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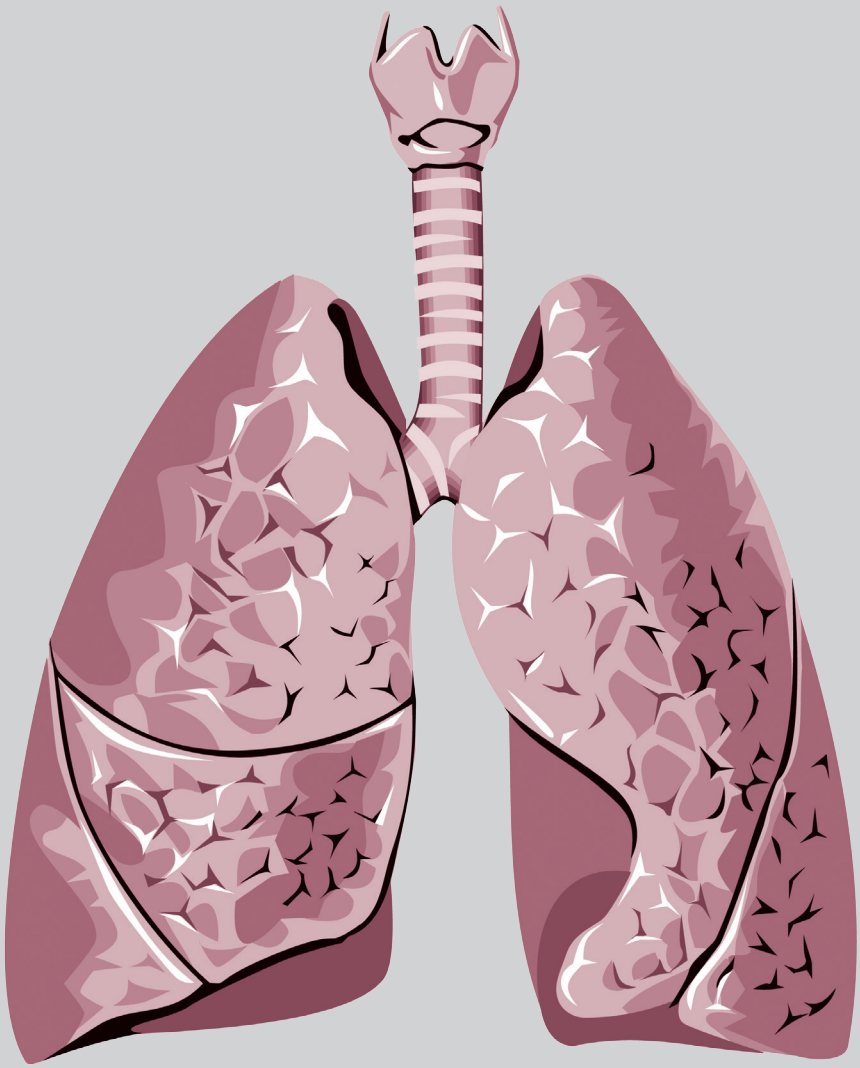

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Prevalence of Chronic Obstructive Pulmonary Disease in Cardiac Outpatient Clinics Using Questionnaire and Spirometry Screening

Ching-Yi Chen[1], Kun-Chou Hsieh[2], Shin-Yi Liang[3], Yi-Ping Hsiang[3], Yu-Feng Wei[1]

Background: Patients who have COPD may visit cardiac outpatient clinics due to having similar symptoms. We aimed to investigate whether a COPD diagnostic questionnaire (CDQ) and spirometry can facilitate the early detection of undiagnosed COPD in individuals who visit cardiac clinics.

Methods: A voluntary screening for COPD was conducted for patients who visited the cardiac clinics of E-Da hospital. Subjects aged ≧35 years and who had at least 1 cardiovascular comorbidity were eligible for COPD screening with the CDQ and spirometry. COPD was defined as a ratio of forced expiratory volume in the first second/forced vital capacity less than 0.7 by spirometry. Clinical data, including the presence of COPD symptoms and questionnaire scores, were collected for analysis.

Results: A total of 808 patients were enrolled in this study. Of these patients, 21 had a confirmed diagnosis of COPD. The prevalence of COPD was only 2.6% in the subjects who visited our cardiac clinics. Compared to the non-COPD group, more of the COPD group were aged ≧70 years and were ex-smokers, and had ≧2 COPD symptoms, higher COPD Assessment Test and CDQ scores, and a smoking history of more than 20 pack/years. The prevalence, sensitivity, and specificity among patients with a CDQ score ≧21.5 were 6.6%, 62%, and 76%, with a low positive predictive value of 7% and a high negative predictive value of 99%.

Conclusion: The prevalence of COPD in patients visiting cardiac clinics was low in this study. A CDQ score ≧21.5 before spirometry screening was more effective for screening COPD in this population. ***(Thorac Med 2020; 35: 96-105)***

Key words: chronic obstructive pulmonary disease, prevalence, questionnaire, screening, spirometry

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease worldwide and is currently the seventh leading cause of death in Taiwan [1]. Since effective interventions and treatment of COPD may reduce morbidity and mortality, an early diagnosis of COPD followed by an appropriate treatment strategy is important to reduce the disease burden. The US Preventive Service Task Force recommended against screening asymptomatic adults for COPD using spirometry. They estimated that 455 adults between 60 to 69 years of age would need to be screened to prevent one exacerbation [2]. Moreover, the prevalence of patients with COPD is still low among adults with respiratory symptoms [3-4]. Several studies have shown that using simple screening tools (e.g., questionnaires, hand-held spirometers) may provide a simple method to identify patients with COPD [5].

It is well known that COPD and cardiovascular disease (CVD) share the same risk factors, such as older age and cigarette smoking, and patients with unrecognized COPD may visit cardiac clinics due to the similarity between cardiac and COPD clinical symptoms, such as dyspnea and chest discomfort. Concomitant chronic cardiac disorders are common in patients with COPD, ranging from 28% to 70% [6]. Similarly, COPD is common and often under-diagnosed among patients with chronic heart disease [6-8]. The aim of the current study was to evaluate the prevalence of patients with COPD who visit cardiac clinics using a questionnaire and a portable spirometry.

Methods

Study population

This prospective, voluntary screening study was conducted at the cardiac clinics of E-Da Hospital in southern Taiwan from May 2012 to November 2012. Subjects aged ≧35 years and who had at least 1 cardiovascular comorbidity (including hypertension, cardiovascular disease, diabetes, and dyslipidemia) were eligible for enrollment in this study. Patients with a previous diagnosis of chronic lung disease such as pulmonary tuberculosis, bronchiectasis, lung cancer, lung fibrosis, or obstructive lung disease (asthma or COPD), and those who could not complete the questionnaire or the spirometry test, were excluded. Informed written consent was obtained from each patient before joining the study. The study protocol was approved by the Human Ethics Committee of this institution.

Questionnaire and spirometry evaluation

Clinical data, including demographic information, smoking status and intensity, comorbidities, and respiratory symptoms including the COPD Assessment Test (CAT) score [9], were collected and recorded by trained study staff and research assistants using a case report form and the Chinese-language version of the COPD diagnostic questionnaire (CDQ) (supplementary Figure S1) [10].

The patients participating in this study underwent spirometry using a portable spirometer (Micro Medical MicroLab 3500 Spirometer). Patients with a ratio of forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC) of < 0.7 were referred for a bronchodilator challenge test. Four puffs of salbutamol (Ventolin, GlaxoSmithKline) were administered after repeating the spirometry test using a body plethysmograph (Vmax 229, SensorMedics, Yorba Linda, CA). All tests were

carried out by the same team of technicians according to the recommendations of the American Thoracic Society/European Respiratory Society [11]. Knudson's reference equations were used to express the predicted spirometry values [12].

Each participant was given at least 3 tests (with at least 2 reproducible and acceptable maneuvers). Results were considered to be reproducible if the second highest FEV_1 and FVC values were within 5% of the highest values. The highest measured FEV_1 value and the corresponding FVC value were used for analysis. The results of these tests were expressed as the percentage of the predicted normal values.

Statistical analysis

Statistical analyses were carried out using SPSS version 24.0 (IBM, Armonk, NY, US). Continuous parameters are presented as mean ± SD, while categorical parameters are presented as the number and percentage. Univariate comparisons between the COPD and non-COPD groups were performed using Student's t-test for independent samples and the Mann–Whitney U-test for normally and abnormally distributed variables, respectively. Fisher's exact test was used for analysis of categorical variables between 2 groups. Sensitivity, specificity, negative predictive values (NPVs), and positive predictive values (PPVs) of symptoms and CDQ scores for the diagnosis of COPD were calculated. Logistic regression was used to estimate the odds ratio (OR) for each symptom, CDQ score, and smoking history of <20, ≥20, ≥30 and ≥40 pack-years (PYs). Two-tailed p values <0.05 were considered to be statistically significant. Receiver operator characteristic (ROC) curve analysis was used to determine the optimal cut-off value of the CDQ score for the diagnostic discrimination of COPD.

Results

A total of 808 patients were enrolled and completed the CDQ and portable spirometry test for this study. Of these patients, 28 met the COPD criteria after spirometry screening; however, only 21 had a confirmed diagnosis of COPD after a bronchodilator challenge test. The prevalence of COPD was only 2.6% among the subjects who visited our cardiac outpatient clinics. Compared to the non-COPD group, significantly more of the COPD group were aged ≧70 years and were ex-smokers, and had ≧2 COPD symptoms and higher CAT and CDQ

Table 1. Clinical Characteristics of the Study Population

Variables	COPD N = 21	Non-COPD N = 787	*P* value
Demographic data			
Mean age, years	67.0±10.2	58.8±10.6	<0.001
Age range, years			
35-39	0(0)	18(2.3)	1.000
40-49	0(0)	124(15.8)	0.059
50-59	7(33.3)	259(37.5)	0.821
60-69	4(19.0)	222(28.2)	0.464

Table 1. Clinical Characteristics of the Study Population

≥70	10(47.6)	128(16.3)	0.001
Male	18(85.7)	668(84.9)	1.000
BMI	25.3±4.8	26.8±8.4	0.419
Spirometric data			
FEV_1 % predicted	54.1±18.3	79.9±15.6	<0.001
FVC (L)	2.4	2.5	0.419
FEV_1/FVC (%)	63.1±7.6	91.5±7.0	<0.001
History of smoking			
Non-smokers	3 (14.3)	244 (31.0)	0.148
Current smokers	5 (23.8)	293 (37.2)	0.208
Ex-smokers	13 (61.9)	250 (31.8)	0.004
COPD symptoms			
Cough	10 (47.6)	300 (38.1)	0.377
Sputum production	13 (61.9)	363 (46.1)	0.152
Shortness of breath	10 (47.6)	296 (37.6)	0.351
≥ 1 symptom	18 (85.7)	563 (71.5)	0.218
≥ 2 symptoms	13 (61.9)	308 (39.1)	0.035
GOLD stage			
1	2 (9.5)	—	—
2	11 (52.4)	—	—
3	7 (33.3)	—	—
4	1 (4.8)	—	—
CAT score			
< 10	17 (81.0)	758 (96.3)	0.008
10–19	4 (19.0)	27 (3.4)	0.007
≥ 20	0 (0)	2 (0.3)	1.000
CDQ score			
< 16.5	3 (14.3)	366 (46.5)	0.003
16.5–19.5	5 (23.8)	155 (19.7)	0.641
> 19.5	13 (61.9)	266 (33.8)	0.008
≥ 21.5	13 (61.9)	185 (23.5)	<0.001
Comorbidities			
Hypertension	12 (57.1)	452 (57.4)	0.979
Cardiovascular disease	13 (61.9)	325 (41.3)	0.059
Diabetes mellitus	5 (23.8)	454 (57.7)	0.002
Dyslipidemia	2 (9.5)	257 (32.7)	0.030

Data are presented as mean ± SD or N (%)

BMI = body mass index; CAT = COPD Assessment Test; CDQ = COPD Diagnostic Questionnaire; GOLD = The Global Initiative for Chronic Obstructive Lung Disease; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity

Table 2. Clinical Presentations and Symptoms of COPD and Non--COPD Groups by Smoking Intensity

Variables	Non-smokers			Smokers < 20 PYs*			Smokers ≥ 20 PYs*			Smokers ≥ 30 PYs*			Smokers ≥ 40 PYs*		
	COPD	Non-COPD	*p* value	COPD	Non-COPD	*p* value	COPD	Non-COPD	*p* value	COPD	Non-COPD	*p* value	COPD	Non-COPD	*p* value
Subject, n (%)	3 (14.3)	244 (31.0)		5 (23.8)	289 (36.7)		16 (76.2)	398 (50.6)		13 (61.9)	321 (40.8)		11 (52.4)	238 (30.2)	
Mean age, years	67.3±10.5	60.8±10.5	0.133	71.0±7.0	59.8±10.6	0.013	65.5±10.8	58.0±10.0	0.002	65.9±11.2	58.9±9.4	0.001	65.8±11.0	59.8±9.2	0.037
FEV_1 % predicted	46.3±13.6	82.7±16.4	0.006	39.2±17.1	81.7±15.9	<0.001	58.7±16.5	78.1±15.0	<0.001	57.3±17.2	77.3±14.9	<0.001	60.9±16.1	77.0±15.3	0.001
BMI	27.5±8.7	26.7±4.1	0.839	26.8±8.1	26.6±4.0	0.884	24.8±3.4	26.9±11.1	0.443	24.3±3.4	26.5±3.7	0.078	24.5±3.6	26.6±3.8	0.076
Symptom															
Cough	1 (33.3)	71 (29.1)	1.000	3 (60.0)	122 (31.4)	0.332	7 (43.8)	178 (44.7)	0.939	5 (38.5)	145 (45.2)	0.633	4 (36.4)	110 (46.2)	0.521
Sputum production	0 (0)	86 (35.2)	0.554	2 (40.0)	142 (36.5)	1.000	11 (68.8)	221 (55.5)	0.296	9 (69.2)	192 (59.8)	0.575	8 (72.7)	150 (63.0)	0.751
Shortness of breath	1 (33.3)	95 (38.9)	1.000	2 (40.0)	153 (39.3)	1.000	8 (50.0)	143 (35.9)	0.252	5 (38.5)	109 (34.0)	0.737	5 (45.5)	80 (33.6)	0.418
Symptom ≥ 1	2 (66.7)	155 (63.5)	1.000	4 (80.0)	249 (64.0)	0.659	14 (87.5)	314 (78.9)	0.541	11 (84.6)	254 (79.1)	1.000	10 (90.9)	191 (80.3)	0.696
Symptoms ≥ 2	0 (0)	79 (32.4)	0.553	2 (40.0)	132 (33.9)	1.000	11 (68.8)	176 (44.2)	0.053	8 (61.5)	144 (44.9)	0.267	7 (63.6)	110 (46.2)	0.357

*Includes current/ex-smokers

BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; PYs = pack-years.

scores (Table 1).

Subgroup analysis by smoking status and intensity showed that smokers in the COPD group had a significantly higher mean age than smokers in the non-COPD group, regardless of intensity, but that there were no significant differences in the clinical symptom presentation between the COPD and non-COPD groups (Table 2). The ORs of the risks for COPD were 3.13, 2.36, and 2.54 for a smoking intensity of ≥20 PYs, ≥30 PYs, and ≥40 PYs, respectively, but this was not significantly associated with clinical symptom presentation (Table 3). The prevalence rates of COPD among patients with a smoking history of >20 PYs combined with more than 1 or 2 COPD symptoms were 4.3% and 5.9%, respectively (Table 4).

The COPD prevalence rate among patients with a CDQ score ≧21.5 was 6.6%. The sensitivity and specificity of clinical symptoms and COPD scores are shown in Table 5. A CDQ score cut-off point of 21.5 had a sensitivity of 62% and specificity of 76%, with a low PPV of 7% and a high NPV of 99% (Figure 1)

Discussion

In this study conducted in cardiac outpatient clinics in Taiwan, the prevalence of patients with COPD was low (2.6%). Among patients with a CDQ score ≧21.5, the prevalence was 6.6%. Use of a CDQ before spirometry was effective for COPD screening in this population.

Previous studies have shown that population screening of asymptomatic smokers for COPD is not cost-effective [2], and that the presence of chronic airway symptoms, including dyspnea, cough, and phlegm, is associated with the incidence of COPD [13-14]. Some studies have focused on screening for COPD in individuals

Table 3. Associations Among Clinical Symptoms and Smoking Intensity in the Diagnosis of COPD

Symptom	All subjects (n=808)	Smokers < 20 PYs (n=394)	Smokers ≥ 20 PYs (n=414)	Smokers ≥ 30 PYs (n=334)	Smokers ≥ 40 PYs (n=249)
Cough	1.48 (0.62–3.52)	3.28 (0.54–19.90)	0.96 (0.35–2.63)	0.76 (0.24–2.37)	0.67 (0.19–2.33)
Sputum production	1.90 (0.78–4.63)	1.16 (0.19–7.02)	1.76 (0.60–5.17)	1.51 (0.46–5.01)	1.56 (0.40–6.05)
Shortness of breath	1.51 (0.63–3.59)	1.03 (0.17–6.23)	1.78 (0.66–4.85)	1.22 (0.39–3.81)	1.65 (0.49–5.56)
Smokers <20 PYs	0.32 (0.12–0.88)				
Smokers ≥20 PYs	3.13 (1.13–8.62)				
Smokers ≥30 PYs	2.36 (0.97–5.76)				
Smokers ≥40 PYs	2.54 (1.06–6.06)				

Data were presented as odds ratio (95% confidence interval)
PYs, pack-years

Table 4. Prevalence of COPD by Symptoms and Smoking Intensity

Variables	N	COPD subjects	Prevalence (%)
All subjects	808	21	2.6
Non-smokers	247	3	1.2
All smokers ≥ 20 PYs	414	16	3.9
All smokers ≥ 30 PYs	334	13	3.9
All smokers ≥ 40 PYs	249	11	4.4
All subjects with 1 or more symptoms	581	18	3.1
All smokers ≥ 20 PYs	328	14	4.3
All smokers ≥ 30 PYs	265	11	4.2
All smokers ≥ 40 PYs	201	10	5.0
All subjects with 2 or more symptoms	321	13	4.0
All smokers ≥ 20 PYs	187	11	5.9
All smokers ≥ 30 PYs	152	8	5.3
All smokers ≥ 40 PYs	117	7	6.0
CDQ score ≥ 19.5	279	13	4.7
CDQ score ≥ 21.5	198	13	6.6

CDQ = COPD Diagnostic Questionnaire; PYs, pack-years.

Table 5. Sensitivity, Specificity, PPVs, and NPVs of Symptoms and CDQ Scores in the Diagnosis of COPD

Symptoms	All subjects (n=808)				Smokers < 20 PYs (n=394)				Smokers ≥ 20 PYs (n=414)				Smokers ≥ 30 PYs (n=334)				Smokers ≥ 40 PYs (n=249)			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Cough	48	62	3	98	60	69	2	99	44	55	4	96	38	55	3	96	36	54	4	95
Sputum production	62	54	3	98	40	63	1	99	69	44	5	97	69	40	4	97	73	37	5	97
Shortness of breath	48	62	3	98	40	61	1	99	50	64	5	97	38	66	4	96	45	66	6	96
One or more symptoms	86	29	3	99	80	36	2	99	88	21	4	98	85	21	4	97	91	20	5	98
Two or more symptoms	62	61	4	98	40	66	1	99	69	56	6	98	62	55	5	97	64	54	6	97
CDQ score ≥ 21.5	62	76	7	99	40	90	5	99	69	63	7	98	69	57	6	98	73	48	6	97

CDQ = COPD Diagnostic Questionnaire; COPD = chronic obstructive pulmonary disease; NPV = negative predictive value; PPV = positive predictive value; PYs = pack-years

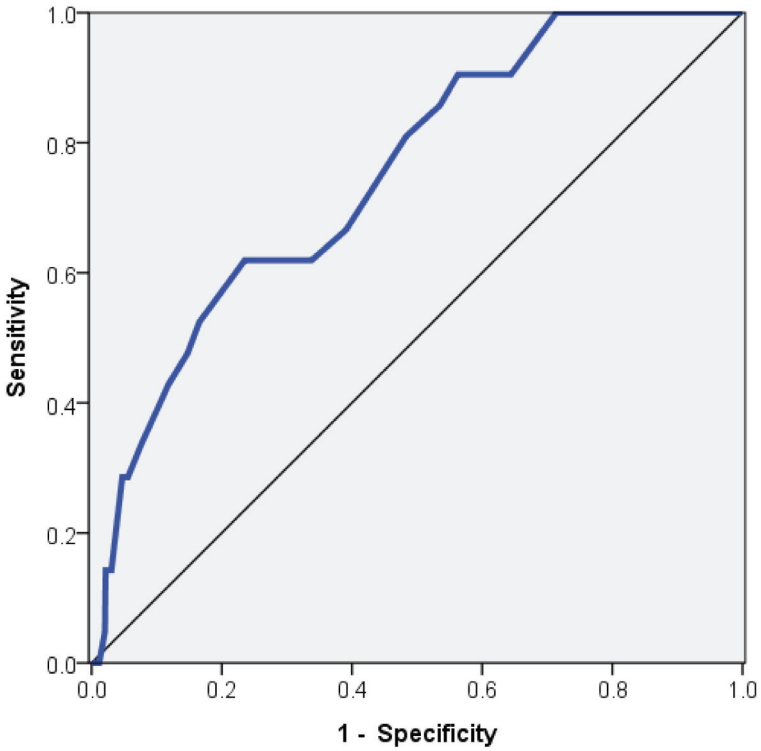

Fig. 1. Receiver operator characteristic (ROC) curves of CDQ scores in the diagnosis of COPD
AUC = 0.752 (0.654, 0.849) (P<0.001)
Cuff-off point 21.5, sensitivity 0.619, specificity 0.765

with chronic respiratory symptoms [3-4,15]. A previous voluntary lung function screening study conducted by Capozzolo *et al* reported a COPD prevalence of 9.8% for subjects aged ≧35 years combined with a smoking history of ≧5 PYs or at least 1 chronic respiratory symptom [15]. However, a population-based cohort study conducted in Canada found that these symptoms were relatively poor at discriminating undiagnosed COPD patients from subjects without COPD in a general population, and that they should be used in conjunction with other factors such as smoking PYs [4]. These findings are consistent with those of the current study, which showed that more of the identified COPD patients were ex-smokers, had a higher mean age and age ≥70 years, and had ≥2 COPD symptoms, higher CAT scores and higher CDQ

scores than the non-COPD patients. However, when stratified by smoking status, there were no significant differences in the clinical symptom presentation, indicating that differences in symptoms per se were relatively minor between the COPD and non-COPD groups. Similarly, another cross-sectional study reported by North *et al* found that the prevalence of COPD in participants with chronic respiratory symptoms was only 2.0% [3]. The prevalence increased slightly to 3% when restricting the cohort to those aged ≧40 years, which is consistent with the finding of a prevalence of 2.6% in the whole population in the current study.

A large proportion of patients with COPD also had chronic comorbidities, especially CVD, with a reported prevalence of up to 70% [6]. Previous studies have also indicated that airflow limitation is common in individuals with CVD, and that it is largely underdiagnosed and undertreated [7-8]. Screening for COPD in this population has therefore been recommended. In addition to chronic airway symptoms, patients who visit cardiac clinic may have a higher risk of having COPD due to cardiovascular comorbidities [16]. However, we found a relatively low prevalence of COPD in the patients who visited our cardiac clinics. This finding suggests that the presence of comorbidities, including CVD, may not be related to GOLD stage airflow severity, and should be treated individually. Although the COPD prevalence was higher in patients with a smoking history of >20 PYs combined with COPD symptoms, this approach to detecting undiagnosed COPD in this population is still not cost-effective. In this study, the risk of developing COPD with a smoking intensity of ≥20 PYs, ≥30 PYs, and ≥40 PYs was similar. Smoking intensity also was not significantly associated with clinical symptom presentation. The prevalence of COPD in patients with a smoking history of >20 PYs combined with more than 1 or 2 COPD symptoms was 4.3% and 5.9%, respectively. Nevertheless, our data showed that a CDQ score ≧21.5 was associated with an increase in the COPD prevalence rate to 6.6%, with a low PPV of 7% and a high NPV of 99%, which supported the use of a questionnaire to select subjects for spirometry screening for COPD [17].

There are several limitations to this study. First, the study population was limited to those individuals who visited cardiac clinics at a single institution, which may have led to selection bias. Second, histories of passive smoking and occupational exposure were not identified in this study. Third, the number of COPD patients could have been under-estimated if they also had a CVD such as heart failure, which may have led to a restrictive spirometric pattern and a falsely normal FEV_1/FVC ratio.

In conclusion, in this study conducted in cardiac outpatient clinics in Taiwan, the prevalence of patients with COPD was low. The use of the CDQ to select a subject for spirometry screening for COPD was more effective. A CDQ score ≧21.5 yielded a 6.6% prevalence rate, and those with a score < 21.5 had a high probability of not having COPD.

Acknowledgements

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Supplementary Figure S1. COPD Diagnostic Questionnaire

ID Nomber

呼吸健康篩檢*

姓名_____ 日期（西元）_____（年）_____（月）_____（日）

填寫說明：針對過去從未有過呼吸道疾病之吸煙者，
請依答題順序對照各項答案之分數，並加總分數於下方。

		計分	
▲ 您今年幾歲？	❑ 40-49 歲 ❑ 50-59 歲 ❑ 60-69 歲 ❑ 70 歲以上	❑ 0 分 ❑ 4 分 ❑ 8 分 ❑ 10 分	CF1
▲ 目前您每天抽幾根？ （假如您目前已經戒菸，那麼 您以前每天抽幾根菸？）	平均一天_____根菸 ❑ 我從來不抽菸	包-年數=（每日吸菸支數／20）×吸菸年齡 0-14 包一年..... ❑ 0分 15-24 包一年..... ❑ 2分 25-49 包一年..... ❑ 3分 50+ 包一年..... ❑ 7分	
▲ 您抽菸總共多少年？	總共_____年 ❑ 我從來不抽菸		CF2
▲ 您體重幾公斤？	_____公斤	BMI= 體重（公斤）／身高²（公尺²）	
▲ 您身高幾公分？	_____公分	BMI< 25.4 ❑ 5分 BMI25.4-29.7 ❑ 1分 BMI> 29.7 ❑ 0分	CF3
▲ 氣候變化是否會影響您目前的咳嗽？	❑ 是 ❑ 否 ❑ 我並沒有咳嗽	❑ 3分 ❑ 0分 ❑ 0分	CF4
▲ 您是否經常在沒有感冒的情況下， 仍會從肺部咳出痰來？	❑ 是 ❑ 否	❑ 3分 ❑ 0分	CF5
▲ 您經常於早上起床後從肺部咳出痰來？	❑ 是 ❑ 否	❑ 0分 ❑ 3分	CF6
▲ 您呼吸會發生喘鳴聲的情況有多頻繁？	❑ 不曾發生 ❑ 偶而或是經常發生	❑ 0分 ❑ 4分	CF7
▲ 您有過敏或曾經發生任何過敏的情況嗎？	❑ 是 ❑ 否	❑ 0分 ❑ 3分	CF8

COPD 篩選結果總分_____

總分	患有COPD之可能性
>19.5	高
16.5-19.5	中
0-16.5	低

您的分數 =

*內容摘自2007慢性塞性肺病治療指引

Use of Radial Probe Endobronchial Ultrasound (EBUS) in Diagnosing Atypical Pulmonary Infection

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Background: Bronchoscopy with radial probe endobronchial ultrasonography (EBUS) has been utilized to assess peripheral pulmonary lesions and to identify parenchymal lung lesions for biopsy. However, there is no information on the use of bronchoscopy with EBUS in the diagnosis of atypical pulmonary infection. Identifying the unknown pathogens responsible for atypical pulmonary infections remain a diagnostic challenge. Therefore, we investigated the usefulness of bronchoscopy with EBUS in the diagnosis and management of patients with atypical pulmonary infection.

Methods: The diagnostic yields of EBUS from patients with atypical pulmonary infection treated in a tertiary university hospital between December 2007 and December 2010 were analyzed retrospectively.

Results: A total of 78 patients with atypical pulmonary infection were enrolled in the study. The majority of those patients (n=57, 73%) also had underlying disease, such as diabetes mellitus (n=26) or malignancy (n=12). A total of 78 microorganisms were isolated or identified by histopathology, including *Mycobacterium tuberculosis* (n=59), Aspergillus (n=8), Cryptococcus (n=6), Pneumocystis jiroveci (n=3), and mucormycosis (n=2). The definitive diagnosis rate using EBUS was 82.1% (n=64), including 86.4% for *Mycobacterium tuberculosis* (51/59), 87.5% for Aspergillus (7/8), 100% for Pneumocystis jiroveci (3/3) and mucormycosis (2/2), and 16.7% for Cryptococcus (1/6). EBUS examination assisted in both the diagnosis (82.0%) and management (78.2%) of patients. Pneumothorax, which occurred in 2 patients (3%), was the only complication.

Conclusion: Bronchoscopy with EBUS is a useful diagnostic tool for patients with atypical pneumonia. This technique can be particularly helpful in diagnosing patients without an identified pulmonary infection pathogen. ***(Thorac Med 2020; 35: 106-115)***

Key words: endobronchial ultrasound, atypical pulmonary infection

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Introduction

The development of a pulmonary infiltrate and/or nodule may represent a particularly ominous sign and remain a diagnostic challenge [1]. Although diagnostic techniques continue to improve, accurate diagnosis of unknown radiologic pulmonary infiltration is still difficult [2-6]. Several diseases may present with a pulmonary infiltrate and mimic bacterial pneumonia [7]. A delay in resolution of the pulmonary infiltrate or a lack of response to initial antibiotic treatment should trigger consideration of an atypical pathogen infection, such as *Mycobacterium tuberculosis*, fungus, or virus. The use of empiric antibiotic therapy can lead to increased mortality and cost [8-10]. Bronchoscopy examination with a smear and culture of the bronchoalveolar lavage fluid (BALF) has been successful in establishing the diagnosis of pulmonary infection [11]. Unfortunately, diagnosis of most invasive pulmonary infections, such as fungal infections, must rely on histology [12-13]. Radial probe endobronchial ultrasonography (EBUS), a recently introduced technique, has been utilized to assess peripheral pulmonary lesions and to identify parenchymal lung lesions for biopsy [14]. EBUS offers the benefits of visualizing the parabronchial structure, confirming the precise location of the peripheral lung lesions, and improving the diagnostic yield of lung cancer [15-16]. However, no studies have focused on the role of EBUS as a diagnostic tool in the diagnosis of non-bacterial pneumonia, also known as "atypical pneumonia". Therefore, a retrospective study was performed to ascertain the value of EBUS in assisting the diagnosis and management of patients with atypical pneumonia.

Methods

Enrolled Patients

A retrospective collection and review of data from patients who underwent bronchoscopy with EBUS at China Medical University Hospital (a 1700-bed tertiary care, university-affiliated hospital) in Taiwan between December 2007 and December 2010 was performed. The study was approved by the China Medical University Hospital Internal Review Board (DMR98-IRB-335), and the requirement for informed consent.

A total of 1,600 patients underwent EBUS during the study period, and 78 patients were finally diagnosed with a non-bacterial pulmonary infection, a so-called "atypical pulmonary infection", including *M. tuberculosis* and fungal infection. These patients underwent bronchoscopy examination with EBUS because of unexplained pulmonary infiltrates or nodular lesions. Prior to EBUS, these 78 patients underwent chest X-ray, chest computed tomography (CT), Gram staining of sputum, bacterial culture of sputum, acid-fast staining of sputum, and M tuberculosis culture without a definitive diagnosis

Bronchoscopy Procedure and Equipment

The location of the lesion was determined initially using traditional posteroanterior chest radiography with or without chest CT. All patients underwent bronchoscopy (IT260; Olympus; Tokyo, Japan). EBUS was performed using an endoscopic ultrasound system (EU-M30; Olympus) and a 20-MHz miniature radial probe (UM-S20–20R; Olympus). After local anesthesia with lidocaine, a bronchoscope was introduced transnasally. An EBUS probe was inserted through the working channel into the target bronchus, based on radiographic findings.

When the location of the target lesion was identified precisely by EBUS, the EBUS probe was marked with colored tape against the orifice of the working channel of the bronchoscope. Then, the EBUS probe was pulled out slowly. When the EBUS probe transducer reached the orifice of the subsegmental bronchus, the distance between the colored tape on the probe and the orifice of the working channel was measured by an assistant. The EBUS probe was then completely withdrawn. Transbronchial biopsy (TBB), brushings, and bronchoalveolar lavage were performed without fluoroscopic guidance. No extended working channel (guide sheath) was left in situ. Bronchoscopy procedures were performed by 2 pulmonary attending physicians, each with more than 4 years of training and experience in bronchoscopy and in performing >200 bronchoscopy procedures per year.

Definition

The definitive diagnosis of pulmonary tuberculosis (TB) was confirmed by the presence of *M. tuberculosis* cultured in sputum or BALF, or a pathologic report of TBB. The diagnoses of invasive fungal infections, including Aspergillosis, Cryptococcal disease, and mucormycosis, were all made by EBUS with TBB. The diagnosis of Pneumocystis jiroveci pneumonia (PJP) was made by EBUS with biopsy and use of polymerase chain reaction (PCR). After the EBUS examinations and interventional procedures were completed, the usefulness of EBUS in assisting the diagnosis of these patients with atypical pneumonia was evaluated. EBUS examinations that met 1 of the following criteria were considered to have had a positive role in the diagnosis: (1) made the diagnosis: a tentative diagnosis was confirmed after EBUS examination; (2) changed the diagnosis: a tentative diagnosis was changed after EBUS examination; (3) provided additional information: provided new information for diagnosis.

EBUS examinations were considered nonbeneficial if they provided no additional information. The EBUS examinations were considered to have helped management if (1) a new decision on a patient's management was made after EBUS examination; or (2) the examination confirmed current management.

Statistical analysis

Data were analyzed using SPSS for Windows, version 12.0 (Chicago, IL, USA). Continuous variables were reported as mean ± standard deviation (SD) and compared using 2-tailed Student's t-tests. Categorical variables were reported as the numbers of patients and percentages.

Results

Patient Characteristics, Underlying Diseases, and Pathogens

During the study period, 78 patients (54 males and 24 females) with a mean age of 60.2 years ± 17.5 years (range, 24-87 years) were diagnosed as having atypical pneumonia (Table 1). Most patients (n=57, 72.8%) had chronic underlying diseases or associated medical conditions; the most common concomitant conditions were diabetes mellitus (33.8%) and malignancy (15.6%). A total of 78 organisms were isolated or identified by histopathology, including *M. tuberculosis* (n=59), Aspergillus (n=8), Cryptococcus (n=6), Pneumocystis jiroveci (n=3), and mucormycosis (n=2) (Table 2). Figure 1 summarizes the diagnostic yield of direct examination of specimens obtained from EBUS-guided smear, culture, and histopathology. Of the 59

Table 1. Characteristics and Underlying Diseases of Patients with Atypical Pneumonia (n=78)

	Number (n, %)
Age (yr)	60.2 ± 17.5
Sex	
Male	54 (69.2)
Female	24 (30.8)
Underlying diseases	
Diabetes	26 (33.8)
Malignancy	12 (15.6)
Hypertensive cardiovascular disease	11 (14.3)
Congestive heart failure	7 (9.1)
Obstructive pulmonary disease	7 (9.1)
Chronic kidney disease	6 (7.8)
Renal transplantation	3 (3.9)
CVA	3 (3.9)
HIV infection	1 (1.3)
Alcoholism	2 (2.6)
Autoimmune disease	2 (2.6)
No underlying disease	21 (27.2)

Table 2. Proportion of Atypical Pneumonia Diagnosed by EBUS-aided TBB or Brushing

	Number (n, %)	Proportion of lesions diagnosed by TBB or brush using EBUS
Type of pulmonary infection	78 (100)	
Pulmonary TB	59 (75.9)	51 (86.4)
Aspergillus	8 (10.3)	7 (87.5)
Cryptococcus	6 (7.7)	1 (16.7)
Pneumocystis jiroveci	3 (3.8)	3 (100)
Mucormycosis	2 (2.6)	2 (100)

patients eventually proven to be infected with *M. tuberculosis*, EBUS-guided smears were positive in 11 patients, cultures were positive in 46 patients, and tissue specimens were positively identified in 29 patients. For the 13 patients eventually diagnosed with fungal infections, none of the EBUS-guided smears or cultures was positive. All of these patients with fungal pneumonia were diagnosed based on EBUS-guided TBB.

Influence of EBUS Examinations on the Diagnosis and Management of Patients

EBUS was considered helpful in reaching a diagnosis for 64 (82.0%) of 78 patients. The diagnostic rates of EBUS for the various

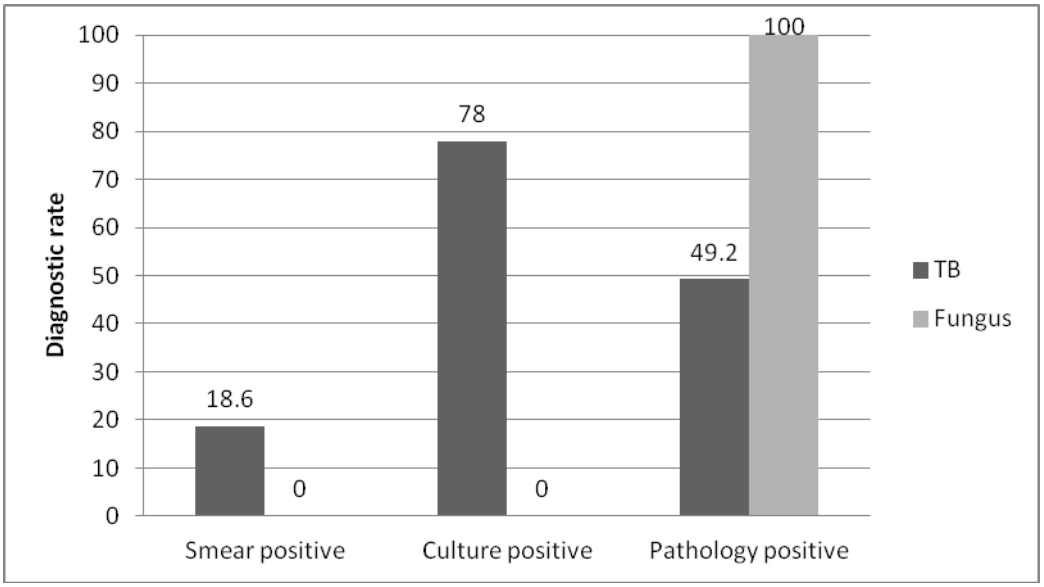

Fig. 1. Comparison of results using EBUS-aided specimens for diagnosis of *M tuberculosis* (TB) or fungal infections by smear, culture, or pathology.

Table 3. Influence of EBUS-aided Examinations on the Diagnosis of Patients with Atypical Infection

Category	Number of patients (n, %)
Assisting diagnosis	64 (82.0)
Made diagnosis	50 (64.1)
Changed diagnosis	14 (17.9)
No benefit	14 (18.0)

pathogens responsible for atypical pneumonia were 86.4% for *M. tuberculosis*, 87.5% for Aspergillus, 100% for mucormycosis, 100% for Pneumocystis jiroveci, and 16.7% for Cryptococcal disease (Table 2). EBUS examinations provided a definitive diagnosis for 50 patients (64.1%) and changed the diagnosis of 14 patients (17.9%). However, 14 patients received no diagnostic benefit from EBUS examinations, including 8 with *M. tuberculosis*, 1 with Aspergillosis, and 5 with Cryptococcal disease (Table 3). The most common diagnostic methods used to confirm the diagnosis in these 14 patients were video-assisted thoracoscopic surgery (VATS) with wedge resection (n=8), CT-guided biopsy (n=3), and sputum culture (n=3).

The EBUS examinations helped in the management of 61 (78.2%) of 78 patients, including in making new decisions for 14 patients and confirming current management in 47 patients. EBUS examinations were not beneficial for 17 patients, including 9 patients with *M. tuberculosis*, 5 with Cryptococcal disease, 2 with Aspergillosis, and 1 with Pneumocystis jiroveci (n=1) (Table 4).

Figure 2 shows the diagnostic effect of ra-

Table 4. Influence of EBUS-aided Examinations on the Management of Patients with Atypical Infection

Category	Number of patients (n, %)
Helped with management	61 (78.2)
Confirmed management	47 (60.3)
Changed management	14 (17.9)
No benefit	17 (21.8)

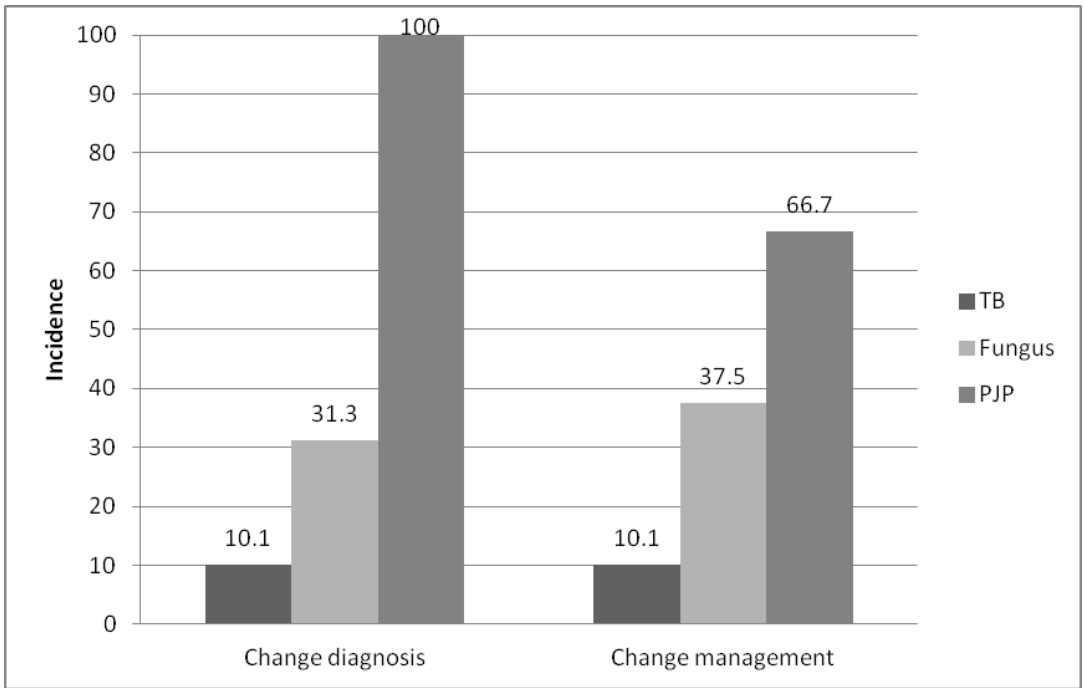

Fig. 2. Benefit of using EBUS-aided specimens in changing the diagnosis or management of *M tuberculosis* (TB), fungal infections, or *Pneumocystis jiroveci* pneumonia (PJP) Use "changed" in the figure below.

dial probe EBUS in changing the diagnosis and management based on the infectious etiology. Patients with Pneumocystis jiroveci received the most benefit from EBUS-guided examinations, while patients with *M. tuberculosis* received the least benefit from the examinations.

Discussion

Bronchoscopy is a helpful tool to determine the etiology of pneumonia. The diagnostic yield of BALF published for patients with neutropenic fever or hematologic malignancy with pneumonia ranged between 13% and 53% [15-19]. The clinical application of EBUS began in the early 1990s [14]. When sonographic images of peripheral lesions are seen all around the probe on the screen, the probe can then be considered situated within the target. EBUS was documented to improve the diagnostic yield for lung cancer because of its ability to navigate to specific pulmonary segments affected by malig-

nancy. In theory, peripheral lung lesions that are not visualized with conventional bronchoscopy can be precisely biopsied under radial EBUS-guidance. EBUS-aided TBB or BALF can navigate to the precise location of the pulmonary infection by direct visualization. However, few studies have focused on the value of EBUS in diagnosing pneumonia, especially atypical pulmonary infections. Our retrospective study has shown that EBUS can be useful in diagnosing and managing patients with atypical pneumonia, especially those patients with underlying disease not responding to empiric antimicrobial therapy. The overall assistance in diagnosis was 80.8%, and in management, 78.2%. This study has shown that the diagnostic rate for cases of atypical pneumonia caused by *M. tuberculosis*, Aspergillosis, mucormycosis, Cryptococcal disease, and PJP was higher than in previous studies [17-19] after the introduction of EBUS (Figure 3).

The definitive diagnosis of active pulmo-

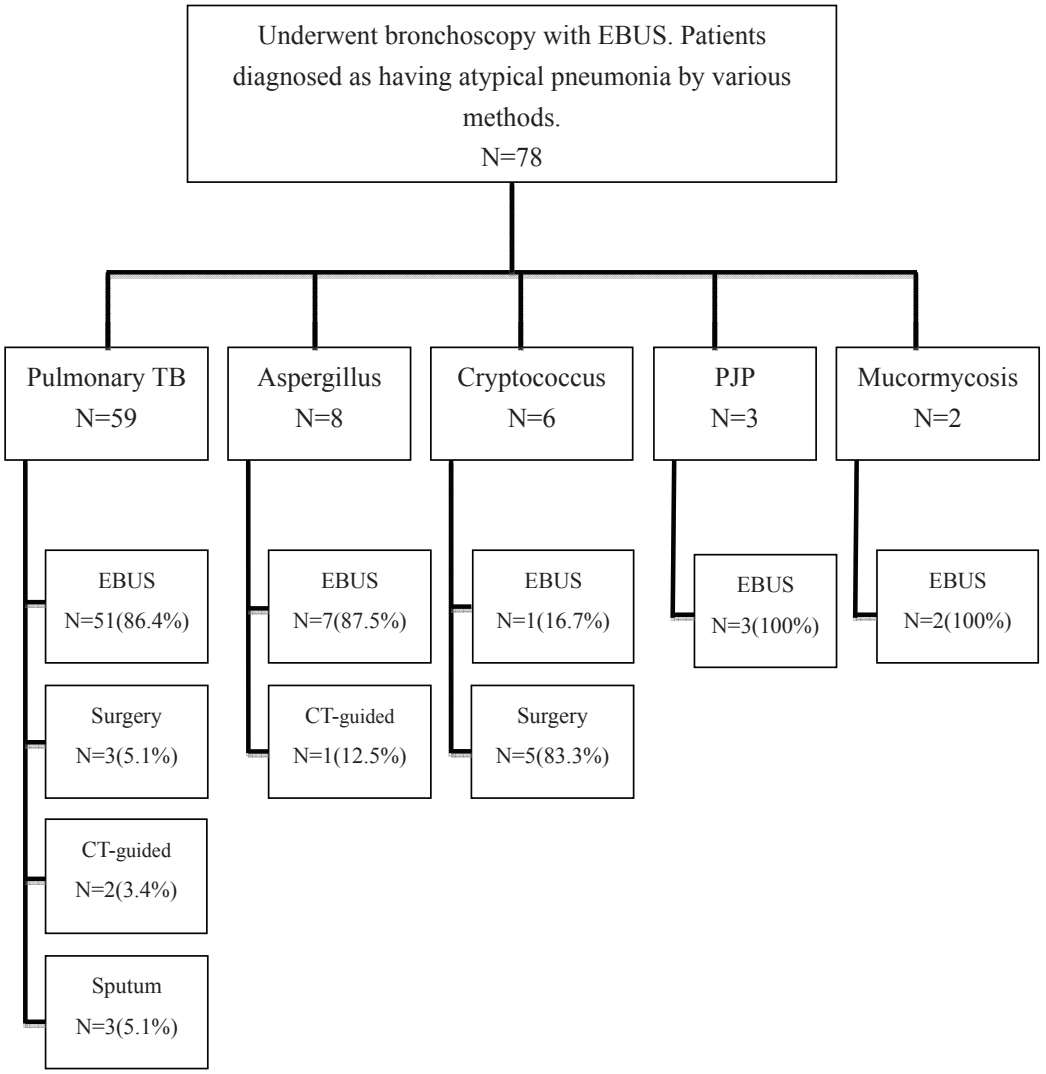

Fig. 3. Summary of diagnostic methods used for all patients with atypical pneumonia.

nary TB usually requires the isolation of *M. tuberculosis* from respiratory secretions, and up to 6 weeks may be required to identify *M. tuberculosis* from culture specimens [18]. Delays in diagnosis and treatment have been recognized as an important cause of death in patients with pulmonary TB [19]. A recent study found that the addition of EBUS to a diagnostic bronchoscopy increases the incidence of a TB diagnosis [20], and the use of EBUS-guided transbronchial needle aspiration can increase the diagnostic yield in the investigation of suspected intrathoracic TB [21]. In our study, 51 (86.5%) patients were diagnosed with pulmonary TB by EBUS with TBB or BALF. As shown in Figure 1, most of our patients (n=46, 78%) were diagnosed from EBUS-guided specimen cultures. However, 11 patients were diagnosed from EBUS-guided specimen smears, and 29 were diagnosed based on the pathology report from the TBB. Pathology or specimen smear studies usually identify *M. tuberculosis* infection within 1 week. Bronchoscopy with EBUS not only increased the diagnostic accuracy of *M. tuberculosis* but also shortened the diagnostic period.

Fungi represent a major cause of nonresolving pneumonia. Fungi may colonize the respiratory tract, and invasive fungal infection must be confirmed by a positive specimen culture from a sterile site or by characteristic histopathology [22]. However, blood cultures are limited in sensitivity, and cultures from nonsterile sites are very difficult to interpret due to contamination or colonization [23]. Bronchoscopy with EBUS can accurately localize the lesion and increase the overall diagnostic yield of invasive pulmonary fungal infection, including Aspergillus and mucormycosis. Therefore, the EBUS-aided diagnosis of all our patients with fungal infection was based on TBB (Figure 1).

Because patients with PJP frequently produce little or no sputum and harbor low numbers of organisms, the method of choice to obtain a specimen is open lung biopsy or bronchoscopy with TBB. Currently, PJP is diagnosed more often in non-HIV immunocompromised patients. The quantities of P jiroveci in these patients are generally low, making detection more difficult [24]. PJP is currently diagnosed by detection of organisms in respiratory secretions or tissue [25]. In our study, 2 of 3 patients were diagnosed by pathology, and 1 was diagnosed by polymerase chain reaction (PCR) testing of EBUS with BALF. These patients all had either leukemia or renal transplantation. An early diagnostic yield of PJP can assist in determining an accurate treatment for these immunocompromised patients. In Figure 2, the infectious pathogens were classified as TB, fungus, and PJP. The diagnosis of PJP benefits more from EBUS-guided procedures than does the diagnosis of TB or fungal pneumonia. Therefore, earlier EBUS-aided TBB or BALF can help physicians accurately determine the diagnosis and management of these immunocompromised patients clinically suspected of having PJP infection.

The diagnostic yield of Cryptococcus infection is small, and the diagnostic rate was low (n=1, 16.7%). Six patients with pulmonary Cryptococcus infection presented with solitary pulmonary nodules that were smaller than the nodules seen with other types of pulmonary infection (1.9 cm vs. 3.3 cm, p=0.015). Most of the patients with non-diagnostic Cryptococcal pneumonia (80%, 4/5) required surgical intervention to confirm the diagnosis. Size is an important factor influencing the diagnostic yield [26], and the smaller size of pulmonary nodules seen with Cryptococcus infection certainly

presents a lower diagnostic yield. Therefore, if the peripheral lung lesions are <2 cm, surgical intervention should be considered to diagnose atypical pneumonia.

Inappropriate use of antibiotics for the treatment of suspected pneumonia is widely prevalent [6]. Empiric antibiotic therapy is often continued despite negative culture results. One study reported that patients who received empiric antibiotics >4 days had increased mortality [10].

Our retrospective study has shown that EBUS can also be useful in assisting the diagnosis and management of an atypical pulmonary infiltrate, especially in those patients with negative bacterial studies. The overall frequency of EBUS assisting the diagnosis is high, and includes assistance in both establishing an accurate diagnosis and changing the diagnosis. The influence of EBUS on the management of an atypical infection was also noteworthy, and involved both confirming and changing the management. In addition, the use of EBUS during bronchoscopy procedures resulted in a low incidence of complications. Pneumothorax occurred in only 2 patients (3%).

Some limitations in this study warrant mentioning. First, this was a retrospective study with a limited number of patients with atypical pulmonary infection, and therefore the sensitivity, specificity, and predictive value cannot be determined. Second, not all patients with atypical pulmonary infection underwent bronchoscopy with EBUS, so the results of our study could not be extended to all patients with atypical pulmonary infection. Third, we began using EBUS routinely in the diagnosis of unknown pulmonary lesions in our hospital after 2007, so we cannot compare the differences in diagnostic rates between conventional bronchoscopy and bronchoscopy with EBUS during this time. Fourth, we had a limited number of cases. Therefore, further study investigating predictors of the diagnostic accuracy of EBUS with regard to atypical pneumonia is suggested.

In conclusion, EBUS-aided TBB or BALF is useful in diagnosing and managing pneumonia that has not responded to empiric antibiotic treatment. EBUS is valuable in assisting with the diagnosis and management of patients with atypical pneumonia, resulting in the avoidance of unnecessary antibiotic usage.

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PD-1/PD-L1 Inhibitors in Stage IV Non-Small Cell Lung Cancer - A Single Medical Center Experience

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Introduction: Information about the real-world efficacy of programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors in the treatment of stage IV lung cancer is limited in Taiwan. Here, we report the experience of a medical center in Taiwan.

Methods: Patients diagnosed with lung cancer and treated with PD-1/PD-L1 inhibitors were identified. We recorded the characteristics of the patients, treatment efficacy, and side effects, and analyzed variables related to treatment outcome.

Results: From September 2016 to October 2019, 52 lung cancer patients received PD-1/PD-L1 inhibitors. After exclusion, 38 patients were included for final analysis. Progression-free survival (PFS) was 6.2 months (95% CI, 5.3 to 7.1 months), and overall survival (OS) had not been reached at the time of analysis. Patients that had progressive disease at 2 months after their first PD-1/PD-L1 inhibitors treatment had significantly shorter PFS and OS than patients with stable disease or a partial response.

Conclusion: The efficacy of PD-1/PD-L1 inhibitors in this real-world analysis was comparable to that reported in previous clinical trials. Response at 2 months after initiation of immune checkpoint inhibitors is a good predictor for PFS and OS. ***(Thorac Med 2020; 35: 116-121)***

Key words: immunotherapy, PD-1/PD-L1 inhibitors, non-small cell lung cancer

Introduction

Lung cancer has a relatively poor outcome. For patients treated with chemotherapy only, the median overall survival (OS) was around 1 year [1]. The discovery of the PD-1/ PD-L1 pathway and PD-1/PD-L1 inhibitors was a breakthrough for lung cancer treatment during this decade, and offers a twilight of hope for lung cancer patients [2-4]. However, our data on the use of immune checkpoint inhibitors (ICIs) in lung cancer is mostly based on clinical trials, with selected patient cohorts. Herein, we report the experience of a medical center in Taiwan using PD-1/PD-L1 inhibitors to treat stage IV non-small cell lung cancer (NSCLC).

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Materials and methods

After approval by the institutional review board of MacKay Memorial Hospital, patients registered in the lung cancer registry program of this hospital who received treatment with PD-1/PD-L1 inhibitors from September 2016 to October 2019 were identified. The PD-1/PD-L1 inhibitors included in this analysis were pembrolizumab, nivolumab, atezolizumab and durvalumab.

The following variables were gathered for analysis: age, sex, smoking history, EGFR or ALK mutation, Eastern Cooperative Oncology Group (ECOG) performance status at the time of first ICI treatment, PD-L1 expression proportion of the tumor, treatment prior to ICIs, combination therapy given with ICIs, response at first evaluation, best response to ICI treatment, and types and grades of immune-related adverse effects (irAE). Dates of the following were also recorded: ICI initiation, first evaluation for treatment response, disease progression after ICI treatment, last OPD follow-up and death.

Response to ICI treatment was defined according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Kaplan-Meier analysis was used to estimate OS and progression-free survival (PFS). OS was calculated from the date of first ICI treatment until the date of death. PFS was calculated from the date of first ICI treatment until the date of growth of a target lesion or the development of a new lesion. Log-rank testing was used to assess the relationship of PFS and OS with the variables. The Pearson correlation coefficient was used to evaluate the correlation of variables. Univariate Cox proportional hazards analysis was used to examine factors associated with increased risk of disease progression and death. Statistical analyses were performed using IBM SPSS Statistics V23.

Results

Between September 2016 and October 2019, 52 lung cancer patients received treatment with PD-1/PD-L1 inhibitors at MacKay Memorial Hospital. We excluded 5 patients that died within 2 months after the first ICI treatment, and 4 small cell lung cancer and 5 stage III NSCLC patients that received ICIs as consolidation therapy after concurrent chemoradiation therapy. Thirty-eight patients were included for final analysis. Patient characteristics are listed in Table 1. Of the 38 patients, 23 (60.5%) received pembrolizumab, 8 (21.1%) received atezolizumab, and 7 (18.4%) received nivolumab; 22 (57.9%) of the 38 patients received ICIs as monotherapy and 16 (42.1%) were given a chemotherapy combination. Patients treated with atezolizumab were more likely to have been given combined chemotherapy, as 6 out of 8 patients that had atezolizumab also had chemotherapy at the same time. In comparison, only 1 out of 7 patients treated with nivolumab and 8 out of 23 patients treated with pembrolizumab had combined chemotherapy. All patients with a high PD-L1 expression (>=50%) received pembrolizumab. Twelve patients had an EGFR mutation, and all of them received ICIs after EGFR tyrosine kinase inhibitor treatment failure.

For the entire cohort, median PFS was 6.2 months (95% CI, 5.3 to 7.1 months), and median OS had not been reached as of this writing (Figure 1). One patient had no measurable lesion at the start of ICI treatment and had not developed a new lesion after that, so that patient

Table 1. Patient Characteristics

	N=38
Age(S.D.)	59.7(13.1)
Gender, male(%)	23(60.5)
Smoker*, n%	16(42.1)
Histology, n(%)	
Adenocarcinoma	26(68.4)
Squamous	5(13.2)
Adenosquamous	3(7.9)
NOS	2(5.3)
Large cell carcinoma	1(2.6)
Sarcomatoid	1(2.6)
PD-L1, n(%)	
0%	7(25.9)
1-50%	11(41.1)
51-100%	9(33.3)
N.D.	11
ECOG, n(%)	
0	17(44.7)
1	14(36.8)
2-4	7(18.4)
Regimen, n(%)	
Pembrolizumab	23(60.5)
Atezolizumab	8(21.1)
Nivolumab	7(18.4)
Combination, n(%)	
Mono	22(57.9)
Chemotherapy	16(42.1)
Previous Tx, n(%)	
0	16(42.1)
1	9(23.7)
2	2(5.3)
>3	11(41.1)

* included 1 ex-smoker and 15 active smokers

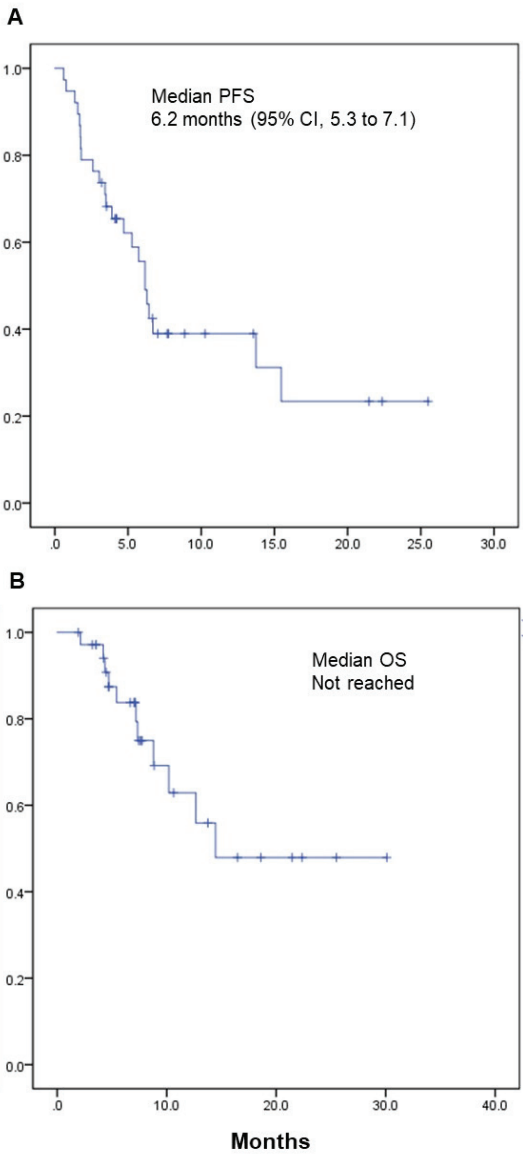

Fig. 1. A. Median PFS, B. Median OS of the whole cohort.

was not evaluable for treatment response. At first evaluation of ICI treatment for the remaining 37 patients, 12 (32.4%) had progressive disease (PD), 14 (37.8%) had stable disease (SD) and 11 (29.7%) had a partial response (PR). The average time from initiation of ICI treatment to first evaluation of treatment response was 2.2 months (S.D. 1.1). As for the best response during ICI treatment, 2 patients with stable disease at first evaluation went on to have a partial response later; the others showed no change. Response at first evaluation correlated very well

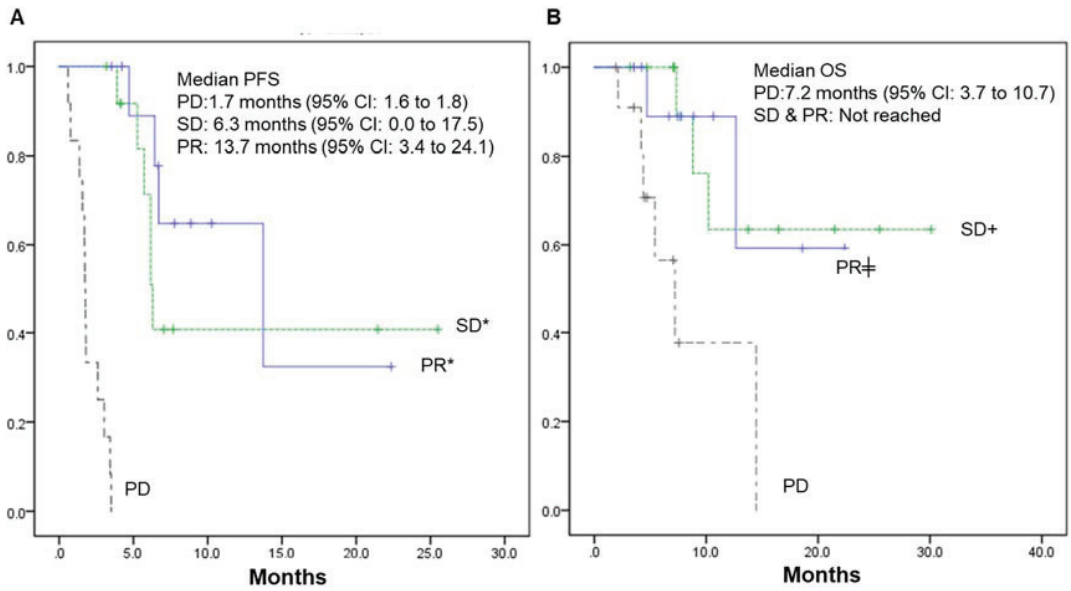

Fig. 2. Kaplan-Meier analysis comparing A. PFS, B. OS in patients with a different response at initial evaluation.
* p <0.001 for SD vs PD and PR vs PD, + p <0.01 for SD vs PD, ╪ p=0.03 for PR vs PD.

with best response to ICI treatment (r = 0.961, p < 0.001).

The median PFS for patients that had PD during the first evaluation was 1.7 months (95% CI, 1.6 to 1.8 months), which is significantly shorter than that of patients with SD (6.3 months, 95% CI, 0.0 to 17.5 months, p <0.001) and PR (13.7 months, 95% CI: 3.8 to 24.1 months, p <0.001). The median OS was also significantly shorter for patients with PD (7.2 months, 95% CI, 3.7 to 10.7 months) compared to those with SD (not reached, p <0.01) and PR (not reached, p =0.03) (Figure. 2).

Univariate Cox proportional hazards analysis (Table 2) revealed that patients with adenocarcinoma or ECOG status 0-1 had better PFS. Patients with ECOG 0-1 also had better OS than those with ECOG 2-4. In our cohort, both PFS and OS were related to age, gender, EGFR mutation status, PD-L1 expression, combined treatment with chemotherapy, or the presence of an irAE.

Thirteen (34.2%) patients had a recorded irAE. The most common irAE was hepatitis in 5 patients, followed by skin rash in 4 patients. In terms of irAE management, 10 patients with a grade 1 irAE received no specific treatment, and 2 patients with a grade 2 irAE were treated with oral steroid. One patient treated with pembrolizumab developed grade 3 colitis with a grade 1 skin rash; IV steroid was given for treatment of the colitis and pembrolizumab was withheld for 2 months. After the patient recovered fully from the colitis, the doctor maintained the oral steroid and resumed pembrolizumab use. There was no recurrent irAE after that.

Discussion

Previous clinical trials have shown that the objective response rate (ORR) of PD-1/PD-L1 inhibitors use in PD-L1-unselected lung cancer patients was around 15% to 30%, and PFS was around 3 to 9 months [2, 3, 5-8]. Although our

Table 2. Univariate Analyses of Covariates Associated with PFS and OS

Variables	PFS			OS		
	HR	95% CI	*p*	HR	95% CI	*p*
Age, < 65 vs >=65	1.06	0.43 to 2.64	0.90	0.69	0.20 to 2.43	0.57
Gender, male vs female	0.78	0.33 to 1.83	0.78	0.44	0.13 to 1.43	0.17
Smoker, ever vs never	1.29	0.56 to 3.00	0.55	0.55	0.16 to 1.83	0.33
Histology Adeno vs non-adeno	0.41	0.18 to 0.94	0.04	0.53	0.15 to 1.82	0.31
PD-L1						
0 vs 1-100 %	1.32	0.49 to 3.93	0.61	1.15	0.28 to 4.68	0.85
0-49 vs 50-100%	3.31	0.93 to 11.78	0.07	1.12	0.27 to 4.63	0.88
ECOG, 0-1 vs 2-4	0.34	0.14 to 0.87	0.02	0.21	0.06 to 0.82	0.02
Mono vs combination	0.68	0.30 to 1.56	0.37	0.94	0.29 to 3.10	0.92
irAE, (+) vs (-)	0.75	0.31 to 1.84	0.54	0.81	0.23 to 2.76	0.73
EGFR mutation, (+) vs (-)	1.10	0.45 to 2.71	0.83	6.49	0.80 to 52.54	0.08
Previous treatment none vs >= 1	0.76	0.33 to 1.76	0.52	1.03	0.31 to 3.40	0.96

study population was heterogeneous and relatively small, our treatment efficacy was comparable to that of previous clinical trials, with ORR of 28% and PFS of 6.2 months. Durable response was also a strength of PD-1/PD-L1 inhibitors [9, 10]. Our study found there was a durable response, with a median duration of response of 13.7 months. Overall, PD-1/PD-L1 inhibitors were shown to be as effective in the real world as in clinical trials.

Lack of a predictive marker has been a major problem in selecting patients for ICI treatment. The tumor PD-L1 level predicted treatment response in some trials, but was not predictive in others. In general, a high PD-L1 expression predicts a better response for pembrolizumab, but not for nivolumab and atezolizumab [4, 8, 11]. In our cohort, we also found that tumor PD-L1 expression was not related to the efficacy of PD-1/PD-L1 inhibitors. Univariate Cox proportional hazards analysis of our cohort showed that patients with a better ECOG performance status had better PFS and OS than those with a poor performance status. As patients with a poor performance status may be less capable of generating an immune response to fight cancer, this is a reasonable finding. Univariate analysis also showed that patients with adenocarcinoma had better PFS than patients with squamous cell carcinoma. But the histology of cancer is related to gender and smoking status, so we performed a multivariate Cox proportional hazards analysis with variables including histology, gender, EGFR mutation, and smoking status. The result showed that the hazard ratio for adenocarcinoma vs non-adenocarcinoma was 1.03 (95% CI, 0.77 to 1.37, p=0.85). So, in our cohort, a better ECOG status was the only predictor for a better outcome before ICI treatment.

We also found a predictor for longer PFS and OS after ICI use. Treatment response evaluated at 2 months after initiation of ICIs is predictive of PFS and OS. Patients with PD had

significantly worse PFS and OS than those with SD or PR. A previous study showed that depth of response correlated well with PFS and OS for NSCLC patients receiving PD-1 inhibitors [12]. However, pseudo-progression had been an issue when evaluating treatment response to ICIs for various types of cancer, including NSCLC [13]. So, some suggested maintaining ICI use after progression. In 2019, Fujimoto *et al* reported a retrospective study of 542 NSCLC patients [14], in which they observed pseudo-progression in 14 (3%) at a median time of 1 month. We found that the response at 2 months correlated very well with best response for the whole treatment course. Two of 14 patients with SD went on to be PR later and both received local radiotherapy between SD and PR. So, for patients treated with ICIs, 2 months may be the optimal time to evaluate treatment response.

Conclusion

The efficacy of PD-1/PD-L1 inhibitors in this real-world analysis was comparable to that reported in previous clinical trials. Response at 2 months after initiation of ICIs is a good predictor for PFS and OS.

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Gender Differences in Caregiver Burden with Ventilator-Dependent Patients

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Introduction: Ventilator-dependent patients require skillful and extraneous care during daily tasks, and this can elevate the stress level and increase the burden of caregivers. This study examined the gender-related differences in caregivers' burden caused by caring for ventilator-dependent patients.

Methods: This retrospective cross-sectional study was conducted on caregivers of ventilator-dependent patients in southern Taiwan. A survey was conducted that included basic demographic information on the patients and caregivers, and used the Burden Assessment Scale (BAS) scores for 4 domains, comprising a total of 21 questions (physical burden, n=5; psychological burden, n=6; social burden, n=6; financial burden, n=4).

Results: A total of 128 caregivers of both genders, aged 50.8±12.8 years, were recruited (men: n=59; women: n=69). Most of these caregivers were children of the patient or the spouse of the patient (83.1% for men and 78.3% for women), and received no social welfare. Female caregivers exhibited significantly higher BAS scores than did male caregivers. The higher physiological burden (P<.016) for women was attributed to lack of sleep and torso pain, whereas the higher psychological burden (P<.021) was attributed to loss of appetite and fear of the patient's disease deteriorating. The higher social burden (P<.041) was due to their being unable to handle household chores and being forced to change personal plans.

Conclusion: The results revealed that female caregivers of ventilator-dependent patients encountered a greater burden than men, including physiological, psychological, and social burdens, yet the financial burden was similar. ***(Thorac Med 2020; 35: 122-131)***

Key words: gender, caregiver burden, ventilator-dependent patient

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Introduction

With the advances in technology, mechanical ventilators have become a life-saving tool, resulting in increased life expectancy. However, the proportion of patients requiring prolonged mechanical ventilation support has increased from 4% to 13%, leaving family members to care for patients after they are discharged from hospital. "Ventilator-dependent patients" refers to patients under mechanical ventilation for more than 6 hours per day and longer than 21 days [1]. Caregivers of ventilator-dependent patients may encounter an excessive physical, psychological, social, and financial burden [2-8].

Studies have shown that caregivers of patients with chronic disease encounter cultural conflicts regarding gender [8-10]. Most caregivers are the wives of chronic patients; they have limited social resources and low psychological health. Their tasks include caring for their family members, performing household chores, and managing the burden resulting from the patients' ailments, mental status, and social life. The burden and stress levels of female caregivers are greater than those of male caregivers, resulting in a higher risk of developing depression [2-3,5,11-14]. Without proper training and education, caregivers for patients with chronic disease can easily develop high-level anxiety and low self-esteem. With limited resources, female caregivers suffer a greater burden, and this may lead to anger, anxiety, depression, panic, uncertainty, loneliness, and decreased well-being [15-17].

However, male caregivers take on more obligations and have limited mental and social support compared with women, despite having higher self-esteem and more socioeconomic support. Male caregivers handle stress by applying more effective strategies, resulting in lower levels of anxiety and depression, and a decreased burden [5-6,18]. The complexity of caring for ventilator-dependent patients requires skill and extraneous care during daily tasks, and places greater stress and more of a burden on caregivers than caring for patients with other diseases. Since the caregiving burden differs between genders, we wanted to investigate the influence of gender on the burden of caring for ventilator-dependent patients.

Materials and methods

Participants

The present retrospective cross-sectional study was reviewed and approved by the Institutional Review Board of the Zuoying Armed Forces General Hospital in Taiwan. Informed consent was obtained from the participants. Questionnaires were distributed to caregivers of ventilator-dependent adult patients who had used a ventilator >6 hours per day for more than 21 days. The caregivers were defined as those who made surrogate decisions, paid the medical expenses, and were the primary family members caring for the patient.

Measures

The structured questionnaire included demographic information on ventilator-dependent patients and their caregivers and Burden Assessment Scale (BAS) scores. Patient characteristics included age, gender, Barthel activities of daily living index scores, Karnofsky performance status scale scores, consciousness status, and hospital readmission rate. Caregiver characteristics were age, marital status, educational degree, income, and current health condi-

tion. The Barthel activities of daily living index contains 10 items of daily living activities, and each item is scored as 0, 5, or 10 points. The Karnofsky performance status scale is a tool for assessing functional impairment and classifies patients into 1 of 4 categories: 4 for normal, 3 for assistance required, 2 for disabilities, and 1 for terminal status.

The BAS comprises 4 domains with a total of 21 questions (physical burden, n=5; psychological burden, n=6; social burden, n=6; and financial burden, n=4). A 5-point Likert scale was used to score the BAS domains, and higher scores represented higher levels of caregiver burden. Sampling adequacy was measured using the Kaiser–Meyer–Olkin coefficient of 0.828, because a value of 0.8–1 indicated adequate sampling. Content validity was examined using Cronbach's α coefficients of 0.941 and 0.923 for reliability and validity, respectively.

Data analysis

Data were analyzed using SPSS (version 23.0, IBM Inc., NY, USA), and presented as means ± standard deviation for continuous variables and as numbers (percentages) for categorical variables. The statistical analysis methods employed were the independent sample t test for continuous variables and chi-square test for categorical variables. $P<.05$ was considered statistically significant.

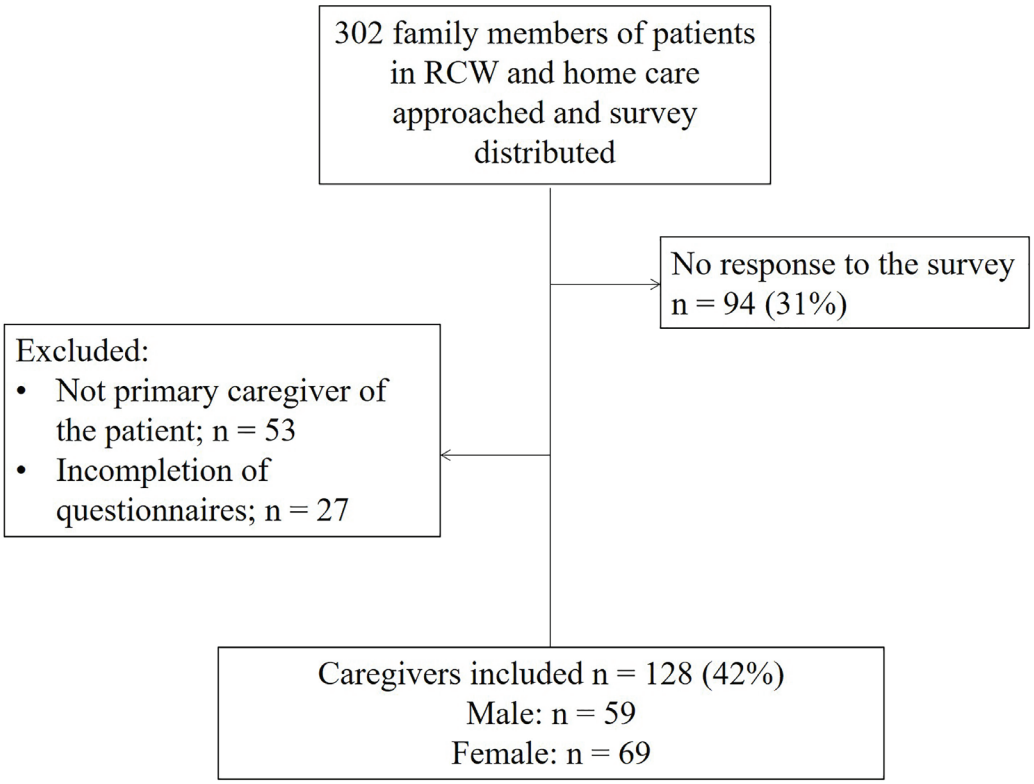

Fig. 1. Flow diagram of caregiver enrollment Use "Incomplete questionnaires" above.

Results

In all, 302 questionnaires were administered to screened caregivers; 174 questionnaires were excluded because they were incomplete or the responders were not the primary caregivers. A total of 128 primary caregivers (59 men and 69 women) for 128 ventilator-dependent patients participated in the survey, with an overall response rate of 42%, as shown in Figure 1.

With regard to demographic characteristics, patients were more likely to be elderly, with a mean age of 80.37±11.67 years for the male caregiver group and 76.07±14.42 years for the female caregiver group. The average ventilator-use duration for patients was 23.64±24.48 months for the male caregivers and 21.36±25.27 months for the female caregivers. Patients were predominantly functionally dependent (Barthel index >20), and categorized as disabled and required physical assistance (Karnofsky scale 1, 2, and 3). Nearly 50% of patients had readmissions within 1 year. No statistical differences between the 2 groups regarding patient characteristics were observed (Table 1).

The mean age of the caregivers was 52.03± 10.96 years for men versus 50.75±12.81 years for women. The caregivers in both groups were

Table 1. Demographic Characteristics of Ventilator-Dependent Patients

Characteristics	Men (N=59)	Women (N=69)	*P*
Age (y)	80.37±11.66	76.07±14.42	0.069
Duration of ventilator use (mo)	23.64±24.48	21.36±25.27	0.606
Barthel index			0.212
0-20	20 (33.90%)	22 (31.88%)	
21-60	24 (40.08%)	37 (53.62%)	
61-90	15 (25.42%)	10 (14.49%)	
Karnofsky Scale			0.409
2- assistance needed	3 (5.08%)	5 (7.25%)	
3- unable to self-care	20 (33.90%)	30 (43.48%)	
4- terminal status	36 (61.02%)	34 (49.28%)	
Consciousness status			0.441
Conscious	20 (33.90%)	31 (44.92%)	
Unconscious	39 (66.11%)	38 (55.08%)	
Readmissions during 1 year			0.355
0	29 (49.10%)	31 (44.92%)	
1	18 (30.15%)	27 (39.13%)	
2	7 (11.86%)	5 (7.25%)	
3	5 (8.47%)	6 (8.70%)	

predominantly the patients' children and did not receive social welfare (93.22% vs. 84.05%). More caregivers had higher educational degrees (52.54 vs. 39.13%). An annual income of >US$ 21,000 was most frequent among male caregivers (52.54% vs. 41.13%). Most caregivers (70% of caregivers in both groups) felt their health status had worsened. However, no statistical differences in caregivers' characteristics between genders were observed (Table 2).

Table 2. Demographic Characteristics of Caregivers

Characteristics	Men (N=59)	Women (N=69)	*P*
Age (y)	52.03±10.96	50.75±12.81	0.548
>65	9 (15.25%)	10 (14.49%)	0.098
46-65	33 (50.93 %)	38 (55.07%)	
<45	17 (28.81%)	21 (30.43%)	
Relation to patient			0.765
Parents	1 (1.69%)	5 (7.25%)	
Spouse	5 (8.47%)	16 (23.19%)	
Child	47 (79.66%)	39 (56.52%)	
Other relatives	6 (10.17%)	9 (12.04%)	
Under social welfare	4 (6.78%)	11 (15.94%)	0.090
	55 (93.22%)	58 (84.06%)	
Education			0.062
Illiterate	0 (0.0%)	3 (4.35%)	
Elementary school	2 (3.39%)	10 (14.49%)	
Secondary school	26 (44.07%)	29 (42.03%)	
College	31 (52.54%)	27 (39.13%)	
Religion			0.528
None	10 (16.95%)	13 (18.84%)	
Buddhism/Taoism	43 (72.88%)	47 (65.12%)	
Christian/Catholic	6 (10.17%)	7 (10.14%)	
Others	0 (0.0%)	2 (2.90%)	
Annual household income (US dollars)			0.095
Below $7,000	8 (13.56%)	10 (14.49%)	
$7,000–$14,000	6 (10.17%)	20 (28.99%)	
$14,000–21,000	14 (23.73%)	12 (17.39%)	
$21,000–28,000	13 (22.03%)	09 (13.04%)	
Above $28,100	18 (30.51%)	18 (26.09%)	
Self-reported health status			0.211
Very poor	10 (16.95%)	19 (27.54%)	
Poor	31 (52.54%	36 (52.17%)	
Normal	14 (23.73%)	13 (18.84%)	
Healthy	4 (6.78%)	1 (1.45%)	

Table 3. Comparisons of Burdon Assessment Scores of Caregivers (Mean ± SD)

Domains/Items	Men (N=59)	Female (N=69)	*P*
Total scores	48.97±12.27	54.01±14.39	0.036*
Physiological burden	9.88±3.58	11.59±4.21	0.016*
Lack of sleep or rest	2.59±1.11	3.12±1.21	0.013*
Constant tiredness/restlessness	2.63±1.04	2.99±1.13	0.067
Torso pain	2.44±0.95	3.00±1.30	0.007*
Worsening of physiological status or illness	2.22±0.94	2.49±1.26	0.168
Psychological burden	14.00±3.85	15.75±4.50	0.021*
Loss of appetite	2.19±0.95	2.62±1.12	0.021*
Feeling pressured and anger	2.58±1.07	2.74±1.20	0.425
Frustration and helplessness	2.69±1.10	3.03±1.15	0.097
Feeling of care insufficiency	3.12±1.19	3.48±1.15	0.086
Fear of patient's disease deterioration	3.42±0.95	3.88±0.97	0.008*
Social burden	12.78±4.22	14.39±4.55	0.041*
Neglecting the care of other family members	2.51±0.97	2.80±1.23	0.148
Unable to handle household chores	2.44±0.93	2.83±1.16	0.043*
Time constraints	2.59±1.05	2.87±1.13	0.158
Change in personal plans	2.56±1.05	2.97±1.08	0.032*
Less interaction with friends and families	2.68±0.99	2.93±1.18	0.202
Financial burden	12.31±4.46	12.28±4.80	0.971
Decreased income due to joblessness	2.25±1.28	2.58±1.49	0.193
High medical bills leading to frugal lifestyle	3.22±1.36	3.14±1.36	0.756
Increased expenses due to caretaker fees	3.61±1.36	3.46±1.39	0.552
Financial difficulties due to medical bills	3.22±1.34	3.09±1.40	0.585

The BAS results (Table 3) revealed that the total BAS score of female caregivers was significantly higher (54.01±14.39 vs. 48.97± 12.27, *P*=0.036) than that of the male caregivers. Figure 2 illustrates the comparisons of the 4 domains of BAS scores between males and females. The physical burden scores were significantly higher in female than in male caregivers (9.88 ± 2.58 vs. 11.59±4.21, *P*=0.013). The factors contributing to physical burden included insufficient sleep and torso pain (*P*=0.013 and *P*=0.007, respectively). The psychological burden for female caregivers was significantly higher than that for male caregivers (15.75±4.50 vs. 14.00±3.85, *P*=0.021), because the female caregivers reported a loss of appetite (2.62± 1.12 vs. 2.19±0.95, *P*=0.021) and fear of the patient's disease deteriorating (3.88 ± 0.97 vs. 3.42±0.95, *P*=0.008). Female caregivers also encountered a greater social burden than men (14.39±4.55

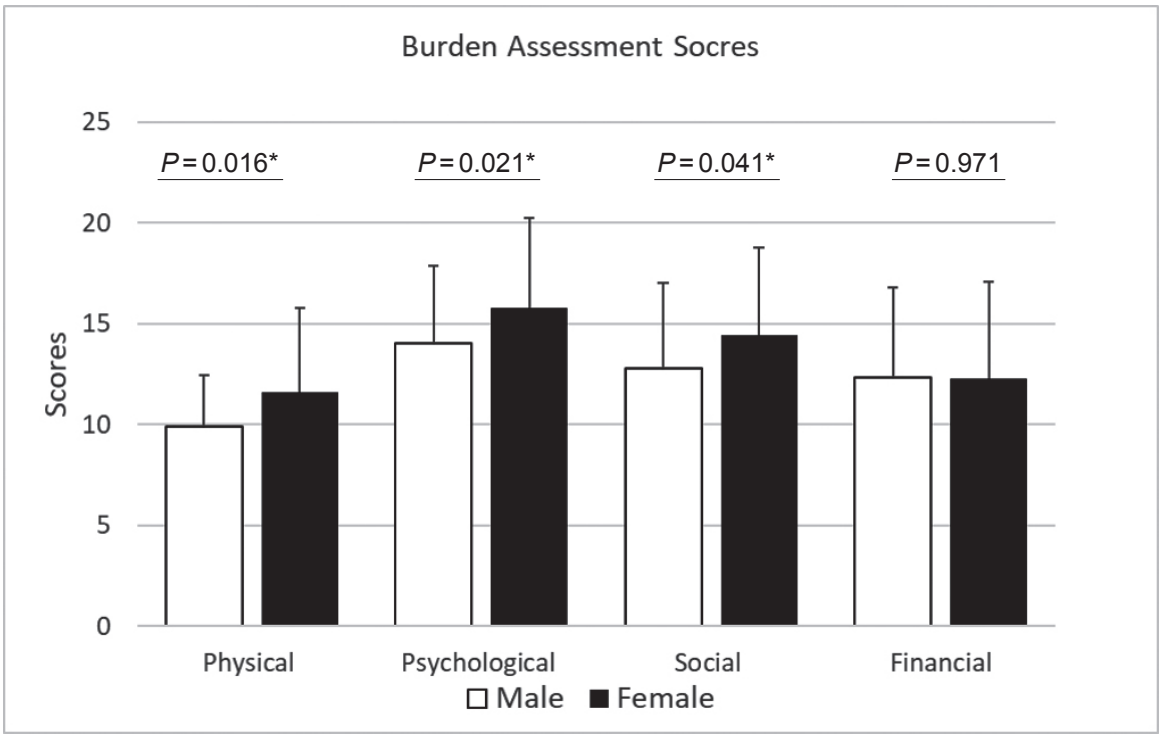

Fig. 2. Burden assessment outcomes between groups
Note: **P* <0.05

vs. 12.78±4.22, *P*=0.041), including being unable to handle household chores (2.83±1.16 vs. 2.44±0.93, *P*=0.043) and having to change their personal plans (2.97±1.08 vs. 2.56±1.05, *P*= 0.032). No significant differences in financial burden were observed between the 2 groups.

Discussion

In this cross-sectional study, we found that female caregivers of ventilator-dependent patients endured greater physiological, psychological, and social burdens than male caregivers, specifically with regard to lack of sleep or rest, torso pain, loss of appetite, fear of the patient's disease deteriorating, inability to handle household chores, and changes in personal plans.

Most caregivers in our study were middle-aged without social welfare, which was similar to the situations of caregivers of patients with multiple chronic conditions [2,18-19]. Compared with male caregivers of ventilator-dependent patients, female caregivers were confronted with a greater overall burden (Table 3). First, their physiological burden was greater because of a lack of rest and sleep as well as torso pain, revealing that they encountered excessive physical work. Studies have shown that female caregivers tend to assume more responsibility and self-sacrifice than male caregivers, which is associated with cultural background [10,20]. In traditional Chinese culture, middle-aged women must typically care for their children as well as their aging parents. They assume more obligations, such as caring for 2 to 3 generations of family members in addition to perform-

ing 5 times the household chores as men [21]. In addition to their daily work, women caring for a ventilator-dependent family member must be constantly alert to life-threatening problems of the patient, leading to a lack of sleep and physical discomfort [4,18,22]. Studies have also reported that the greater burden on female caregivers of chronic patients increases the likelihood that the female caregivers will become ill, and jeopardizes their physical condition, leading to chronic fatigue, insomnia, gastric ulcers, back pain, or weight changes [3-4,18,23-25]. Female caregivers have reported a greater psychological burden than men, with loss of appetite and fear of the patient's condition deteriorating. Studies have revealed similar concerns for female caregivers because they tend to develop a stronger bond with the patient and are reluctant to leave them alone [25-26]. Thus, they have a greater emotional burden that may be expressed as anger, anxiety, depression, sadness, pain, uncertainty, or reduced well-being. The psychological burden can be reflected in temperament and appetite [15-16, 25].

The social burden of female caregivers was greater than that of male caregivers because the female caregivers sacrificed their personal plans and neglected household chores. This may be attributed to the complexity of caring for ventilator-dependent patients who have a high mortality rate and a higher complication and readmission rate, which demands greater caring skills1. Ventilator-dependent patients require frequent physiotherapy and ventilator troubleshooting, in addition to feeding and changes in position. Caregivers must constantly be aware of secretion problems to prevent suffocation and hypoxemia, and prioritize this above household chores. Second, culture influences personal behavior and roles. Female caregivers face multiple role conflicts, being wives, daughters, daughters-in-law, mothers, and employees. Most elderly ethnic Chinese people receive care from their adult children, primarily the daughter or daughter-in-law. When a female caregiver cannot fulfill the expected responsibility of her role, she often feels anxiety and stress and expresses her feelings of guilt to other family members [22,25]. Finally, because of the excessive work required for caring for ventilator-dependent patients, female caregivers will adjust their career plans and free time to be able to take care of the patients. Ethnic Chinese women tend to be passive, and their own emotional and physical needs are frequently overlooked to avoid family conflicts [26]. These results reflect the unique characteristics of ethnic Chinese caregivers.

Several methodological limitations should be considered when deriving the implications of our findings. This cross-sectional study was conducted in 1 center; therefore, this 1-time assessment of the caregivers of ventilator-dependent patients may have been influenced by various assessment conditions on a particular day. Our study had a response rate of <50%, so the results could vary with a higher response rate. In addition, there is a lack of qualitative interview data to gain an in-depth understanding of gender differences in the care of ventilator-dependent patients.

Conclusion

Female caregivers of ventilator-dependent patients in our study reported greater physical, psychological, and social burdens, but no difference between genders was observed in financial burden. Supporting strategies and programs for female caregivers should be developed, as well

as respite care services. Future studies are warranted to ascertain the association between cultural experience and caregiver burden between the genders.

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Spontaneous Posterolateral Lung Hernia

Yi-Han Lin[1,2], Han-Shui Hsu[1]

Lung herniation is defined as the protruding of the lung parenchyma outside the thoracic cage through a defect in the chest wall or diaphragm. A spontaneous posterolateral chest wall hernia is extremely rare. This report presents the case of a patient with chronic obstructive pulmonary disease who suffered from persistent cough and right back ecchymosis. The ecchymosis progressed and a protruding mass was noted the next day. Chest plain film and chest computed tomography revealed that the right lower lobe parenchyma had protruded from the thoracic wall. Conservative treatment was given and the lung hernia gradually regressed. ***(Thorac Med 2020; 35: 132-135)***

Key words: lung hernia, chronic obstructive pulmonary disease, chest wall defect

Introduction

Lung herniation is defined as the protruding of the lung parenchyma outside the thoracic cage through a defect in the chest wall or diaphragm [1]. Lung herniation is considered to be congenital or acquired, based on the etiology [2]. Acquired lung hernias are divided into traumatic, spontaneous and pathologic herniations. A spontaneous lung hernia is relatively rare and occurs at a site of localized weakness in the thoracic cage without previous injury. These hernias occur mostly at the anterior chest wall, especially the costochondral junction, because there is only 1 layer of intercostal muscle at that site. Herein, we report the case of an extremely rare spontaneous posterolateral chest wall hernia.

Case Report

A 72-year-old male was a heavy smoker and had been diagnosed with chronic obstructive pulmonary disease (COPD) for years. He was given theophylline, montelukast, budesonide and steroid for COPD control in daily life. This time, he had suffered from persistent cough for 3 days and visited the emergency department for help. Physical examination initially revealed wheezing in the bilateral lungs and mild ecchymosis, about 10x5 cm in size, on his right back. No protruding mass was noted in the initial physical examination. The first chest plain film revealed increasing infiltration at bilateral hila without obvious an bone or diaphragm problem. The laboratory examination showed a white blood cell count of 8,600/ul (4,500-

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11,000/ul) and C-reactive protein of 0.14mg/dl (0-0.5mg/dl). The creatine kinase (CK) level was elevated to 399 units/liter (24-168/units/liter), but the MB isoenzyme of the CK (CK-MB) level was 13 units/Liter (<25units/Liter). The electrocardiogram showed normal sinus rhythm. He denied any recent traumatic injury or coagulopathy. Under the diagnosis of COPD with exacerbation, he was admitted for further evaluation.

After admission, he complained of exacerbated cough and a protruding mass on his right back. The physical examination showed there was a 15x10 cm protruding mass, more obvious when coughing. Meanwhile, the ecchymosis region increased to 30×20cm in size, with a large range of subcutaneous emphysema (Figure 1). The next day, a second chest plain film and chest computed tomography (CT) were performed to evaluate the chest wall condition. The second chest plain film showed an infiltrative patch at the right lower lobe and subcutaneous emphysema (Figure 2). The chest CT revealed a lung parenchyma protruding from the 7th intercostal space on the right posterolateral side, without rib fracture (Figure 3). He was then given cough suppressants and analgesics for symptom treatment. For management of the herniated lung parenchyma, a lumbosacral support corset belt was applied for external com-

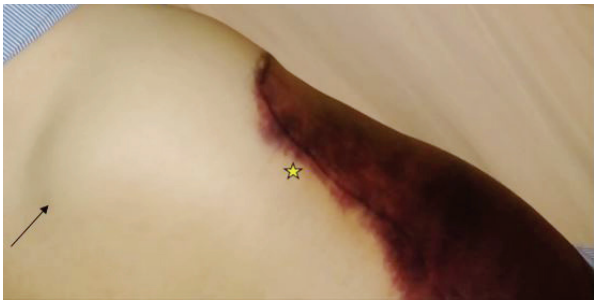

Fig. 1. Arrow: A 15x10 cm mass protruded when coughing. Star: The progressive ecchymosis region.

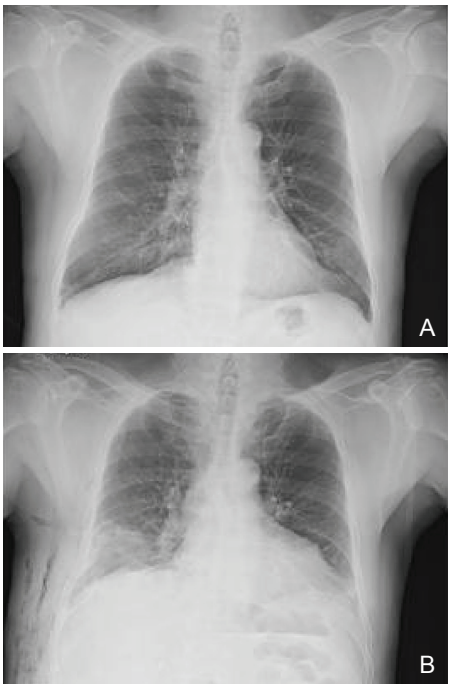

Fig. 2. A: The first chest plain film at the emergency department. B: The second chest plain film on the next day. There was an infiltrative patch at the right lower lobe, complicated with subcutaneous emphysema.

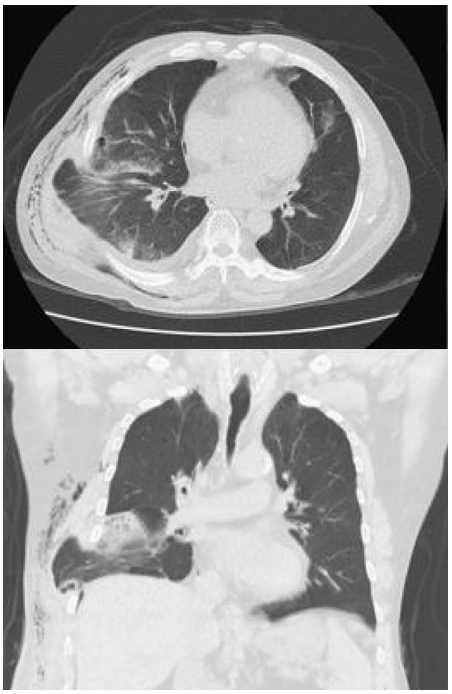

Fig. 3. Chest computed tomography: Lung parenchyma protruding at the 7th intercostal space on the right posterolateral side without rib fracture.

Fig. 4. The lumbosacral support corset belt.

pression (Figure 4). As a result, the parenchyma did not protrude from the thoracic cage, so the defective intercostal muscle could recover gradually. Conservative treatment was given for 14 days and the cough symptoms were relieved. Following this, no obvious mass protrusion was noted during the patient's daily activities. Meanwhile, the third chest plain film showed the size of the herniated lung was had less than in the previous CT image. The fourth chest plain film 3 weeks later revealed a regressed protruding mass (Figure 5). In this case, a good therapeutic outcome was achieved with conservative treatment.

Discussion

Traumatic or post-operative factors are usually the main causes of lung hernia; spontaneous posterolateral lung hernia is extremely rare. According Maeda and colleagues, only 16 patients were reported to have spontaneous lung hernia from 1968 to 2000 [3]. Most of these spontaneous lung hernia patients suffered from

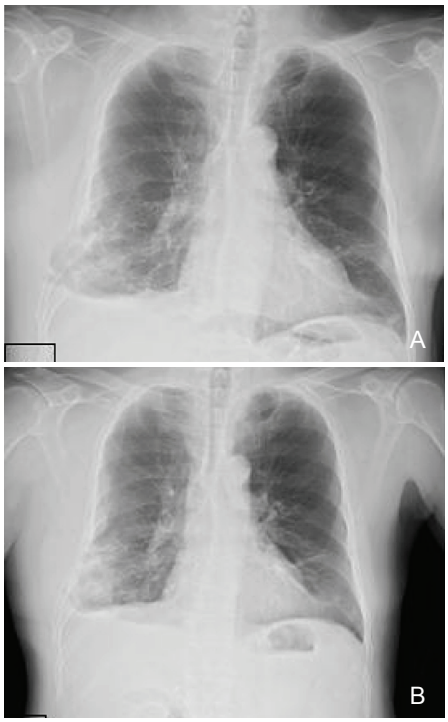

Fig. 5. A: The third chest plain film, 2 weeks after noting the initial lung hernia. The herniated lung parenchyma was smaller when compared with the previous computed tomography image. B: The fourth chest plain film, 3 weeks after noting the initial lung hernia, in which regression of the lung hernia was seen.

anterior or lateral lung hernia because the chest wall is weaker in these directions. The muscle power of the posterolateral chest wall is greater than that of the anterior chest wall, so at posterolateral lung hernia is a rarer subtype of lung hernia.

This case illustrates some particular symptoms and signs that induce spontaneous lung hernia. First, there was an episode of persistent cough. Although productive cough is a common symptom of COPD patients, an episode of severe persistent cough may be a cause of lung hernia [4]. Second, spontaneous ecchymosis was noted. About 44% of spontaneous lung hernia patients are complicated with ecchymosis [4]. A lung hernia usually combines with an intercostal vessel or muscle injury and a

subcutaneous hematoma appears as ecchymosis. Third, an unexplainable non-cardiogenic elevated CK level was also noted [3]. An elevated CK level is a hint of myopathy, rhabdomyolysis or a large area of muscular damage. A patient with spontaneous lung hernia may develop a large muscular laceration when coughing. A persistent cough combined with an unexplainable elevated CK level is a hint of spontaneous lung hernia. Fourth, a painful bulging mass at the protruding site was observed. Almost all spontaneous lung hernia patients present a mass bulging sign [4]. This sign may emerge later than other signs because the defect should first be large enough to make the patient aware of the lesion. The chest wall protruding mass in our patient was found on the second day. However, this sign has high specificity. A chest plain film or CT should be arranged if the previously mentioned symptoms or signs are noted. The role of image investigation is to confirm the presence of the herniated lung and hernia sac and to exclude possible complications such as lung tissue strangulation [5].

Treatment for spontaneous lung hernia includes both conservative and surgical options. Conservative treatments include symptoms control such as antitussive agents and pain control. A coarse belt, compressive pad or truss bandages are used for external compression of the herniated parenchyma [4,6]. A chest wall defect would undergo self-repair gradually if there was no consistent damage like coughing or a protruding mass. Tack and colleagues suggested that the surgical indications for spontaneous lung hernia are pain, recurrent infection, hemoptysis and interference with daily activities [6]. Brock et al suggested that all anterior lung hernia patients should undergo surgical repair to prevent extension of the hernia to the abdominal wall resulting in a thoracoabdominal hernia [4]. Our patient received conservative treatment for 3 weeks and the chest plain film showed a regressing lung hernia. Physical examination revealed no obvious protruding mass on his right back. He denied pain, dyspnea or interference in daily activities. Conservative treatment resulted in a good therapeutic outcome for this patient.

Conclusion

A spontaneous posterolateral lung hernia is rare and usually occurs in patients who suffer from an episode of severe persistent cough. A mass protruding from the thoracic cage is the most specific feature of lung hernia. A chest plain film or CT can be used to diagnose the lung hernia. Conservative care including antitussive agents and external compression works for most patients. But for those complicated with pain, recurrent infection, hemoptysis and interference with daily activities, surgical intervention should be considered.

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Pulmonary Mucormycosis Diagnosed by Ultrasound-Guided Transthoracic Biopsy in a Mechanically Ventilated Patient in the Intensive Care Unit – A Case Report

Han-Ching Yang, Chun-Kai Huang

Pulmonary mucormycosis, a fatal fungal infection characterized by a rapid progressive clinical course, often occurs in immunocompromised patients. Due to its varied presentations, early diagnosis is very difficult, and histopathological examination is necessary to reach a diagnosis. Here, we report the case of a 68-year-old man with newly diagnosed acute myeloid leukemia and pneumonia with acute respiratory failure. Computed tomography of the chest showed a mass-like lesion with internal low attenuating necrosis at the left upper lung field. A bedside ultrasound-guided transthoracic biopsy was performed and revealed an active mucormycosis infection. With this case, we would like to emphasize the concept that diagnosis of pulmonary mucormycosis usually requires a biopsy of the affected site. Furthermore, for mechanically ventilated patients in the intensive care unit with peripheral subpleural lung lesions, ultrasound-guided transthoracic biopsy is a suitable diagnostic tool that is effective and safe if performed cautiously. ***(Thorac Med 2020; 35: 136-142)***

Key words: pulmonary mucormycosis, ultrasound-guided transthoracic biopsy

Introduction

Mucormycosis is a serious and potentially life-threatening fungal infection caused by a group of molds that belong to the class Zygomycetes, order Mucorales. It presents in a variety of forms including rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated disease. Pulmonary mucormycosis is the second most common presentation in patients with hematologic malignancy, diabetes mellitus, and hematopoietic stem cell/solid organ transplant [1-2]. Patients with pulmonary mucormycosis often present nonspecific symptoms such as fever, cough, and dyspnea. Owing to the low culture yield and the variety of chest computed tomography (CT) patterns, the diagnosis of pulmonary mucormycosis remains challenging. Here, we report a case of histology-proven pulmonary mucormycosis that was

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diagnosed by bedside ultrasound-guided transthoracic biopsy in a mechanically ventilated patient in a critical care setting.

Case Report

A 68-year-old man with a medical history of diabetes mellitus and thalassemia was hospitalized due to newly diagnosed acute myeloid leukemia. During the period of cytoreduction, he developed a fever with dyspnea and was intubated for pneumonia. The patient required mechanical ventilation for 1 week. Although he was weaned from mechanical ventilation successfully on the 17th day of admission, respiratory failure occurred again and he required reintubation on the 22nd day of admission. He was then transferred to the intensive care unit (ICU).

The patient was a heavy smoker and drinker. He had no relevant exposure history in his work as a businessman. Before reintubation and transfer to the ICU, his blood pressure was normal, but he had prominent sinus tachycardia (heart rate 128 beats per minute) and tachypnea (about 37 breaths per minute). He was febrile and was then treated with intravenous ceftazidime, tigecycline, inhaled colistin, and oral prophylactic co-trimoxazole.

The patient had diffuse rhonchi and crackles. Physical examination further revealed peripheral pitting edema and bilateral inguinal ecchymosis. Relevant serum analysis included a white blood cell count of 23.86 K/μL (with a differential of 85% blasts, 4% promyelocytes, 1% metamyelocytes, 1% neutrophils, 8% lymphocytes, 1% monocytes, 0% eosinophils, and 0% basophils), anemia with a hemoglobin level of 7.2 g/dL, and thrombocytopenia with a platelet count of 30 K/μL. Hemoglobin A1c was 7.9%. His ferritin level had increased to 6,347.6 ng/mL. The human immunodeficiency virus serologies were non-reactive. Furthermore, the galactomannan antigen test, cryptococcal antigen, Pneumocystis jirovecii sputum polymerase chain reaction results, and 3 consecutive sputum smears for acid-fast bacilli were all negative. All blood and sputum cultures yielded no growth.

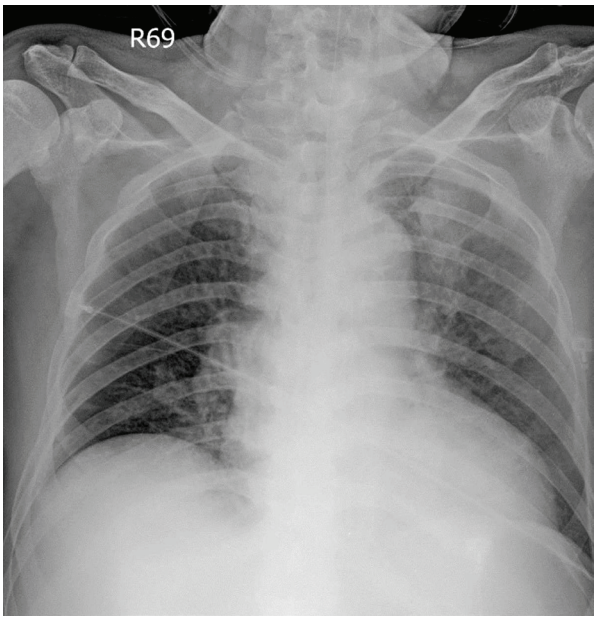

Fig. 1. Chest radiograph revealed a new ill-defined hazy opacity at the left upper lung.

A chest radiograph on the 22th day of admission (Figure 1) revealed a new ill-defined hazy opacity at the left upper lung (LUL), which was not seen 6 days before. Subsequent CT of the chest with contrast revealed a mass-like lesion at the LUL, measuring 5.7cm in diameter with internal low attenuating necrosis and focal air-densities, suggesting abscess formation (Figure 2). Furthermore, a small left-sided pleural effusion was also found.

Due to his worsening condition, the patient was treated with intravenous voriconazole (400 mg every 12 h×2 doses, then 200 mg every 12 h) empirically. A bedside ultrasound-guided trans-

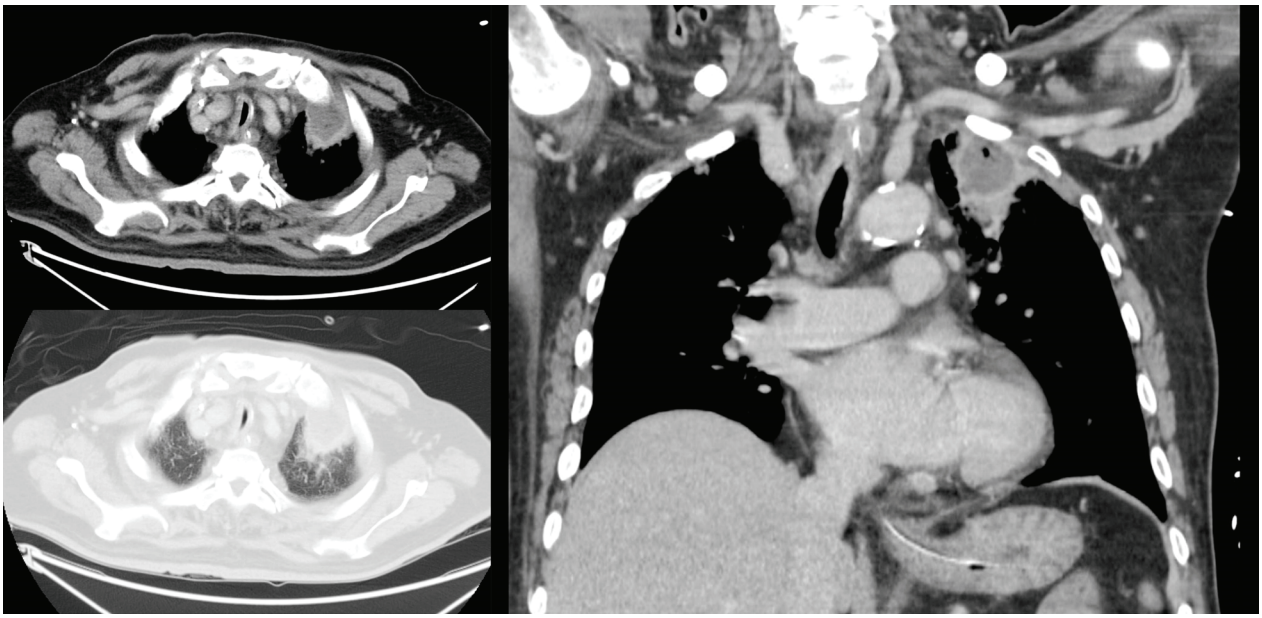

Fig. 2. CT of the chest revealed a mass lesion at the LUL, measuring 5.7cm in diameter with internal low attenuating necrosis and focal air-densities. Also, a small amount of left-sided pleural effusion was found.

thoracic biopsy was performed immediately after ICU transfer the next day (the 23rd day of admission). Histopathological examination of the biopsy specimen showed the presence of extensive necrosis with hyphae in the necrotic background. The hyphae were large and lacked septa, suggestive of mucormycosis active infection (Figure 3). The organism did not grow on echo-guided biopsy culture for species identification.

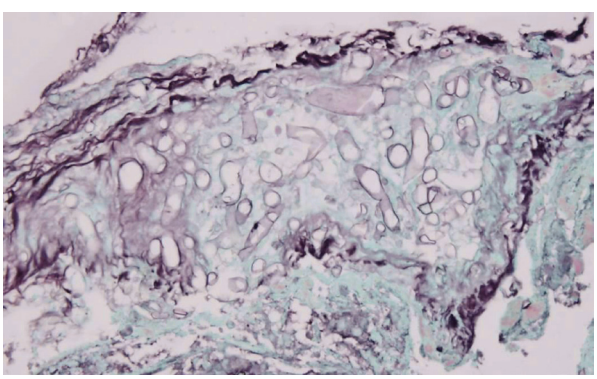

Fig. 3. Histopathological examination of the lung biopsy specimen revealed extensive necrosis with hyphae in the necrotic background, highlighted by periodic acid-Schiff (PAS) and Grocott's methenamine silver (GMS) stains. The hyphae were large and lacked septa, and were morphologically highly suggestive of Mucorales.

Because pulmonary mucormycosis was suspected, voriconazole was discontinued and the patient was started on intravenous liposomal amphotericin B (400mg every 24 h, 5mg/kg) on the 26th day of admission. Surgical resection for a LUL lesion and tracheostomy were also arranged 2 days later. However, an unexpected desaturation with severe respiratory acidosis developed during the operation. Intraoperative bronchoscopy was then performed immediately and revealed a great deal of blood that was suspected to be infection-related had emerged from the LUL apical segment. Although the bleeding episode resolved on its own, the surgical resection was held due to the patient's unstable condition.

The patient underwent operation again on the 34th day of admission, and a left upper lobectomy using video-assisted thoracic surgery was performed smoothly (Figure 4). The pa-

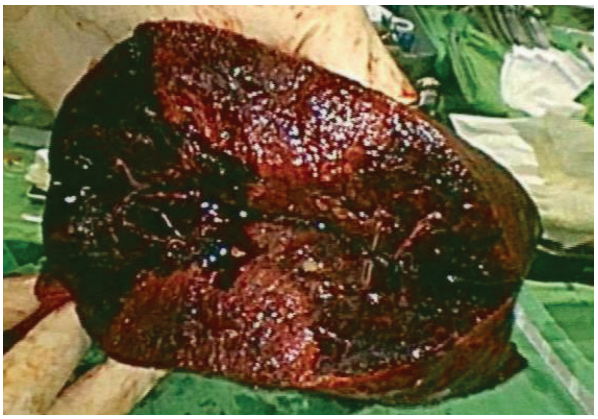

Fig. 4. A gross specimen, pink-red and soft, from the LUL lobectomy. On cutting, a red-brown necrotic nodule, measuring 5.5cm×5.5cm×3.2cm in size, was found. The remaining lung parenchyma was congested and focally hemorrhagic.

thology report confirmed the diagnosis of pulmonary mucormycosis with leukemia involvement. Cultures from the left upper lobe were positive later for a Rhizopus species. To assess the disease extent thoroughly, a CT scan of the head and sinuses was performed, and revealed no concomitant nasal, sinus, orbital, or cerebral involvement.

Despite early treatment and extensive life support, the patient's condition deteriorated during the next few days, including the development of multiple organ failure, presumably due to ventilator-associated pneumonia and septic shock caused by enterococcal bacteremia. On the 41st day of admission, the patient's family asked to discontinue all life-sustaining measures and turn to palliative care. The patient passed away a few hours later.

Discussion

Mucormycosis is a fungal infection caused by fungi of the order Mucorales. They are ubiquitous in nature and can be found in the soil and on decaying vegetation. Species in the Mucor, Rhizopus, Absidia, and Cunninghamella genera are most often found in human infections. Common risk factors for developing mucormycosis include uncontrolled diabetes mellitus, ketoacidosis, hematologic malignancies, renal insufficiency, treatment with glucocorticoids or immunosuppression, hematopoietic cell/solid organ transplantation, iron overload, and treatment with deferoxamine [1]. Recent studies have shown an increasing incidence of these infections, especially in patients with hematologic malignancies [2]. The increasing incidence was not related to the prior use of voriconazole; rather, it was probably associated with an increasing number of patients who had an underlying hematologic malignancy [3].

Mucormycosis manifests clinically in a variety of organs. Of all manifestations, rhino-orbital-cerebral and pulmonary infections are the most common. Pulmonary mucormycosis was first described in 1876 by Furbringer [4]. It is a rapidly progressive disease with a very high mortality rate of up to 40-76% [5-6]. The most common presenting clinical findings are fever, neutropenia, dyspnea, cough, chest discomfort, and hemoptysis. The progression of mucormycosis is rapid. Erica *et al*. reported a retrospective study conducted at Mayo Clinic between 2000 and 2015 that enrolled 35 patients with pulmonary mucormycosis. The majority were hematologic, with 16 cases of leukemia (45.7%), 8 cases of lymphoma (22.9%), and 7 cases with diabetes mellitus (20%). About 22.9% of patients needed acute mechanical ventilation, and there was no statistically significant association between mortality and need for mechanical ventilation [7].

The radiological manifestations of pulmonary mucormycosis differ, with the most common being solitary nodules/masses, focal

consolidations, cavitating lesions, and ground glass infiltrates. A previous study reported that the lesions are often peripherally located and upper lobe predominant [8]. In addition, there is a high frequency of pleural effusion (60-77%) [7, 9], which is usually absent in patients with pulmonary aspergillosis. The halo sign, reversed halo sign, and central necrosis/abscess formation within the cavitation were also found in some cases. The presence of a reversed halo sign, defined by a focal round area of ground-glass attenuation surrounded by a ring of consolidation, was highly suggestive of pulmonary mucormycosis. In a retrospective study that included 189 patients with proven or probable fungal pneumonia, the reversed halo sign was seen in 7 of 37 patients with pulmonary mucormycosis (19%), 1 of 132 patients with invasive aspergillosis (<1%), and in none of 20 patients with fusariosis [10]. In another study, the reversed halo sign was found in 15 of 16 (94%) leukemia patients with pulmonary mucormycosis, when chest CT was performed in the first week [6]. As for central necrosis, Choo *et al*. reported that the pattern appeared more frequently in follow-up CT than in initial CT [11]. Nam *et al*. observed that the majority of patients with pulmonary mucormycosis had sequential morphologic changes on serial CT follow-ups, and central necrosis often evolved from a consolidation or nodule/mass with a halo or reversed halo sign [9]. Our patient did not present with the typical reversed halo sign but rather a huge mass with central necrosis and abscess formation. This pattern was described in a previous study [9], and it might be explained by the late chest CT scan arranged at that time.

Early and accurate diagnosis of pulmonary mucormycosis is very important, because a delay in treatment potentially results in a very poor outcome. Histopathological examination of biopsy specimens remains the mainstream method to diagnose pulmonary mucormycosis, which is characterized by the presence of broad (6-16 μm) non-septated hyphae branching at right angles. Cultures of sterile biopsy tissue with abundant Mucorales hyphal growth can also have positive results; however, diagnostic sensitivities were low and the yield rate was less than 50% [12-13]. Serological tests of (1-3)-β-D-glucan or galactomannan antigen are often negative and have no diagnostic value. Pleural effusion and sputum culture have poor diagnostic sensitivities, and only a few cases have been reported [7-8]. Although mucormycosis is an angio-invasive fungal infection, blood cultures usually produce negative results. Documented mucormycosis fungemia is very rare, and only 5 cases have been reported up to this time [14-18]. Overall, the methods used most commonly to reach a diagnosis were fiberoptic bronchoscopy, transthoracic needle aspiration, and open lung biopsy. All bronchoscopy specimens, including those obtained through bronchoalveolar lavage (BAL), bronchial washing, bronchial brushing, and endobronchial/transbronchial biopsy, have roles in the diagnosis, but have different success rates [19-20]. If patients suffer from severe thrombocytopenia, bronchial brushing or biopsy may not be feasible, and BAL may be the more suitable modality. A previous study reported that BAL was diagnostic in 3 of 5 patients (60%) with pulmonary mucormycosis, with typical hyphae identified in the BAL fluid [19].

Pulmonary mucormycosis was diagnosed in our patient by real-time ultrasound-guided transthoracic biopsy rather than bronchoscopy. The reason we chose ultrasound-guided transthoracic biopsy is that the patient had prominent

hypoxic respiratory failure and a high demand for oxygen. Furthermore, the LUL lesion was located in the subpleural region, which is difficult to approach with bronchoscopy.

Ultrasound-guided transthoracic biopsy is rapid, convenient, and easily available compared with CT-guided lung biopsy in the ICU setting. Also, it avoids the need for radiation exposure. Considering safety, the risk of pneumothorax and fatal hemoptysis is acceptable, and can be minimized by avoiding puncturing the normal aerated lung tissue and adjacent blood vessels through using real-time image guidance techniques.

The recommended treatment for pulmonary mucormycosis includes antifungal therapy, surgery, and control of underlying conditions. A multidisciplinary approach is required, and both early initiation of amphotericin B and early surgical treatment greatly reduced mortality [1, 6, 8]. Surgical treatment in conjunction with antifungal therapy has been shown to significantly improve survival when compared with antifungal therapy alone in patients with pulmonary mucormycosis. A review of cases of pulmonary mucormycosis showed that the mortality rate in patients who received antifungal agents and surgery was 27% versus 55% in patients who received antifungal agents alone [1]. In our patient, although surgical debridement of infected tissue was performed on an urgent basis, hyphal invasion of blood vessels caused unexpected massive hemorrhage and interfered with the surgical procedure; the patient then needed to undergo a second operation. In spite of aggressive care and treatment, the patient had an unfavorable outcome. Treatment failure could be attributed to the underlying refractory neutropenia.

In conclusion, the diagnosis of pulmonary mucormycosis is challenging. There are varied radiographic patterns, and sputum and blood cultures usually yield false negative results; therefore, biopsy of the affected site is needed. For mechanically ventilated critical patients, those for whom CT-guided or transbronchial biopsy is usually not feasible, real-time ultrasound-guided transthoracic biopsy is an effective and safe diagnostic tool when performed cautiously.

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Where is the Subcarinal Lymph Node? Case Report of Bronchial Obstruction Due to Broncholithiasis

Lu-Chia Lee[1], Jen-Jyh Lee[1,2], Po-Pin Cheng[1], Chih-Bin Lin[1,2]

Broncholithiasis is an uncommon airway disease. It presents as calcified material in or adjacent to the tracheobronchial trees due to extrusion and erosion of the calcified lymph nodes into the airway. Calcified lymphadenitis due to mycobacterial infections is the most important cause of broncholithiasis, and may lead to airway obstruction. Here, we reported a patient who had calcified subcarinal lymph nodes 3 years ago on chest computed tomography. She was admitted to our hospital this time with the finding of calcified lymphadenitis in the left main bronchus, causing obstruction. The calcified lymphadenitis was successfully removed by flexible bronchoscopy, with basket. ***(Thorac Med 2020; 35: 143-146)***

Key words: bronchial obstruction, broncholithiasis, calcified lymph node, bronchoscopic extraction

Introduction

Broncholithiasis is defined as the presence of calcified material in the lumen of the tracheobronchial tree, emanating mostly from the mediastinal lymph nodes, that erodes into the airway, causing obstruction and inflammation. In Taiwan, pulmonary tuberculosis (TB) is among the most common etiologies of broncholithiasis [1]. The most common radiographic findings are the presence of a calcified nodule causing airway obstruction, such as atelectasis, bronchiectasis, or air trapping [2]. Most common clinical presentations include chronic cough (100%), fever (50%-60%), hemoptysis (45-50%), localized wheezing (25-60%), chest pain (20%), and stone expectoration (15-26%) [3]. Other rare complications, such as recurrent pneumonia, massive hemoptysis and fistulas between the bronchi [8] and adjacent mediastinal structures [9], have been reported [4]. We report here a case of broncholithiasis caused by erosion of subcarinal lymph node calcification into the left main bronchus (LMB) that was extracted by flexible bronchoscopy.

Case Presentation

This 65-year-old female patient was referred to our hospital because of chronic cough

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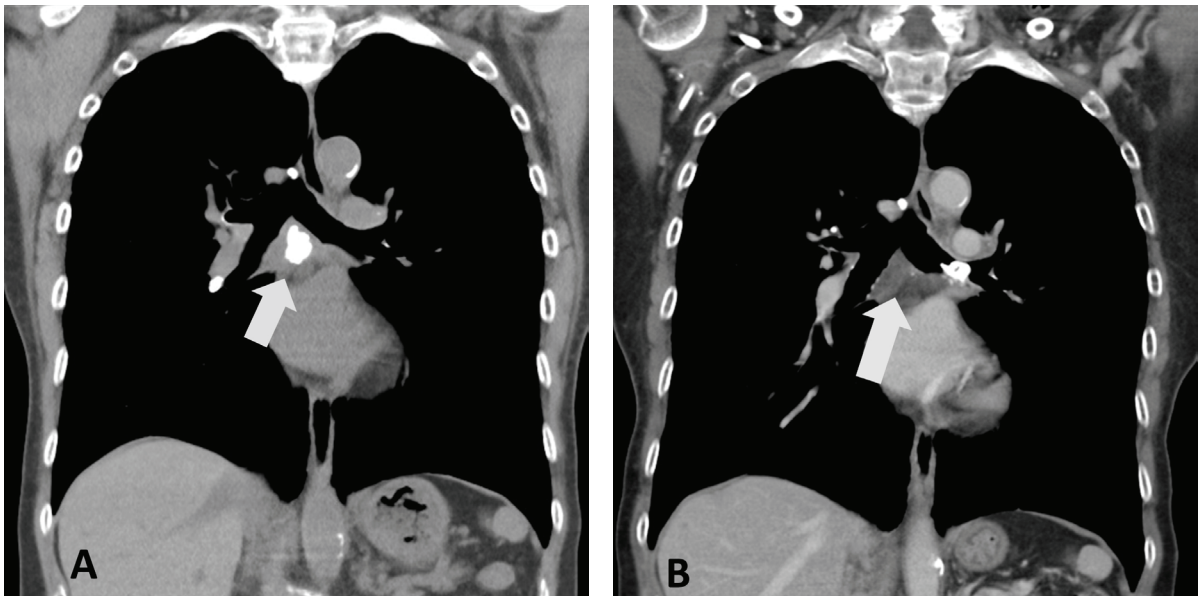

Fig. 1. A. Presence of subcarinal lymph node calcification on chest CT 3 years prior to this hospitalization; B. Disappearance of the subcarinal calcification during this hospitalization.

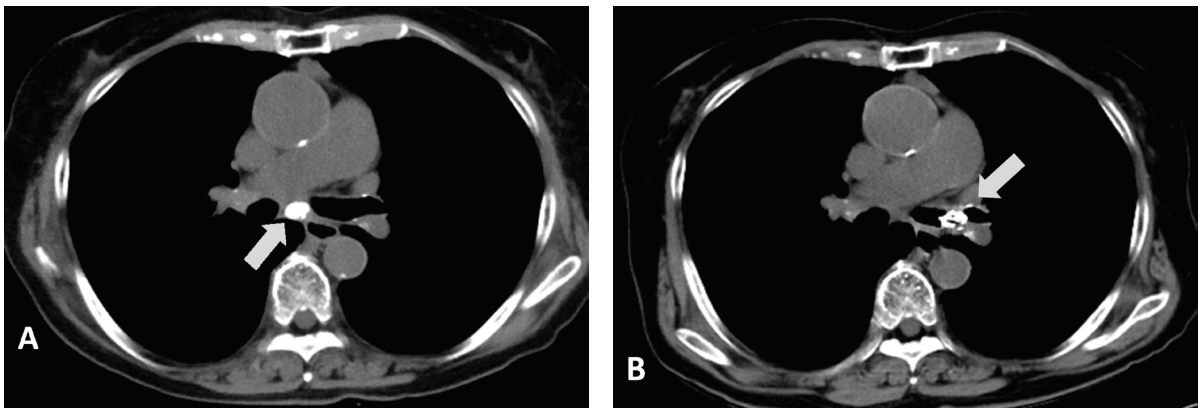

Fig. 2. A. Calcified subcarinal lymphadenopathy on chest CT 3 years ago. B. Broncholithiasis obstructing the left main bronchus during this hospitalization.

for 2 years. The cough had aggravated in the past 3 weeks with new symptoms of localized left-side wheezing and dyspnea. The patient had a previous history of pulmonary TB and regular follow-up at a local clinic. She also had a history of intermittent cough with hemoptysis 3 years prior to this referral that subsided gradually after symptomatic treatment.

The chest radiography (CXR) and computed tomography (CT) of the patient from the referral hospital showed a radiopaque lesion at the LMB, with no calcified mediastinal lymph nodes at the subcarinal area (Figure 1). The chest CT of this patient 3 years ago revealed a calcified lymph node at the subcarinal area, with no evidence of abnormal findings at both bronchial trees and the lung parenchyma (Figure 2).

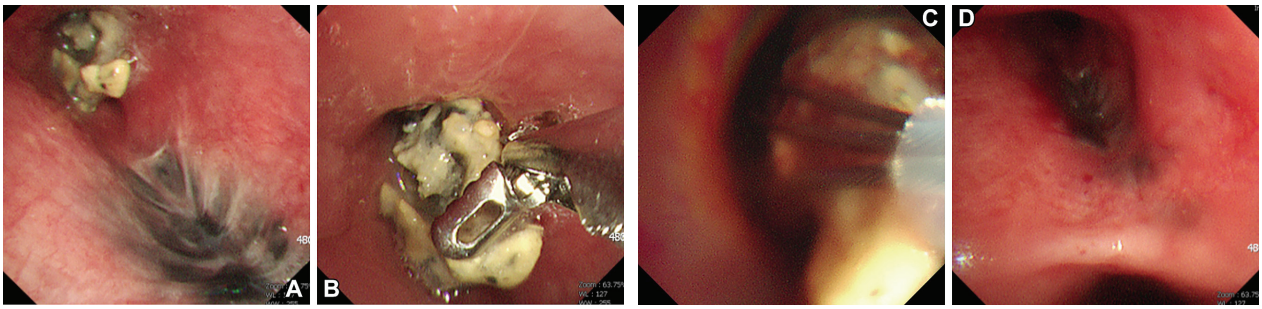

Fig. 3. A. Foreign body obstructing the left main bronchus, from flexible bronchoscopy. B. Failed removal of the broncholithiasis by forceps. C. The broncholith was removed by basket. D. Absence of a broncholith after removal, with the presence of anthacotic-fibrotic mucosa at the medial side of the left main bronchus.

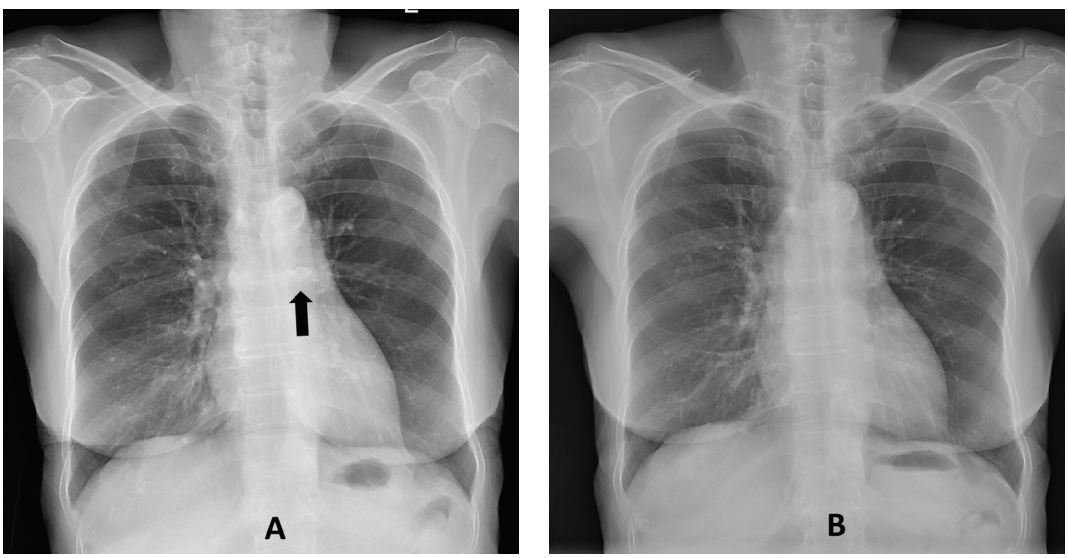

Fig. 4. A. Before therapeutic bronchoscopy, a tiny radiopaque lesion at the left main bronchus. B. After therapeutic bronchoscopy, the broncholith vanished from the chest radiography.

Flexible bronchoscopy was performed after hospitalization, revealed the impacted white-grey and irregular-shaped material at the distal portion of the LMB. The broncholithiasis was mobile during the removal procedure using forceps, and then a basket for retrieval was successfully implemented (Figure 3). The procedure was smoothly completed without any complications. At the proximal and medial aspect of the LMB, the mucosa revealed an anthracotic, fibrotic and irregular surface that must have been the site where the calcified material entered the tracheobronchial tree (Figure 3). The CXR before and after therapeutic bronchoscopy showed an obviously vanished radiopaque lesion at the LMB (Figure 4).

Discussion

Broncholithiasis is defined as the presence of calcified material in the lumen of the tracheobronchial tree. The etiology of the majority of broncholiths is erosion of the adjacent calcified peribronchial lymph nodes into the lumen, and the causes of these calcifications are relatively different: TB, histoplasmosis, actinomycosis,

coccidioidomycosis, cryptococcosis, non-TB mycobacterium and fungus. Other causes include aspiration of bone tissue, in situ calcification of a foreign body, and calcified cartilage extruding and becoming sequestrated inside the bronchial tree [4].

The clinical presentations of the patient are related to the degree of inflammation and obstruction of the adjacent structures. Chronic cough, purulent phlegm, hemoptysis, chest pain and fever are common. Lithoptysis -- expectoration of bronchial stones -- also can occur in some cases [5-6]. Our patient presented with chronic cough and wheezing as symptoms of the obstruction.

CXR and chest CT usually can identify the calcified lesion "in" the tracheobronchial tree or in the adjacent structure, causing parenchymal infiltrates such as atelectasis, bronchiectasis, expiratory air trapping and mucoid impaction [2]. Our patient presented with calcified mediastinal lymphadenopathy in her previous chest CT, but 3 years later, during this hospital visit, her chest CT revealed the disappearance of the calcified subcarinal lymph node and the presence of a new calcified foreign body at the LMB.

The management strategy for broncholithiasis can be divided into conservative, bronchoscopic removal and surgical resection [4]. Use of bronchoscopic broncholithectomy is not suggested initially, due to a concern about complications, including bleeding, displacement of the broncholith causing obstruction, or iatrogenic creation of a fistula [4]. Flexible bronchoscopy is considered the most important diagnostic test for broncholithiasis, but it is indicated only for cases with loose and movable broncholiths, and removal by extraction [7]. Surgery is reserved for those symptomatic patients for whom the airway obstruction cannot be relieved by flexible bronchoscopy. However, some complications may occur during and after surgical intervention, such as pulmonary artery laceration during operation, hemothorax and empyema after surgery [4]. In our patient, removal of the endobronchial calcification from the LMB using flexible bronchoscopy with a basket was successful (Figure 3).

In conclusion, we reported a case of broncholithiasis caused by erosion of subcarinal lymph node calcification into the LMB, causing airway obstruction. The calcified lymphadenitis was extracted successfully by flexible bronchoscopy. From this case, we learn that if a patient has a history of TB with a calcified lymph node at the mediastinum, and there are symptoms of aggravating cough, dyspnea, a suspicious airway obstruction, or obstructive pneumonia, broncholithiasis should be a concern.

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A Case of Granulomatosis with Polyangiitis Presenting with Bronchus Ulceration

Cheng-Te Wang, Ching-Yao Yang

Granulomatosis with polyangiitis (GPA), formerly known as Wegner's granulomatosis, is a form of systemic vasculitis that involves primarily the upper and lower airways and the kidneys. The most frequent airway manifestations include subglottic stenosis and inflammation, and tracheal and bronchial stenosis, while ulcerations in tracheobronchial mucosa are uncommon findings. Here, we reported the case of a 77-year-old man who presented with cough, hemoptysis, and progressive joint pain in all 4 limbs for about 2 months, accompanied with intermittent low-grade fever in the evening for 2 weeks. Bronchial ulcerations were found by bronchoscopy, and biopsy yielded a non-specific granulomatous inflammation without positive staining for relevant pathogens. Due to a contact history with tuberculosis patients and unresolved fever despite antibiotics treatment, the tracheobronchial granulomatous inflammation was diagnosed as tuberculosis at first. However, his symptoms did not improve in spite of empirical anti-tuberculosis antibiotics treatment. Later, other symptoms developed, including otitis media and acute glomerulonephritis, which manifested with hematuria and acute kidney injury. The serological test revealed elevation of cytoplasmic antineutrophil cytoplasmic antibodies. Thus, the patient was diagnosed with GPA with airway, ear, and kidney involvement. After immunosuppressive therapies with cyclophosphamide and glucocorticoid for GPA, his symptoms improved, and the follow-up bronchoscopy showed resolution of the bronchial ulcerations. ***(Thorac Med 2020; 35: 147-151)***

Key words: granulomatosis with polyangiitis, bronchus ulceration, endobronchial tuberculosis

Introduction

Granulomatosis with polyangiitis (GPA), (formerly known as Wegener's granulomatosis) is a form of systemic vasculitis that involves primarily the upper and lower airways and the kidneys [1]. GPA occurs mostly in older age adults; there is no sex preference and the disease is much more commonly seen in Caucasians [2]. The most frequent airway manifestations include subglottic stenosis and inflammation, and tracheal and bronchial stenosis; ulcerations in the tracheobronchial mucosa are uncommon findings [3]. Constitutional but non-specific symptoms of GPA include fever, migratory arthralgia, malaise, anorexia, and weight

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loss [4]. Common airway symptoms of GPA include cough, hemoptysis, stridor, sibilant rales, and dyspnea [5-6].

Granuloma formation could be seen as a pathological presentation of GPA, and might also be found in other diseases, such as tuberculosis (TB) infection and fungal infections, and granulomatous non-infectious diseases, including sarcoidosis, Crohn's disease, and rheumatoid arthritis [7]. Here, we report a patient with GPA presenting with uncommon bronchus ulcerations, which was misdiagnosed as TB infection initially.

Case Report

This 77-year-old man presented to our clinic with cough, hemoptysis, and progressive joint pain in all 4 limbs for about 2 months. Intermittent low-grade fever in the evening for 2 weeks was also reported.

Laboratory data showed no leukocytosis as a sign of infection. Neither thrombocytopenia nor coagulopathy was noted as a reason for hemosputum. Renal function and liver function tests were normal. Chest x-ray (CXR) and chest computed tomography (CT) revealed no active lung lesions, such as tumor or infection (Figure 1). Sputum acid-fast stains were negative for 3 sets. Bronchoscopy was then performed for surveillance of hemoptysis, and revealed ulceration at the right main bronchus; no other abnormality was noted (Figure 2). Biopsy of the ulceration was then done. Pathology disclosed some granuloma formation with multi-nucleated giant cells; there were no acid-fast stain-positive bacilli or Grocott's methenamine silver stain pathogens.

Although there was no microbiological evidence, TB infection was still highly suspected because of the patient's contact history (his son-in-law had TB pleurisy), the symptoms of body weight loss and night sweating, and a positive interferon-gamma release assay (IGRA). Anti-TB medications (isoniazid 300 mg per day, rifampin 600 mg per day, ethambutol 1,200 mg per day, pyrazinamide 1,500 mg per day) were empirically administered. However, another fe-

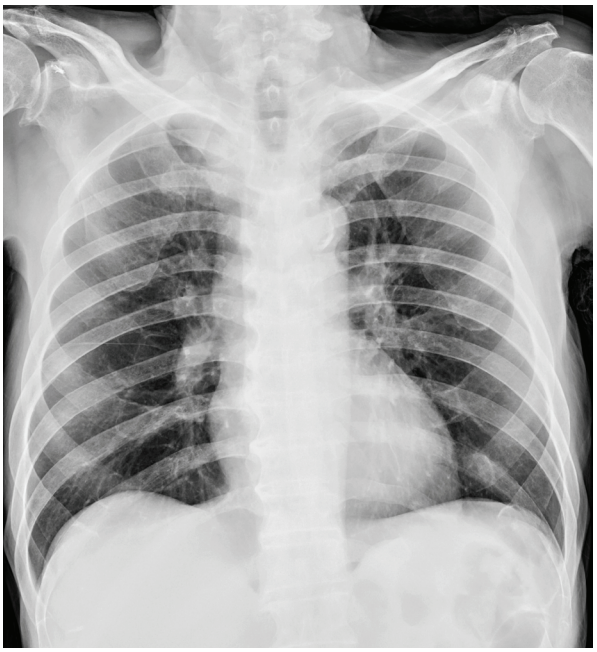

Fig. 1. CXR of the patient, which showed no remarkable findings.

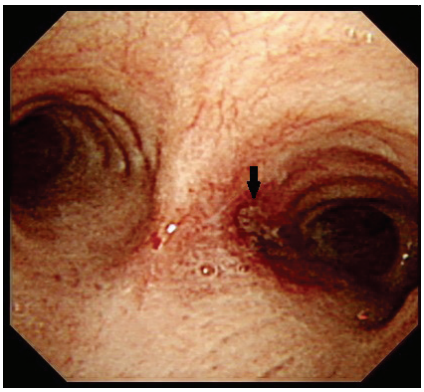

Fig. 2. Flexible bronchoscopy revealed an ulceration at the patient's right main bronchus (the ulcer is marked by an arrow).

ver spike was noted despite 10 days of anti-TB treatment. Fluorodeoxyglucose-positron emission tomography (FDG-PET) was performed for a suspected malignancy work-up, and revealed no malignant tumor; however, a hot spot was found at the left Eustachian tube, which was diagnosed as otitis media. Augmentin was then prescribed.

Six weeks later, an episode of acute nephritis developed, as manifested by an elevation of serum creatinine to 2.4mg/dL, and hematuria, as revealed by urinalysis (dysmorphic red blood cells (RBC) and ≧100 RBC/high power field). Work-up of the glomerulonephritis showed elevation of cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) (73.97 IU/ml). GPA was diagnosed based on all the clinical pictures and serological evidence, though there was no pathological proof. Cyclophosphamide (400mg infusion once) and methylprednisolone (10mg IV Q8H) were administered, and his symptoms of fever, cough, hemoptysis, otitis media and glomerulonephritis improved gradually. Bronchoscopy follow-up about 1 year after treatment revealed the ulceration at the right main bronchus had recovered completely (Figure 3).

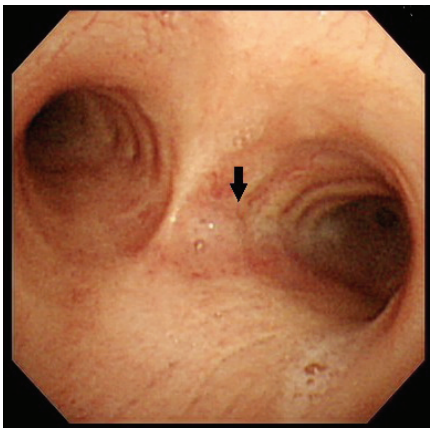

Fig. 3. Flexible bronchoscopy follow-up revealed the ulceration at the patient's right main bronchus had healed (the healed ulcer is marked by an arrow).

Discussion

In this case, since the patient had a contact history and the symptoms of body weight loss, hemoptysis, and night sweating, a positive IGRA assay, and granulomatosis formation in the bronchial ulcer pathology, he was diagnosed initially as having TB infection. However, once otitis media and glomerulonephritis had developed, GPA was finally diagnosed with the elevated C-ANCA. His symptoms improved and the bronchial ulceration recovered after cyclophosphamide and corticosteroid administration. In our review of related articles, we found that GPA was seldom manifested with bronchus ulceration, but mostly with subglottic stenosis [3], so we share this rare case.

GPA was first described in 1936 [8] as characterized by granulomatous inflammation and necrotizing vasculitis involving mainly the small arteries, arterioles, capillaries and venules of the upper and lower airways and the kidneys [4]. The condition could be limited to the respiratory system without affecting the renal system, and was referred to as limited GPA, which is seen in 25% of patients [9]. One of the major characteristics of GPA is involvement of the airways, which is reported to occur in 15%-55% of patients and cause cough, hemoptysis, stridor, sibilant rales, and dyspnea as common symptoms [5-6]. The manifestations of GPA in the respiratory tract include nasal stenosis, tracheal and bronchial stenosis, granulomatous nodules and masses, alveolar infiltrates and cavities [10-11]. In our case, the patient presented with right main bronchus ulceration.

Pulmonary infiltrates and nodules are the most common radiologic findings of GPA (67%

and 58%, respectively). The nodules are usually multiple, bilateral and with cavitation in approximately 50% of cases. In 43%-63% of patients, chest CT reveals infiltrates and nodules not observed on conventional chest plain film. Ground glass opacity and consolidation were found in up to 50% of patients. Nevertheless, there are also some less frequent manifestations, including pleural effusion (5%-20%), mediastinal masses, and enlarged lymph nodes, usually in association with parenchymal infiltrates [4]. In our case, there were none of the above radiologic findings.

There have been a few large studies on endoscopic findings of GPA by bronchoscopy examination. For instance, Cordier et al. reported that 41 (55%) of 74 patients who underwent bronchoscopy showed abnormal findings. The findings included bronchial stenosis (13 patients), ulcerations or pseudo-tumor (7 patients), inflammatory lesions without stenosis (10 patients), isolated hemorrhage (10 patients), and isolated purulent secretions (1 patient) [12].

In our case, pathology of the bronchial ulceration reported granuloma formation, which was suspected to be TB infection at first, and then turned out to be GPA. Granulomatous reactions are seen in a wide variety of diseases, both infectious, such as mycobacteria, fungi, and parasites, and non-infectious, such as sarcoidosis, Crohn's disease, GPA, rheumatoid arthritis, drug reactions and foreign body aspiration. In countries with a high incidence of TB, the initial consideration in the differential diagnosis of granulomatous diseases is usually TB, so detailed history-taking and physical examination should be included for the differential diagnosis [7].

Since our patient was suspected of having endobronchial TB (EBTB) infection, we also reviewed relevant articles. EBTB seems to be predominant in females 20-30 years old [13-14]. However, van de Brande *et al*. reported EBTB in an elderly population with a mean age of 70 years [15]. Symptoms of EBTB include productive cough, chest pain, hemoptysis, lethargy, fever and dyspnea. Clinical manifestations are heterogeneous, and can include a focal wheeze and decreased air entry on auscultation [13]. As long as the symptoms and signs are non-specific, and despite clinical suspicion, the diagnosis of EBTB should be based on a combination of clinical findings, radiology and sputum/tissue analyses.

Unless there is remarkable airway obstruction that induces atelectasis of the distal pulmonary segment, or concurrent parenchymal or pleural disease, CXR of EBTB patients may seem normal. Chest CT would disclose more detail, such as irregularities or stenosis of the airways, as well as other features of TB in the chest such as mediastinal lymphadenopathy, nodules, cavities and pleural effusion [16]. In our case, there was no significant finding on CXR or chest CT.

Contrary to clinical expectations, sputum analysis in EBTB has a variable diagnostic yield, with reports ranging from 17-79% if combined with specimens obtained via bronchoscopy [17-18]. Possible reasons for this include the lack of ulceration in the mucosal wall of the bronchus, or difficulties in expectoration [19].

Although any part of the tracheobronchial tree can be affected, EBTB tends to impact mainly the right upper and right main bronchi [17]. Differences in endoscopic appearances have been described as the following: actively caseating, edematous-hyperemic, fibrostenotic, tumorous, granular, ulcerative and nonspecific

bronchitis [19].

Different subtypes have different clinical outcomes. On analyzing bronchial lavage fluid samples, the granular subtype appeared to yield the highest smear and culture positivity for *Mycobaterium tuberculosis*, whereas both tests were negative for the fibrostenotic and nonspecific subtypes [20]. The presence of caseating granulomas or acid-fast bacilli would confirm the diagnosis of EBTB.

In conclusion, in the clinical case that came to our attention, bronchial ulceration was highly suspected to be TB infection at first, then turned out to be a manifestation of GPA, which then healed after cyclophosphamide and corticosteroid administration.

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