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Case report

Efficacy of combination antibiotic therapy including inhaled tobramycin on *Burkholderia cepacia* pneumonia in a non-cystic fibrosis patient

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ABSTRACT

Burkholderia cepacia complex (BCC) has been recognized as a serious cause of pneumonia in patients with cystic fibrosis. BCC infection has also been reported in non-cystic fibrosis patients. Notably, the mortality rate of bacterial pneumonia caused by BCC is high. Nonetheless, therapeutic management of BCC infection remains to be established. Recent reports have indicated successful treatment of BCC pneumonia with combination antibiotic therapy. However, no reports have detailed the efficacy of combination antibiotic therapy for both initial and recurrent BCC pneumonia management. We herein describe a rare case of BCC pneumonia in a non-cystic fibrosis patient that was successfully treated with a combination of intravenous, inhalational and oral antibiotics. Furthermore, antibiotic therapy including inhaled tobramycin has been continued after discharge from hospital, and no side effects or recurrence of bacterial pneumonia has been observed, although BCC has been detected in sputum. The findings of the present case suggest that combination antibiotic therapy including inhaled tobramycin may be effective for recurrent bacterial pneumonia caused by BCC. In the management of BCC infection, early diagnosis should be made based on sputum culture results, and combination antibiotic therapy should be initiated promptly.

Introduction

Burkholderia cepacia complex (BCC) is ubiquitously found in the environment, and is known as a significant cause of pulmonary infection, particularly in patients with cystic fibrosis (CF) and immunocompromised patients [1]. Moreover, BCC infection in non-cystic fibrosis (non-CF) patients has also been reported [2]. However, management of BCC infection is challenging, often leading to a high mortality rate. This difficulty persists irrespective of the presence of CF [2]. We herein report a case of recurrent bacterial pneumonia caused by BCC in a non-CF patient, which was successfully treated with combination antibiotic therapy including inhaled tobramycin, demonstrating its potential as an effective strategy for both initial and long-term management of BCC pneumonia.

Case report

A 71-year-old woman presented to our department due to fever, chronic productive cough, and dyspnea. She was diagnosed with bronchiectasis at age of 43 years, and had since been treated with oral erythromycin (200 mg, twice daily) at our department. She had no history of smoking or allergies, and had no relevant family history. She had experienced repeated bacterial pneumonia since the age of 70 years. Erythromycin was thus changed to azithromycin (250 mg, daily); however, bacterial pneumonia in which no causative organism was identified occurred three times over the next 6 months, and did not improve with outpatient treatment of oral sitafloxacin (50 mg, twice daily), resulting in hospitalization in our hospital.

Physical examination on admission showed a fever of 38.0 °C and bilateral coarse crackles, and oxygen saturation was 97 % on 0.5 L/min

Abbreviations: BCC, *Burkholderia cepacia* complex; CF, cystic fibrosis; CRP, C-reactive protein; CT, chest computed tomography; non-CF, non-cystic fibrosis; ST, trimethoprim/sulfamethoxazole.

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of oxygen. As shown in the Table 1, laboratory findings on admission revealed elevated white blood cell count of 13,000/μL (normal range, 3300–8600/μL), C-reactive protein (CRP) of 4.33 mg/dL (normal range, 0–0.30 mg/dL), and immunoglobulin G of 3390 mg/dL (normal range, 861–1747 mg/dL). Immunoglobulin A, immunoglobulin M, procalcitonin, and β-D glucan levels were normal. Serum *Aspergillus* antigen was 0.3 (normal range, 0–0.5), and T-SPOT.TB test, an interferon-gamma release assay, was negative. Chest computed tomography (CT) on admission showed bilateral granular shadows and consolidation with left lower lobe dominance (Fig. 1A). Phagocytosis of gram-negative rod-shaped bacteria and BCC were detected in sputum obtained two week before admission (Fig. 2A). Antimicrobial susceptibility testing for BCC showed susceptibility to meropenem, ceftazidime, tobramycin, and trimethoprim/sulfamethoxazole (ST), and resistance to cefozopran, ciprofloxacin, and levofloxacin. Two sets of blood cultures on admission were negative for bacteria.

We suspected bacterial pneumonia caused by BCC based on the clinical findings, and initiated antibiotic treatment with intravenous meropenem (1 g, 3 times daily) on the first day of admission (Day 1). Her body temperature reduced on Day 4. On Day 7, meropenem was switched to ceftazidime (1 g, 3 times daily), to which the bacterial strain was susceptible. The patient's condition improved, and her white blood cell count and CRP levels on Day 14 were decreased to 6000/μL and 0.62 mg/dL, respectively; thus, the antibiotic treatment was discontinued. However, bacterial pneumonia recurred along with an elevation of body temperature, white blood cell count (14,000/μL) and CRP levels (13.4 mg/dL) on Day 18. Therefore, intravenous meropenem was restarted. Additionally, based on a previously reported BCC eradication protocol in CF patients [3], a combination treatment consisting of inhaled tobramycin (300 mg, twice daily), oral ST (800/160 mg, twice daily) and oral azithromycin (250 mg, daily) was initiated. Thereafter, chest CT revealed improvement of granular shadows and consolidation (Fig. 1B), and sputum gram staining showed the absence of phagocytosis of gram-negative rod-shaped bacteria (Fig. 2B). The patient was discharged from our hospital, and has since been treated with a 28-day-on, 28-day-off cycle of inhaled tobramycin, as well as daily oral ST and azithromycin. At the time of writing, one year after discharge, no side effects or recurrence of bacterial pneumonia has been observed, despite BCC still being detected in the patient's sputum.

Discussion

To the best of our knowledge, to date there have been no reports describing the efficacy of combination antibiotic therapy not only in initial treatment but also in long-term management of recurrent bacterial pneumonia caused by BCC in non-CF patients. BCC is a group of multidrug-resistant gram-negative bacteria, and has been recognized as a cause of significant morbidity and mortality in patients with CF [2] and/or chronic granulomatous disease [4]. Although BCC infection is rare in immunocompetent patients without CF [5], it has also been reported in non-CF patients, and is associated with a high mortality rate, particularly in those with BCC bacteremia [2,6–8]. While risk factors for BCC bacteremia in non-CF patients include renal failure needing dialysis, previous abdominal surgery, and tracheostomy placement [9], none of these predisposing factors were present in our case; nor was immunosuppression. Although the patient in the present case was immunocompetent, her history of bronchiectasis may have contributed to an increased risk of BCC infection.

The optimal treatment and management of BCC infection have yet to be determined. Intravenous antibiotic treatment (cefepime or doripenem) without inhaled antibiotics showed no effect on pneumonia caused by BCC in non-CF patients with systemic arterial hypertension and type 2 diabetes [7]. On the other hand, in a previously reported case of sepsis secondary to pneumonia caused by BCC in a non-CF patient, a combination therapy of meropenem, levofloxacin and inhaled amikacin was effective [10]. In addition, treatment with intravenous meropenem as well as inhaled meropenem and tobramycin has been reported to be effective for BCC pneumonia in a CF patient [11]. The results of these previous reports of successful treatment suggest that combination antibiotic therapy including inhaled amikacin or tobramycin is effective for BCC pneumonia. Furthermore, a study on a BCC eradication protocol in CF patients reported that a 2-month treatment with a combination of inhaled tobramycin (300 mg, twice daily), ST (800/160 mg, twice daily) and azithromycin (250 mg, daily) was effective in preventing exacerbations [3]. The results of this previous study [3] supports the treatment strategy of above-mentioned previous successful cases [10,11]. Similarly, in the current case, treatment with the above-mentioned antibiotic combination may have contributed to the prevention of bacterial pneumonia exacerbation even though BCC could not be completely eradicated from the patient's sputum. Although further accumulation of cases is necessary, this treatment may be effective against repeated exacerbations due to BCC, regardless of the presence of CF.

Furthermore, a recent study has demonstrated that long-term administration of inhaled tobramycin for 12 months in patient with bronchiectasis infected by different pathogens, such as *Pseudomonas aeruginosa* and *Haemophilus influenzae*, contributed to the reduction of exacerbation frequency and improvement of quality of life with high tolerance [12]. The results of that trial support the current case, in which

Table 1
Laboratory data on admission.

Hematology			Blood chemistry			Biological test		
White blood cell	13,000	/μL	Total protein	9.3	g/dL	β-d glucan	< 6.0	pg/mL
Neutrophils	78	%	Albumin	3.5	g/dL	Aspergillus antigen	0.3	
Lymphocytes	18	%	AST	15	U/L	T-SPOT (IGRA)	(-)	
Monocytes	4	%	ALT	7	U/L	MAC antibody	< 0.5	U/mL
Eosinophil	0	%	LDH	154	U/L	Immunologic test		
Red blood cell	329	$\times 10^4$/μL	Total bilirubin	0.3	mg/dL	IgG	3390	mg/dL
Hemoglobin	9.8	g/dL	BUN	11	mg/dL	IgA	450	mg/dL
Hematocrit	32.3	%	Creatinine	0.33	mg/dL	IgM	105	mg/dL
Platelet	43.0	$\times 10^4$/μL	Na	136	mEq/L	Arterial blood gas	(0.5 L/min of oxygen)	
Coagulation test			K	3.5	mEq/L	pH	7.45	
PT	100	s	Cl	99	mEq/L	PaO_2	93.9	mmHg
PT-INR	1.00		CRP	4.33	mg/dL	$PaCO_2$	38.3	mmHg
APTT	26.4	s	BNP	61.8	pg/mL	HCO_3^-	25.8	mEq/L
Fibrinogen	494	mg/dL	Glucose	100	mg/dL	BE	1.7	mEq/L
FDP	3.3	μg/mL	HbA1c (NGSP)	5.8	%			
D-dimer	1.7	μg/mL	PCT	< 0.02	ng/mL			

PT: prothrombin time, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrinogen degradation products, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, CRP: C-reactive protein, BNP: brain natriuretic peptide, HbA1c (NGSP): hemoglobin A1c (National Glycohemoglobin Standardization Program), PCT: procalcitonin, IGRA: interferon-gamma release assay, MAC: mycobacterium avium complex, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, BE: base excess.

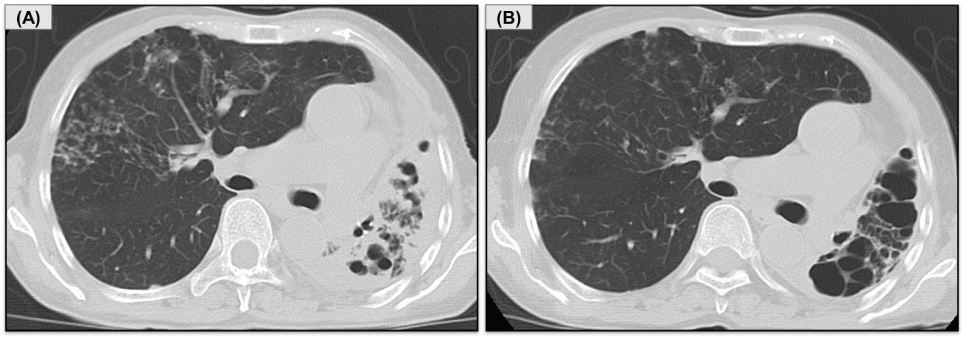

Fig. 1. Chest CT before and after combination antibiotic therapy with inhaled tobramycin, oral trimethoprim/sulfamethoxazole and oral azithromycin. (A) Chest CT findings on admission. There were bilateral granular shadows and consolidation with left lower lobe dominance. (B) Chest CT findings after initiation of combination antibiotic therapy. Improvement in bilateral granular shadows and consolidation is observed. CT, computed tomography.

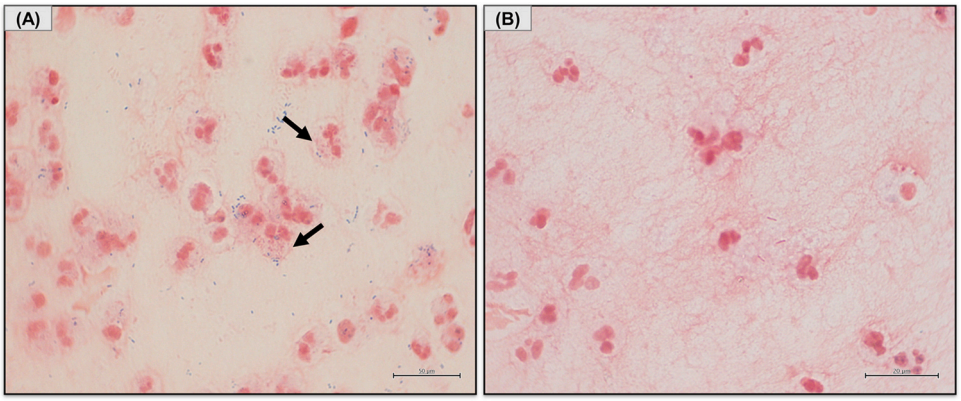

Fig. 2. Sputum gram staining images before and after combination antibiotic therapy with inhaled tobramycin, oral trimethoprim/sulfamethoxazole and oral azithromycin. (A) Sputum gram staining image two week before admission. Phagocytosis of gram-negative rod-shaped bacteria is observed (arrows). (B) Sputum gram staining image after initiation of combination antibiotic therapy. No phagocytosis of gram-negative rod-shaped bacteria is observed.

there was no recurrence of bacterial pneumonia without side effects after discharge.

In conclusion, the findings of the current case suggest that combination antibiotic therapy including inhaled tobramycin is effective not only in initial treatment but also in the long-term management of recurrent bacterial pneumonia caused by BCC. Early diagnosis from sputum cultures along with swift initiation of combination antibiotic therapy is important for effective management of BCC infection.

CRediT authorship contribution statement

Junpei Saito: Writing – review & editing. **Ryuichi Togawa:** Conceptualization, Writing – review & editing. **Takefumi Nikaido:** Writing – review & editing. **Yuki Sato:** Writing – review & editing. **Julia Morimoto:** Writing – review & editing. **Mami Rikimaru:** Writing – review & editing. **Takaya Kawamata:** Writing – review & editing. **Natsumi Watanabe:** Writing – review & editing. **Yoko Shibata:** Conceptualization, Writing – original draft, Writing – review & editing. **Hikaru Tomita:** Writing – review & editing. **Yoshinori Tanino:** Writing – review & editing. **Ryuki Yamada:** Writing – review & editing. **Kenya Kanazawa:** Writing – review & editing. **Riko Sato:** Writing – review & editing. **Tomoyoshi Lee:** Conceptualization, Writing – original draft, Writing – review & editing. **Hiroyuki Minemura:** Writing – review & editing. **Yasuhito Suzuki:** Conceptualization, Writing – original draft, Writing – review & editing.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

Not needed.

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Declaration 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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Declaration of competing interest

All authors declare no conflict of interest associated with this manuscript.

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