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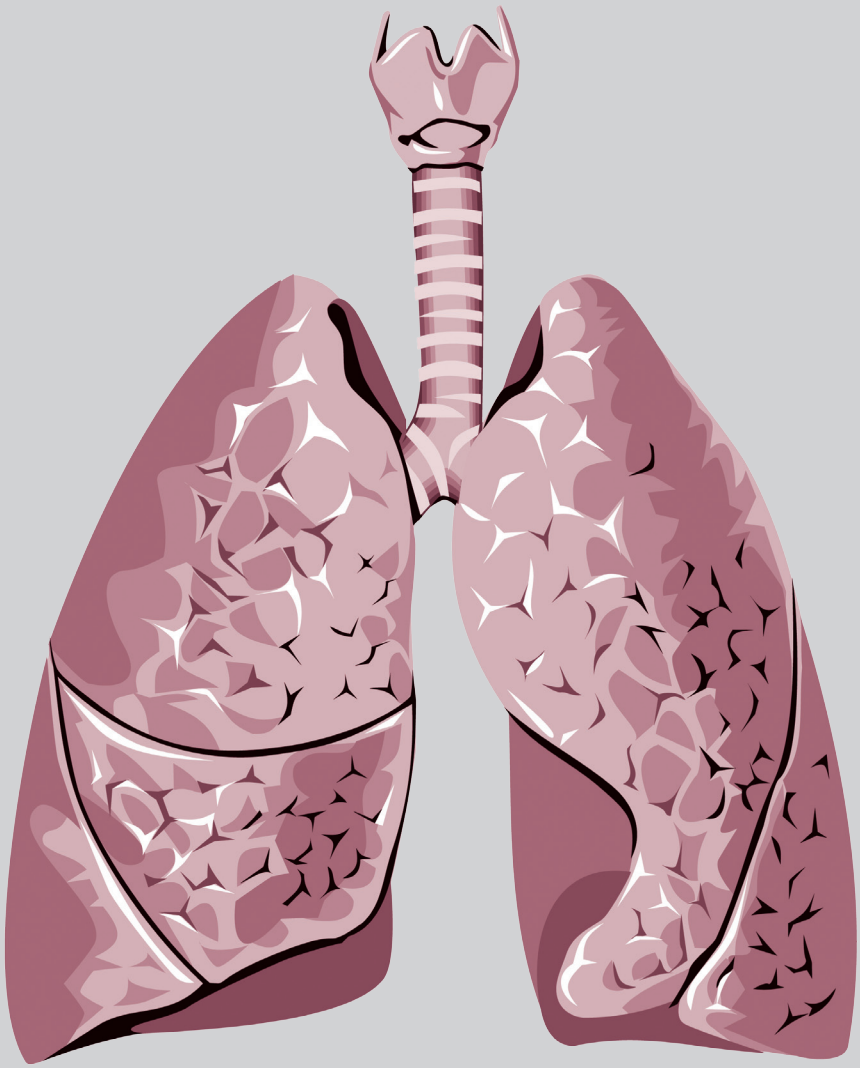

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CONTENTS

Review article: Protective effects of bacillus Calmette-Guérin vaccination against COVID-19

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Abstract: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a major impact worldwide. Although researchers have made every effort to find ways to avoid its spread and to find the best way to treat the disease, there are still no effective options up to now. From the current point of view, vaccination seems to be a good way to prevent the spread of COVID-19. However, studies on the use of vaccination for COVID-19 are still on-going, and the safety of the vaccines is still questioned. It is interesting that epidemiological studies have shown that countries with bacillus Calmette-Guérin (BCG) vaccination programs have less spreading of COVID-19, less severity of infections, and a higher recovery rate. The striking association between BCG vaccination and COVID-19 supports the possible protective effects of BCG vaccine against COVID-19. Experimental studies suggest that BCG vaccine enhances trained immunity with cellular and molecular mechanisms against various viral infections, including single-strand RNA viruses. SARS-CoV-2 is a single-strand RNA virus. Therefore, we reviewed studies on immunity against various viral infections using BCG vaccination. Well-designed clinical studies are still necessary to define the effects of BCG vaccine relative to COVID-19 in the future. ***(Thorac Med 2021; 36: 207-215)***

Key words: bacillus Calmette-Guérin, coronavirus disease 2019, pandemic, vaccination policy

Introduction

Coronavirus disease 2019 (COVID-19) is a global health crisis that has had a major impact worldwide. According to the WHO website, there have been 226,844,344 confirmed cases and 4,666,334 deaths- due to the global spread of COVID-19 as of September 17,2021. COVID-19 has been found to be caused by a new coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. SARS-CoV-2 is transmitted by droplets from

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the respiratory tract that are spread by coughing and sneezing [1]. It is also transmitted by contaminated secretions through the nose, eyes, and mouth [1]. It is therefore easy to spread in the family, the community, and in the hospital.

The severity of COVID-19 is wide ranging. Most individuals remain asymptomatic or develop only mild disease with upper respiratory tract symptoms such as cough with some sputum, fever and dyspnea [2]. However, some cases of COVID-19 may progress to pneumonia or acute respiratory distress syndrome (ARDS), and become complicated with respiratory failure [2]. Older patients or those with comorbidities are often at a higher risk of severe illness [2].

Even though aggressive measures have been adopted in many countries, the case numbers of COVID-19 have continued to increase [3]. COVID-19 is expected to continue to spread during the next few years. Efforts have been made to find ways to stop the spread of the virus and to uncover the best treatment methods, but there are still no effective options till now [3]. However, many studies have reported that the spreading and severity of COVID-19 are quite different in countries with different bacillus Calmette-Guérin (BCG) vaccination polices [1,4-7]. These analyses suggested that the BCG vaccination may decrease the spreading and severity of COVID-19 [1,4-7]. This review, therefore, explores the possible protective effects and mechanisms of BCG vaccination relative to COVID-19.

Introduction of BCG vaccine

The BCG vaccine was derived via attenuation of Mycobacterium bovis [8]. It was first used in humans in 1921 for cross-protection from and prevention of Mycobacterium tuberculosis (TB) infection [9]. The BCG vaccine is usually administered to infants intradermally around the first year of life [1]. A BCG vaccination policy is used with groups that are at high risk of TB. The World Health Organization (WHO) recommends that all newborns in countries with a high prevalence of TB should be vaccinated with BCG vaccine [1]. Therefore, the implementation of BCG vaccination programs around the world depend on the incidence of TB, and on health policies, and community perception. BCG vaccination programs are used in high-prevalence countries, but not in low-prevalence countries [6]. A total of 131 countries, including Afghanistan, India, Nepal, China, Bhutan, Bangladesh, Pakistan and etc have universal BCG vaccination programs [4]. Twenty-one countries, such as the United States of America (USA), Spain, the United Kingdom (UK), Italy and etc do not have universal BCG vaccination programs [4]. Twenty-six countries have an unknown BCG vaccination status [4].

Status of COVID-19 in countries with different BCG vaccination policies

There are great differences in the spreading and severity of COVID-19 among different countries, and BCG vaccination is considered to be one of the factors contributing to this difference [1,4-7]. Many global epidemiological analytical studies have focused on the linkage between COVID-19 and BCG vaccination [1,4-7]. Sharma et al. showed that the COVID-19 infection rate was lower in countries with BCG vaccination, such as China, Brazil, Chile, Cuba, Finland, India, and Indonesia, than in countries without BCG vaccination, such as the USA, UK, Canada, Italy, Germany and Iceland [1]. Desouky and colleagues reported that countries

with universal BCG vaccination programs have fewer cases of COVID-19 than the countries without BCG [4]. They found that the incidence of COVID-19 was 38.4 cases per million people in countries with BCG vaccination programs compared to 358.4 cases per million people in countries without in 2020 [4]. They also found that BCG vaccination reduced the severity of COVID-19 [4]. The mortality rate was 4.28 cases per million people in countries with BCG vaccination programs compared to 40 cases per million people in countries without [4]. Many other studies have shown a similar result, that the incidence of COVID-19 and deaths due to the virus are strongly associated with universal BCG vaccination programs [5,6]. Madan *et al*. also noted an interesting finding, in which the UK reported lower mortality due to COVID-19 among Asians and blacks who have received BCG vaccinations [7]. In addition, the percentage of recovered cases in BCG-implementing countries is also higher (about 43%), than that in non-implementing countries (about 35%) [1]. In a recent study, Paul *et al*. also found that the map of countries that were most affected by COVID-19 in Europe bears striking resemblance to the map of countries that had no national BCG vaccination programs [10].

However, latent TB in these countries may also be one of the factors in the innate immunity of these populations. Some studies have indicated the possibility that people who have latent TB infection may also have innate immunity against COVID-19 [11-12]. This innate immunity further decreases the infection rate and the severity of COVID-19 infection in those countries. Inoue et al. found that an inverse relationship existed between the past epidemic indicators of M. tuberculosis and the current impact of COVID-19 [11].

It would be interesting to know something about the protective effects of BCG vaccination relative to 2 other recent coronavirus infections, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). However, to the best of our knowledge, there are no published articles on the protective effects of BCG vaccination against SARS and MERS. In 2002, the first lethal coronavirus, SARS-CoV appeared in Guangdong Province, China. During the 2002-2004 outbreak, SARS-CoV infected 8,098 patients before it disappeared. It caused 774 SARS-related deaths in 29 countries [13]. In 2012, MERS-CoV emerged in Saudi Arabia; then, there were a few outbreaks in South Korea in 2015, and again in Saudi Arabia in 2018. There are still reports of sporadic cases nowadays. As of January 2020, there were 2,519 confirmed MERS-CoV cases and 866 deaths in 27 countries [14]. The present SARS-CoV-2 emerged in Wuhan, China in 2019. Compared with SARS-CoV and MERS-CoV, SARS-CoV-2 is highly contagious, and is able to spread through asymptomatic patients. SARS-CoV-2 is a globally infectious disease, and has infected more than 226 million people and caused more than 4.66 million deaths in 235 countries around the world. Compared with SARS-CoV-2, SARS-CoV and MERS-CoV have far fewer cases and regions of infection. Therefore, it is difficult to analyze the impact of BCG vaccination on SARS-CoV and MERS-CoV in different countries.

According to these studies [1,4-7], populations of countries with universal BCG vaccination have less spreading of COVID-19, less severity, and a higher recovery rate. This result supports the notion that BCG vaccination protects subjects from SARS-CoV-2 infection. Therefore, it may be recommended as a pos-

sible way to fight COVID-19.

Protective effects of BCG vaccination against TB infection

The attenuated BCG vaccination is primarily used for protection from TB, especially severe TB such as miliary TB and TB meningitis [1]. Severe TB often leads to severe sequelae and high mortality. BCG vaccination was found to prominently decrease the number of cases of severe TB in Argentina [6].

Although there are many studies on the effect of BCG vaccination on TB, its protective effect is still being controversial, especially for adults [15]. One systematic review revealed the protective effect against TB appeared to be the greatest in children or infants who are strictly tested for tuberculin [16]. However, the protective effect for adolescents without a pre-test and for adults was low. The probable reason is that those previously infected with TB or non-TB mycobacteria may have protection similar to BCG vaccination.

Protective effects of BCG vaccination against bacterial and fungal infection

Besides the protection against TB, BCG vaccine also confers broad protection against other bacterial and viral infections [8] (Fig. 1). BCG vaccination conferred protection in multiple animal models experimentally challenged with Herpesvirus hominis, Staphylococcus aureus, Yersinia pestis, Klebsiella pneumonia, Schistosoma mansoni, or Candida albicans [10,17-18]. Another animal study found that vaccinated animals had better survival when infected with bacterial pathogens [19]. The same study found that survival among animals with or without BCG vaccination was 40% vs 73%, respectively, in those infected with Streptococcus pyogenes, and 7% vs 93%, respectively, in those with Staphylococcus aureus infection [19].

Protective effects of BCG vaccination against viral infection

In humans, limited clinical evidence suggests that BCG vaccination may have non-targeted protective effects against viral infections [20]. Animal studies showed that BCG protected mice from herpes simplex virus (HSV) and influenza A [21,22].

Epidemiological analysis revealed BCG vaccination can decrease mortality by 50% in infants, and this cannot be fully explained by reducing the TB infection rate [3]. In Spain, children who have been vaccinated with BCG have fewer hospitalizations for respiratory infections than children who have not been vaccinated with BCG [1]. It is well known that common pathogens of respiratory tract infections in children are viral pathogens. Therefore, the idea that the BCG vaccine can reduce the spreading of virus infections has been strengthened [23]. Similar evidence suggests that BCG vaccination has reduced respiratory infections in elderly people in Japan, Indonesia and Africa [24-26].

SARS-CoV-2 is a kind of ribonucleic acid (RNA) coronavirus with a single -strand [17]. In the Netherlands, BCG vaccine is reported to decrease the viremia of yellow fever by 71% [27]. It also prominently decreased the severity of mengovirus infection in mice [28]. Both yellow fever virus and mengovirus are RNA viruses with a single -strand [29,30]. Although there is no study on the effects of BCG vaccine on COVID-19, epidemiological studies showed a lower prevalence and severity of COVID-19

in countries with universal BCG vaccination programs [31].

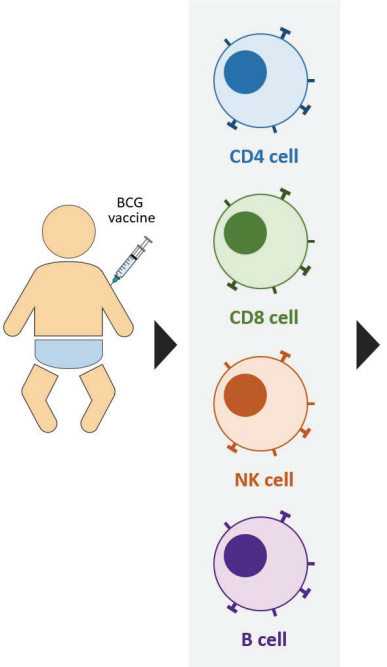
Animal studies also suggested that BCG vaccine provides protection against viral infections such as RNA viruses. Taken together, this evidence suggests that BCG vaccination may potentially provide a protective effect from COVID-19 [1].

According to a previous study, after adjusting for age, the protective effects of BCG vaccination still existed. The retrospective study enrolled 6679 health care workers for analysis of the correlation between previous BCG vaccination and COVID-19 infection [18]. They found that a history of BCG vaccination was associated with SARS-CoV-2 IgG seroconversion, after adjusting for sex or age [18]. However, these effects were not found with meningococcal, pneumococcal, or influenza vaccination.

The effects of non-specific innate immunity against viral or bacterial infection with BCG vaccination are summarized in Fig. 1.

BCG vaccination in cancer immunotherapy

BCG vaccination is known to prevent infectious diseases, and it also has been administered to treat non muscle-invasive bladder cancer (NMIBC) for many years [4]. It has also been administered intra-vesically for NMIBC [8]. BCG immunotherapy reduces bladder cancer recurrence and progression, and is defined as the gold-standard therapy [8]. Its possible mechanism is the presenting of BCG or cancer cell antigens to the human immune system [4,32]. Trained immunity is then activated to destroy the bladder cancer cells [31]. Immune



Non-specific immunity		Ref.
Yellow fever	Viremia 71% ↓	16
RSV	Lower nfection rate	23
Newborns mortality	Mortality 50% ↓ Lower sepsis and respiratory tract infection	3
COVID-19 ?	Mortality rate Non-BCG vaccine area (40/million) vs. BCG vaccine area (4.28/million)	4
Specific immunity		**Ref.**
TB	In newborns, 70-80% prevention efficacy.	38

Fig. 1. BCG vaccination confers broad and non-specific innate immunity against viral or bacterial infection

system cells involved in BCG cancer immunotherapy have been reported, and include natural killer cells, lymphocytes, granulocytes, dendritic cells and macrophages [4,32].

The cancer immunotherapy of BCG vaccination is more evidence that BCG vaccine can enhance an immune response that is not related to anti-TB effects [3]. Below, we further address details on the immunological responses of BCG vaccination that may provide immunity against COVID-19.

Mechanisms: BCG vaccination and immunological responses

There are many studies on the protective mechanism of BCG vaccination against various infections and cancers. The extensive protection of BCG vaccine against unrelated pathogens is due to its role in enhancing innate immunity [3,8].

Studies have also addressed the mechanisms of BCG vaccination in the immunological system [3]. BCG vaccine provides protection from TB and other infections by boosting cellular immunity [31]. The first line of defense against pathogens is innate immunity [31]. The BCG vaccine acts on the innate immune system and produces a training immunity that is a memory-like response. These non-specific effects (NSEs) help in rapid recognition, and trigger a quick immune response [8]. Therefore, BCG vaccine is not only a vaccine for TB, but also a general immune-system enhancer. This enhancing response is very characteristic of BCG vaccine [33].

Many of the mechanisms underlying the NSEs of the BCG vaccine have been explored. The BCG vaccine induces NSE that are stimulated by microorganisms through mediation from epigenetic changes in the cells of the innate and adaptive immune system [8]. These epigenetic changes in the immune cells enhance the immune response to secondary challenges, and the immune cells (dendritic cells, macrophages, and neutrophils) are activated and interact with viruses or bacteria [1]. Subjects vaccinated with BCG can have enhanced innate antimicrobial immunity with long-term activation [9]. This effect can inhibit virus replication and reduce the viral load, thereby reducing the severity of inflammation [3]. Studies involving humans and mice have shown that BCG vaccination can trigger trained immunity to eliminate various infections, including candidiasis, staphylococcus, influenza and yellow fever [10,17].

Immune cells that have pathogen recognition receptors (PRR) can recognize pathogens from different pathogen-related molecular patterns (PAMP), such as peptidoglycans, cell wall proteins, lipopolysaccharides, mycolic acids, and glycoproteins [1]. PAMPs bind with PRRs and present these molecules to immune cells [1]. Toll-like receptors (TLRs) and dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) also play roles in pathogen recognition after BCG vaccination [1]. Antigens expressed on the TB or BCG surface are known to induce interaction of DC-SIGN and PAMPs [1].

Antigen-presenting cells (APCs) and T cells-related adaptive immunity are also important mechanisms of BCG vaccination. APCs present antigen peptides with major histocompatible complex (MHC) molecules and activate CD4+and CD8+ T cells. This further initiates the immune response and the expression of interferon gamma (IFN-γ) and other pro-inflammatory cytokines such as tumor necrosis factor (TNF-α), interleukin (IL)-1 and IL-6 [1,5,34].

IFN-γ is an important cytokine that mediates activation of macrophages [24]. These further increase the potential ability against other bacterial or viral infection. After BCG vaccination, IFN-γ increases the potential of macrophages to work against TB or other viruses. Activated CD8+ T cells also proliferate into specific CD8+ T cells which against TB [1,34]. These CD8+T cells further express granzymes and perforins, which have cytotoxic activity [1,34]. CD4+ and CD8+ T cells, with their functional features of cytotoxic activity, further convert into effector memory cells [1,34]. IFN-γ is also involved in the activation and differentiation of B cells into plasma B cells, which further produce antibodies against viral or bacterial antigens [1].

Clinical trial of BCG vaccination

Although epidemiological studies suggest a protective effect of BCG vaccination, in those countries without universal BCG vaccination have much higher and severer COVID-19 infections [35], these published studies are observational studies that cannot show definitive causality. There may be confounding issues, including differences in genetic and demographic features [3-4]. Well-designed studies are necessary to define the role of BCG in protecting against COVID-19. There are currently clinical studies in progress in Australia, the Netherlands, the United States, and Greece investigating the effect of BCG vaccination on COVID-19 [3,9]. These studies are being performed among health-care workers and elderly patients [9].

Safety of BCG vaccination

BCG vaccine has been used for the prevention of TB for many years. Its safety is well-proven [8]. However, BCG still has a few side effects, and the most common is swelling at the injection site [1]. The other side effects are joint pain, nausea, vomiting, dysuria and hematuria [1]. These side effects occur more often in pregnant women and immune-compromised subjects [1]. The most worrisome side effect is the possibility of TB infection after BCG vaccination; patients receiving intravesical BCG immunotherapy are also a concern [15]. However, the issue of side effects can be more serious among immunocompromised people. It is suggested to carefully provide BCG vaccination to these populations [15].

Clinical implications

COVID-19 has had a devastating impact worldwide, and measures to attenuate the spread and severity of COVID-19 are urgently needed. Researchers have been exploring effective vaccines for COVID-19, and there are now many new vaccines; however, the safety of these vaccines is still questioned. Two scientific studies establishing a causal relationship between the AstraZeneca COVID-19 vaccine and severe thrombotic complications have been published [36-37]. The safety of these vaccines should be closely monitored, since there are no long-term follow-up reports. Second, the vaccines are too expensive for many poor countries, so their populations can not be vaccinated, and new variants of SARS-COV-2 could evolve in the future. Third, we already know that not all of these vaccines are protective against new variants of SARS-COV-2, and that some vaccinated people have died due to variants of COVID-19. Fourth, the virus is a RNA virus, similar

to the influenza virus. We may have to consider the possibility of receiving SARS-COV-2 vaccine every year. Nevertheless, the effectiveness and safety are still questioned. Finally, we need time to do the research to develop new vaccines during new virus outbreaks. However, many people have already died from the new virus before the vaccines are developed. Therefore, considering the training immunity of the BCG vaccine and the lesser severity noted in those countries that use BCG vaccine, it might therefore have a role as an alternative vaccine to prevent the spread of COVID-19 or a new virus outbreak in the future.

Conclusions

SARS-COV-2 has been spreading rapidly around the world. Countries without universal BCG vaccination programs are severely affected, and countries with these programs are less affected by COVID-19. Experimental studies have shown that the mechanism of BCG vaccine is trained immunity against viral infections, including single-strand RNA virus. Clinical studies on the effects of BCG vaccination on COVID-19 are ongoing in many countries. BCG vaccine is safe and worth considering as a possible preventive strategy for COVID-19.

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Competing interests

The authors declare no conflicts of interest.

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Risk Factors for Readmission among Sepsis Survivors

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Introduction: Readmission within 90 days after hospital discharge is common among sepsis patients, and is second only to readmission among congestive heart failure patients. Readmission results in a reduced quality of life, increased patient mortality, and higher medical costs. Although several studies have been conducted to identify the reasons and risk factors for sepsis readmissions, only a few have focused on critically ill patients, and these studies have reported heterogeneous results.

Methods: This was a single-center, prospective cohort study with 129 patients.

Results: Of the 129 sepsis survivors, 62 had a readmission within 90 days of index discharge. The patients who were readmitted within 90 days were significantly older than those who were not, with a mean age of 75.97 versus 67.96 years, $p < 0.05$. Infection (79.03%) was the primary cause of readmission, and among these patients, 75.5% were readmitted for the same infection source as during the index hospitalization. There was a higher percentage of infection with drug-resistant Gram-negative bacilli (odds ratio [OR] 15.840, 95% CI [1.993–125.885]) in the readmission group.

Conclusion: About half of the survivors with sepsis had re-hospitalization within 90 days after discharge from their index admission. Factors that contributed to the higher odds of re-hospitalization were older age and infection with drug-resistant Gram-negative bacilli. The majority of these unplanned readmissions were due to infection. By reducing the rate of infection by drug-resistant Gram-negative organisms, the 90-day readmission rate among sepsis survivors might be reduced. ***(Thorac Med 2021; 36: 216-224)***

Key words: sepsis, critical care, readmissions, prevention

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Despite recent advances in the treatment of critically ill patients, adverse events due to sepsis remain high. Furthermore, readmission within 90 days of hospital discharge is common among sepsis patients. In fact, index admissions for sepsis result in the second highest readmission rate, second only to admissions for congestive heart failure [2].

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These re-hospitalization events may be indicative of unresolved acute illness, ongoing chronic illness, new medical problems, or gaps in outpatient care [3]. Readmissions result in a reduced quality of life, increased patient mortality, and increased medical costs.

In recent years, studies have been conducted to identify the reasons and risk factors for sepsis readmission. Although statistical models have been developed to predict readmission risk for many hospitalized patient groups, few have specifically assessed the intensive care unit (ICU) populations with risk factors related to episodes of critical illness. Moreover, study results concerning risk factors are heterogeneous and the overall certainty of evidence is low. We found that most studies aimed to survey 30-day re-hospitalization events after critical illness. While readmissions within 30 days of discharge can be influenced by the quality of care received at the hospital and the coordination of discharge, readmissions occurring at a later time (such as 90 days) may not only be related to the care provided during the index admission, but also to outpatient care and the patients' individual health. Most of these studies were conducted outside of Asia, which indicates the necessity of ICU-specific, Taiwan-based local research.

In this study, we sought to identify the most common readmission diagnosis after hospitalization for ICU septic patients, as well as the risk factors for 90-day readmissions after sepsis discharge, and whether these factors are modifiable.

Methods

Subjects

This study was a secondary analysis of our previous cohort study and was approved by the Institutional Review Board of Chang Gung Memorial Hospital (98-1682C, 201700223BO). The requirement for informed consent was waived. Patients admitted to the medical ICU at Keelung Chang Gung Memorial Hospital for sepsis from July 2007 to June 2010 were recruited for analysis. The following data were recorded within the first 3 days after admission: age, sex, medical history, the Acute Physiology and Chronic Health Evaluation (APACHE II) score, and adverse events during admission.

Enrollment

Altogether, 494 patients were admitted to our medical ICU between April 2007 and July 2010 (Figure 1). One hundred and twelve patients were excluded for repeated admissions, having been lost to follow-up, or having missing mortality records; 245 patients died during the index admission, and there were 137 survivors. Two of the survivors were excluded because they were transferred to another hospital at index admission, and 6 were excluded because of scheduled readmission for cancer survey or treatment. The final case number was 129 patients, with 62 patients in the readmission group and 67 in the non-readmission group.

Definitions and Description

Sepsis, according to the Third International Consensus Definitions for Sepsis (Sepsis-3), is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Hospitalization of our patients in the prior year was verified by hospital records. We traced back 1 year preceding the index hospitalization to identify any recorded admission episodes. Patients with chronic kidney disease were defined as those with glomerular filtration

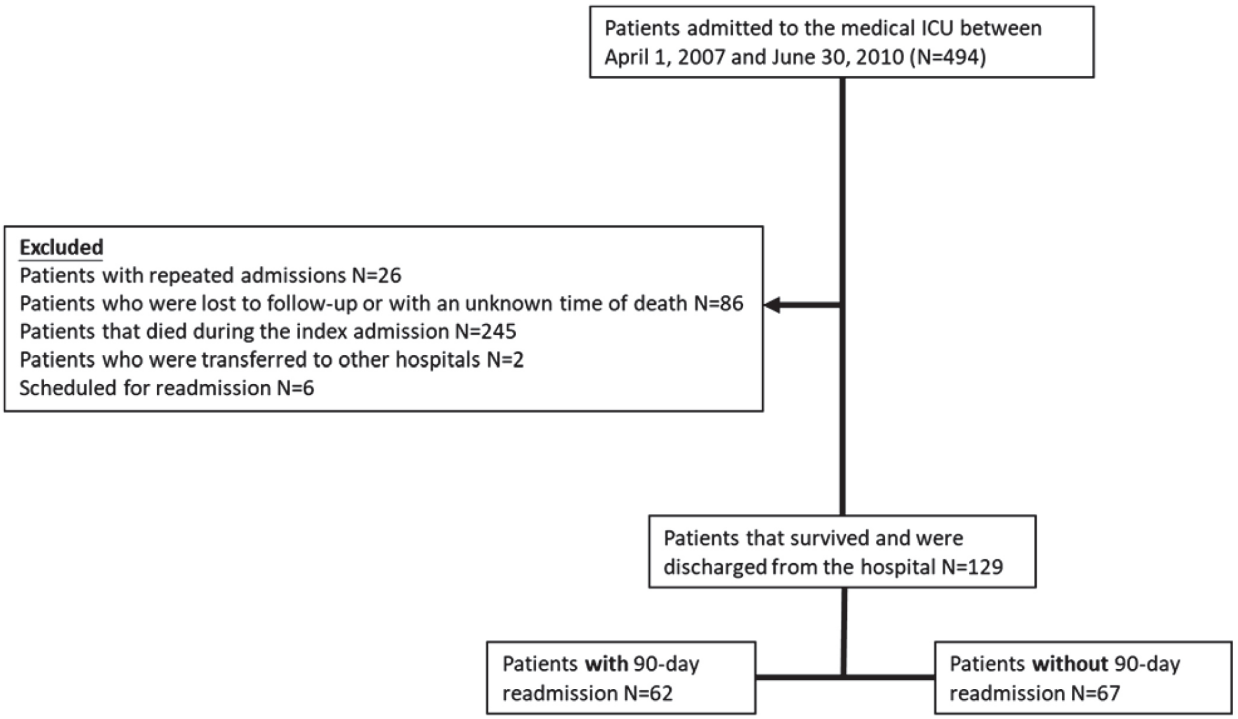

Fig. 1. Flow chart of patients' enrollment

rate (GFR) categories 4 and 5.

Coinfection was defined as the identification of more than 1 infection focus, while multiple infection was the infection of a host by multiple pathogen species. Resistant Gram-positive cocci (GPC) included methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus spp. (VRE). Resistant Gram-negative bacilli (GNB) included extended-spectrum beta-lactamase (ESBL)-producing GNB or plasmid-encoded ampC (pAmpC)-producing Enterobacteriaceae, and resistant Acinetobacter baumannii (AB). Multidrug-resistant (MDR) Acinetobacter baumannii (MDR-AB) (previously called pandrug-resistant Acinetobacter baumannii, PDR-AB) was defined as A. baumannii with full or intermediate resistance to amikacin, gentamicin, cefepime, ceftazidime, piperacillin, piperacillin-tazobactam, aztreonam, ciprofloxacin, and carbapenems [4]. MDR organisms (MDRO) were defined by the Centers for Disease Control and Prevention (CDC) as bacteria that are resistant to 1 or more classes of antimicrobial agents. Although the names of certain MDROs describe resistance to only 1 agent (such as MRSA and VRE), these pathogens are frequently resistant to most available antimicrobial agents [4].

Statistical Analyses

Statistical analysis was performed using SPSS version 22 statistical software. Continuous variables between the 2 groups were compared using the Mann Whitney U test. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Binary logistic regression analysis was performed to identify independent factors of readmission. $P < 0.05$

was considered to be statistically significant.

Results

In our study, the rate of all cause re-hospitalization within 90 days was 48%. Patients who were readmitted within 90 days were significantly older than those in the non-readmission group, with a mean age of 75.97 versus 67.96 years, $p < 0.05$. The mean APACHE II scores were 23.40 and 22.85 for the 90-day readmission group and non-readmission group, respectively. The mean hospitalization days during the index admission were 50.73 and 41.08 for the 90-day readmission and non-readmission groups, respectively. Baseline patient characteristics, sepsis-related parameters, and the use of additional treatment showed no significant differences between the 2 groups. Sepsis-related parameters included underlying medical history, foci of infection, and acute sepsis-related adverse events such as respiratory failure, septic shock, acute kidney injury, bacteremia, use of renal replacement therapy, and use of steroids and antibiotics at discharge (Table 1).

Although there was no significant difference between the 2 groups regarding infection with GPC or GNB (data not shown), patients with a 90-day readmission had a higher percentage of infection with drug-resistant GNB. Meanwhile, the percentage of drug-resistant GPC was similar between the 2 groups.

Binary logistic regression analysis (Table 2) revealed that age and infection with drug-resistant GNB were both significant independent factors associated with 90-day readmission. Readmission of patients (Table 3) was mostly due to an infection (79.03%), and 75.5% of these patients were re-admitted for the same infection source as during the index hospitalization. Other readmission diagnoses included 4 cardiovascular events, 2 respiratory events other than pneumonia, 2 gastrointestinal/hepatobiliary events, 2 sugar control issues, 1 cerebrovascular event, 1 renal disease, and 1 musculoskeletal problem.

Discussion

Our study is the first in Taiwan to discuss the risk factors for readmission among sepsis survivors. In our single-center, prospective cohort study, about half of the survivors had a re-hospitalization within 90 days after discharge from their index admission. Factors that contributed to the higher odds of re-hospitalization were older age and an infection with drug-resistant GNB; most of these unplanned readmissions were due to an infection.

According to a systematic review by Shankar-Hari et al., the mean re-hospitalization proportion for sepsis survivors at 90 days was 38.1% (95% CI, [34.3%-42.0%], N=14 studies, 388,044 patients) [5]. Analysis of our data on septic patients who were admitted to our medical ICU between April 2007 and July 2010 revealed that the 90-day readmission rate after index hospital discharge was 48%. The difference in readmission rates between our study and previous studies (as in the systematic review) may be due to the difference in patient severities. While the systematic review by Shankar-Hari et al. included studies with septic patients of varying severities, we only focused on critically ill patients.

Previous studies on sepsis have discussed multiple risk factors; however, the results were heterogeneous and the overall certainty of evidence was low [5]. In our study, 2 major factors were identified. We found that older age is a

Table 1. Clinical Characteristics of Patients with and Without 90-day Readmission After the Index Hospitalization (Number, Percentage, Mean ± Standard Deviation)

	No 90-day readmission (n=67)	90-day readmission (n=62)	*P-value**
Gender			0.283
Male	44 (65.67%)	35 (56.45%)	
Female	23 (34.33%)	27 (43.55%)	
Age	67.96 ± 17.605	75.97 ± 12.302	0.003
APACHE score	22.85 ± 7.498	23.40 ± 6.418	0.406
Length of stay at the hospital (days)	41.08 ± 28.792	50.73 ± 36.501	0.050
Hospitalization in the prior year	35 (52.24%)	40 (64.52%)	0.158
Medical history			
CVA	22 (32.84%)	26 (41.94%)	0.285
Hypertension	37 (55.22%)	38 (61.29%)	0.485
Heart diseases	17 (25.37%)	24 (38.71%)	0.104
COPD	10 (14.93%)	16 (25.81%)	0.124
Cirrhosis	7 (10.45%)	5 (8.06%)	0.642
Chronic kidney disease	4 (5.97%)	8 (12.90%)	0.230
End-stage renal disease	5 (7.46%)	3 (4.84%)	0.719
Diabetes mellitus	27 (40.30%)	21 (33.87%)	0.450
Malignancy	11 (16.42%)	14 (22.58%)	0.376
Adverse events			
Acute respiratory failure	58 (86.57%)	54 (87.10%)	0.929
Septic shock	25 (37.31%)	20 (32.26%)	0.547
Acute kidney injury	29 (43.28%)	31 (50.00%)	0.830
Co-infection	32 (47.76%)	37 (59.68%)	0.175
Bacteremia	8 (11.94%)	10 (16.13%)	0.493
Nature of infection			
Pneumonia	53 (79.10%)	53 (85.48%)	0.344
Additional treatment			
Renal replacement therapy	14 (20.90%)	11 (17.74%)	0.651
Use of low-dose steroid	32 (47.76%)	30 (48.39%)	0.943
Antibiotics at discharge	12 (17.91%)	8 (12.90%)	0.432
Pathogens			
Resistant GPC	11 (16.42%)	9 (14.52%)	0.766
Resistant GNB	1 (1.49%)	12 (19.35%)	0.001
Multiple infection	13 (19.40%)	15 (24.19%)	0.510

* $p < 0.05$, as compared between groups using the Mann Whitney U test, chi-square test, or Fisher's exact test.

ICU = intensive care unit, APACHE = acute physiology and chronic health evaluation, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, GPC = Gram-positive cocci, GNB = Gram-negative bacilli

Table 2. Results of Binary Logistic Regression Analyzing Independent Factors for 90-day Readmission

	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Age	1.037 (1.011–1.064)	0.006	1.034 (1.007–1.062)	0.013
Resistant GNB	15.840 (1.993–125.885)	0.009	13.845 (1.727–111.004)	0.013

OR = odds ratio, CI = confidence interval, GNB = Gram-negative bacilli

Table 3. Etiologies of Patients who Were Readmitted Within 90 Days

Etiology	Patient numbers (percentage)
Infection	49 (79.03%)
Respiratory tract	34
Genitourinary	7
Skin/soft tissue	3
Others	5
Other medical conditions	13 (20.97%)
Cerebrovascular	1
Cardiovascular	4
Respiratory system other than pneumonia	2
Gastrointestinal, hepatobiliary	2
Renal	1
Musculoskeletal	1
Sugar control	2

risk factor for readmission, which is identical to the findings of several other studies. Liu *et al*. found that increased age was associated with a 1.2% hazard ratio for early readmission [6]. Studies by Hua et al. and Lone *et al*. showed that older age increased the risk of re-hospitalization among critical illness survivors [3,7]. Wang *et al*. reported that advanced age was associated with an increased risk of post-discharge infections and post-discharge hospitalizations [8]. The study by Prescott *et al*. revealed that the proportion of septic patients experiencing a 90-day hospital readmission was 37.3% (95% CI, 36.4%–38.2%) among those < 65 years of age, and 39.2% (95% CI, 38.4%–39.9%) among those aged ≥ 65 years [9]. Another study by Dietz *et al*. found that older patients who survived their index hospitalization for sepsis were more likely to expire or be transitioned to a hospice during the 30-day readmission [10].

However, some studies reported contradictory results. The study by Jones *et al*. showed that younger age was associated with an increased risk of re-hospitalization [11]. Chang *et al.* also reported that younger age (OR 1.34; 95% CI, 1.29-1.39, between the youngest and oldest age categories) was associated with higher odds of 30-day readmission following hospitalization for sepsis [12]. Another study by Goodwin et al. found that patients aged < 80 years were associated with an increased chance

of readmission (adjusted odds ratio [aOR] of 1.14; 95% CI, 1.08-1.21) [13]. Increasing age generally leads to more comorbidities, increased frailty, and weaker immunity; therefore, the readmission rate should increase with age. The 3 earlier studies that showed contrary results were all conducted in the United States. We hypothesize that the difference in the results is possibly due to subsequent readmission avoidance related to old age-associated palliative care-related decisions and health insurance policy in the United States. The observation that survivors older than 80 years were more likely to be discharged to hospice care, as shown in the observational cohort by Goodwin et al. supports this hypothesis [13]. Palliative care was statistically significantly associated with less emergency department use and less hospitalization compared to usual care, as shown in the systematic review by Quinn *et al* [14].

Some studies identified underlying medical history as a risk factor for readmission. No single underlying disease was identified as a significant risk factor in our study; therefore, the influence of the underlying medical history needs further investigation.

For sepsis-specific characteristics, illness severity with resultant organ dysfunction has been identified as a risk factor for readmission in previous studies. However, since we included patients who were all critically ill, the APACHE II score, use of mechanical ventilation, or use of vasopressors did not show any significant difference between patients who were readmitted and those who were not.

Regarding the type of infecting pathogen, we found that an infection with drug-resistant GNB was a risk factor for readmission. The organisms that were identified in our study included ESBL Escherichia coli, ESBL Klebsiella pneumoniae, and MDR-AB (PDR-AB). Our results are similar to those of Dicks *et al* [15]. Patients with MDR-Gram-negative rod (MDR-GNR) infections had 2.03 higher odds of 30-day readmission than patients with non-MDR-GNR infections (95% CI, 1.04–3.97, p=0.04). A study by Zilberberg et al. reported that ESBL-producing bacteria increased the risk of 30-day readmission after sepsis hospitalization [16]. Another cohort showed an increased 30-day readmission risk for infections with MRSA, Escherichia coli ESBL, Klebsiella pneumoniae ESBL, and carbapenem-resistant Pseudomonas aeruginosa [17].

While the study by Ignacio et al. found that MRSA infection had a 2.78 (1.30–5.96) OR for readmission, another study showed no difference in readmission rates between methicillin-susceptible Staphylococcus aureus (MSSA) and MRSA when adjusting for other comorbidities and severity of illness [17-18]. The difference in the influence of MRSA between our study and the study by Ignacio *et al*. is suspected to be related to differences in patient groups and sources of infection. About half of the patients in the study by Ignacio *et al*. were from the surgical unit, and less than 20% of the patients were from the ICU. In addition, most of the patients in our study were infected with pneumonia, while the majority of the patients in their study had urinary tract infection or surgical site infection.

The main readmission etiology in our study was an infection (79.03%), and 75.5% of these patients were admitted for the same focus of infection as during the index hospitalization. The relationship between infection at the index sepsis admission and the infection diagnosis at re-hospitalization was reported in 1 study as recurrent or unresolved in nearly 50% of the

cases [19]. It can be reasonably hypothesized that increased readmissions from infectious causes could represent either an unresolved prior infection or the acquisition of a new infection stemming from immunosuppression caused by sepsis.

The 2 identified risk factors in our study were age and infection with drug-resistant GNB. Age is a time-invariant predictor. We thus suggest that prevention of infection with drug-resistant GNB could lower the risk of 90-day readmission among sepsis survivors, and is a goal that we could work on. The methods to control MDRO include standard care (STD), an antimicrobial stewardship program (ASP), environmental cleaning (ENV), and source control (SCT) [20]. An analysis of subgroups showed that the core strategy for prevention of ESBL-producing Enterobacteriaceae was ASP. For PDR-AB or MDR-AB, ENV plays a crucial role in its reduction; Acinetobacter baumannii has been noted for its ability to survive on dust and other particles in the environment for a prolonged period, even under dry conditions. By incorporating SCT, including drainage of infected fluids, debridement of infected soft tissues, removal of infected devices or foreign bodies, and definite measures to correct anatomic derangement resulting in ongoing microbial contamination, prolonged antibiotic use could be avoided and antibiotics could quickly be de-escalated. Moreover, the hands of healthcare personnel can transmit MDROs, resulting in infections; therefore, optimal hospital ENV combined with careful SCT from healthcare personnel is essential [18]. By incorporating the above methods into infection control in our hospital, we hope to reduce the infection rate of MDRO and thus reduce the readmission risk among sepsis survivors.

For sepsis survivors previously infected with MDRO, other methods of SCT, such as daily baths with chlorhexidine or decolonization could possibly reduce further colonization and the readmission rate after discharge [4, 20]. Another concern is that MDR-GNB infections are common among nursing home residents; consequently, providing appropriate management to lower the prevalence of MDR-GNB colonization in this group may be beneficial.

This study has some limitations. First, this was a single-center cohort study with relatively small case numbers. Second, we did not include certain data that were shown as risk factors in other studies, including blood transfusion, discharge hemoglobin level, nutrition status (such as albumin level), use of total parenteral nutrition, duration of treatment with antibiotics during index admission, and discharge disposition, among others. Further studies with larger sample sizes and multi-center data are necessary to confirm our results and to identify other possible preventable risk factors for sepsis readmissions.

Conclusions

In our single-center, prospective cohort study, age and infection with drug-resistant GNB were risk factors for 90-day readmission among ICU sepsis survivors. Since age is a time-invariant predictor, the modifiable risk factor is the rate of infection with drug-resistant GNB. By reducing the infection rate of drug-resistant Gram-negative organisms, we might reduce the 90-day readmission rate among sepsis survivors. Further studies are needed to confirm these results and to identify other possible risk factors.

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Value of Aspergillus Galactomannan Antigen Assay from Endobronchial Ultrasonography-guided Bronchial Washing Fluid for Diagnosis of Invasive Pulmonary Aspergillosis

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Introduction: Invasive pulmonary aspergillosis (IPA) is a frequent and increasingly common cause of morbidity and mortality in immunocompromised patients. To improve the outcome of these often fatal infections, early diagnosis of IPA is of utmost importance. The primary aim of this study was to establish the value of the Aspergillus galactomannan (GM) antigen assay from endobronchial ultrasonography (EBUS)-guided bronchial washing (BW) fluid for the diagnosis of IPA.

Methods: The diagnostic yields of EBUS for patients with suspected IPA between December 2012 and December 2017 were retrospectively analyzed.

Results: A total of 106 patients with suspected IPA were enrolled in the study. The mean age was 52.9±17.1 years and the most common underlying disease was hematological malignancy (n=36, 34%). Among these patients, 29 were diagnosed as having proven aspergillosis and 6 as having probable IPA infection. At a cut-off index value of 0.5, GM detection in BW fluid had a sensitivity of 97.14% and specificity of 78.57%. The positive predictive value (PPV) and negative predictive value (NPV) were 69.39% and 98.21%. Applying a cut-off index of 1.0, as is proposed for adults, resulted in a sensitivity, specificity, PPV and NPV, respectively, of 96.97%, 95.89%, 91.43% and 98.59%.

Conclusion: The Aspergillus GM antigen assay from EBUS-guided BW fluid is a useful diagnostic tool for pulmonary aspergillosis. It offered a high sensitivity, specificity, PPV and NPV at a cut-off index value of 1.0. This technique can be particularly helpful in avoiding delayed treatment for immunocompromised patients who are suspected of having pulmonary aspergillosis. ***(Thorac Med 2021; 36: 225-235)***

Key words: invasive pulmonary aspergillosis (IPA), endobronchial ultrasonography (EBUS), bronchial washing (BW), galactomannan (GM)

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Introduction

Invasive pulmonary aspergillosis (IPA) is a frequent and increasingly common cause of morbidity and mortality in immunocompromised patients. To improve the outcome of these often fatal infections, early diagnosis of IPA is of utmost importance [1]. The detection of Aspergillus from respiratory tract samples is very important for reaching a precise diagnosis of each form of pulmonary aspergillosis. However, the roles of conventional diagnostic tools, such as cultures obtained from respiratory tract samples, are limited by their low sensitivity.

The serum galactomannan (GM) antigen has been recognized as a useful tool for the diagnosis of IPA, and various methods of detecting GM have been investigated. Several studies [2-5] have evaluated the use of the Platelia assay in detecting bronchoalveolar lavage fluid (BALF) GM in adult patient populations, and have reported sensitivities ranging from 60% to 100%, and specificities from 87.8% to 100% using a cut-off index of >1.0. Bergeron et al [6] reported a sensitivity and a specificity of 57.6% and 95.6%, respectively, when using a cut-off index of BALF GM > 0.5.

Endobronchial ultrasonography (EBUS), a newly introduced technique, has been used in the assessment of peripheral lung lesions [7-8]. Compared with conventional bronchoscopy, EBUS offers the benefits of visualizing the parabronchial structure, confirming the precise location of peripheral lung lesions, and therefore improving the diagnostic yield [9-10]. The BALF GM obtained in the above studies was usually from conventional bronchoscopy; the role of bronchoscopy with the aid of EBUS in the diagnosis of invasive pulmonary aspergillosis has still not been reported. The primary aim of this study was to establish the value of the Aspergillus GM antigen assay from EBUS-guided bronchial washing (BW) fluid in the diagnosis of IPA.

Materials and methods

Patients

Patients at Chinese Medical University Hospital who were clinically suspected of having pulmonary aspergillosis between December 2012 and December 2017 were enrolled in this study. The study was approved by the China Medical University Hospital Internal Review Board (DMR98-IRB-335) and the requirement for informed consent was waived. The cases were immunocompromised patients who matched the revised definitions for proven or probable IPA based on EORTC/MSG [11] criteria, without the use of BALF GM results. In brief, proven IPA requires cytopathologic or histopathologic evidence of acute branching septate hyphae in biopsy samples or aspiration of sterile regions with evidence of tissue damage and a positive Aspergillus culture result.

The probable IPA group required the presence of at least 1 host factor (neutrophil count< 500/μl for more than 10 days, allogeneic stem cell transplant, consumption of glucocorticoid at a dose of 0.3 mg/Kg/day of prednisone equivalent for more than 3 weeks, treatment with immunosuppressive drugs in the last 3 months or inherited immunodeficiency diseases), 1 clinical feature (a dense, well-circumscribed lesion with or without air crescent sign, halo sign or cavity on pulmonary CT scan, or tracheobronchitis evidence using bronchoscopy), and evidence of mycological infection (positive fungal culture in the sputum or BALF sample, the presence of fungal elements indicating a mold in the BALF

sample, or positive GM in serum).

The possible IPA group consisted of patients who met both host factor and clinical criteria, but without mycological evidence. All other patients were considered not to have IPA. Exclusion criteria included prolonged usage (more than 1 week) of antifungal agents and use of the antibiotics piperacillin/tazobactam as a cause of a false positive result of GM testing, at the time of bronchoscopy.

Bronchoscopic procedures and equipment

The probable location of the lesion was determined initially by using traditional posterior anterior chest radiography with chest computed tomography (CT). A flexible fiberoptic bronchoscope (BF-P260; Olympus, Tokyo, Japan) was then inserted through the nostril after local spray with 2% lidocaine for anesthesia. The heart rate and oxygen saturation of each patient were monitored using a pulse oximeter during the procedure. A 20 MHz, radial, mechanical-type ultrasonographic probe (model UM-S20-S20R, Olympus) and an ultrasound unit (Endoscopic Ultrasound System, Olympus) were used in the procedure.

The EBUS catheter was advanced into the fourth- to sixth-order bronchi to assess lesions at the periphery of the lung. Once the lesion was located using EBUS, the neighboring bronchiolar orifices were also examined to ensure the precise location of the lesions. The EBUS procedure was performed without a guide sheath. BW was performed by instilling 50 mL of 0.9% sterile saline into the segment that showed an abnormal shadow on the EBUS, and then as much of the saline as possible was recovered to act as BW. The lung specimens obtained by transbronchial lung biopsy (TBLB) came from the same lesion as that which underwent BW. The Platelia Aspergillus enzyme immunoassay (EIA) (Bio-Rad Laboratories, Hercules, CA, USA) was performed by SRL, Inc. (Tokyo, Japan) to measure the BW and serum GM antigen levels. Serum sampling for the GM was obtained the day bronchoscopy was performed. The BW samples that were obtained for the GM antigen detection test were used also for the fungal and bacterial culture and cytology examinations.

Statistical Analysis

Data were compiled and analyzed using commercial statistical software (SPSS for Windows, version 17.0, Chicago, IL, USA). All continuous variables were reported as the mean±standard deviation (SD) and compared using a 2-tailed Student's t-test. Categorical variables were reported as numbers of patients and percentages. Differences in categorical variables were examined using Fisher's exact test. All tests of significance were 2-sided and a p value ≤ 0.05 was considered statistically significant. Diagnostic performance was expressed as sensitivity, specificity and the receiver operating characteristic (ROC) curve. The optimal cut-off levels for the GM antigen detection tests were determined by the ROC curves.

Results

Characteristics of patients with pulmonary aspergillosis

During the study period, 697 patients were highly suspected of having IPA. Of these, 312 did not undergo diagnostic bronchoscopy due to the poor condition of the patient or family refusal. Seventy-eight patients did not have serum GM on the same day as the performance of bronchoscopy; 103 were excluded due to pro-

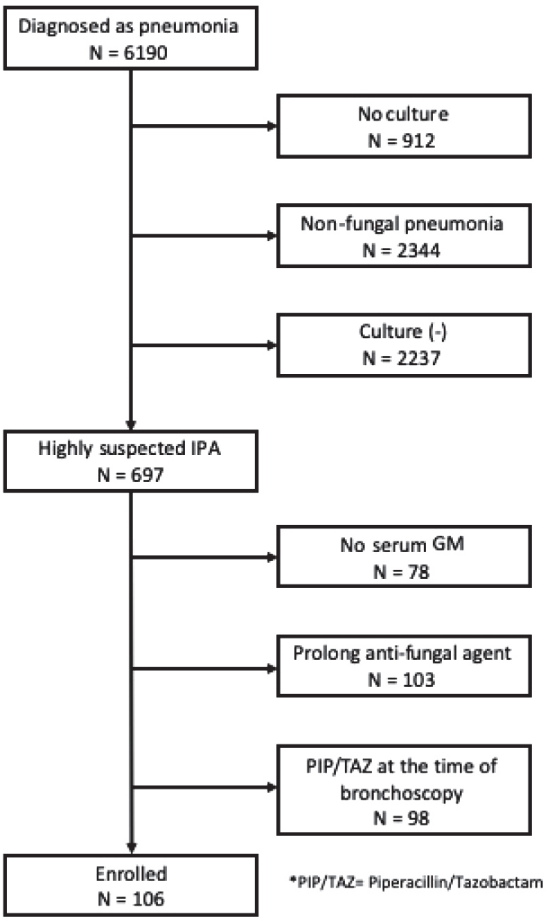

Fig. 1. Patients included in this study—use "Prolonged" below

longed usage of antifungal agents and 98 were excluded due to use of the antibiotics piperacillin/tazobactam at the time of bronchoscopy. The remaining 106 patients were analyzed for this study (Figure 1). According to the EORTC/MSG host factors criteria, 49 (46.2%) patients had a neutrophil count < 500/μl for more than 10 days, 6 (5.7%) had allogeneic HSCT, 11 (10.3%) had consumed glucocorticoid (a prednisone equivalent) at a dose of 0.3 mg/Kg/day for more than 3 weeks, and 6 (5.7%) had an HIV infection with an AIDS status.

According to the EORTC/MSG criteria, 29 patients were classified as having proven IPA, including 21 by means of the bronchoscopic biopsy specimen, 6 by operation and 2 by blood culture. Another 6 patients were classified as probable IPA and 37 patients as possible IPA. We classified patients with proven IPA and probable IPA as the IPA infection group (n=35, 33%), and the others as the non-IPA infection group (n=71, 67%). The IPA infection group comprised 10 women and 25 men, with a mean age of 52.3±14.7 years. The 3 most common underlying diseases of the patients with IPA were hematological malignancy in 18 patients (51.4%), solid tumor in 6 patients (17.1%), and HIV infection with AIDS in 3 patients (8.6%). Compared with the non-diagnostic IPA group, patients with the underlying disease of hematological malignancy had a higher incidence of IPA infection (51.4% vs. 25.4%, *P*=0.008). There were no other statistically significant differences in underlying disease between patients with or without pulmonary aspergillosis infection (Table 1).

The duration from symptoms to treatment in the IPA group was shorter than for the non-diagnostic IPA group, but without statistical significance. In our study, voriconazole was the major treatment in both groups. Compared to the non-diagnostic IPA group, the hospital mortality of the diagnostic IPA group was lower, though without a statistically significant difference, and this may be due to the patient number (Table 2).

The complications of bronchoscopy are known to be pneumothorax, pulmonary hemorrhage and infection. In our study, pneumothorax was diagnosed in 2 patients, and 1 patient suffered from hemoptysis. No patient died after the procedure.

Results of the EBUS-guided BW and serum GM antigen detection tests

Table 1. Baseline Clinical Characteristics of the Study Population

	Total (n=106)	Aspergillus (n=35)	Non-Aspergillus (n=71)	*P* value
Age	52.9±17.1	52.3±14.7	53.1±18.3	0.819
Sex, male, n (%)	77 (72.6%)	25 (71.4%)	52 (73.2%)	0.844
Underlying disease				
Hematological malignancy	36 (34%)	18 (51.4%)	18 (25.4%)	0.008
Solid tumor	11(10.4%)	6 (17.1%)	5 (7%)	0.172
Organ transplantation	8 (7.5%)	1 (2.9%)	7 (9.9%)	0.266
Tuberculosis	12 (11.3%)	2 (5.7%)	10 (14.1)	0.329
HIV infection with AIDS	6 (5.7%)	3 (8.6%)	3 (4.2%)	0.394
Liver cirrhosis	13 (12.3%)	2 (5.7%)	11 (15.5%)	0.212
COPD	7 (6.6%)	1 (2.9%)	6 (8.5%)	0.421
DM	6 (5.7%)	0 (0%)	6 (8.5%)	0.175
ESRD under dialysis therapy	8 (7.5%)	1 (2.9%)	7 (9.9%)	0.266
Autoimmune disease	4 (3.8%)	1 (2.9%)	3 (4.2%)	0.728

Table 2.

	Total (n=106)	Aspergillus (n=35)	Non-Aspergillus (n=71)	*P* value
Admission days	39.3±35.5	33.4±33.3	44.8±36.9	0.144
In-hospital mortality	33 (31.1%)	7 (20.0)	26 (36.6%)	0.118
Antibiotic treatment				
Voriconazole	90 (84.9%)	29 (82.8%)	61 (85.9%)	0.249
Ampho-B	1 (0.9%)	1 (2.9%)	0 (0.0%)	
Lipo-AmphoB	3 (2.8%)	0 (0.0%)	3 (4.2%)	
Anidulafungin	7 (6.6%)	2 (5.7%)	5 (7.0%)	
Itraconazole	1 (0.9%)	1 (2.9%)	0 (0.0%)	
Posaconazole	2 (1.9%)	2 (5.7%)	0 (0.0%)	
From symptom to treatment (days)	8.6 ±5.4	8.0±5.8	9.2±4.9	0.497

The sensitivity and specificity of the EBUS-guided BW GM and serum GM antigen detection tests at various interpretive cut-offs are presented in Table 3. The EBUS-guided BW GM antigen detection test maintained a relatively high sensitivity and specificity at all evaluated cut-off points, while the serum GM antigen detection test failed to maintain an acceptable sensitivity and specificity. At a cut-off index value of 0.5, GM detection in EBUS-guided BW had a sensitivity of 97.14% and a specificity of 78.57%. PPV and NPV were 69.39% and 98.21%, respectively. Applying a cut-off index of 1.0, as is proposed for adults, resulted in a sensitivity, specificity, PPV and NPV, respectively, of 96.97%, 95.89%, 91.43% and 98.59%.

Table 3. The Sensitivity, Specificity, and Positive and Negative Predictive Values Classified from the BAL, Serum GM Antigen Test, Tissue Histology and Bronchial Wash Culture

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
BAL GM > 0.5	97.14%	78.57%	69.39%	98.21%
BAL GM > 1.0	96.97%	95.89%	91.43%	98.59%
Serum GM >0.5	58.70%	85.71%	93.10%	73.24%
Serum GM >1.0	64.15%	98.11%	97.14%	74.65%
Histology	53.12%	97.62%	97.14%	57.75%
Culture	49.25%	94.87%	63.21%	94.29%

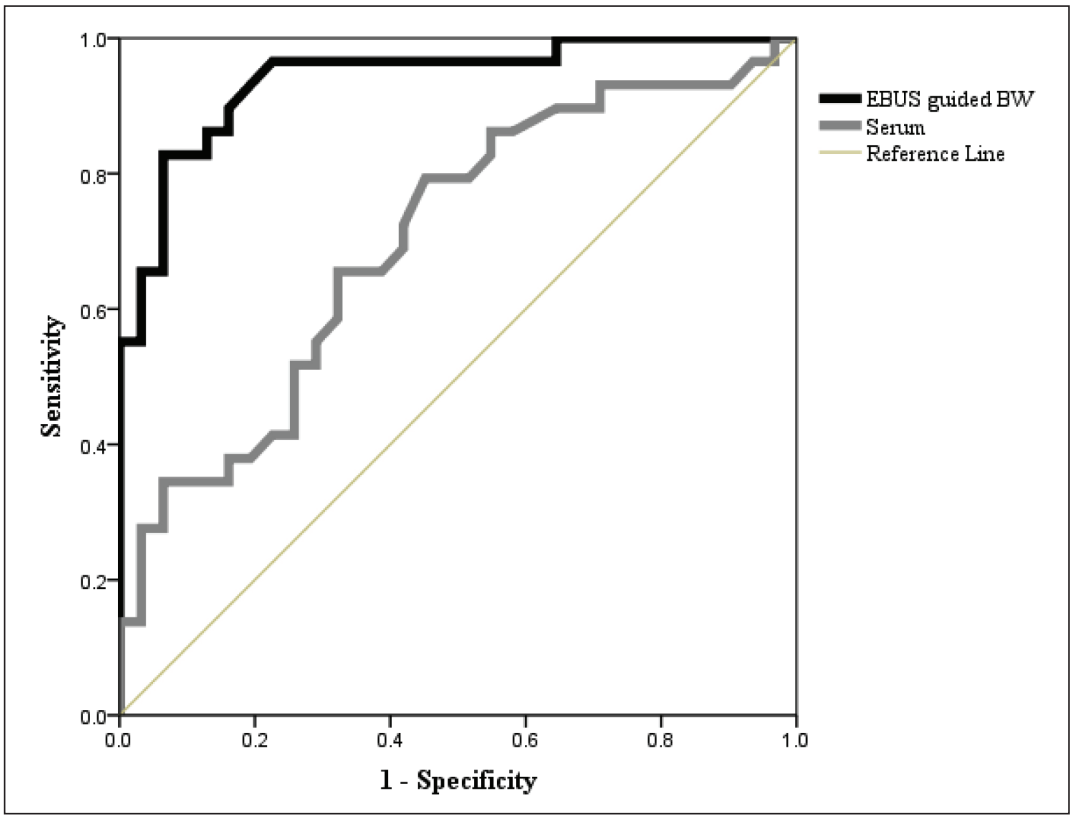

Fig. 2. ROC curve of EBUS-guided BW and serum GM antigen test for diagnosis of IPA—use "EBUS-guided" below

The serum GM antigen detection test had a relatively low sensitivity, but maintained a high specificity, Applying a cut-off index value of 0.5 resulted in a sensitivity, specificity, PPV and NPV, respectively, of 58.70%, 85.71%, 93.10% and 73.24%, and applying a cut-off index value of 1.0 resulted in a sensitivity, specificity, PPV and NPV, respectively, of 64.15%, 98.11%, 97.14% and 74.65%.

The ROC curves constructed for the EBUS-guided BW and serum GM antigen detection tests are presented in Figure 2. The areas under

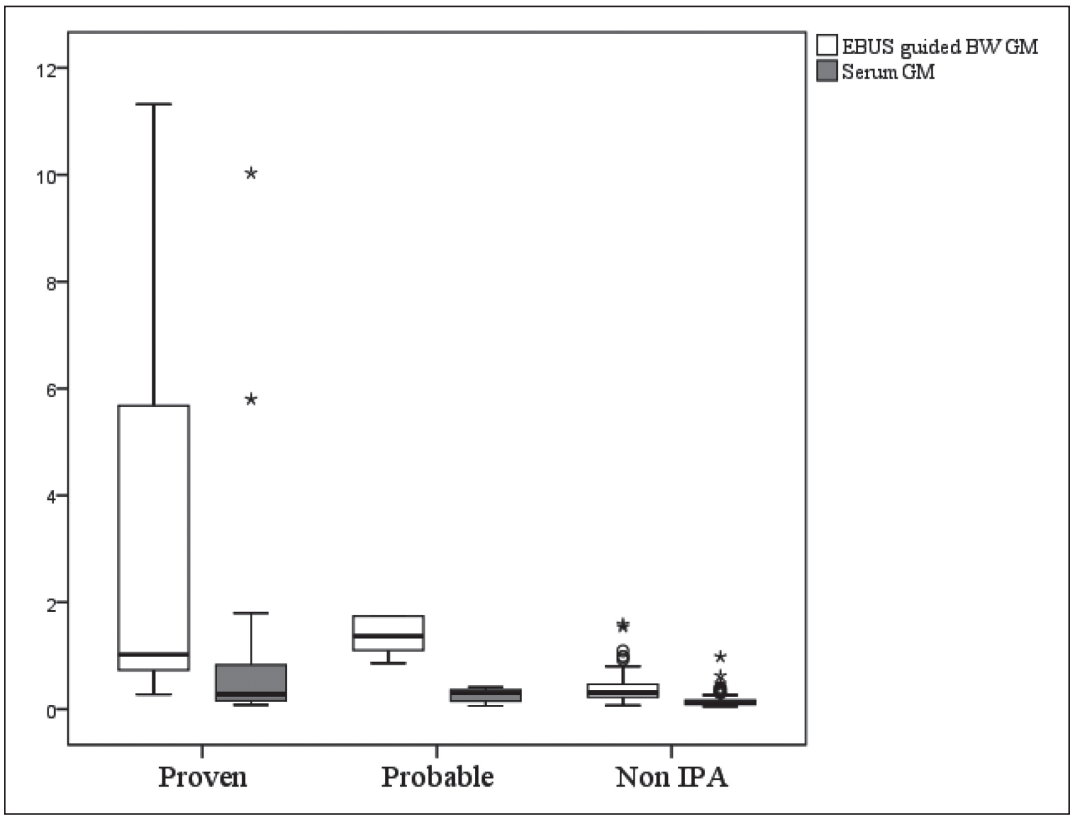

Fig. 3. Distribution of EBUS-guided BW and serum GM antigen tests in different groups of patients—use "EBUS-guided" below

the ROC curves were 0.94 for the EBUS-guided BW GM antigen detection test, and 0.70 for the serum GM antigen detection test, thus suggesting that the EBUS-guided BW antigen detection test has a high accuracy, while the serum antigen detection test is less useful for diagnosing IPA. Figure 3 shows the distribution of the EBUS-guided BW and serum GM antigen test in different groups of patients. The median GM value among proven and probable IPA patients was significantly higher with EBUS-guided BW (Proven: median: 1.02, interquartile range: 5.10; Probable: median: 1.36, interquartile range: 0.70) than with the serum GM antigen test (Proven: median: .0278, interquartile range: 0.723; Probable: median: 0.305, interquartile range: 0.245).

Discussion

This study investigated the utility of EBUS-guided BW GM antigen detection tests for detecting pulmonary aspergillosis, compared to serum GM. We suggest that the EBUS-guided BW GM antigen test is a valuable tool for diagnosing IPA in adults, with a higher sensitivity, specificity, PPV and NPV than serum GM.

Previous studies investigating the BAL GM antigen test confirmed that this test had good diagnostic value in patients suspected of having IPA [12-15]. Another study suggested that BW may have a higher diagnostic yield than BAL for GM detection [16]. However none of these studies used an EBUS-guided tool to obtain the BW GM samples. In our study, we used EBUS-

guided BW for the respiratory tract sample, because EBUS-guided BW can obtain a more precise sample than conventional bronchoscopy, due to its ability to avoid blind washing and lavage. Once the lesion is not visible with conventional bronchoscopy, BAL and TBLB are performed in a best-guess fashion [17], and the diagnostic yield may be reduced. Otherwise, EBUS allows confirmation of the precise location of the lesions by means of direct visualization. The image characteristics of EBUS also provide clues in determining the nature of peripheral abnormalities, such as atelectasis, tumor, and inflammation, based on their different ultrasonic features [18]. Therefore, with the aid of EBUS, we can accurately localize the lesion more easily and increase the overall diagnostic yield for pulmonary aspergillosis. In our study, 21 (72.4%) proven IPA patients could be diagnosed by bronchoscopic biopsy. The above might explain why, in our study, using a higher cut-off index value of 1.0, we still had a higher sensitivity, specificity, PPV, and NPV than other studies using conventional bronchoscopy for the BW GM antigen test [12-15].

Although the FDA has approved a cut-off index as low as 0.5 for serum GM, there has been a lot of controversy regarding the optimal cut-off value of GM as applied to BAL. Several studies reported a low specificity and PPV of BAL GM using a cut-off value of 0.5, due to the high frequency of false positive results, so the value recommended to define positivity has historically been ≥ 1 [12, 19-21]. But with the higher values, the sensitivity and NPV may be reduced significantly. Given the increased mortality risk associated with missing IPA cases, recent studies have suggested that using a lower index cut-off may help detect disease earlier in its course [22].

In our study, using EBUS-guided BW GM to diagnose IPA, we did not need to lower the index of the cut-off value and still had a higher sensitivity, specificity, PPV, and NPV. The high diagnostic yield of EBUS-guided BW GM for early diagnosis of aspergillosis infection might therefore avoid a delay in the administration of antifungal treatment or the need for further invasive procedures, such as CT-guided or surgical biopsy, to reach a definite diagnosis. A high NPV can also contribute to the avoidance of an overuse of antifungal drugs.

Some studies found that the effect of antifungal therapy on BAL GM sensitivity was not remarkable [14-15], other studies described a rapid decrease in BAL GM after initiation of therapy [23], and still others have shown an improvement in the sensitivity of the assay [24]. Hence, we excluded patients with prolonged usage of antifungal agents to avoid any effect on sensitivity. Moreover, the false-positive GM results related to piperacillin–tazobactam (TZP) administration were also considered an important problem affecting the accuracy of the test [25]. A recent study revealed that the original brand of TZP is no longer related to false-positive GM assay results [26]. We have both generic compounds and the original brand of TZP in our hospital, but we still excluded patients with TZP use to avoid possible false positive results for GM testing.

The effect of neutropenia is also a topic of interest. Although some studies have reported no difference in the sensitivity of BAL GM between patients with or without neutropenia [14], in most of the other published studies the sensitivity of the assay was significantly better in neutropenic patients [27]. In our study, 26 (89.6%) proven and 4 (66.7%) probable patients with neutropenia underwent EBUS-guided BW

GM to determine a diagnosis of IPA. The sensitivity of our study may therefore have been increased.

Both univariate and multivariate analyses were used to evaluate factors predicting the diagnostic yield. With univariate analysis, size with location (PPLs ≥ 3 cm with positive bronchus signs, PPLs < 3 cm with negative bronchus signs), and the position of the probe (within the PPLs) were identified as significant factors predicting diagnostic yields. Using multivariate analysis, the following were identified as independent factors predicting the diagnostic yield: EBUS probe within the lesion (HR = 7.224; 95% CI = 4.39-15.44; p<0.001), and *PPLs* < 3 cm with negative bronchus signs (HR = 0.412; 95% CI = 0.23-0.83; p=0.007) (Table 4).

lower diagnostic yield than when the probe is inside a lesion. Hence, we recommend that the bronchoscopist identify the lesion via a different bronchus until the probe is within the PPLs.

Size is also an important factor that affects the diagnostic yield. In our study, a large lesion size (≥ 3 cm) had a higher diagnostic yield than a smaller size. This was because the EBUS probe could be placed inside a larger-sized lesion more readily than in a smaller-sized lesion, and as a result, had a higher diagnostic yield. The location also affected the diagnostic yield. In our study, a positive bronchus sign on CT scan had a higher diagnostic yield than a negative bronchus sign. This was also because the EBUS probe could be placed more readily within a lesion with a positive bronchus sign

Table 4. Univariate and multivariate analyses in the evaluation of factors predicting diagnostic yield of EBUS for IPA. (n=35)

Variable	Univariate		Multivariate	
	HR(95% CI)	P Value	HR(95% CI)	P Value
Lesion size				
Bronchus sign + & > 3 cm vs. others	2.793(1.10-6.23)	0.003	1.131(0.88-3.28)	0.181
Bronchus sign - & < 3 cm vs. others	0.313(0.22-0.48)	<0.001	0.412(0.23-0.83)	0.007
Lesion location				
Right apical and left apical posterior segment vs. other location	0.538(0.41-0.90)	0.007	0.88(0.679-1.15)	0.125
Position of the probe				
Within vs. not within	8.46(5.04-14.76)	<0.001	7.224(4.39-15.44)	<0.001

Previous studies have shown that the diagnostic yield was affected by the position of the EBUS probe. In our study, when the EBUS probe was introduced into a lesion, there was a higher diagnostic yield than when the probe was adjacent to a lesion or outside of a lesion. Therefore, specimen sampling when the probe is either adjacent to or outside of a lesion has a

than in one with a negative bronchus sign, and certainly had a higher diagnostic yield. Hence, we found that PPLs < 3 cm with negative bronchus signs in CT scan images had significantly lower diagnostic accuracies. To improve the diagnostic yield, the use of novel advanced diagnostic bronchoscopy systems, such as a virtual bronchoscopic navigation system, to precisely

identify the proper bronchial route to a lesion, has been reported and might improve the diagnostic yields for PPLs < 3 cm with a negative bronchus sign. Therefore, we found that a larger-sized lesion, a positive bronchus sign, and a probe that could be positioned within a lesion would yield a better diagnostic field. EBUS is suggested to be used for patients with the above characteristics.

Certain limitations of our study deserve to be acknowledged. First, the number of patients with pulmonary aspergillosis was small, which would impede robust conclusions about an optimal cut-off point. Second, we used retrospective data. Clinician-based decisions on bronchoscopy and timing of the bronchoscopy relative to aplasia onset are potential sources of selection and observation biases. It is obvious that the timing of BAL has an influence on the BAL GM antigen test result, since performing bronchoscopy too early may result in false-negativity. This may be of considerable importance in patients diagnosed with possible IPA. Third, bronchoscopy with EBUS is used to detect pulmonary lesions in our department. EBUS was prescribed for all the patients in this study. Therefore. This study cannot evaluate the differences between EBUS and non-EBUS bronchoscopy. Fourth, our patients had different underlying diseases. The fungal burden and the development of pulmonary aspergillosis might depend on the underlying diseases. Although many reports suggest that BAL GM antigen detection tests add sensitivity to cytology and culture in immunocompromised hosts, it has also been reported that the BAL GM antigen detection test does not add sensitivity and only increases the likelihood of obtaining false positive results in non-immunocompromised hosts [28]. Therefore, underlying diseases might influence the utility of the GM antigen detection test.

In conclusion, this is the first report to focus on the usefulness of the EBUS-guided BW GM antigen test for the diagnosis of pulmonary aspergillosis. Aspergillus GM antigen assay from EBUS-guided BW fluid is a useful and safe diagnostic tool for pulmonary aspergillosis. It offered a high sensitivity, specificity, PPV and NPV at a cut-off index value of 1.0. The addition of EBUS-guidance to the BW GM antigen test can be particularly helpful with immunocompromised patients who are suspected of having pulmonary aspergillosis, and avoid delayed treatment.

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Association of B-type Natriuretic Peptide and Exercise Capacity with Cheyne-Stokes Respiration in Heart Failure Patients - a Pilot Prospective Study in Taiwan

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Background: Cheyne-Stokes respiration (CSR) frequently occurs in patients with heart failure (HF). We aimed to evaluate the association between plasma B-type natriuretic peptide (BNP) levels in HF patients with the presence of CSR, and assess functional exercise capacity in HF patients with and without CSR.

Methods: From June 2018 to June 2019, we enrolled 39 patients from a cardiac outpatient clinic who had an ejection fraction <50% and stable HF conditions. All the participants underwent echocardiography, portable sleep monitoring, and blood tests. Twenty-two of the 39 patients received an overnight polysomnography and 19 of the 39 patients underwent a cardiopulmonary exercise test to assess exercise capacity and ventilator response.

Results: Of the 39 enrolled participants, 12 (30.7%) had CSR, and 27 (69.2%) had no significant CSR using a portable monitoring device. BNP levels were significantly higher in the HF patients with CSR than in those without CSR (median: 270.8 pg/ml vs 120.6 pg/ml; P= 0.03). However, there were no significant differences in the parameters of the cardiopulmonary exercise test in HF patients with or without CSR in our study.

Conclusion: Plasma BNP level is significantly associated with the presence of CSR in HF patients. The plasma BNP level can be considered as a parameter to evaluate for detecting central sleep apnea in HF patients. However, we failed to identify whether exercise capacity and ventilator response were associated with CSR in HF patients. ***(Thorac Med 2021; 36: 236-245)***

Key words: Cheyne Stokes respiration, heart failure, B-type natriuretic peptide, exercise capacity, cardiopulmonary exercise test

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Introduction

Cheyne-Stokes respiration (CSR) occurs frequently in patients with heart failure (HF), and the presence of CSR worsens the overall prognosis [1-3]. Although studies have shown that the prevalence of CSR is high, it remains highly variable [1,4,5].

The frequency of CSR is correlated with the severity of HF [1]. Some studies have reported that an increase in the B-type natriuretic peptide (BNP) concentration is directly proportional to the severity of HF and is also associated with an advanced New York Heart Association (NYHA) functional class and disease prognosis [2,6]. BNP levels are significantly related to the central apnea/hypopnea index (AHI), which is a marker for the severity of central sleep apnea (CSA) [7]. Low ejection fraction (EF) and low exercise capacity were associated with the presence of CSR in HF patients [8].

The present study aimed to evaluate the prevalence of CSR in HF patients. We also wanted to evaluate the association between plasma BNP levels and CSR, and between functional exercise capacity and CSR in HF patients.

Materials and Methods

Patients

This protocol was approved by the institutional review board of Chang Gung Memorial Hospital (IRB No. 201701305A3). Patients who visited the cardiac outpatient clinic from June 2018 to June 2019 were screened for this study. The inclusion criteria were age at least 20 years old, a left ventricular ejection fraction (LVEF) <50% on echocardiogram that was performed within 6 months before enrollment, and a stable condition under medication control (absence of hospitalization due to acute decompensation for at least 3 months prior to study entry). Participants who had an EF >50%, instability of chronic HF (CHF) during the study, and acute myocardial infarction during the previous 3 months were excluded from the study. Forty-one patients who fit the criteria were included initially in the study. Written informed consent was obtained from each participant prior to enrollment in the study.

Study protocol

Participants underwent the following tests within 1 month after enrollment in the study: (1) echocardiography to confirm LVEF <50%, (2) sleep study using a portable sleep monitoring device to evaluate any sleep breathing disorder, (3) blood sample evaluating, including BNP level, lipid profile and renal function, (4) overnight polysomnography (PSG) to confirm sleep apnea and (5) a cardiopulmonary exercise test to evaluate exercise capacity. Twenty-two patients underwent overnight PSG, and 19 underwent a cardiopulmonary exercise test. Some participants refused to do an overnight PSG and/or cardiopulmonary exercise test due to time consumption, inconvenience, post-knee joint surgery, disability, or old stroke.

Echocardiography

Echocardiographic studies were performed by 2 experienced cardiologists within 1 month after patient enrollment in the study, using a GE Vivid Q machine (GE Healthcare, United Kingdom). M-mode, 2-dimensional echocardiography was performed in standard views (i.e., long-axis, short-axis, apical 2-chamber, 4-chamber, and subcostal) with the patient in the supine or left lateral position. The parameters of left ven-

tricle (LV) dimensions and function were measured using standard procedures, and the EF was determined using Simpson's method. Two patients were excluded because their EF was higher than 50% on echocardiographic studies after enrollment.

Portable respiratory monitor

A type 3 portable monitoring (PM) device (Medibyte, Braebon Medical Corporation, Canada), which complied with the guidelines of the Center for Medicare and Medicaid Service, was used to detect sleep breathing disorder [10]. The Medibyte consists of the following: 2 respiratory effort bands (chest and abdomen), a nasal cannula pressure transducer to detect airflow, a finger pulse oximetry sensor (oxygen saturation and heart rate) and a body position sensor [11]. Uncalibrated inductance plethysmography was used to identify respiratory effort. Medibyte has high sensitivity and can detect moderate and severe obstructive sleep apnea (OSA) [11] but there is a lack of information on the device's ability to detect CSA. However, manual checking of the readings of the PM was done by a well-trained pulmonologist to obtain accurate results in detecting sleep apnea in this study.

According to the American Academy of Sleep Medicine (AASM) standards guideline version 2.5, the diagnosis of CSR is made if there are episodes of at least 3 consecutive central apneas and/or central hypopneas separated by a crescendo and decrescendo change in breathing amplitude with a cycle length of at least 40 seconds, combined with 5 or more central apneas and/or central hypopneas per hour associated with a crescendo/decrescendo breathing pattern recorded over a minimum of 2 hours of monitoring. Apnea is defined as the cessation of inspiratory airflow >10 s. Hypopnea is defined as a decrease in the oronasal airflow >30% of baseline for >10 seconds combined with 3% oxygen desaturation or arousal events. The number of apneas and hypopneas per hour of sleep is referred to as the AHI. CSA is defined as the absence of a rib cage and abdominal excursions with the absence of airflow. OSA is defined as the absence of airflow in the presence of a rib cage and abdominal excursions.

Blood tests

Blood samples were collected after undergoing echocardiography. Venous blood samples were collected from the forearm and introduced into tubes containing ethylenediaminetetraacetic acid (1.5 mg/mL). Total cholesterol levels, triglyceride levels, glycohemoglobin levels, renal and liver function tests and BNP levels were checked. The BNP levels were determined using a fluorescence immunoassay technique.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed using an electronically braked cycle ergometer. Patients were strongly encouraged by the technician to achieve the point of maximal exercise. Expired air was continuously analyzed using the MedGraphics cardiopulmonary diagnostic system (Breeze Suite 6.0A; Medical Graphics Corporation; St Paul, MN, USA) to assess the physiologic response to exercising. To assess exercise capacity and ventilatory efficiency, the variables of oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation (VE), respiratory exchange ratio (RER), respiratory rate, hemoglobin saturation by pulse oximeter (SpO_2), electrocardiogram, heart rate and blood pressure were measured continuously during the exercise test. Pulmonary

function tests were performed by spirometry (Model 2130 spirometer, SensorMedics, CA, USA) following the standards of the American Thoracic Society. Peak VO_2 was expressed as the 10-second average value obtained during the final stage of the exercise test. Ten-second averaged VE and VCO_2 data were written into spreadsheet software (Microsoft Excel, Microsoft Corp, Bellevue, Wash) as time-down columns from the start of exercise to the peak. The VE/VCO_2 slope was calculated using the slope calculation option of the spreadsheet software package.

Full overnight polysomnography (PSG)

Overnight PSG with an attending technician was performed, and the data were analyzed according to the recommendations of the AASM Scoring Manual, Version 2.5, which are the same as for scoring with the PM device. The PSG sensors include continuous polygraphic recordings of the body position, eyes and leg movements, electroencephalography, oronasal airflow, chest and abdominal effort, and pulse oximetry for confirmation, for a whole night. The AHI for sleep apnea was the number of apneas and hypopneas per hour of total sleep time on the PSG and the total recording time for PM. CSR was considered present when at least 3 regular cycles of increasing and decreasing air flow (crescendo and decrescendo change in breathing amplitude) with a cycle length of at least 40 seconds were observed, as well as increasing and decreasing thoracic and abdominal efforts combined with 5 or more central apneas and/or central hypopneas per hour over a minimum of 2 hours of monitoring [9].

Statistical Analysis

Descriptive statistical analysis was performed. The data are presented as median (25%-75% interquartile range) and percentage of numbers, including all performance metrics. Statistical analyses were performed using Prism version 5 (GraphPad Software Inc., La Jolla, CA, USA) and SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA). The 2 groups were compared using unpaired Student's t test for normal distribution and Mann-Whitney U Test for non-normal distribution; p values less than 0.05 were considered statistically significant. The primary outcome of the study was an evaluation of the prevalence of CSA in patients with HF, and the secondary outcome was an evaluation of the association between plasma BNP levels and functional exercise capacity in HF patients with or without CSR.

Results

Of the 41 patients initially enrolled in the study, 2 were excluded because their echocardiography, done 1 month after enrollment, showed an EF >50%. The study comprised 34 men and 7 women with a median age of 58 years (IQR: 45-68) and median EF of 32% (IQR: 26-39). The basic characteristics of the patients are presented in Table 1.

All of the 39 patients were subjected to PM to evaluate sleep apnea using manual scoring, but only 22 patients were confirmed with overnight PSG. Twelve patients (30.7%) had CSR, and 27 (69.2%) had no significant CSR on the PM device. The 2 groups did not differ significantly in terms of sex, but the presence of CSR was more common in older patients with HF. No significant difference was found in the etiology of HF, severity of HF (NYHA functional class) or comorbidities such as atrial fibrillation, hyperlipidemia, hypertension and diabetes

Table 1. Baseline characteristics of heart failure patients with or without Cheyne-Stokes respiration

Characteristics	All patients (N=39)	CSR group (N=12)	No CSR group (N=27)	*P* value
Age, y	58 (45-68)	64.5 (57.3-69.8)	53 (41-66)	0.06
Male n (%)	33 (84.6%)	11 (91.7%)	22 (81.5%)	0.42
BMI kg/m2	26.2 (23.5-29.1)	26.3 (22.1-27.7)	25.9 (23.7-29.3)	0.79
Comorbidities				
Atrial fibrillation, n (%)	12 (30.8%)	5 (41.7%)	7 (25.9%)	0.34
Chronic kidney disease (GFR), n (%)	81 (58-102)	74 (56.7-99.5)	82 (59-105)	0.49
Diabetes mellitus, n (%)	9 (23.1%)	2 (16.7%)	7 (25.9%)	0.54
Hypertension, n (%)	20 (51.3%)	7 (58.3%)	13 (48.1%)	0.56
LV ejection fraction%	32 (26-39)	33.9 (26.8-46.3)	31 (26-37)	0.25
B-type natriuretic peptide (pg/ml)	123.1 (48.3-265.7)	270.8 (72.3-1438.3)	120.6 (35.1-211.5)	0.03*
TG (mg/dl)	135 (94-183)	126 (75-187)	135 (96-183.3)	0.76
Total cholesterol (mg/dl)	166 (132-182.5)	166 (130-188)	165 (141-181.8)	0.88
LDL (mg/dl)	96 (69-118)	84 (61.3-112.8)	97 (78.5-121.5)	0.51
NYHA heart failure functional class, n (%)				0.37
I	1 (2.6%)	1 (8.3%)	0	
II	34 (87.2%)	10 (83.3%)	24 (88.9%)	
III	4 (10.3%)	1 (8.3%)	3 (11.1%)	
Heart failure, n (%)				0.15
Ischemic	13 (33.3%)	6 (50%)	7 (25.9%)	
Non-ischemic	26 (66.7%)	6 (50%)	20 (74.1%)	

Data presented as median (IQR; 25%-75% interquartile) or as a number (percentage).

* $p< 0.05$ considered significant. BMI: body mass index, LV: left ventricle, TG: triglyceride, LDL: low density lipoprotein. CSR: Cheyne-Stokes respiration, N: number.

mellitus between the 2 groups. The plasma BNP levels were significantly higher in HF patients with CSR (median: 270.8 pg/ml (IQR: 72.3-1438.3)) than in patients without CSR (median: 120.6 pg/ml (IQR: 35.1-211.5) pg/ml) (*P* value = 0.03) (Figure 1)

Of the 39 participants, only 22 underwent overnight PSG. Twelve patients had CSR, and 10 had no CSR on the full overnight PSG. The parameters of PSG in the CSR groups and no CSR groups are presented in Table 3. Nineteen of the 39 participants underwent the cardiopulmonary exercise test, and the other patients refused because of time consumption, knee joint surgery, disability, old stroke, or inconvenience. However, the parameters of the cardiopulmonary exercise test (peak oxygen consumption, RER, O_2 pulse, slope VE/VCO_2, VE/VCO_2), which are related to exercise capacity, ventilator efficiency and cardiac stroke volume, were not significantly different between the 2 groups (Table 2).

Discussion

Our study results showed that the presence of CSR in patients with CHF is high (30.1%), and that a higher BNP concentration was observed in HF patients with CSR. Although an advanced NYHA functional class and lower EF

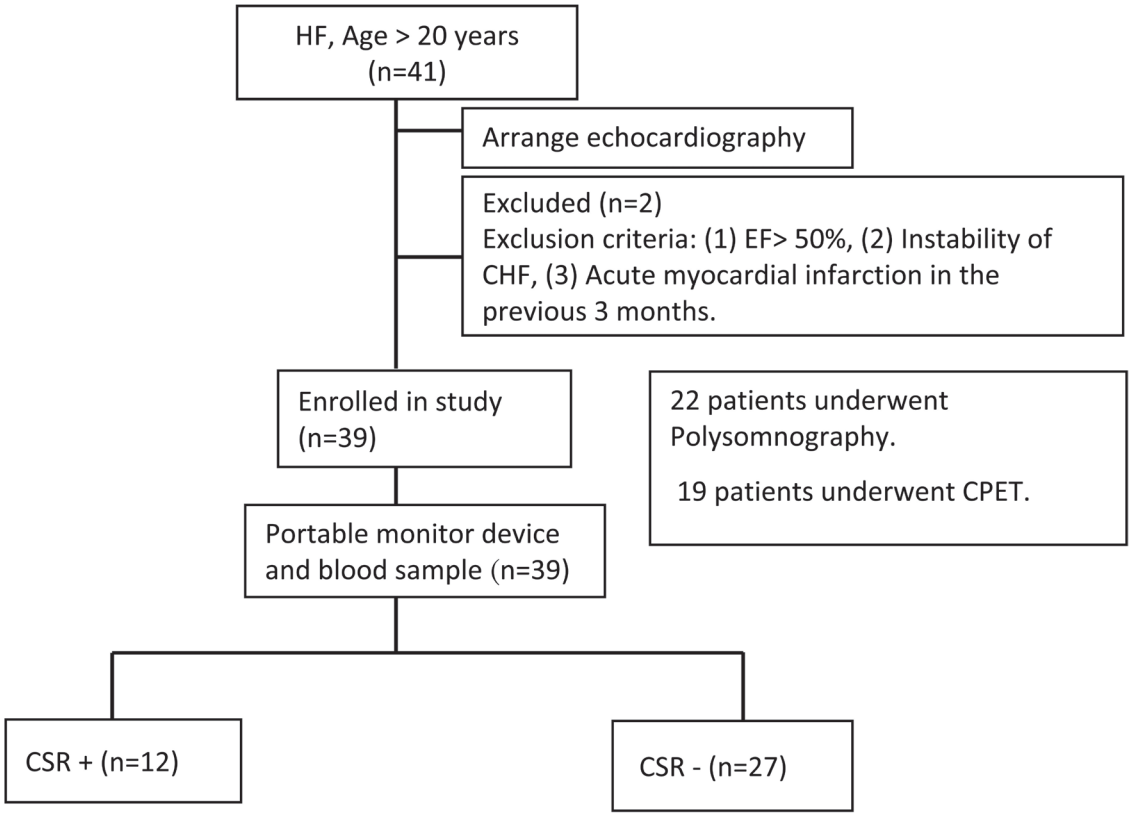

Fig. 1. Flow chart of study protocol

Table 2. Cardiopulmonary Exercise Test Results of Chronic Heart Failure Patients with or Without CSR

CPET variables	All patients (N=19)	CSR group (N=10)	No CSR group (N=9)	*P* value
RER	1.06 (0.99-1.22)	1.05 (0.95-1.2)	1.08 (1.0-1.1)	0.72
HR response	69 (62-83)	76 (56.5-86.8)	68 (63-70.5)	0.78
Peak O_2 pulse (% pred)	94 (64-115)	71.5 (61-120)	101 (90-114.5)	0.31
Peak $V\dot{}O_2$ (ml/min/kg)	15.1 (13.7-20.4)	13.9 (10.1-21.3)	17.3 (14.4-20.5)	0.21
ATVO2 (ml/min)	650 (510-1050)	610 (337.5-875)	650 (575-1125)	0.40
$V\dot{}E/V\dot{}O_2$ (ratio)	35 (27.8-38.2)	32.9 (27.4-37.4)	35.7 (28.1-41.4)	0.60
$V\dot{}E/V\dot{}CO_2$ (ratio)	34.1 (27.4-36.6)	30.5 (28.1-35.6)	33.1 (28.1-36.3)	0.66
Slope of $V\dot{}E/V\dot{}CO_2$	34.1 (27.4-36.6)	33.6 (27.3-38.2)	34.1 (27.8-35.9)	0.54
FEV1, L	2.8 (2.4-3.2)	2.8 (2.3-3.2)	2.8 (2.4-3.4)	1.00

Data are expressed as median (IQR; 25%-75% interquartile). Mann-Whitney U Test was used and *P value <0.05 represents a significant difference. N: number; CSR: Cheyne-Stokes respiration; RER: respiratory exchange ratio (i.e., $V\dot{}CO_2/V\dot{}O_2$); AT: anaerobic threshold; oxygen pulse: $V\dot{}O_2$/HR; % pred: percent of predicted value; slope of $V\dot{}E$ versus $V\dot{}CO_2$: $V\dot{}E$ as a function of $V\dot{}CO_2$; $V\dot{}CO_2$: carbon dioxide output per min; $V\dot{}E$: minute ventilation; $V\dot{}E/V\dot{}CO_2$: ratio of $V\dot{}E$ to $V\dot{}CO_2$; $V\dot{}O_2$: oxygen uptake per minute.

Table 3. Median and Interquartile Range of Sleep Parameters Using Overnight Polysomnography

PSG parameters	Total (N=22)	CSR (N=12)	No CSR (N=10)	*P* value
TST (minutes)	268.8 (178.1-308.8)	234.5 (152.6-302.9)	276.5 (247-318.8)	0.49
AHI	37.2 (21.3-52.7)	44.7 (33.6-69.3)	25.6 (9.2-45.7)	0.03*
Hypopnea index	24.2 (11.3-37.6)	26.2 (16.7-35.9)	22.9 (7.8-40.2)	0.58
OSA index	2.4 (11.3-37.6)	2.7 (0.5-9.7)	1.8 (0.3-6.2)	0.62
CSI	0.4 (0.3-6.3)	3.7 (0.4-16.3)	0 (0-0.3)	<0.01*
RDI	20.8 (15.6-44.9)	39.6 (17.9-46.3)	17.8 (10.2-22.9)	0.02*
ODI	13.7 (4.6-29.6)	27.1 (8.6-44.2)	8.2 (2.5-15.9)	0.01*

Data are expressed as median (IQR; 25%-75% interquartile). *P value <0.05 represents a significant difference. TST: total sleep time; AHI: apnea-hypopnea index, OSA: obstructive sleep apnea index; CSI: central sleep apnea index; RDI: respiratory disturbance index; ODI: overnight desaturation index.

were associated with HF with the presence of CSR in some studies, there was no significant difference in HF patients with or without CSR in this study. There was also no difference in functional exercise capacity assessment using cardiopulmonary exercise testing between the HF with and without CSR groups.

CSR is an abnormal breathing disorder during sleep that is commonly found in HF patients, and is an independent risk factor for increased mortality in patients with HF [7]. The pathophysiology of CSR in HF is associated with an increase in pulmonary venous pressure and pulmonary congestion that stimulates pulmonary stretch receptors to aggravate the ventilatory response and instability of the respiratory control system, predisposing patients to CSR [12-14]. Although our study includes only a few cases, it is the first study on CSR in HF patients in Taiwan. The high prevalence of CSR in HF patients found in our study was similar to that of previous studies in which CSR was detected in 30%-50% of CHF patients [12,15]

BNP release is stimulated by myocyte stretch, and higher concentrations are closely related to ventricular pressure and fluid volume [7,16,17]. Elevated pulmonary capillary wedge pressure is associated with hypocapnia, and both have been identified as risk factors for CSR. Previous studies have suggested that BNP is effective in detecting HF and may be a valuable diagnostic marker in the diagnosis of CSR [1,18-20]. In addition, the plasma BNP level reflects the degree of LV dysfunction, and a high BNP level in HF is associated with a poor outcome [7]. Low BNP level appears to indicate a low risk for CSR in HF patients [20]. One study reported that there was a 2-fold increase in BNP levels in CHF patients with CSA, compared to those without CSA, and even with a similar NYHA functional class and LVEF [2].

Some studies reported a lower EF (EF <40%) and that an advanced NYHA functional class was significantly associated with the occurrence of CSR in HF patients [8,23], but most studies showed that NYHA functional class and EF used to assess the severity of CHF do not considerably differ between CHF patients with and without sleep breathing disorder [4,7,22]. NYHA functional class and lower EF are unreliable criteria for determining CSR risk in HF patients [7,22], as CSR has also been found in CHF patients with preserved EF [4]. In our study, there was no association between lower

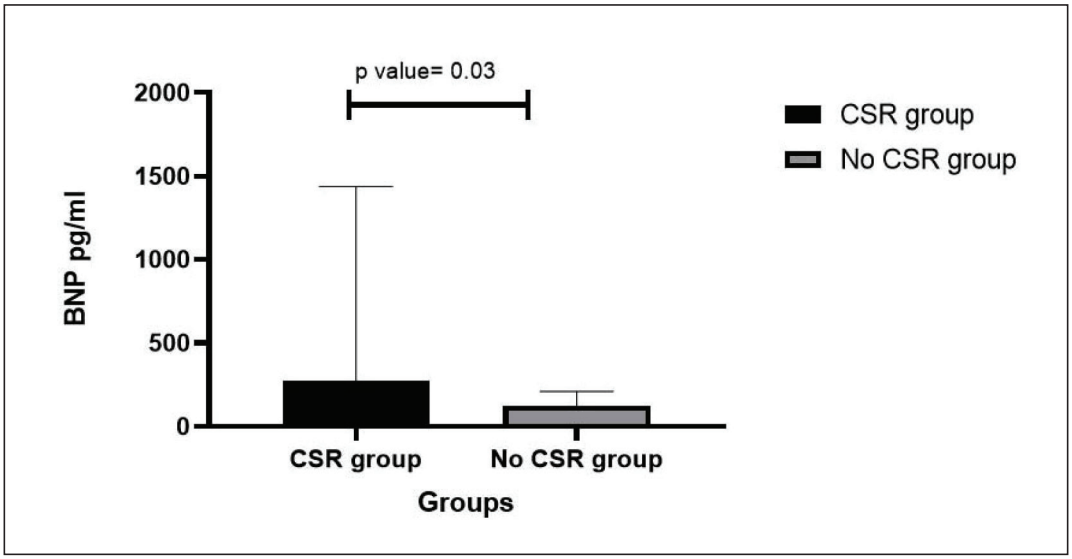

Fig. 2. Vertical scatter plot showing that the BNP levels were significantly higher in HF patients with CSR than in those without CSR (median 270.8 [IQR 72.3-1438.3] vs 120.6 [IQR 35.1-211.5]; *P*= 0.03). The horizontal bars indicate the median with interquartile range for each group.

EF and advanced NYHA functional class in HF and the presence of CSR in HF patients. It may be associated with the low EF of selected patients in both groups (median EF: 33.9% in the CSR group and 31% in the no CSR group).

Exercise intolerance is a cardinal manifestation of HF and a direct consequence of decreased cardiac function [4]. Objective assessment of exercise functional capacity using cardiopulmonary exercise testing could be used as a diagnostic tool to evaluate HF. Several studies have reported that the peak oxygen uptake (VO_2) and slope of VE/VCO_2, which represent exercise capacity and ventilator response, respectively, are powerful prognostic markers for CHF [23]. The severity of CSA and ventilator response (VE/VCO_2 slope) were significantly correlated, and a high VE/VCO_2 slope can predict a poor prognosis in patients with CHF [21]. Exercise capacity (VO_2) and cardiac function were not associated with the severity of CSR in CHF patients [22]. In this study, there was no significant association between low functional exercise capacity and the presence of CSR in HF.

Using a PM device, we found a high prevalence of CSA in HF patients (30%), similar to other studies. Even though PSG is the gold standard method to detect sleep apnea, it is both time-consuming and with a high cost for patients, which can, in turn, delay the diagnosis of CSA. The plasma BNP level can be a valuable alternative parameter to evaluate for early detection of CSA in HF patients.

Limitations

There are a few limitations in this study. First, there was a small sample size and inadequate data on overnight PSG and cardiopulmonary exercise testing for all participants, since some participants refused to undergo PSG due to time consumption, inconvenience, discomfort due to status post-knee joint surgery,

or disability. Also, we were well aware of the fact that the Medibyte is a type 3 PM device and there is a lack of information on the device's ability to detect CSA in previous studies. Moreover, a limitation of PM is its inability to distinguish between sleep and wake periods. So, it is likely that PM underestimates the numbers of apnea and hypopnea incidences due to the use of total recording time instead of total sleep time [24]. The current AASM guideline recommends performing a confirmatory PSG in patients with a negative result on the PM device [24]. However, some studies reported that the diagnostic accuracy of PM is better in a sleep laboratory setting than at home. In our study, PM was performed in a sleep laboratory and each PM reading was manually checked to obtain accurate results in detecting CSA. Even so, the PSG and PM readings in our study could not be compared since they were conducted at different times, unlike in previous studies in which both devices were worn by the same patient at the same time. Furthermore, our study was not intended to validate the accuracy of the PM device in detecting CSR. Further validation of type 3 PM for detecting CSA is needed.

Conclusions

In summary, our study found that the plasma BNP level is significantly associated with the presence of CSR in HF patients. The plasma BNP level can be used as a parameter to evaluate in detecting CSA in HF patients. However, we failed to identify whether exercise capacity and ventilator response were associated with CSR with HF patients.

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Activity Endurance of Patients with Chronic Obstructive Pulmonary Disease after Attending Pulmonary Rehabilitation

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Introduction: Chronic obstructive pulmonary disease (COPD) is a major public health problem and a leading cause of morbidity and mortality worldwide. Long-term exposure to ambient particulate matter 2.5 μm ($PM_{2.5}$) is associated with an increased risk of COPD incidence. Studies have shown that pulmonary rehabilitation (PR) can improve the exercise tolerance and quality of life of patients with COPD. Little is known about the effect of PR on patients with COPD in Taiwan. The purpose of this study was to investigate the activity endurance of COPD patients after undergoing PR training.

Methods: This was an observational study in the thoracic medical clinic of a teaching hospital in southern Taiwan. Sixty-six patients aged 42-90 years (71.45±11.74) and diagnosed with COPD groups B, C, or D, who had completed 6 training sessions, were enrolled. Measurements included a 6-minute walk test (6MWT), a modified Borg scale (mBorg), a modified Medical Research Council dyspnea scale (mMRC), a COPD Assessment Test (CAT), and pulse oximeter oxygen saturation (SpO_2). Measurements were taken to assess the degree of dyspnea while the patients were performing rehabilitation exercises. The collected data were analyzed using the Statistical Package for the Social Sciences 22.0 (SPSS 22.0) for Windows software.

Results: The results of the study revealed that the variables affecting the 6MWT were the mMRC score, the CAT, home exercise habits and home exercise frequency (p<0.05). The results of hierarchical regression showed that the 6MWT was affected by age, the mMRC score, and BMI, and the 6MWT % predicted (6MWT %pred) was affected by the mMRC score and age. The changes in vital signs during the 6 training sessions indicated that the severity of COPD had an impact on the mBorg score, while the changes in diastolic blood pressure in patients with severe COPD had a significant influence.

Conclusion: The mMRC score and age were the main factors affecting activity endurance, the 6MWT and the 6MWT %pred for COPD patients undergoing PR. During PR training, monitoring changes in the diastolic blood pressure of patients with mild to severe COPD is an important measure. ***(Thorac Med 2021; 36: 246-260)***

Key words: pulmonary rehabilitation; activity endurance; COPD

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Introduction

Chronic obstructive pulmonary disease (COPD) is a clinical syndrome of lung disease characterized by irreversible airway obstruction. It is currently the third-leading cause of death in the world. COPD patients suffer from airflow limitation, exacerbations, and hospitalization [1]. With an estimated prevalence of 6.1% in the general population, the number of patients with COPD in Taiwan has been underdiagnosed [2]. Hypertension, or cardiovascular disease, is the most common comorbidity of COPD. Arterial stiffness, which is an important predictor of cardiovascular risk, was increased in patients with COPD. The symptoms of COPD occur in the morning, and include coughing, sputum production and shortness of breath, which result in limited physical activity [3-4]. Fatigue reduces the individual's motivation to engage in daily and social activities, which impacts their overall quality of life. COPD is not a curable disease.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommends that, other than maintenance therapy, pulmonary rehabilitation (PR) is "a comprehensive intervention that includes exercise training, education, and self-management", that is designed to improve the physical and psychological condition of COPD patients [5]. Several studies have confirmed that PR programs for COPD patients obviously increase their activity endurance and improve the degree of dyspnea after exercise training [6-8], and they decrease the rate of hospitalization [9-10]. However, the proportion of hospitalized elderly COPD patients receiving PR is low in Taiwan [11]. In recent years, many hospitals in Taiwan have established medical teams to perform PR therapy for these COPD patients. However, there are few domestic studies on the activity endurance of COPD patients after participating in PR. Thus, the purpose of this study was to explore the activity endurance of COPD patients after finishing 6 PR sessions. The results of this study could provide a practical reference for the clinical treatment of COPD.

In the GOLD guidelines, assessment of combined COPD can be classified into 1 of 4 categories: Group A, B, C or D. Patients in Groups B, C, and D should be encouraged to take part in a formal PR program [5]. Implementing PR after hospitalization, due to exacerbation, could specifically alleviate the dyspnea symptoms and improve the physical activity of COPD patients [12]. To understand the COPD patient's conditions and the current level of symptoms, the modified Medical Research Council dyspnea scale (mMRC) or COPD Assessment Test (CAT) is frequently used [5]. PR treatment for more than 8 weeks is required to improve the physical activity and quality of life of COPD patients; to improve the patients' functional exercise capacity, continuation of treatment for more than 12 weeks may be necessary [13]. However, no matter what physiological or psychological factors may contribute directly or indirectly to exercise tolerance, the timing of PR depends on the clinical status of the individual patient. Most programs are for 8 or 12 weeks, with an overall range of 4 weeks to 52 weeks [14-15].

The 6-minute walk test (6MWT), a standardized self-paced and timed walking test, is useful for measuring functional capacity in clinical practice and provides additional information regarding the patient's prognosis. A shorter measured distance of the 6MWT will indicate a greater risk of death in patients with

COPD, interstitial lung disease, and pulmonary artery hypertension [16]. The results of a previous study based on a 12-month PR for COPD patients in Taiwan showed that both forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV_1) in the experimental group increased, and the 6MWT increased from 402.5 to 410.4 meters [17]. The results after a 12-week PR for patients with moderate COPD showed that there was no significant improvement in FVC and FEV_1, but that the 6MWT increased from 254±38 to 322±42 meters, and the modified Borg scale (mBorg) decreased from 20.2±0.4 to 14.9±0.3 points [18]. In another study, COPD patients at GOLD Stages 1-4 were treated with PR for 6 months, and the changes in the mMRC, Borg scale and 6MWT were measured at the initial PR, at 3 weeks and at 6 months after PR in each group. A comparison of the degree of dyspnea within each group initially, at 3 weeks and at 6 months after the PR showed that the average decrease in the mMRC scale was -0.39 units and the average difference in the Borg scale was -0.76 units. The improvement in the 6MWT average value was over 40 meters at 3 weeks and 6 months after PR in each group. Therefore, the mMRC scale and the 6MWT are predictors of the survival rate of COPD patients [8].

The predicted walking distance value is calculated based on the subject's gender, height, weight and age, and the percentage of the predicted value (6MWT %pred) is calculated by using the patient's actual 6MWT and the predicted value. A higher 6MWT %pred value indicates better exercise endurance [19]. Male patients with moderate to severe COPD had their oxygen uptake and heart rate (HR) recorded during a muscle strength test with a continuously increasing load. The results showed that the HR during training was moderately negatively correlated with the 6MWT and the 6MWT (%pred) [20]. Age and inspiratory capacity at rest were independent factors that were used to predict the 6MWT in COPD patients with lung hyperinflation [21]. A study reported that a 6MWT <350 meters was positively associated with age and mMRC, but negatively associated with resting SpO_2 and FVC %pred [22]. Based on the above literature, the factors affecting 6MWT are age, mMRC, resting SpO_2, and FVC %pred. Therefore, this study employed a cross-sectional design to explore the activity endurance on the 6MWT among elderly patients with COPD after participating in PR, as well as explore the related influencing factors.

Methods

Study design and population

In this study, purposive sampling and a structured record for collecting data were used. COPD patients who were to receive PR treatment were recruited from the thoracic medicine outpatient department in a regional teaching hospital in southern Taiwan. After passing a review by the Institutional Review Board (No.: 201800526B0D001), we began collecting data. The participants needed to meet the following conditions: (1) having been diagnosed as COPD Group B, C, or D by a physician and continuously receiving PR treatment; (2) using low-flow nasal cannula oxygen (<5 L/min); (3) able to communicate in Mandarin Chinese and having a stable gait; and (4) agreeing to participate in this research project after filling in the informed consent form. Exclusion criteria were: (1) using a nasal cannula or home ventilator oxygen (>5 L/min); (2) having a confused consciousness and difficulty in communicating; (3)

having an unstable gait or being unable to walk; (4) having COPD in acute exacerbation; and (5) being in combined treatment for other lung diseases (e.g., tuberculosis, pneumonia, or lung cancer).

In accordance with the report on the GOLD proposal, the PR treatment in the study was designed around performing breathing muscle training exercises for individual patients. The procedures included warm-up exercises for 5 minutes, breathing exercises for 5 minutes, upper limb exercises for 5 minutes, lower limb resistance exercises (aerobic exercise applied on the bike ergometer) for 25 minutes, and relaxation exercises for about 5 minutes. To avoid the risk of life-endangering accidents, oxygen inhalation with 2-4 L/min of a nasal cannula was supplied during the rehabilitation exercise and walking tests. The target HR was determined to be 60% of the patients' maximum heartbeat. The total execution time for a single training session was about 45-50 minutes, depending on the patient's exercise load status and the ability to adjust (shorten or extend) the exercise time, as long as the longest execution time did not exceed 60 minutes. PR was performed 6 times within 2 months. At the first session, the mBorg, height and weight data of the participants were collected, and at the completion of each training session, medical data, such as heartbeat, respiration, SPO_2 and blood pressure, were gathered. Oxygen therapy was given during each training exercise. The 6MWT, which reflects the functional exercise level of patients with COPD, was measured after finishing the sixth session.

Research tools

Data on basic attributes were collected using the patients' demographic and disease characteristics. The former included their age, sex, and education, while the latter included their height, weight, BMI (body mass index), smoking history, smoking years, exercise habits at home, exercise frequency at home, use of nutritional supplements, COPD grouping, chronic disease comorbidities, number of hospitalizations due to acute exacerbation, years of illness, use of oxygen at home, hemoglobin, FEV_1 %pred, FVC %pred, FEV_1/FVC %, mMRC, and CAT. Both the mMRC and the CAT are clinical assessment tools that were included in the guidelines of the Taiwan Society of Pulmonary and Critical Care Medicine [23]. The mMRC is divided into 5 grades (Grades 0-4). A higher mMRC score indicates more difficult breathing. The CAT assesses the health impairment of COPD patients, including coughing, sputum volume, chest tightness, wheezing, quality of life at home, confidence, sleep, and vitality. It has 8 questions with a score of 0 to 5 points for each, for a total score of 0 to 40 points. A high CAT score means that the subject has more symptoms, and indicates poor health and quality of life.

The 6MWT is a reliable test, with intraclass correlation coefficients ranging from 0.72 to 0.99 [24], and it was therefore used as a dependent variable in this study. According to the guidelines proposed by the American Thoracic Society in 2002 [19], the test requires a 30-meter hallway to measure the distance that a patient can walk on a flat, hard surface during a period of 6 minutes. The self-paced 6MWT assesses the sub-maximal level of the patient's walking capacity and allows them to choose their own intensity of exercise, and to stop and rest during the test. In this study, when the 6MWT test was performed, a finger pulse oximeter was worn by each patient throughout

the entire process to monitor the patient's blood oxygen concentration and HR. If the patient had symptoms of physical discomfort during the test, it was stopped immediately and appropriate medical treatment was provided. After finishing the test, the 6MWT %pred of each patient was calculated, with higher values representing a better activity endurance.

Statistical analysis

Data were checked for normality prior to analysis. All data were expressed as numbers and percentages for nominal or ordinal variables and mean ± standard deviation (SD) for continuous variables. Comparisons were carried out using Pearson's chi-squared test for categorical variables and the Mann-Whitney U test and Kruskal-Wallis test for continuous variables. Hierarchical regression was used to analyze factors affecting the 6MWT and 6MWT %pred. The Generalized Estimating Equation (GEE) was used to analyze the variables for repeated measurements during 6 training sessions. A 2-sided p value of <0.05 was indicated as the statistical difference. All statistical analyses were performed using SPSS 22.0 for Windows software.

Results

During the acceptance period of this study (May 2018 to May 2019), a total of 66 COPD patients completed the test. The average age of the subjects was 71.45±11.74 years. Most of the subjects were male (95.5%), with an elementary or junior high school education (71.2%). The average anthropometric measurements were 62.37±12.31 kg for weight, 163.50±6.33 cm for height, and 23.36±4.96 kg/m^2 for BMI. The number and percentage of subjects in Groups B, C, and D were 36 (54.6%), 22 (33.3%), and 8 (12.1%), respectively. The majority of patients in this study had quit smoking (81.8%), had previously smoked for more than 20 years (68.2%), had suffered from COPD for 1 to 5 years, had experienced an acute attack in the past year, had more than 1 chronic comorbidity (83.3%), did not use oxygen at home (78.8%), did not take formula supplements, had exercise habits at home (90.9%), and engaged in exercise ≥5 times a week at home (59.1%). In terms of the patients' lung function, the average FVC was 76.47±19.00%pred, the average FEV1 was 49.36±18.22%pred, and the average FEV1/FVC was 53.61±11.56%. The average hemoglobin level was 13.67±2.17 g/dl. In all, 48.5% of the patients had mMRC scores of 0-1 point, and 57.5% had ≥2 points. Regarding CAT scores, 57.6% had 0 to 9 points, and 42.4% had ≥10 points (Table 1).

Only age, education level, mMRC score, CAT, exercise habits, and exercise frequency at home were significantly different from the 6MWT (p <0.05) (Table 2). The patients in the COPD groupings had differences in lung function (FEV_1, FEV_1/FVC) and symptoms (mMRC score, CAT, use of oxygen at home), but there was no difference in 6MWT and 6MWT %pred (Table 3). This study first ensured that there was no collinearity problem among these variables in the study. The influencing factors of the 6MWT and 6MWT %pred were then predicted by hierarchical regression, and independent variables (age, education years, height, weight, BMI, CAT, mMRC score, FEV_1, FVC, and FEV_1/FVC) were analyzed.

As shown in Table 4, Model 3 indicated that age, mMRC, and BMI could predict the 6MWT with 36.6% of the explained variance, and these 3 items all had a significant negative

Table 1. Basic Attributes (N=66)

Item		n	%	Mean ± SD	Minimum	Maximum
1. Demographic characteristics						
Age (yrs)				71.45 ± 11.74	42.0	90.0
Age (yrs)	<70	28	42.4			
	≧70	38	57.6			
Sex	male	63	95.5			
	female	3	4.5			
Education level	literacy	9	13.6			
	elementary school	32	48.5			
	junior high school	15	22.7			
	senior high school (vocational) or above	10	15.2			
Height (cm)				163.50 ± 6.33	144.0	178.0
Weight (kg)				62.37 ± 12.31	41.0	92.0
BMI (kg/m^2)				23.36 ± 4.96	15.3	43.2
2. Disease characteristics						
Smoking history	never smoked	8	12.1			
	quit smoking	46	69.7			
	still smoking	12	18.2			
Smoking years (yrs)	0	8	12.1			
	7-19	13	19.7			
	≧20	45	68.2			
COPD grouping	Group B	36	54.6			
	Group C	22	33.3			
	Group D	8	12.1			
Years of illness (yrs)	1-5	35	53.0			
	6-9	19	28.8			
	≧10	12	18.2			
mMRC (units)	0-1	32	48.5			
	≧2	34	57.5			
CAT (units)	0-9	38	57.6			
	≧10	28	42.4			
Exacerbation admissions in the last year (times)	0	12	18.2			
	1	36	54.5			
	2-3	18	27.3			
Chronic disease comorbidities (numbers)	0	11	16.7			
	1	32	48.5			
	2	15	22.7			
	≧3	8	12.1			
Use oxygen at home	No	52	78.8			
	Yes	14	21.2			
Formula nutrition supplement	No	49	74.2			
	Yes	17	25.8			
Exercise habits at home	No	6	9.1			
	Yes	60	90.9			

Table 1. Basic attributes (N=66) (cont')

Item		n	%	Mean ± SD	Minimum	Maximum
Exercise frequency at home (times/week)	0	6	9.1			
	1-4	21	31.8			
	≧5	39	59.1			
FEV_1 (%pred)				49.36 ± 18.22	22.0	100.0
FVC (%pred)				76.47 ± 19.00	41.0	130.0
FEV_1/FVC (%)				53.61 ± 11.56	31.6	68.3
HB (g/dl)				13.67 ± 2.17	9.7	17.9
6MWT (m)				338.76 ± 72.11	172	555
6MWT (%) / predicated value				73.09 ± 13.54	53	109

Table 2. Comparison of Basic Attributes and 6MWT (N=66)

Items (n)		6MWT		
		mean±SD	Z/χ^2 value	*p* value
Age (yrs) [a]	<70 (28)	377.79±67.73	-3.634	0.000
	≧70 (38)	310.00±61.52		
Education level [b]	literacy (9)	300.89±74.83	9.680	0.021
	elementary (32)	326.50±76.62		
	junior (15)	362.60±64.03		
	senior or above(10)	376.30±38.62		
BMI (kg/m^2) [b,c]	< 18.5 (9)	335.33±74.97	1.328	0.722
	18.5-24 (33)	341.27±69.20		
	24.1- 27 (12)	324.83±62.68		
	≧27.1 (12)	354.67±79.44		
Smoking history [b]	never smoked (8)	298.38±48.25	4.654	0.098
	quit smoking (46)	340.20±76.14		
	still smoking (12)	360.17±61.90		
Smoking years (yrs) [b]	0 (8)	293.38±48.25	4.014	0.134
	7-19 (13)	353.15±66.37		
	≧20 (45)	341.78±75.78		
COPD grouping [b]	Group B (36)	342.33±78.84	0.090	0.956
	Group C (22)	332.59±69.67		
	Group D (8)	339.63±49.56		
Years of illness (yrs) [b]	1-5 (35)	337.60±69.10	0.080	0.961
	6-9 (19)	335.26±80.10		
	≧10 (12)	338.92±78.33		
mMRC (units) [a]	0-1 (32)	358.09±60.94	-2.336	0.019
	≧2 (34)	320.56±77.78		
CAT (units) [a]	0-9 (38)	352.05±59.31	-2.200	0.028
	≧10 (28)	320.71±84.33		

Exacerbation admissions in the last year (times) [b]	0 (12)	375.25±97.18	1.952	0.377
	1 (36)	333.03±58.42		
	2-3 (18)	320.06±76.23		
Chronic disease comorbidities (numbers)[b]	0 (11)	346.46±44.81	1.113	0.774
	1 (32)	346.50±85.43		
	2 (15)	325.00±53.99		
	≧3 (8)	323.00±78.79		
Use oxygen at home [a]	No (52)	345.42±73.67	-1.436	0.151
	Yes (14)	314.00±62.18		
Formula nutrition supplement[a]	No (49)	333.51±72.24	-0.858	0.391
	Yes (17)	347.71±69.96		
Exercise habits at home [a]	No (6)	239.67±53.58	-3.235	0.000
	Yes (60)	346.92±67.44		
Exercise frequency at home (times/week) [b]	0 (6)	239.67±53.58	15.448	0.000
	1-4 (21)	324.95±71.41		
	≧5 (39)	361.44±60.40		

[a]: Mann-Whitney U test; [b]: Kruskal -Wallis test, [c]: BMI groupings were less than normal (<18.5), normal (18.5-24), overweight (24.1-27) and obese (≧27.1).

influence on the 6MWT. Among them, the predictive powers were BMI (ß=-0.297), mMRC score (ß=-0.419), and age (ß=-0.442). The results showed that being older, having a more serious mMRC score, and having a higher BMI value would lead to a worse 6MWT. In Table 5, Model 2 indicated that the mMRC score and age could predict the 6MWT %pred with 16.5% of the explained variance, and mMRC score and age had a significantly negative influence on 6MWT %pred. Age (ß= -0.261) had the highest predictive power, followed by the mMRC score (ß=-0.410). This result indicated that being older and having a more severe mMRC score would lead to a worse 6MWT %pred. The regression equations were as follows:

6MWT=700.796 + (-2.714) × age (years) + (-40.212) × mMRC (score) + (-4.323) ×BMI (kg/m^2) (F=13.497, p=0.000)

6MWT%pred=63.894 + 0.301 × age (years) + (-7.398) × mMRC (score) (F=7.403, p=0.001)

In order to explore the changes in the repeated measurements during the 6 training sessions, the patients' HR, number of breaths (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and mBorg data were analyzed. The GOLD grouping was used as an independent variable, while the HR, RR, SBP, DBP, MAP, and mBorg were dependent variables. GEE statistical analysis was performed and revealed the following: Groups B, C, and D showed significant differences after repeated measurements of mBorg, indicating that the varying disease severity had an impact on the patients' dyspnea during exercise. Group D also showed a significant difference after repeated measurement of DBP, but Groups B and C were not influenced by DBP. This result indicated that the severity of the disease had a high impact on the DBP of the patients during exercise. However, Groups B, C, and D were not influenced by the HR, RR, SBP, and MAP after repeated measurements. This result indicated that disease severity had no influ-

Table 3. Comparison of the Basic Attributes of the COPD Groupings (N=66)

Items		Group B (36)	Group C (22)	Group D (8)	χ^2 value	*p* value
		n (%)/mean±SD				
Age (yrs)[a]	＜70	15 (41.7)	9 (40.9)	4 (50.0)	0.217	0.897
	≧70	21 (58.3)	13 (59.1)	4 (50.0)		
Sex[a]	male	33 (91.7)	22 (100)	8 (100)	2.619	0.270
	female	3 (8.3)	0 (0.0)	0 (0.0)		
Education level[a]	literacy	4 (11.1)	4 (18.2)	1 (12.5)	5.966	0.427
	elementary	17 (47.2)	11 (50.0)	4 (50.0)		
	junior high	10 (27.8)	5 (22.7)	0 (0.0)		
	senior or above	5 (13.9)	2 (9.1)	3 (37.5)		
Height (cm)[b]		163.97±6.61	160.43±4.57	169.75±1.39	16.662	0.000
Weight (kg)[b]		66.14±13.08	56.58±8.34	61.35±12.83	7.307	0.026
BMI (kg/m^2)[b]		24.75±5.63	21.85±3.43	21.30±3.61	6.007	0.050
Smoking history[a]	never smoked	6 (16.7)	2 (9.1)	0 (0.0)	4.372	0.316
	quit smoking	26 (72.2)	15 (68.2)	5 (62.5)		
	still smoking	4 (11.1)	5 (22.7)	3 (37.5)		
Smoking years (yrs) [a]	0	6 (16.7)	2 (9.1)	0 (0.0)	4.801	0.308
	7-19	9 (25)	2 (9.1)	2 (25.0)		
	≧20	21 (58.3)	18 (81.8)	6 (75.0)		
FEV_1(%pred)[b]		56.58±17.17	41.10±14.01	39.63±20.67	18.826	0.002
FVC(%pred)[b]		78.86±17.74	74.41±19.51	69.63±17.76	2.575	0.276
FEV_1/FVC(%)[b]		61.28±6.92	44.23±6.70	44.90±14.21	32.980	0.000
HB(g/dl)[b]		13.21±2.32	14.44±1.72	13.69±2.14	4.007	0.135
Years of illness (yrs)[a]	1-5	22 (61.1)	11 (50.0)	2 (25.0)	5.405	0.248
	6-9	10 (27.8)	5 (22.7)	4 (50.0)		
	≧10	4 (11.1)	6 (27.3)	2 (25.0)		
mMRC (units)[a]	0-1	23 (63.9)	7 (31.8)	2 (25.0)	7.633	0.022
	≧2	13 (36.1)	15 (68.2)	6 (75.0)		
CAT (units)[a]	0-9	25 (69.4)	11 (50.0)	2 (25.0)	6.069	0.048
	≧10	11 (30.6)	11 (50.0)	6 (75.0)		
Exacerbation admissions in the last year (times)[a]	0	8 (22.2)	3 (13.6)	1 (12.5)	3.727	0.444
	1	21 (58.3)	12 (54.5)	3 (37.5)		
	2-3	7 (19.5)	7 (31.8)	4 (50.0)		
Chronic disease comorbidities (numbers)[a]	0	6 (16.7)	3 (13.6)	2 (25.0)	1.330	0.970
	1	18 (50.0)	11 (50.0)	3 (37.5)		
	2	7 (19.4)	6 (27.3)	2 (25.0)		
	≧3	5 (13.9)	2 (9.1)	1 (12.5)		

[a]: Pearson's chi-squared test; b: Kruskal-Wallis test.

Table 3. Comparison of the Basic Attributes of the COPD Groupings (N=66) (cont.)

Items		Group B (36)	Group C (22)	Group D (8)	χ^2 value	*p* value
		n (%)/mean±SD				
Use oxygen at home[a]	No	34 (94.4)	12 (54.5)	6 (75)	13.085	0.001
	Yes	2 (5.6)	10 (45.5)	2 (25)		
Formula nutrition s upplement[a]	No	29 (80.6)	13 (59.1)	7 (87.5)	4.127	0.127
	Yes	7 (19.4)	9 (40.9)	1 (12.5)		
Exercise habits at home[a]	No	3 (8.3)	2 (9.1)	1 (12.5)	0.137	0.934
	Yes	33 (91.9)	20 (90.9)	7 (87.5)		
Exercise frequency at home (times/ week)[a]		0	3 (8.3)	2 (9.1)	3.850	0.427
		1-4	13 (36.1)	4 (18.2)		
		≧5	20 (55.6)	16 (72.7)		
6MWT(m)[b]		342.33±78.85	332.59±67.67	339.63±45.96	0.090	0.956
6MWT (%) predicated value		73.09 ± 13.54	72.85 ± 12.50	76.46 ± 15.63	3.460	0.177

[a]: Pearson's chi-squared test; b: Kruskal-Wallis test.

Table 4. Regression Analysis of 6MWT (N=66)

Model	Independent value	B value	Standard error	ß distribution	*t* value	Tolerance	VIF
1	(constant)	541.041	43.375		10.958***		
	Age	-2.830	0.682	-0.461	-4.151***	1.000	1.000
2	(constant)	562.829	46.801		12.026***		
	Age	-2.387	0.654	-0.388	-3.647**	0.953	1.049
	mMRC	-32.078	10.226	-0.334	-3.137**	0.953	1.049
3	(constant)	700.796	66.654		10.562***		
	Age	-2.714	0.632	-0.442	-4.291***	0.921	1.086
	mMRC	-40.212	10.137	-0.419	-3.967***	0.875	1.143
	BMI	-4.323	1.544	-0.297	-2.280**	0.865	1.156

Model 3 dependent variable is 6MWT; R=0.629, R2=0.395, Adj.R2=0.366, F=13.497, d.f.=3/62

*P<0.05, **P<0.01, ***P<0.001

mMRC: modified medical research council dyspnea scale; BMI: body mass index

Table 5. Regression Analysis of 6MWT %pred (N=66)

Model	Independent value	B value	Standard error	ß distribution	*t* value	Tolerance	VIF
1	(constant)	83.727	3.848		21.759***		
	mMRC	-6.383	2.108	-0.354	-3.028**	1.000	1.000
2	(constant)	63.894	9.580		6.670***		
	mMRC	-7.398	2.093	-0.410	-3.535**	0.953	1.049
	Age	0.301	0.134	-0.261	2.248*	0.953	1.049

Model 2 dependent variable is 6MWD %pred; R=0.436, R2=0.190, Adj.R2=0.165, F=7.403, d.f.=2/63

*P<0.05, **P<0.01, ***P<0.001

Table 6. GEE Analysis Comparing the COPD Groupings in Terms of Vital Sign Changes During Exercise Training (N=66)

Items	Parameter	βvalue	Standard error	Wald χ^2	*p* value
mBorg	Group B	-0.063	0.0084	56.541	0.000
	Group C	-0.067	0.0159	17.918	0.000
	Group D	-0.062	0.0195	9.995	0.002
HR	Group B	-0.014	0.0106	1.838	0.175
	Group C	0.004	0.0200	0.040	0.841
	Group D	-0.018	0.0270	0.433	0.511
RR	Group B	0.006	0.0138	0.193	0.661
	Group C	0.018	0.0227	0.637	0.425
	Group D	0.027	0.0146	3.486	0.062
DBP	Group B	-0.026	0.0153	2.983	0.084
	Group C	-0.003	0.0280	0.014	0.904
	Group D	-0.032	0.0134	5.750	0.016
SBP	Group B	-0.009	0.0141	0.452	0.501
	Group C	-0.005	0.0154	0.108	0.742
	Group D	-0.020	0.0201	1.023	0.312
MAP	Group B	-0.003	0.0412	0.005	0.946
	Group C	-0.033	0.0449	0.555	0.456
	Group D	-0.023	0.1056	0.046	0.830

mBorg: the modified Borg scale; DBP: diastolic blood pressure; HR: heart rate; RR: respiration rate; SBP: systolic blood pressure; MAP: mean artery pressure

ence on the participants during exercise (Table 6).

The above results revealed that, although some repeated measurements showed no statistical difference between the vital signs and the severity of disease, the variables for HR, RR, SBP, DBP, and MAP still had a mutual influence on the interaction of the heart and lung systems. Therefore, the vital signs affected the patient's mBorg performance. In other words, during the training sessions, when the individuals felt tachypnea, laborious breathing, a faster heartbeat, and high blood pressure, they would feel more dyspnea. Therefore, monitoring vital signs during exercise is a necessary measure to maintain the life safety of patients.

Discussion

The 6MWT range of the sample in this study was 172~555 meters, with an average of 338.76±72.11 meters, and the average 6MWT %pred was 73.09±13.54%. According to Lee *et al*. [9] and Spruit et al. [16], the mobility of patients with 6MWT ≧350 meters is better, indicating that the subjects in these 2 studies had moderate or above-average mobility. To establish the trajectories of PR training for COPD patients, the average 6MWT in the low activity group was 347±91 meters [25]. Donaire-Gonzalez *et al*. [26] found that FEV_1, FEV_1/FVC, and 6MWT in elderly patients with severe and very severe COPD were 41±5/25±4

%pred, 47±11/35±8 %, and 395±102/349±103 meters, respectively. The 6MWT in this study was 338.76±72.11 meters, which was close to that of the previous results [25]. Therefore, the subjects in this study belonged to the low activity group, and their disease level was between moderate and very severe.

In the study by Lee *et al*. [9], the 6MWT of the experimental group increased from 402.5±18.3 to 410.4±17.8 meters after 12 weeks of PR training (p<0.05), while in the study by Nilesh et al. [27], the average 6MWT of 60 COPD patients increased from 350.95 to 419.91 meters after 4 weeks of PR training (p<0.001). In our study, the 6MWT was not measured before PR, so the change in 6MWT between pre- and post-PR could not be compared.

Saglam *et al*. [28] found that the 6MWT, SpO_2, and FEV_1/FVC of COPD patients with hypoxia were 445.29±92.96 meters, 85.61±8.54%, and 56.53±13.26%, respectively. A comparison of results between our study and that study [28] showed that: (1) the 6MWT values in both studies were quite different; (2) the SpO_2 of some patients in this study was between 85% and 88% at the beginning of PR, and remained above 88% during subsequent PR training, which was higher than that in the above study; and (3) the FEV_1/FVC in both studies were similar. Since PaO_2 is not routinely measured at this research site, it could be estimated that the subjects in this study were hypoxemic patients.

In a clinical setting, the 6MWT %pred was 70%, and the average 6MWT %pred of the subjects in the current study exceeded this value. The study of Güngör *et al*. concluded that 6MWT %pred was better correlated with the respiratory function of COPD patients than the actual 6MWT [29]. The study found that the 6MWT value was from 226 to 393 meters, and that the 6MWT %pred value was about 60% [29]. The 6MWT value in the Güngör *et al*. study was close to that in this study, but the 6MWT %pred values in both studies were quite different. The variances in both studies were due to the different study designs, the disease condition and the age of the subjects. In this study, the subjects were an average of 71.45±11.74 years old and underwent 6MWT after finishing 6 training sessions, while in the Güngör *et al*. study, COPD patients were about 65 years old, they used a non-invasive respirator at home due to chronic hypercapnic respiratory failure, and they underwent the 6MWT measurement without PR therapy.

This study found that the variables affecting the 6MWT were mMRC score, CAT, home exercise habits and home exercise frequency (p <0.05). This finding was similar to that of Li *et al*. [30], who found that there were differences in the 6MWT, CAT and mMRC scores between the PR-at home group and usual care group. This indicated that an important key point was the patient's motivation to practice exercises at home. For the effect of PR, the subjects in the current study were encouraged to continue to implement their exercise practicing skills at home, as it was beneficial for the maintenance of patients' functional exercise capacity.

Zeng *et al*. [31] designed a cross-sectional study on the predictors of 6MWT distance for COPD patients. The results showed that mMRC score, age and CAT score were significant predictors in the final model for 6MWT distance. The above result was a little different from that of this study. The reason for this might be the differences in COPD severity and age in our study group. Spruit *et al*. [16] studied the factors affecting a 6MWT <350 meters in COPD

patients, including the severity of obstructed airflow in GOLD groups, mMRC scores ≧2, the degree of emphysema, the presence of depression symptoms, and whether oxygen was used during and after the 6MWT test. However, in this study, the different groups of COPD patients showed no differences in the 6MWT and 6MWT %pred. No data on emphysema or depression were collected; therefore, it was impossible to explore these 2 influencing factors in patients with 6MWT <350 meters in this study.

Previous literature that explored the factors that influence the 6MWT in the normal elderly found that age and height were significantly correlated with the 6MWT (p<0.01) [32], and that height and FEV_1 were independent predictors [33]. However, the 6MWT %pred can better explain the mobility of COPD patients, and it is known that 6MWT %pred =218 + (5.14 × height–5.32 × age)–(1.80 × weight + 51.31 × gender) [32]. There are many study results on the 6MWT formula for predicting healthy people [24]. The short 6MWT of COPD patients is related to an increased risk of death, but predictions of the influencing factors of 6MWT in COPD patients in many models are inconclusive. Age was found to be a common factor in the regression formula of the 6MWT and 6MWT %pred in this study. This coincided with the results of Singh *et al*. [24] and Güngör *et al*. [29], who found that age and gender are the most important predictors of the 6MWT in healthy people.

There was no difference in the SBP, DBP, MAP, and HR in COPD patients before and after 8 weeks of PR training [34]. The Borg score of COPD patients after 4 weeks of PR training decreased from 12.26 to 10.26 (p<0.001) [27]. The results of both of these studies [27, 34] were similar to those of our study, with the Borg score being significantly decreased in the 3 COPD groups. In the current study, the subjects performed low-intensity PR, and the target HR was about 50-60% of the patient's maximum heartbeat. In each training session, the mean SBP of the total subjects changed from 110 mmHg at the beginning to 147 mmHg at the end, and the mean DBP changed from 68 mmHg at the beginning to 86 mmHg at the end. In this study, there was no difference in the SBP, DBP and MAP among the 3 groups of COPD patients between the initiation and ending of the PR. These results were different from those of Gale *et al*. [35], who found that PR reduced SBP by 10 mmHg and DBP by 5 mmHg, but the results were the same as those of Kaliaraju *et al*. [36] and Canavan et al. [37], in which the PR did not significantly reduce blood pressure.

In this study, elderly subjects with moderate to severe COPD were recruited, and 83.3% of them had 1 or more comorbidities, which were mostly related to cardiovascular diseases. These conditions were in accordance with the findings of Qvist *et al*. [38] that showed that COPD patients with GOLD 3-4 and age ≧60 were associated with an increase in arterial stiffness. In the current study, the pulse pressure of 66 subjects during training increased from 41 mmHg at the beginning to 61 mmHg at the end, showing that arterial stiffness existed. Vanfleteren *et al*. [39] showed that central arterial stiffness was increased in subjects with COPD and that peripheral blood pressure (SBP and DBP) did not change, while pulse pressure increased, following PR. These results were the same as those in the current study. A significant change was found in the DBP of the Group D patients in this study during 6 training sessions. The reason

for this phenomenon may be the state of arterial stiffness response to PR. However, the number of COPD patients with GOLD D in this study should be increased, in order to gain further understanding of DBP changes in older patients.

Conclusions

The 6MWT or 6MWT %pred is considered a primary outcome for COPD patients participating in a PR program. Age, mMRC score, and BMI had a significantly negative influence on predicting the 6MWT results. The mMRC score and age had a significantly negative influence on predicting the 6MWT %pred. In addition to medication, PR should be also included in the routine treatment of COPD patients. Low-intensity PR had a positive effect on the exercise capacity and dyspnea scores of COPD patients.

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Bronchoscopic Cryotherapy for Removal of an Intubation-related Tooth in the Trachea---a Case Report

Meng-Yun Tsai[1], Yu-Mu Chen[1], Yu-Ping Chang[1], Wen-Feng Fang[1], Meng-Chih Lin[1]

A 54-year-old man was admitted due to acute respiratory failure. Secretion obstruction occurred in the endotracheal tube, and re-intubation was performed. A tooth was found to be missing after intubation, and the follow-up chest X-ray revealed a foreign body stuck in the left main bronchus. Emergency bronchoscopy was performed and a tooth was removed using bronchoscopic cryotherapy. ***(Thorac Med 2021; 36: 261-265)***

Key words: pulmonary alveolar microlithiasis; SLC34A2 gene; sodium-phosphate co-transporter

Introduction

Tooth injuries during intubation have been reported, with an incidence of about 1.13%; if the patient has loose teeth, the incidence would up to 12.1%[1]. Foreign body aspiration, including a tooth, may lead to pneumonia, airway obstruction or atelectasis. Bronchoscopic cryotherapy is a technique for the treatment of endobronchial tumor, a mass, blood clot or infection, and also has been used for the removal of a foreign body[2]. We present the case of a tooth found to be missing after intubation that was later removed from the trachea by bronchoscopic cryotherapy.

Case Description

A 54-year-old man was admitted to our intensive care unit (ICU) due to acute respiratory distress syndrome(ARDS), which was caused by influenza infection. During admission, an acute onset of respiratory distress occurred, even under full ventilator support. Auscultation revealed bilateral decreased breathing sounds and a low tidal volume. Extubation was performed due to a suspicion of obstruction of the endotracheal tube, and impaction of secretion at the tip of the endotracheal tube was discovered at that time. Respiratory distress presented after extubation, and re-intubation was planned. Pre-

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oxygenation with a bag-valve mask and premedication with a midazolam 5mg IV push were performed. A 7.5 Fr. endotracheal tube was emplaced, after which, the patient's respiratory distress resolved, with clear consciousness and a stable hemodynamic status. But after the procedure, a missing tooth was noted, and a chest X-ray examination was arranged, which revealed a foreign body at the left main bronchus (Figure 1). The patient was placed in a Trendelenburg position and an emergency bronchoscopic examination was arranged. The bronchoscopy examination was performed with an Olympus BF-160 bronchoscope, which had an insertion tube 4.9mm in diameter and a working channel 2.0mm in diameter. During the examination, a tooth was found in the trachea.CO_2 cryotherapy was performed using an ERBE cryoprobe, 1.9mm in diameter. The duration of the attachment was about 30 seconds, and then it was extracted slowly. The ventilator setting during the procedure was a pressure control mode, PEEP 10cmH_2O, FiO_2 100%, with SPO_2 maintained around 95%. The tooth, which was an incisor, was removed smoothly (Figure 2) with the endotracheal tube, for the diameter of the tooth was larger than that of the endotracheal tube. Re-intubation was performed smoothly and chest X-ray follow-up revealed no residual foreign body in the lower respiratory system(Figure 3).

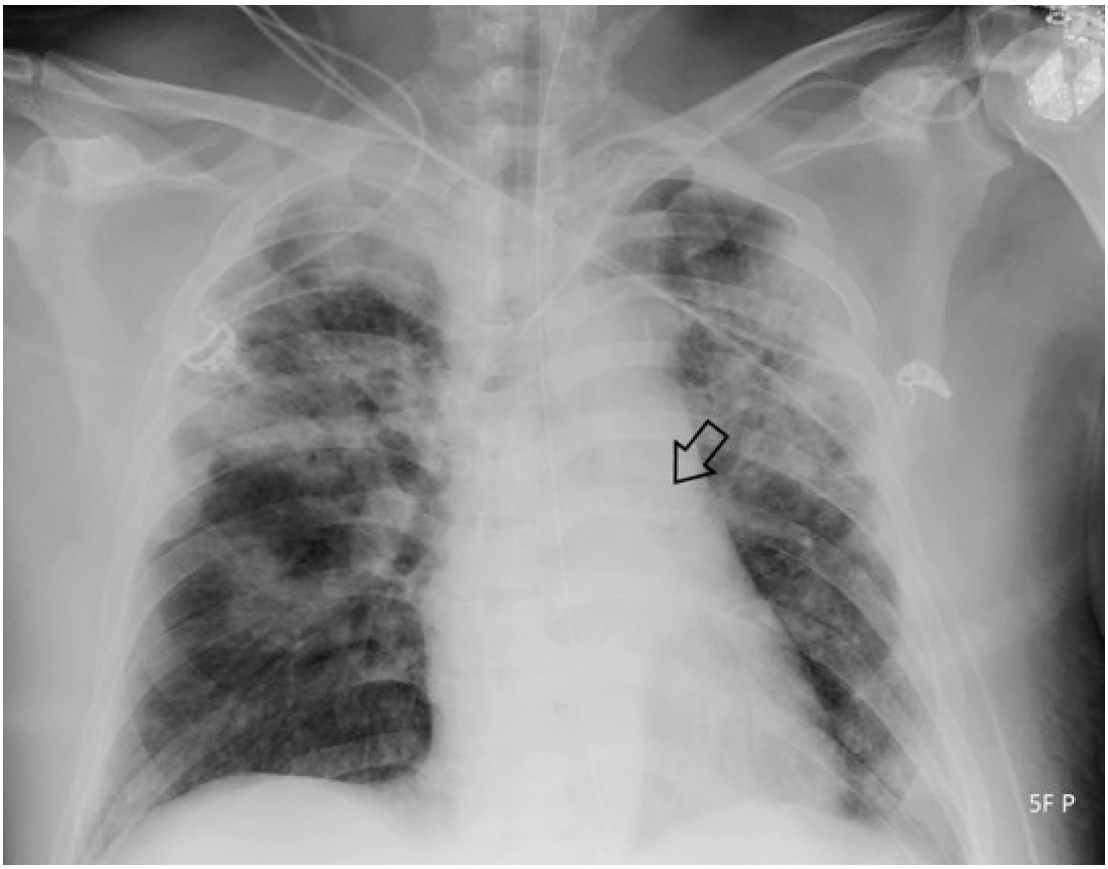

Fig. 1. A foreign body stuck in the left main bronchus (as the arrow) after intubation.

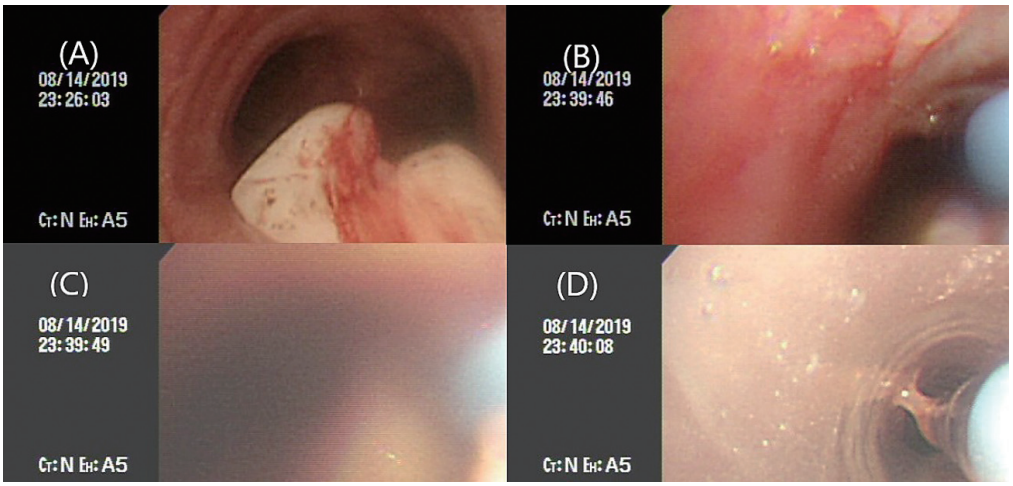

Fig. 2. (A)A missing tooth was found at the main trachea by bronchoscope. (B)A cryo-probe was used in an attempt to attach to the tooth.(C)(D)The tooth was attached to the cryo-probe and was removed from the trachea.

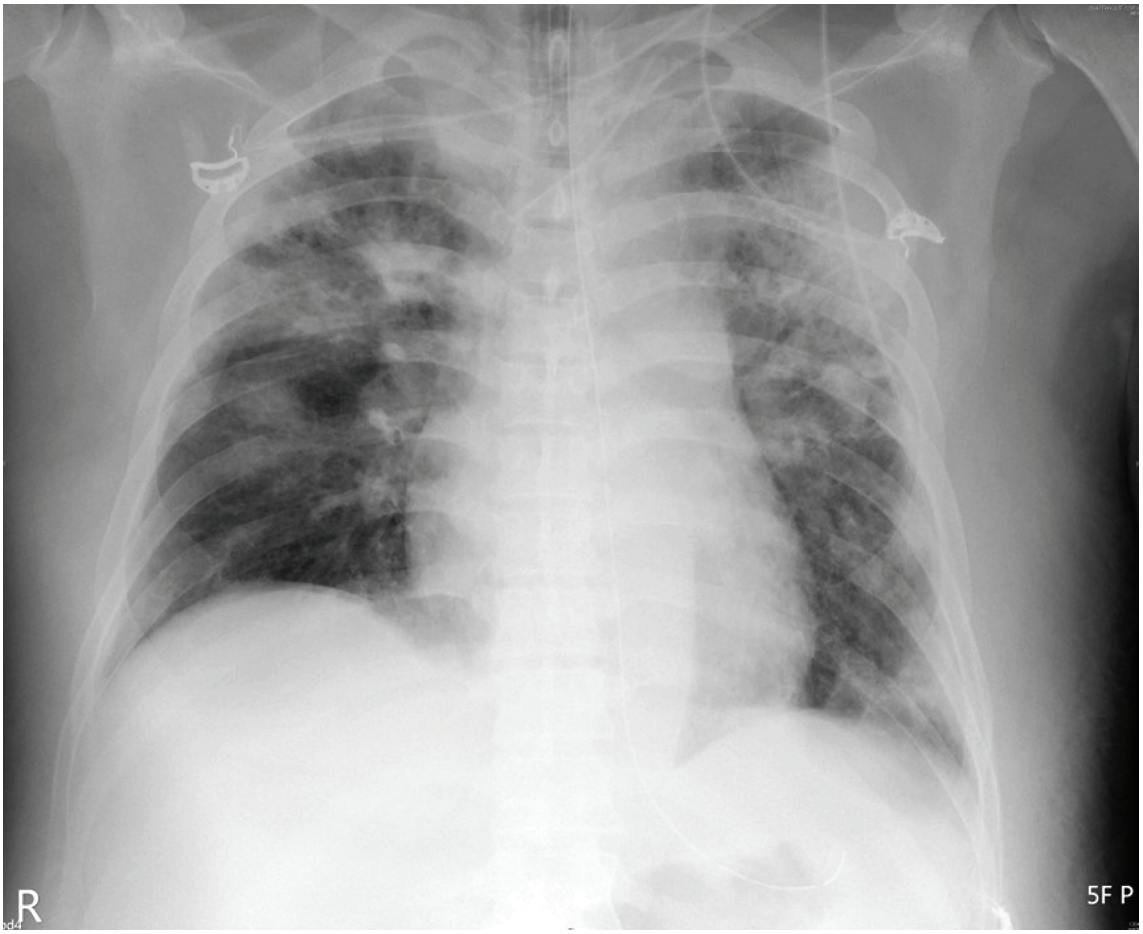

Fig. 3. After bronchoscopic cryotherapy, no foreign body was seen in the chest X-ray.

Discussion

Foreign body inhalation occurs mostly in children [3], but cases among adults have been reported[4]. Only 1 report of tooth inhalation after intubation was found in the literature [5]. Bronchoscopy is the gold standard for the diagnosis and is the therapeutic technique used to remove the foreign body. Prior to the procedure, a Trendelenburg positioning of the patient can prevent the foreign body from falling into the lower respiratory airway and increasing the difficulty of further management[6]. In our case, after Trendelenburg positioning, the tooth moved from the left main bronchus into the main trachea.

Rigid bronchoscopy was performed to treat foreign body inhalation in the past[7], but flexible bronchoscopy has been used instead recently and is considered to be a preferred initial procedure for management of airway foreign bodies in adults[4].However, there are limitations to the use of flexible bronchoscopy for foreign body removal, since the working channel may not be large enough if there is a larger foreign body, and in these cases, rigid bronchoscopy may be a better choice. In our case, the surface of the foreign body was smooth and lacked an edge or ridge for our instrument to grasp, and there was also a lot of secretion on the surface, which enhanced the difficulty of removal by forceps.

Bronchoscopic cyrotherapy is a technique that is used for a variety of conditions, such as malignant and benign central airway obstruction and low-grade airway malignancy, foreign body removal or cryoextraction, endobronchial biopsy, and transbronchial biopsy[8]. Cryotherapy for the removal of a foreign body that has been inhaled by children has been reported and proved to be a safe, easy and effective method[2].Sehgal et al. reported using a cryoprobe for the successful removal of a foreign body in the left main bronchus in an adult patient [9]. Although cryotherapy may prove to be an effective method for the removal of a foreign body in the adult population, there is a lack of reports on critically ill patients who are under mechanical ventilator support. Bronchoscopic cryotherapy may be a safe and successful alternative method for the removal of a foreign body in a critically ill patient under mechanical ventilator support, but the limitations of cryotherapy should be considered. First, hypoxemia may develop during or after the procedure, thus full oxygen support with the ventilator is required to lower the risk. Second, in patients with endotracheal tube intubation, the foreign body would need to be removed with the endotracheal tube simultaneously if the diameter of endotracheal tube is smaller than that of the foreign body, thus there is a greater risk of hypoxemia in patients with respiratory failure, and a re-intubation should be performed right after the foreign body is removed with the endotracheal tube. Finally, risks such as pneumothorax, hemoptysis or unstable hemodynamics during the procedure should also be considered. More studies on the effectiveness, safety and efficacy of bronchoscopic cryotherapy for foreign body removal in critically ill patients are needed.

Conclusion

For patients with respiratory failure and with post-intubation foreign body inhalation, bronchoscopic cryotherapy may be a good and safe choice for the removal of the foreign body.

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Tracheal Schwannoma with Central Airway Obstruction Rescued by Flexible Bronchoscopy

How-Yang Tseng[1], Bing-Ru Wu[1], Wei-Chih Liao[1,2], Chia-Hung Chen[1,2], Chih-Yen Tu[1,2]

A 68-year-old male patient, presented to our hospital because of progressive shortness of breath for 4 months. A primary tracheal tumor with central airway obstruction was noted. The tumor was finally diagnosed as a tracheal schwannoma. It was treated with flexible bronchoscopic tumor excision and stent implantation, and later was surgically resected. ***(Thorac Med 2021; 36: 266-271)***

Key words: Tracheal tumor, Flexible bronchoscopy

Introduction

Primary tracheal tumors are rare, and primary neurogenic tumors of the trachea presenting as schwannomas or neurilemmomas are extremely uncommon. Due to the rarity and nonspecific symptoms, primary tracheal tumors are almost always misdiagnosed and treatment is delayed. Open and curative resection is preferable in treating primary tracheal neurogenic tumors. Bronchoscopy plays an important role in diagnosis and treatment, and in the management of complications caused by tracheal tumors. Here, we report a case of central airway obstruction caused by a tracheal schwannoma that was treated with flexible bronchoscopic tumor excision and stent implantation, and later, surgical resection.

Case Description

A 68-year-old male patient with a history of right buccal cancer, status post operation at Taipei Veterans General Hospital 20 years ago, hypertension, type 2 diabetes mellitus, and chronic kidney disease, presented to our hospital because of progressive shortness of breath for 4 months.

He had a history of cigarette smoking, 2 packs per day for 20 years, but had quit. He also complained of cough with sputum and dyspnea on exertion for months. There was no

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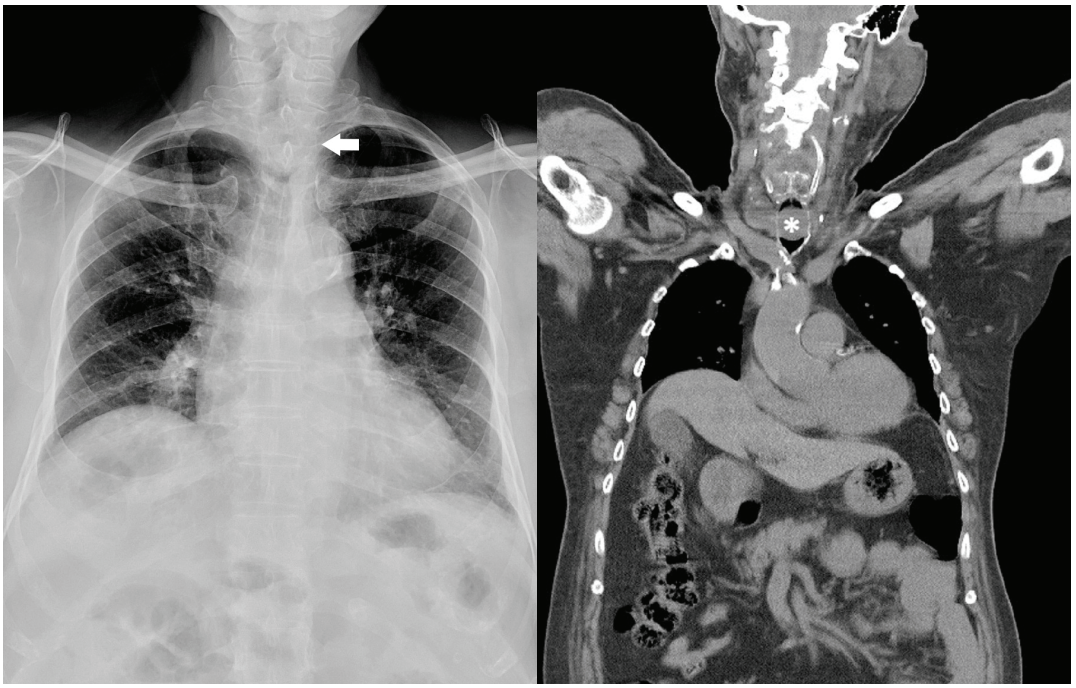

Fig. 1. Chest radiograph(arrow) and computed tomography of the chest(asterisk) showing a mass lesion at the upper trachea.

fever, chest tightness, chest pain, orthopnea, or dysphagia. One week before admission, the symptoms progressed. He visited a local clinic and was treated as having asthma initially, but the symptoms didn't improve after bronchodilator use.

He then came to our hospital for a second opinion, and physical examination revealed stridor at the neck. The chest radiograph and computed tomography of the chest showed a mass lesion at the upper trachea (Figure1). Due to severe dyspnea with a high risk of acute respiratory failure, flexible bronchoscopy was performed and disclosed a firm tracheal tumor in the upper trachea with the lumen nearly totally obstructed (Figure2-A). We performed flexible bronchoscopy with electrocautery and cryosurgery for tumor excision (Figure2-B.D) to remove the airway obstruction. A tracheal stent (BTB-200409, 20mm*4mm) was implanted for residual stenosis (Figure2-C). After the procedure, the patient's symptoms were relieved and he was discharged smoothly.

The pathologic report of the bronchoscopic biopsy revealed a mixture of mucus and dyskeratotic cells with relatively enlarged nuclei; squamous cell carcinoma(SqCC) was suspected initially. Serial survey of the tracheal tumor was arranged. Magnetic resonance imaging of the neck (Figure 4) revealed a tumor around 4.1×3.5 cm in size in the left dorsal aspect of the trachea and 5.5 cm distal to the vocal cords, which had invaded the trachea and possibly the left lobe of the thyroid gland. Positron emission tomography–computed tomography showed an FDG-avid tumor in the central lower neck region, seemingly blurring the margin of the esophagus and thyroid gland, and destroying the posterior wall of the trachea. Endoscopic ultrasound showed a peri-esophageal mass with hypoecho-

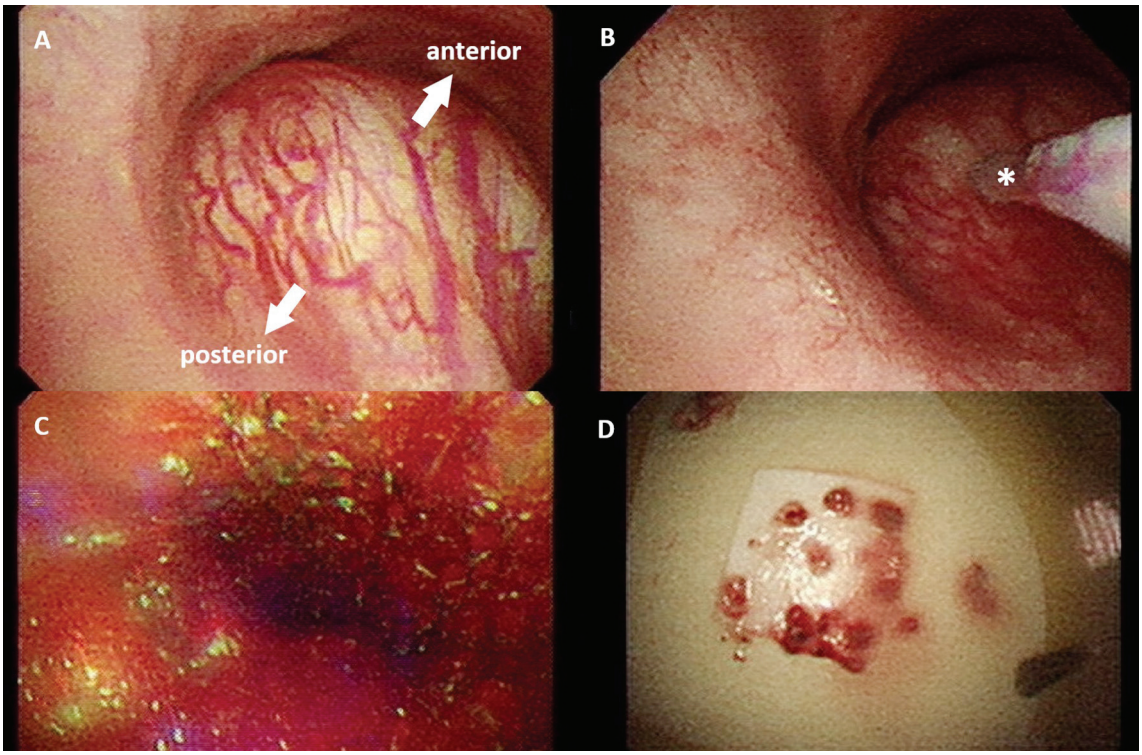

Fig. 2. (A) Bronchoscopy revealed a firm tumor, with a smooth and glossy appearance, located in the upper trachea with the lumen nearly totally obstructed. (B.D) Flexible bronchoscopy with electrocautery and cryosurgery (asterisk: the cryoprobe) were performed for tumor excision. (C) Tracheal stent implantation (20 mm*4 mm) for residual tracheal stenosis.

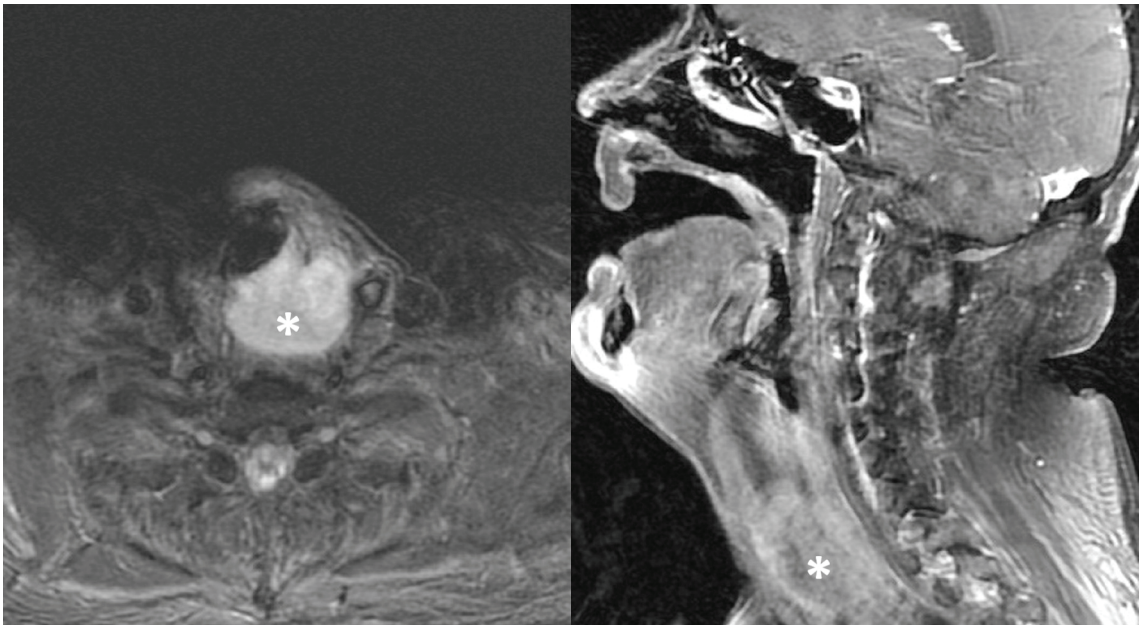

Fig. 3. Magnetic resonance imaging of the neck revealed a tumor (asterisk) at thyroid gland level which had invaded the left dorsal aspect of the trachea and possibly the left lobe of the thyroid gland.

genicity, distinct margins, and external compression. Thyroid aspiration was negative for malignancy. For the above reasons, we arranged tumor resection with laryngopharyngectomy, esophagectomy, resection of the upper posterior part of the trachea and flap reconstruction. The post operative specimen consisted of a well-defined, sessile tumor, measuring 5.0×3.7×3.5 cm in size, located at the upper trachea. The adjacent organs were free of tumor invasion. The microscopic examination of the post operative specimens revealed a schwannoma composed of a predominantly hypocellular (Antoni type B) area and scattered hypercellular areas (Antoni type A) of spindle cells appearing as elongated and wavy with tapered ends and an absence of mitotic activity (0/10 HPF). Immunohistochemical study revealed the tumor cells were diffusely positive for S100 and CD34 and negative for CK, desmin and smooth muscle actin, compatible with the immunoprofile of schwannoma. The patient was relatively stable after a 1-year follow-up.

Discussion

Primary tracheal tumors are rare [1]. The most common histologic types is SqCC, which accounts for more than half of tracheal tumors. Adenoid cystic carcinoma (ACC), which represents about 10%–15% of tracheal tumors, is the second most common type. Primary tracheal tumors other than SqCC and ACC are very rare. There are only a few reported cases of tracheal schwannoma in the literature. One retrospective analysis of tracheal tumors was conducted at Massachusetts General Hospital. A tracheal histologic appearance other than SqCC or ACC was found in a quarter of patients, with a highly heterogeneous histologic appearance (33 different histologic diagnoses in 90 patients). Schwannomas were extremely rare and represented less than 1.1% in this retrospective study[2]. They originate from the peripheral nervous system and are derived from well differentiated Schwann cells. The lesions typically are solitary, encapsulated and attached to a nerve, but have no neurites.

The gross appearance of SqCC, the most common tracheal tumor, is rough and uneven due to the tumor's invasion of the epithelium. ACC, the second most common type, is smooth and glossy. A tracheal schwannoma is also smooth, because it originates from the peripheral nervous system and the tumor is covered with normal epithelium. Schwannomas rarely undergo malignant transformation[3]. However, a review of the literature between 1950 and 2013, found that 3.9%(2/51) of patients presented with malignant schwannoma. Most of these cases occurred in the distal third of the trachea, followed by the proximal, and then the middle third of the trachea. It was slow growing and the type of symptoms depended on the anatomical location, size and degree of airway obstruction caused by the tumor[4].

Primary tracheal schwannomas can occur at any age and have a predilection for female patients[3]. Due to the rarity and non-specific symptoms, primary tracheal tumors are almost always misdiagnosed and treatment is delayed[5]. These tumors are frequently attributed to a respiratory disease such as asthma or bronchitis, but always are refractory to medical therapy. They are not investigated as an endotracheal lesion until suspected flow-volume loops appear or if the symptoms progress to stridor [6-7].

The choices of treatment depend on the clinical characteristics of the tumor (pedun-

culated or sessile), the presence of an extratracheal component or not, and the risk of tracheal resection[8]. Bronchoscopic resection is applicable to pedunculated lesion without extratracheal extension[4]. However, there lesions have been associated with a high rate of residual tumor; a rate of 46.2% has been reported [9]. Thus, open and curative resection for the tumor is always needed and is preferable in low-risk patients with sessile tumors or with extratracheal extension[5,10]. Nevertheless, bronchoscopy plays an important role in the diagnosis, and in the therapy for tracheal tumors. Local complications such as bleeding and central airway obstruction may be treated on an emergency basis under general anesthesia with rigid instruments[11]. Silastic airway stents are useful in patients with central airway obstruction caused by a tracheal tumor, including schwannoma, who are under general anesthesia and undergoing rigid bronchoscopy[12]. However, if rigid bronchoscopy is not available at the facility, flexible bronchoscopy is also an effective procedure for symptomatic central airway obstruction, due to its almost immediate effect[13]. Insertion of self-expandable metallic stents (SEMS) for patients with central airway obstruction is an effective palliative treatment for malignant or nonmalignant disease[14]. Bronchoscopy also plays a role in postoperative follow-up, diagnosis and treatment of secretion, or in cases with anastomotic wound healing disorders.

In conclusion, primary tracheal tumors are rare. Primary neurogenic tumors of the trachea, such as schwannomas or neurilemmomas, are extremely uncommon. We reported a case of central airway obstruction caused by a tracheal schwannoma, that was treated with flexible bronchoscopic tumor excision and SEMS implantation, followed by surgical resection.

Conclusion

For patients with respiratory failure and with post-intubation foreign body inhalation, bronchoscopic cryotherapy may be a good and safe choice for the removal of the foreign body.

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Delayed Presentation of Airway Injury after Blunt Trauma: Case Report and Literature Review

Ping-Chung Tsai[1], Wen-Hu Hsu[1]

Trauma-induced airway injury is catastrophic and results in early mortality. Injuries that are not immediately life-threatening and are missed at initial presentation may later become symptomatic and require medical attention. Delayed diagnoses of traumatic tracheobronchial injuries with damaged distal lung might occur, although early injuries can often be repaired without sacrifice of the distal lung parenchyma. We herein report the case of a 56-year-old female with delayed total occlusion of the left main bronchus due to an accident in which she fell. She recovered very well during an 8-month follow-up after receiving sleeve resections of the left main bronchus. ***(Thorac Med 2021; 36: 272-276)***

Key words: Delayed presentation, airway injury

Introduction

Tracheobronchial injuries are life-threatening conditions that may result from blunt or penetrating injuries to the neck and chest, as well as from medical procedures [1]. Iatrogenic tracheal lacerations are rarely accompanied by esophagus rupture, whereas blunt or penetrating injuries of the tracheobronchial tree are most often accompanied by a variety of different and sometimes life-threatening injuries [2]. The presence of concomitant severe airway injuries may delay the diagnosis and lead to an early fatal outcome. Radiographic and clinical signs of tracheal rupture include pneumothorax, pneumo-mediastinum, subcutaneous emphysema, and respiratory distress, all of which can present without tracheal rupture [3]. A 25% rate of blunt trauma deaths due to thoracic trauma has been reported in the United States [4]. Prompt diagnosis is mandatory for the survival of these patients. The goals of treatment are to restore the integrity of the airway, minimize the loss of pulmonary parenchyma, maintain vocal function and avoid permanent tracheostomy [5]. Patients with a delayed or missed diagnosis could present after weeks or months, and even longer, with complaints that range from respiratory distress to repetitive pneumonia or systemic sepsis caused by pulmonary infections [6]. The diagnosis may be made retrospectively, when bronchial stenosis and its complications develop after chest trauma.

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Case Description

This 55-year-old female was well without systemic disease. On 28 October 2018, she accidently fell 20 meters while climbing a mountain. The impact was partly relieved by a tree, and there was no initial loss of consciousness or focal weakness. She was soon transferred to a local hospital with suspected right hemothorax, pneumothorax, left main bronchus (LMB) laceration, multiple rib fractures with flail chest, left humerus head fracture, and a left patella fracture as seen on the initial imaging survey. In November 2018, during a 20-day treatment in this hospital, right-side 3rd ~ 6th lateral ribs fixation and left humerus head open reduction internal fixation were performed (Figure 1). After discharge, mild shortness of breath on exertion with wheezing sounds was noted. A white-out area in her left lung was noted in the chest CT scan on 8 January 2019. Decreased breathing sounds in the left lung field were also noted. She then came to our hospital. Bronchoscopy on 29 January 2019 revealed complete obstruction of the LMB with scarring formation 2 cm below the carina (Figure 2A). CT scan of the

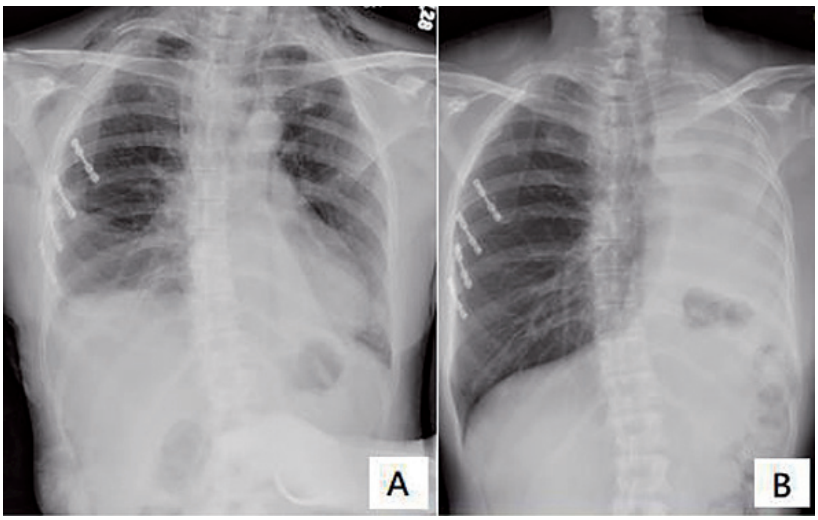

Fig. 1. Patient's chest X-ray. (A). November 2018. (B). January 2019.

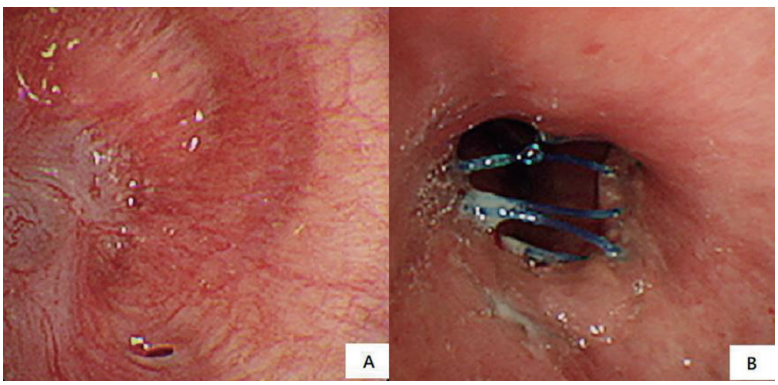

Fig. 2. Patient's bronchoscopy. (A).Complete obstruction with scarring at the left main bronchus 2 cm below the carina in January 2019. (B). Patency of the left main bronchus with some local Prolene stitches in October 2019.

chest with 3D reconstruction for mapping was performed (Figure 3), and showed complete obstruction of the LMB after trauma. The pulmonary perfusion ratio study showed just 3.46% of pulmonary volume in the left side of the total lung.

About 4 months after her trauma, on 22 February 2019, the patient underwent sleeve resection and reconstruction of the LMB by thoracotomy, enforced by a mediastinal pleural flap for LMB laceration with connective tissue totally separated from it. Surgical pathology reported fibrosis and chronic inflammation. The postoperative period was uneventful, and the chest tube (28 Fr) was removed on postoperative day 5. Compared with the previous LMB occlusion and total collapse of left lung status, further chest CT revealed good expansion of the left lung with focal narrowing of the LMB (Figure 4A.4B). Bronchoscopy revealed some prolene stitches at the LMB anastomotic site (Figure 2B) with luminal patency.

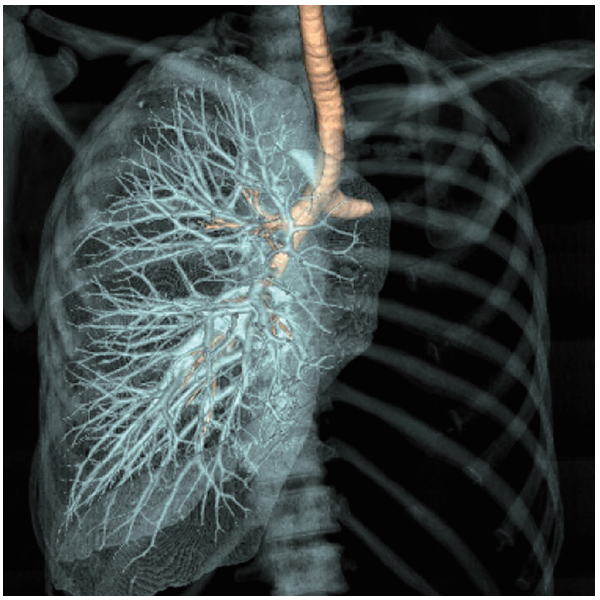

Fig. 3. Chest CT 3D reconstruction image: left main bronchus total occlusion.

Discussion

The true incidence of tracheobronchial injuries is still unknown, since many individuals die before reaching the intensive medical care unit. Blunt or penetrating trauma and iatrogenic injury are the most common causes of tracheobronchial injuries. For all endotracheal intubations, the incidence of airway injury is estimated to be 0.005% [7]. For patients with blunt tracheobronchial injuries, a higher incidence of right bronchial injuries may be due to the

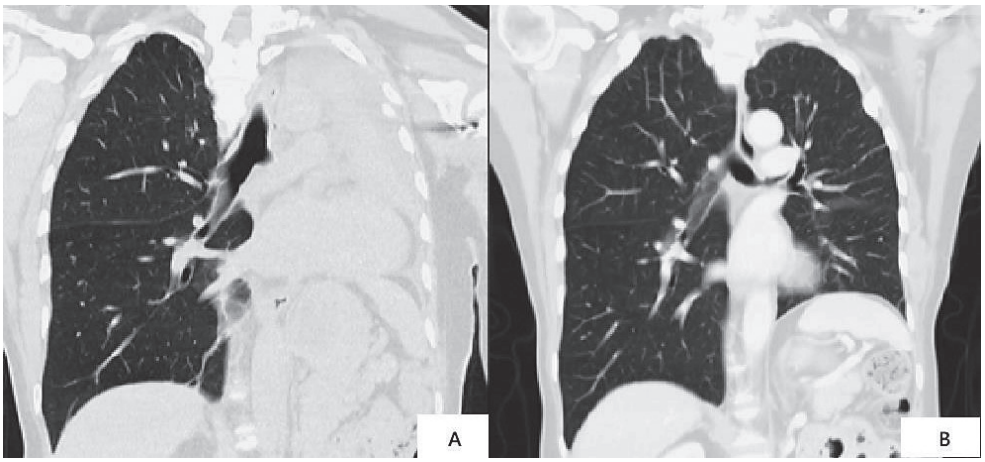

Fig. 4. Pre- and post-operation chest CT scans (A). Left main bronchus occlusion and total collapse of the left lung in January 2019. (B). Slight focal narrowing of the left main bronchus with full expansion of the left lung in November 2019.

shorter length of the right main bronchus (RMB) compared to the LMB (8). Right-side injuries may be detected earlier, while injuries to the left bronchus are more protected by adjacent structures in the mediastinum. The heavier right lung on the shorter RMB may also play an important role in the amount of traction force experienced in accidents. In the Kiser *et al* study, 76% of the 265 airway injuries occurred within 2 cm of the carina, and 43% occurred within the first 2 cm of the RMB [8].

Assuming the patient survives the initial trauma, nearly half of tracheobronchial injuries are missed during the first 24–48 hours [9]. In our case, the patient, who suffered from blunt trauma, was diagnosed with LMB total occlusion around 3 months after the injury and underwent surgical approaches 4 months after the injury. In cases with a high degree of clinical suspicion of acute respiratory distress, radiographic imaging may reveal pneumo-mediastinum, subcutaneous emphysema, pneumothorax, or a tracheal tear, which would help in reaching a diagnosis of tracheal injury. Bronchoscopy remains the "gold standard" for diagnosis of tracheal injury, almost universally [10]. In the event of a complete laceration of the tracheal wall, it is important to assess for concomitant esophageal injury. Stenotic bronchi that are not completely obstructed tend to develop post-obstructive pneumonia and bronchiectasis. Once the airway is completely obstructed, the distal lung may become filled with mucus and protected from infection, and separated from the other bronchi.

The prognosis of a patient after tracheobronchial injury depends on various factors related to the underlying clinical status of the patient. Although tracheobronchial injury is more common among females, males tend to have a higher risk of mortality [10]. This might due to the underlying cause of respiratory failure, rather than being directly related to the tracheobronchial injury. Delayed diagnosis of tracheobronchial injury may lead to a 2-fold increase in mortality, even after undergoing surgical repair [7]. The longer the interval between injury and repair, the more fibrosis becomes prominent. In canine models, bronchi that were experimentally occluded for 5 to 7 months could be surgically repaired and reaerated with a return of physiologic function [11-12]. Despite distal pulmonary parenchymal injury and apparent destruction on radiological images, proximal airway repair via bronchial sleeve resection or end-to-end anastomosis can successfully save the distal lung parenchyma, even after an extended delay in diagnosis [9].

In summary, tracheobronchial injury is a less frequently occurring condition with significant morbidity and mortality, and remains a big challenge for most clinicians. Surgical repair can be a successful treatment to recover pulmonary function, even with delayed treatment of the bronchi in patients with total occlusion of the main bronchi. The optimal time of surgery that would lead to a return of physiologic pulmonary function after bronchial total occlusion still needs to be determined.

Acknowledgements

Not applicable

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

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Lobular Capillary Hemangioma of the Right Bronchus Intermedius with Multilobar Atelectasis–A Case Report and Literature Review

Li-Ting Cheng, Chien-Peng Huang[1], Chi-Hao Shen, Kun-Lun Huang, Chung-Kan Peng, Sheng-Huei Wang

Lobular capillary hemangioma (LCH), also called pyogenic granuloma, is a benign vascular tumor often observed in the cutaneous and oral mucosa and nasal cavity. The precise etiology of LCH is unknown. LCH can present rarely in the gastrointestinal tract and even less frequently in the tracheobronchial tree, according to the literature. The tumor size of most tracheobronchial LCH ranges from several millimeters to a few centimeters. Imaging findings from chest radiography or computed tomography are nonspecific for the diagnosis of tracheobronchial LCH. Flexible bronchoscopy is indicated for early detection of these small lesions, which may be treated endoscopically with a good prognosis. Here, we report a patient living with a tracheostomy who presented with fever and right middle and lower lobar atelectasis. Bronchoscopic biopsy confirmed the diagnosis of tracheobronchial LCH with total occlusion of the right bronchus intermedius. The patient recovered well after conservative treatment. ***(Thorac Med 2021; 36: 277-284)***

Key words: lobular capillary hemangioma, pyogenic granuloma, right bronchus intermedius, multilobar atelectasis

Introduction

Atelectasis is among the most common abnormal findings on chest radiography (CXR), and may not show obvious clinical signs or symptoms if only a small area of the lung is affected. Fever, cough, dyspnea, wheezing, and difficulty breathing may occur in multilobar atelectasis. Atypical radiologic features of multilobar atelectasis can lead to pitfalls in interpretation. Atelectasis can be pathophysiologically divided into obstructive and non-obstructive types. The most frequent combination of multilobar atelectasis is right middle and lower lobar atelectasis, because a solitary endobronchial lesion can obstruct the bronchus intermedius. The common causes of obstructive atelectasis include mucus plugs, bronchogenic carcinoma, foreign body impaction, and carcinoid tumors. Rare obstructive causes include hamartomas,

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endobronchial tuberculosis, histoplasmosis with fibrosing mediastinitis, broncholithiasis, and inflammatory pseudotumors [1]. Herein, we present the case of a rare diagnosis of lobular capillary hemangioma (LCH) of the right bronchus intermedius with multilobar atelectasis, and also review the literature. To the best of our knowledge, this is the first reported case of tracheobronchial LCH in Taiwan.

Case Description

A 62-year-old Taiwanese female nonsmoker presented with a 2-week spiking fever and poor appetite, but no dyspnea, cough, or hemoptysis was noted. She had undergone tracheostomy because of supraglottic stenosis with airway obstruction, and had been living with a long-term tracheostomy for 6 years. She had a good performance status and consumed food without a feeding tube. She also had a history of hypertension and bullous pemphigoid (cicatricial type) under regular medication control. She denied foreign body aspiration, smoking, hormonal supplementation, any recent travel, or contact with any ill person or animal.

Physical examination on admission showed a respiratory rate of 18 breaths/min, temperature of 38.6°C (101.5°F), pulse rate of 92 beats/min, blood pressure of 118/70 mmHg, and oxygen saturation of 98% in ambient air. Auscultation revealed bilateral clear breathing sounds without stridor or rhonchi.

Laboratory test results showed an elevated white blood cell count with predominant neutrophils and C-reactive protein. Viral serology for chlamydia antigen and specific serology for mycoplasma were negative. Sputum bacterial, fungal, and blood cultures were negative. The polymerase chain reaction test for tuberculosis was negative. Tumor markers, including carcinoembryonic antigen and squamous cell carcinoma antigen, were within normal levels. CXR (Figure 1) and chest computed tomography (CT) (Figure 2) revealed consolidation and multilobar atelectasis of the right middle and lower lobes.

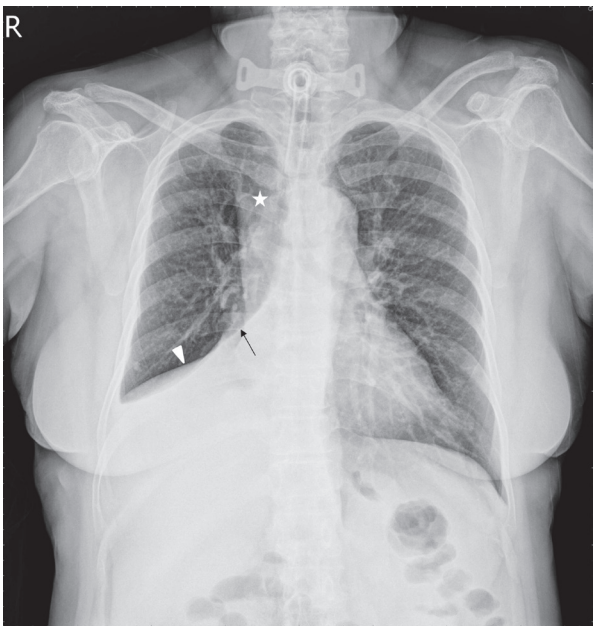

Fig. 1. The displaced minor fissure (arrow head) forms a straight interface between the hyper-expanded right upper lobe and the atelectatic right middle lobe. The inferomedial displacement of the right major fissure (arrow) obscures the right hilar structures. The star marks the upper triangle sign.

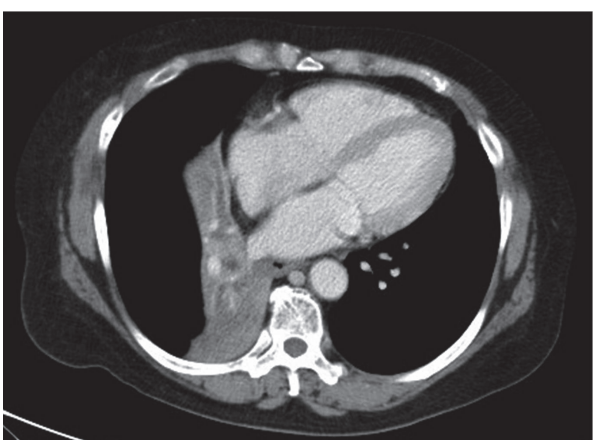

Fig. 2. Consolidation and multilobar atelectasis of the right middle and lower lobes.

After admission, she received an empiric antibiotic for suspected obstructive pneumonitis, and the fever gradually subsided. Flexible bronchoscopy revealed a white granular mucosal lesion totally occluding the right bronchus intermedius. Endobronchial biopsy was performed with easy-touch bleeding, and epinephrine was sprayed in the area for vasoconstriction (Figure 3). Histopathology showed a lobular pattern of numerous capillaries, granulation tissue formation with necrosis, and fibrosis of the pulmonary tissue without evidence of vasculitis or malignancy (Figure 4, A and B). Immunohistochemical analysis was positive for the CD34 antibody (Figure 4, C), confirming the nature of the blood vessels. Histopathology led to the diagnosis of LCH in the tracheobronchial tree. On hospital day 12, the patient was discharged without any respiratory symptoms. One week after discharge, the thoracic surgeon arranged admission for flexible bronchoscopy and explained the possible complications of tumor resection by bronchoscopic laser to the patient and her family. Even with explanation and discussion in detail, the patient and her family felt they could not afford to take any of the possible risks of undergoing bronchoscopic laser resection for the airway tumor, and refused the procedure. The patient was then given conservative treatment and was discharged uneventfully. Since the patient declined to undergo further bronchoscopic examination and had greatly improved symptoms, follow-up bronchoscopy was not performed. Eight months after her initial presentation, CXR (Figure 5) and chest CT were performed, and showed atelectasis of the

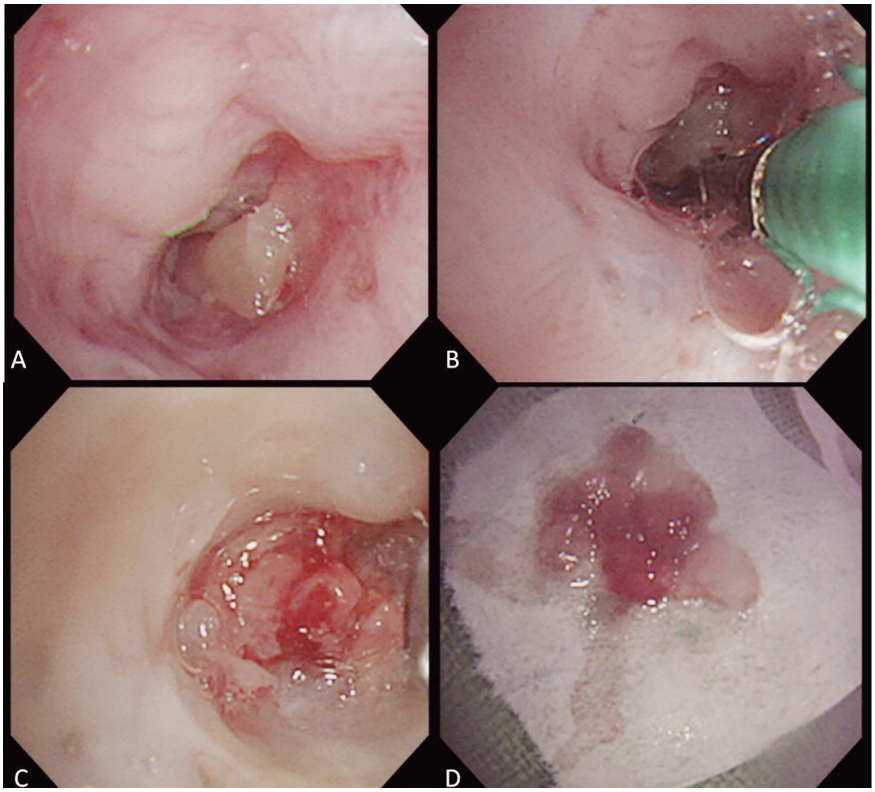

Fig. 3. (A) Bronchoscopy showed total occlusion of the right bronchus intermedius by the soft tissue mass. (B, C, D) Bronchoscopic biopsy was performed and easy-touch bleeding of the soft tissue mass was noted.

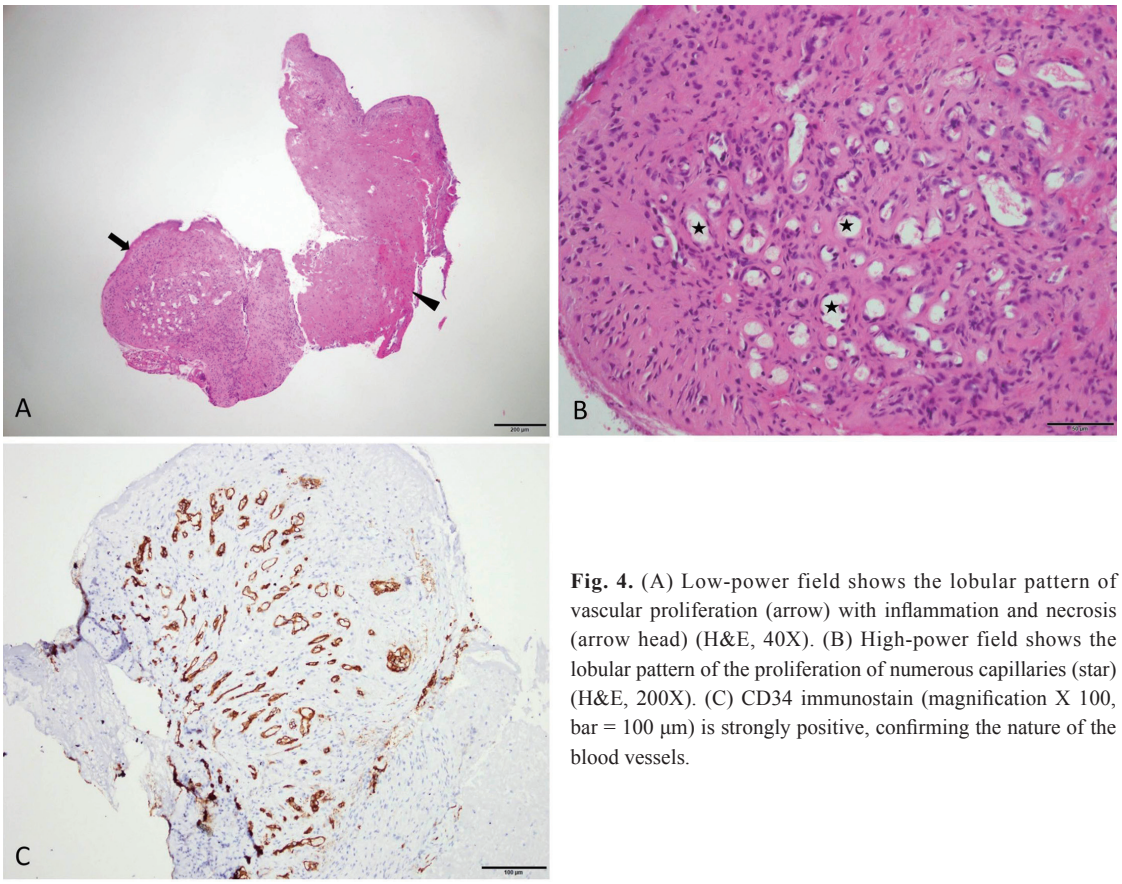

Fig. 4. (A) Low-power field shows the lobular pattern of vascular proliferation (arrow) with inflammation and necrosis (arrow head) (H&E, 40X). (B) High-power field shows the lobular pattern of the proliferation of numerous capillaries (star) (H&E, 200X). (C) CD34 immunostain (magnification X 100, bar = 100 μm) is strongly positive, confirming the nature of the blood vessels.

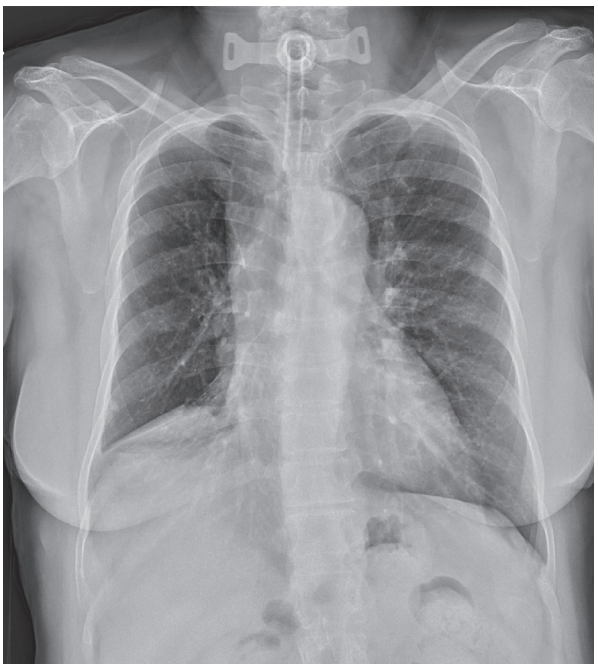

Fig. 5. Follow-up CXR, 8 months after initial presentation.

right middle lobe (Figure 6 A) and centrilobular opacities of the right lower lobe (Figure 6 B). Based on the imaging findings, gradual resolution of LCH of the bronchus intermedius was considered. The patient then followed up at our outpatient department regularly.

Discussion

LCH, also called pyogenic granuloma, is a benign lesion and is 1 of the inflammatory hyperplasias often observed in the cutaneous and oral mucosa and nasal cavity [2-3]. The term "pyogenic granuloma" was first introduced by Hartzell in 1904 [4]. Although pyogenic organisms seem to be the cause of LCH and may play a role in recurrent LCH, large groups of LCHs showed no evidence of infectious organisms

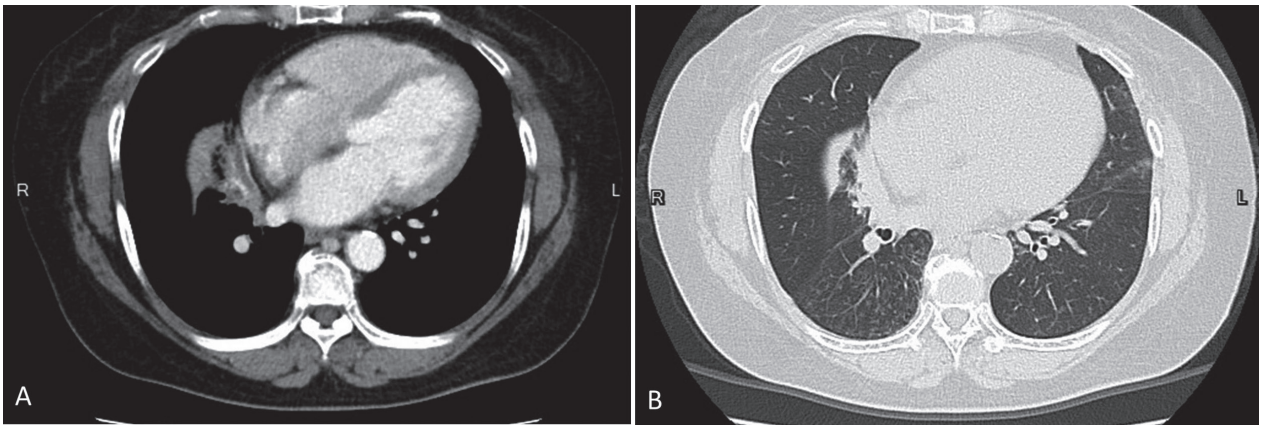

Fig. 6. Follow-up CT, 8 months after initial presentation. (A) Contrast CT. (B) High-resolution CT.

[5]. The most common anatomic locations of LCHs are the head and neck area (36%), upper limb (33%) (especially the fingers), trunk (15%), and lower limb (8%) [6]. A retrospective study of 408 LCH cases showed that the mean age was 40.5 years (range, 5–90 years) with a peak incidence in the 2nd and 3rd decades of life. LCH has is slight male preponderance, especially among children [6-8]. However, the trend is reversed in mucosal LCHs in adult women, especially during pregnancy [9]. Although mucosal LCHs are usually noted in the oral cavity (especially the lip and gingival mucosa) [10], they are rarely reported in the gastrointestinal tract, and patients may be asymptomatic or have overt bleeding, anemia, or dysphagia [11].

According to the literature, the first proven tracheobronchial LCH was reported by Irani in 2003 [2], and only 19 tracheobronchial LCH cases have been reported to date (Table 1) [2, 13-29]. The precise etiology of LCH is unknown. Potential etiologies, such as chronic low-grade local irritation, traumatic injury, hormonal factors, and drug use, have been considered [3]. The most common pathogenesis of LCH is a hyperplastic and neovascular response to an angiogenic stimulus with an imbalance of promoters and inhibitors [6, 12]. Because the CXR and CT imaging findings are nonspecific for the diagnosis of tracheobronchial LCH, flexible bronchoscopy is indicated for early detection of these small lesions, which may be treated endoscopically with low morbidity [2, 13-29]. The definite diagnosis of tracheobronchial LCH depends on the histopathological findings of the specimen from bronchoscopic biopsy or surgical excision. The histopathological features have revealed superficial stromal edema, numerous dilated capillaries in a lobular pattern, inflammation, and granulation tissue.

Surgical excision is usually required, because LCH of the skin or mucous membrane causes frequent bleeding and rarely resolves spontaneously. Nonsurgical treatments include laser therapy, cryotherapy, sodium tetradecyl sulfate sclerotherapy, and intralesional injection of ethanol [3]. Determining which of the abovementioned treatment options to use depends on whether the lesions are in cosmetically or noncosmetically sensitive areas [30]. For tracheobronchial LCH, the use of similar treatment methods, including endoscopic excision, snare electrocautery, laser therapy, plaque radiation, brachytherapy, cryotherapy, argon plasma co-

Table 1. Summary of Case Reports and Characteristics of Tracheobronchial LCH

	Author	Age (year), M/F	Symptoms	Location	No.	Size (cm)	Treatment	Follow-up
1	Irani et al.[2]	72, F	Cough, hemoptysis	3 cm below the vocal cords	1	0.2–0.3	Endoscopic excision	Good (1 year)
2	Madhumita et al.[13]	40, F	Foreign body sensation, hemoptysis	Right anterolateral wall of the upper third of the trachea	1	0.5 × 1.0	Endoscopic excision	Good (1 year)
3	Porfyridis et al.[14]	17, M	Hemoptysis	Left anterolateral wall of the upper third of the trachea	2	0.1 and 0.3	Endoscopic excision	Good (1 year)
4	Chawla et al.[15]	62, M	Hemoptysis	Right wall of the distal trachea	1	ND	Endoscopic excision and laser therapy	ND
5	Udoji and Bechara.[16]	55, M	Cough, hemoptysis	Left lateral wall of the distal trachea	1	0.4 × 0.5	Cryoprobe	Good (3 months)
6	Amy and Enrique[17]	22, M	Cough, hemoptysis	Left posterior wall, 3 cm from the carina	1	1.0–1.5	Electrocautery	Good (ND)
7	Jie et al.[18]	35, M	Cough, bloody sputum	Left lateral wall of the proximal trachea	1	1.5 × 2.0	Brachytherapy	Good (2 years)
8	Xu et al.[19]	64, M	Cough, hemoptysis	Left anterolateral wall of the trachea	1	0.3–0.4	Endoscopic excision	Good (8 months)
9	Prakash et al.[20]	23, F	Acute respiratory failure	Posterior trachea wall	1	2–4	Surgical debulking	Good (ND)
10	Liu et al.[21]	17, M	Cough, hemoptysis, dyspnea	Right wall of the middle of the trachea	1	0.5–1.0	Argon plasma coagulation	Good (11 months)
11	Liu et al.[21]	15, F	Cough, hemoptysis, dyspnea	Lower segment of the trachea	1	1.5–2.0	Argon plasma coagulation, cryotherapy	Good (6 months)
12	Qiu et al.[22]	39, M	Cough, hemoptysis	Right bronchus intermedius	1	1.0	Endoscopic excision, cryotherapy	Good (2 years)
13	Zambudio et al.[23]	66, F	Massive hemoptysis	Between the first and third tracheal rings	1	Occluding 30–40% of the airway	Embolization	Good (1 year)
14	Chen et al.[24]	14, F	Cough, hemoptysis	Lower third of the anterior tracheal wall	1	1.5–2.0	Cryotherapy and argon plasma coagulation	Good (3 months)
15	Kalanjeri et al. [25]	57, M	Cough, hemoptysis	Posterior middle tracheal wall	1	Occluding 70% of the airway	Electrocautery	ND
16	Shen et al. [26]	35, M	Hemoptysis	Lateral wall of the proximal left main bronchus	1	1.5–2.0	Brachytherapy	Good (2 years)
17	Dabó et al. [27]	51, F	Hemoptysis	Lower third of the left lateral tracheal wall	1	ND	Endoscopic resection and laser photocoagulation	Good (27 months)
18	Putora et al. [28]	64, M	Cough	Distal tracheal wall	Multiple	ND	Spontaneous complete remission after cessation of erlotinib.	Good (1.5 months)
19	Acharya et al. [29]	56, F	Hemoptysis	2 cm below the vocal cords on the right tracheal wall	1	0.7	Endoscopic resection and electrocautery	Good (ND)
20	Present case	62, F	Fever, poor appetite	Right bronchus intermedius	1	Occluding 100% of the airway	Observation	Good (8 months)

agulation, and interventional radiology with embolization, have been reported [2, 13-29]. In a critical patient presenting with acute respiratory failure, endotracheal tube intubation with a mechanical ventilator and even extracorporeal membrane oxygenation support have also been reported [9]. Of the 20 reported cases, including ours, 18 had a good prognosis and no further symptoms during follow-up.

A summary of the characteristics and treatment methods of the 20 reported tracheobronchial LCH cases are presented in Table 1. The tumor size of the tracheobronchial LCHs ranged from several millimeters to a few centimeters, and they sometimes occluded 30–70% of the airway [2, 13-29]. The average age at diagnosis of tracheobronchial LCH was 43.3 years (range, 14–72 years), and they were more common in men than in women (M:F = 11: 9). They usually presented with hemoptysis and cough. Most reported cases were solitary lesions. One patient had 2 polypoid tracheal nodules (0.1 cm and 0.3 cm) [14], and another had multiple white granular mucosal lesions of the distal tracheal wall [28]. The most common locations were the proximal and distal trachea. Only 2 cases of right bronchus intermedius LCH were reported [22], including our case.

Putora et al. reported a 64-year-old male exsmoker with a diagnosis of squamous cell carcinoma of the lung who presented with a vigorous cough after 8 months of erlotinib treatment. Bronchoscopy revealed multiple white granular mucosal lesions of the distal tracheal wall, and histopathology of the biopsy confirmed the diagnosis of LCH. Although the authors have no direct proof that tracheal LCHs were a side effect of erlotinib, they made a diagnosis based on the exclusion of other causes. After discontinuing erlotinib, the symptoms improved within 2 weeks, and the lesions of multiple LCHs spontaneously resolved within 6 weeks [28]. Zambudio et al. reported a 66-year-old woman with a history of idiopathic thrombocytopenic purpura presenting with massive hemoptysis. The tracheal LCH occluded 30–40% of the lumen between the first and third tracheal rings. The patient was treated successfully with interventional radiology with embolization, and subsequently had a good prognosis [23].

To the best of our knowledge, this is the first reported case of tracheobronchial LCH occluding 100% of the right bronchus intermedius that resulted in multilobar atelectasis of the right middle and lower lobes. Since the patient was living with a tracheostomy, we supposed that the possible cause of the LCH was minor trauma by a suction catheter at home. Although follow-up CXR and CT still showed atelectasis of the right middle lobe, no further invasive procedure or other treatment procedures were performed, because the patient had no symptoms of fever, dyspnea, or hemoptysis during the 8-month follow-up.

Conclusion

LCH is a benign lesion that is extremely rare within the tracheobronchial tree, and this is the first reported case in Taiwan. This case reminds readers that LCH should still be kept on the list of differential diagnoses of obstructive atelectasis. With awareness of this infrequent benign lesion, we can quickly diagnose and appropriately treat the condition.

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