DOI：10.6314/JIMT.202012_31(6).07 內科學誌 2020：31：432-436

Klebsiella Pneumoniae in Diffuse Panbronchiolitis

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Abstract

Diffuse panbronchiolitis (DPB) is a chronic, idiopathic, rare but lethal inflammatory airway disease resulting in distal airway dilation, obstructive lung disease, hypoxemia, and increased in the susceptibility of bacteria colonization. The case reports that a patient with destructive lung gets pneumonia by *Klebsiella pneumoniae* cured by bactericidal antibiotics, but *K. pneumoniae* in the airway is eradicated with erythromycin, which therefore highlights not only the importance to the testing for DPB in suspicious patients, but also the therapeutic strategies in managing DPB with *K. pneumoniae* in the airways. (J Intern Med Taiwan 2020; 31: 432-436)

Key Words: *Klebsiella pneumoniae*, Panbronchiolitis

Introduction

Diffuse panbronchiolitis (DPB) is a chronic inflammatory disease of the airways, and the diagnosis depends on the clinical symptoms, physical signs, typical chest radiographic findings, low FEV1 (< 70%) in pulmonary function tests, low arterial partial pressure (< 80 mmHg), elevated cold hemagglutinin (> 64X), and history or coexistence of chronic paranasal sinusitis. Early and accurate diagnosis is crucial to promptly deliver erythromycin that distinguishably improves patients' survival[1].

Bacteria, such as *Haemophilius influenzae*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*, are frequently isolated from the sputum in the patients with DPB[2]. Erythromycin that improves the survival of the patients with DPB in the literature also reduces *P. aeruginosa* isolated from the sputum. *P. aeruginosa* in sputum appears to accelerate the destructive process[3]. However, the role of *Klebsiella pneumoniae* in DPB has never been reported. We present a patient with DPB and *K. pneumoniae* isolated from sputum, refractory to ampicillin/sulbactam, but eradicated by erythromycin.

Case Report

A 71 year-old female, a non-smoker, with history of bronchiectasis was presented in outpatient clinic with the chronic productive cough and chest tightness for 4 years. She got dyspnea since one month ago and was admitted to our hospital. Physical examination showed that height 156 cen-

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timeter, weight 42.4 kilogram, temperature 37.8°C, blood pressure 136/79 mm Hg, heart rate 108/min and regular, and respiration rate 18/min. Breathing sound revealed crackles in both lungs. Cardiac and abdominal examinations were unremarkable. In the room air, SaO_2 was 97%, and $PaCO_2$ was 40 mmHg. Chest radiography displayed bilateral diffuse small nodular shadows and focal tram-like or linear opacities with mild hyperinflation (Fig.1). Sputum culture revealed *K. pneumoniae* which suspectible to third and fourth generation of cephalosporins, aminoglycosides, ertapenem, imepenem and resistant to ampicillin, ampicillin/sulbactam, and quinolones. After two-week therapy with ceftriaxone for her pneumonia, the symptoms improved and she was discharged.

One month later, dyspnea, cough, and sputum reurred. Serum white cell count was 6700/unit and 68.7% was neutrophil, which were in normal limits. SaO_2 was 91%, and $PaCO_2$ was 39 mmHg in the room air. Chest CT revealed diffuse centrilobular nodules with branching opacities (tree-in-bud pattern), bronchiectasis, bronchiolectasis and mosaic attenuation of lung parenchyma (Fig. 2). *K. pneumoniae* was found in sputum culture and bronchoalveolar lavage. No tuberculosis, non-tuberculosis mycobacterium, or fungus was detected in the lavage.

Cold hemagglutinin titer was 1024x (normal value: < 32X) with normal anti-Mycoplasma antibody titre. Pulmonary function test revealed FEV1/FVC 61%, FEV1 0.93L and 45% of the prediction value. Radiography of paranasal sinuses revealed increased haziness at left maxillary sinus, compatible with sinusitis (Fig. 3).

The diagnosis of DPB was confirmed. Long term low dose erythromycin(250mg two times a day) was subsequently delivered. Initially, she visited outpatient clinics, emergency department, and required hospitalization frequently. Decreased sputum volume, decrease C-reactive protein, and improvement of pulmonary function test (Fig. 4) was noted during treatment. No more *K. pneumoniae* in serial sputum cultures and decrease WBC in sputum gram stain smear was noted after 6 weeks treatment of low dose erythromycin. Her symptoms dramatically improved including not only the frequency but

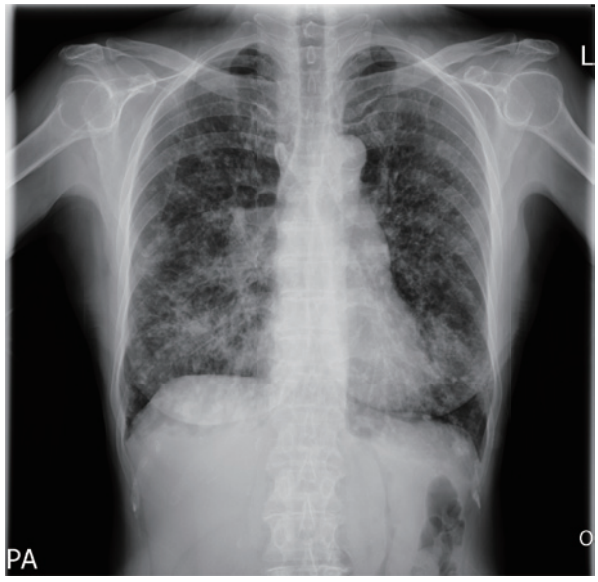

Figure 1. Chest radiography displays bilateral diffuse small nodular shadows and focal tram-like or linear opacities with mild hyperinflation.

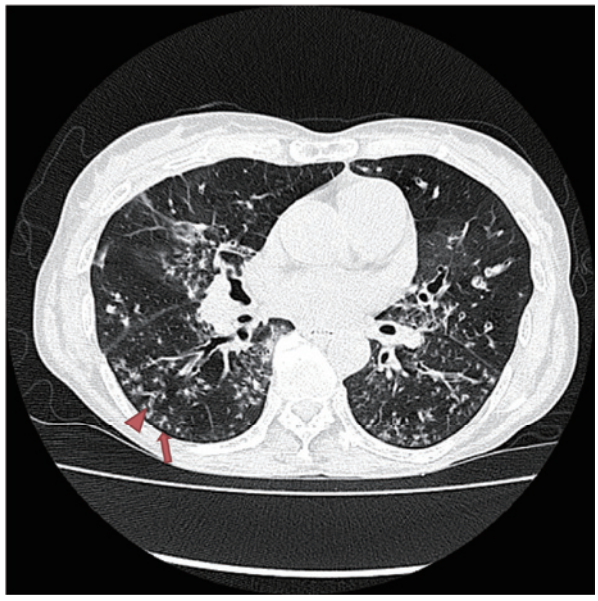

Figure 2. Chest CT reveals diffuse centrilobular nodules with branching opacities (tree-in-bud pattern) (arrow), bronchiectasis, bronchiolectasis (arrow head) and mosaic attenuation of lung parenchyma.

also severity of acute exacerbation and she received regular medical care in outpatient clinics afterward for 8 months.

Discussion

DPB is a rare clinicopathologic syndrome of unknown etiology that affects the distal airways and predominantly the transition zone between the respiratory bronchioles and alveoli. It is a rare disease, mostly not limited in Asian patients[2]. Yamanaka first describes DPB in Japan in 1969 as a suppurative and obstructive airway disease that coexists with sinusitis[1,3]. It usually occurs between the 2nd and 5th decades, and two-thirds of patients are nonsmokers. The symptoms include exertional dyspnea, cough with expectoration, and sinus affectation. Erythromycin or macrolide is potentially effective therapy[3, 4].

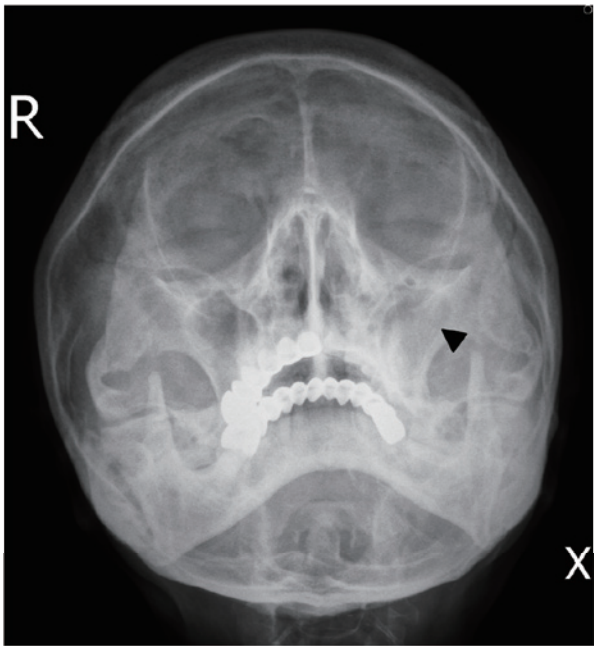

Figure 3. Radiography of paranasal sinuses shows increased haziness at left maxillary sinus (arrow head), compatible with sinusitis.

Bacteria easily colonize in respiratory tract in DPB. *H. influenzae* represents the most common colonized microbiological agent, followed by *P. aeruginosa*[5]. *P. aeruginosa* possesses a large array of virulence factors such as flagella, formation of biofilms, and production of elastase and protease[6-8]. The high ability of *K. pneumoniae* to form biofilms and thus to colonize tissues is a main factor contributing to infections [9].

This is the first case represented the role of *K. pneumoniae* persistent in the sputum in a patient with DPB. *K. pneumoniae* is a gram-negative pathogen. It colonizes human mucosa surface, including nasopharynx and the gastrointestinal tract, once

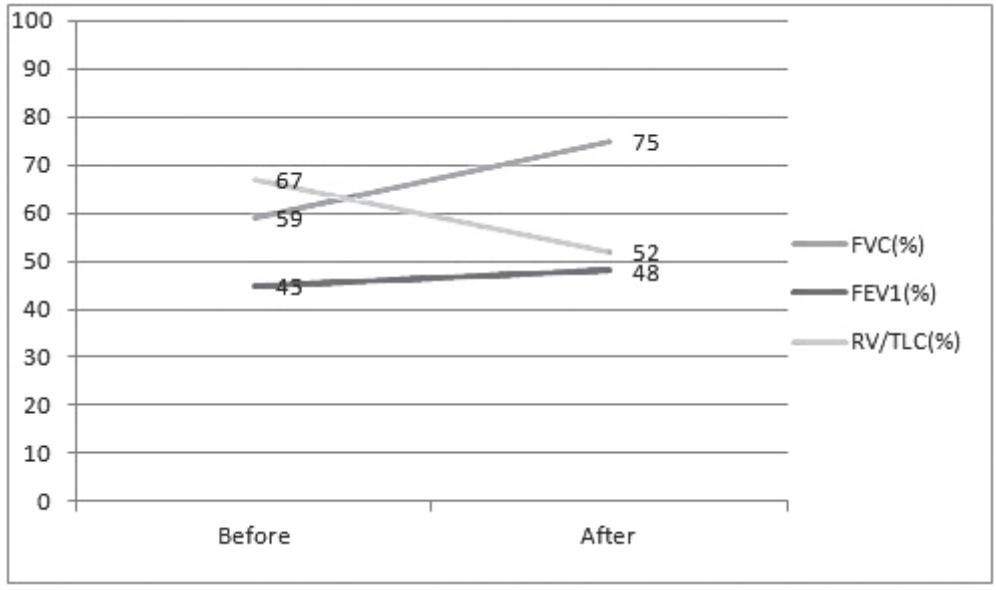

Figure 4. Comparison of pulmonary function tests before and after erythromycin therapy. FVC, FEV1 were improved by erythromycin therapy and RV/TLC decreased.

acquired from the environment[10]. Although the mechanism of progression into infection in colonizing *K. pneumoniae* strain remains unclear, evidence shows that certain plasmids and chromosomal gene loci determine the virulence of *K. pneumoniae*[11], as well as the status of host defense, such as cancer, diabetes mellitus, and alcoholism, influencing the host susceptibility to *K. pneumoniae* infection[12,13]. Bronchiectasis and DPB result in thickening and inflammation of the respiratory airways of this patient, which may have increased the susceptibility to acquired *K. pneumoniae* from the environment, and subsequently colonizes in the respiratory mucosa and causes pneumonia and sepsis. Erythromycin therapy reduced the number of other organisms and induced reversion to normal flora in DPB by antiinflamation and immunomodulation[14,15]. Previous studies reported that the therapeutic benefits of macrolides against *P. aeruginosa* are mediated by inhibition of adherence, inhibition of biofilms formation[16]. Similarly, we hypothesize that erythromycin exposure tended to inhibit biofilms formation in *K. pneumoniae*. After long-term erythromycin therapy, the bacteria in our patient was cleared from the airways. Other virulence factors of *K. pneumoniae* such as cell wall receptors, capsular polysaccharide remain unclear and there is room for further investigation.

Low body mass index (17.4), low FEV1 (45% of the prediction value), concomitant with bronchiectasis of this patient pose more risk of acute exacerbation of DPB. Macrolides are common antibiotics used in patients with respiratory infection; however they were thought to have weak or no activity against *K. pneumoniae*. Nevertheless, the introduction of long-term low dose erythromycin therapy in our patient has resulted in dramatic clinical improvement with eradication of *K. pneumoniae* colonization and improving the prognosis of the patient. There have been no reports of macrolide resistant bacteria in DPB patients treated with long term macrolides. It is hoped that modern technologies will identify a target molecule to clarify the core mechanism of the macolide's anti-inflammatory action.

In summary, we report a case that colonization of *K. pneumoniae* in the airways is significantly associated with the frequency of DPB acute exacerbation, subsequent infections, and requirement of hospitalization. Options of therapy including antibiotics targeting lung infection by *K. pneumoniae* or immunomodulation with erythromycin against underlying DPB are both optimal, depending on the presentation of the clinical situation. Clearance of *K. pneumoniae* in the airways is essential to stabilize the clinical conditions of DPB, which may improve the prognosis of the disease.

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肺炎克雷伯菌在瀰漫性泛細支氣管炎的角色及處置—病例報告

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摘 要

瀰漫性泛細支氣管炎(Diffuse panbronchiolitis, DPB)是一種慢性，特發性，罕見但會致命的發炎性呼吸道疾病。瀰漫性泛細支氣管炎可導致廣泛性遠端細支氣管擴張，阻塞性肺疾病，低氧血症和細菌定植敏感性增加。本病例報告了一位瀰漫性泛細支氣管炎患者，殺菌性抗生素治癒了病人的肺炎克雷伯菌(*Klebsiella pneumoniae, K. pneumoniae*)導致的肺炎，但仍需要紅黴素來根除患者已被破壞肺部內的肺炎克雷伯菌菌落。因此，本病例不但指出了瀰漫性泛細支氣管炎的臨床診斷特徵，也提出針對肺炎克雷伯菌在瀰漫性泛細支氣管炎患者的治療策略。