruginosa* remained sensitive to tobramycin in the antibiotic sensitivity test. One month after the completion of tobramycin course, she was readmitted with severe respiratory failure and mechanical ventilation assistance was initiated. Since she had several acute respiratory failure episodes despite NIMV support, her continuous ventilatory support was changed to positive pressure ventilation via tracheostomy. After 7 months of her discharge from the hospital, she had one infectious exacerbation requiring hospitalization and quantitative tracheal aspirate culture revealed 80.000 cfu/mL *P. aeruginosa*. Her last hospital stay was 5 months ago and since then she has been regularly followed-up at home and has remained free of any acute exacerbation and respiratory failure episode.

DISCUSSION

The prognosis of PCDs is generally considered good with usually a normal life expectancy. Bronchiectasis tends to be age dependent with the decline in lung function of PCD patients. PCD is considered milder than CF; a significant portion of PCD patients has severe disease with respiratory failure. Sputum flora resembles that of CF with the detection of *P. aeruginosa* in respiratory samples. This suggests that chronic failure of mucociliary apparatus may predispose to colonization and/or infection. Accordingly, it seems reasonable to recommend that patients with PCDs should be treated like patients with CF. Directed antibiotic therapy is appropriate.^{2,4,5} In most patients with bronchiectasis, airway damage is related to a combination of infection and the associated release of inflammatory mediators. By releasing proinflammatory cytokines, pseudomonal colonization is associated with more severe disease. Control of *P. aeruginosa* colonization is an important goal, as

pseudomonal infections are associated with more rapid decline in lung function.⁶ Based on the success of inhaled tobramycin for treating *P. aeruginosa* infection in patients with CF, with the improvement in pulmonary function and decreased concentration of *P. aeruginosa*, the use of inhaled tobramycin in patients with other types of bronchiectasis was assessed in some studies. The results showed symptomatic improvement, decrease in hospital admissions, as well as reduction in *P. aeruginosa* concentration in sputum, suggesting that some patients with non-CF bronchiectasis may benefit from inhaled tobramycin therapy.⁷⁻¹⁰ Considering this, we administered inhaled tobramycin treatment to our patient in order to control *P. aeruginosa* infections, which result in a decrease in the number of exacerbations and hospital admissions. During the inhaled tobramycin course, she stayed at home for 6 months, which was a relatively long hospital admission-free period taking into account her frequent hospitalizations in the previous years. In addition, sputum *P. aeruginosa* concentration was decreased without developing resistance to tobramycin. The patient tolerated well the inhalation antibiotic administrations.

Another current approach for patients with CF chronically infected with *P. aeruginosa* is to consider oral azithromycin treatment, which may be beneficial in terms of decrease in numbers of exacerbations and improvement of lung function, possibly due to the anti-inflammatory effects of macrolide antibiotics.¹¹⁻¹³ Although we decided to benefit from the positive effects of oral azithromycin in the management of our patient, she had severe infectious exacerbations requiring RICU admission when she was on azithromycin.

As mentioned previously, respiratory failure is a major problem in the management of patients with bronchiectasis and its treatment is based on the limited data in the literature. During the acute phase of chronic obstructive pulmonary disease (COPD), NIMV has been suggested as an alternative to endotracheal ventilation to aid in weaning from mechanical ventilation and as long-term ventilatory assistance at home to defer the need for tracheostomy. Some of these beneficial effects have

also been shown in patients with chronic respiratory failure due to bronchiectasis and respiratory failure.¹⁴ The hospitalization period was significantly reduced after institution of NIMV in patients with bronchiectasis, even though any effect on PaO₂ evolution and on the overall median survival could not be shown. However, a beneficial effect was observed with reduction of hospitalizations and improvement of functional status. The causes of death were mostly related to respiratory failure and cor pulmonale. Thus, long-term respiratory assistance may be required. Moreover, the results showed a rise in PaO₂ without any improvement in PaO₂.¹⁵ The probability of continuing NIMV therapy at 3 years was 48%;¹⁶ another study revealed poor results in patients with severe disease with 54% of mortality within the first year.¹⁷ In patients with CF, NIMV was able to improve respiratory status and general condition of patients with end-stage CF.¹⁸ In our case, NIMV was used to provide long-term respiratory support at home, and it allowed deferring the need for tracheostomy for up to a year. However, our patient's continuous ventilatory support necessitated a change to positive pressure ventilation via tracheostomy, since she had several acute respiratory failure episodes despite NIMV support and copious secretions were difficult to manage even with daily physiotherapy. The results of ventilation via tracheostomy were poor in patients with bronchiectasis compared with those with chronic respiratory failure secondary to other etiologies in a French series published in 1983.¹⁹ Our patient had some benefit from this treatment modality. She had only one hospitalization in the last year due to an infectious exacerbation.

Very few cases of lung transplantation were described for patients with KS. Successful heart-lung,^{20,21} en bloc double lung,²² and bilateral²³ lung transplants were reported previously. We considered this patient for lung transplantation during her first hospital admission, but this procedure is not commonly available, and the patient's socioeconomical status did not allow her to apply for another transplantation program in other locations.

In conclusion, we reported an adult patient with KS suffering from a very severe disease complicated with chronic respiratory failure and frequent acute infectious exacerbations due to *P. aeruginosa*. These patients are difficult to manage and the treatment strategies are not evidence based. This case report represents that inhaled an-

tibiotics may have beneficial effects to control acute exacerbations in patients chronically infected with *P. aeruginosa*, and long-term ventilatory assistance strategies should be given consideration. NIMV appears to be the treatment of choice and positive pressure ventilation via tracheostomy should be considered when NIMV fails.

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