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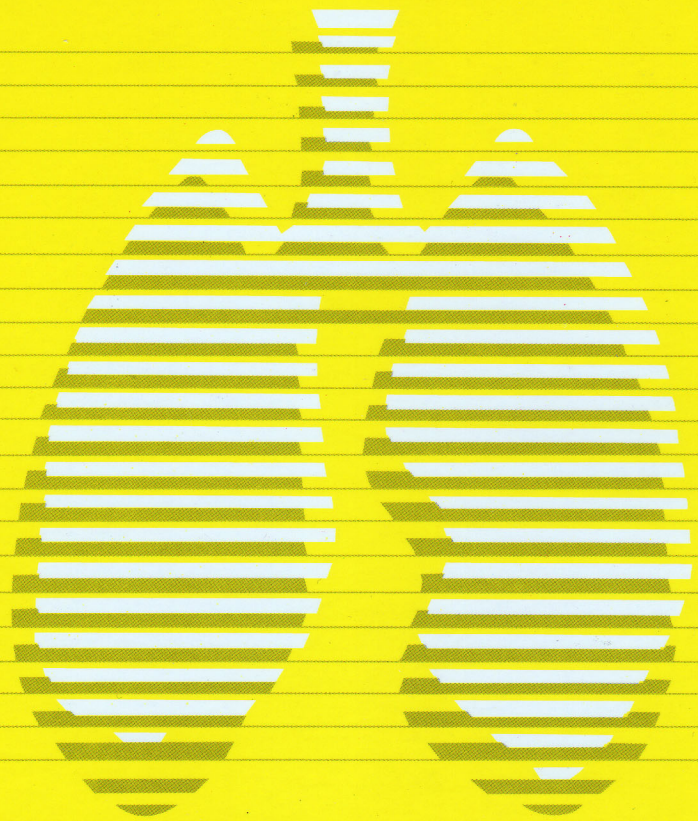

台灣胸腔暨重症加護醫學會

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Orginial Articles

Case Reports

Correlation of the New GOLD Classification (2013 Version) with Exercise Capacity and Mortality Risk

Po-An Chou*, Nai-Ying Kuo**, Ching-Wan Tseng**, Chin-Chou Wang*,**, Chien-Hung Chin**,***, Meng-Chih Lin*,**,***, Shih-Feng Liu*,**,***

Background and Objective: The new GOLD guideline published in 2013 recommends assessing the severity of COPD by a combination of FEV_1, symptom scoring, and exacerbation frequency. The objective of this study was to compare the association of COPD severity stratification with exercise capacity and mortality using both the old and the new GOLD guidelines.

Methods: The correlations of the 6-minute walking distance (6MWD) and mortality rate with different COPD staging methods (the old and new GOLD classifications) were compared in a cohort of 114 clinically stable COPD patients.

Results: Patients were initially stratified into stage I (17 patients, 14.9%), stage II (36 patients, 31.6%), stage III (50 patients, 43.9%), and stage IV (11 patients, 9.6%) using the old GOLD classification system. Using the new GOLD classification, they were re-grouped into group A (29 patients, 25.4%), B (21 patients, 18.4%), C (14 patients, 12.3%), and D (50 patients, 43.9%). Age, gender, body mass index, and cigarette pack-years showed no significant difference among the groups and stages. There was a significant difference in the 6MWD between groups A and D (447.5 vs. 361.9 meters, p=0.003) and stages I and III (477.1 vs. 365.9 meters, p=0.001). The Kaplan-Meier method showed that the new GOLD classification was associated with mortality risk (p=0.02), but not the old GOLD classification (p=0.58).

Conclusions: The new GOLD classification is better than the old one in the estimation of exercise capacity and 2-year mortality risk in stable COPD patients. ***(Thorac Med 2014; 29: 263-271)***

Key words: GOLD classification, 6-minute walking distance, mortality, exercise capacity, COPD

Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by poorly reversible airflow limitation [1]. It is widely accepted that forced expiratory volume

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in 1 second (FEV_1) is essential for the diagnosis and quantification of respiratory impairment in COPD [1-3], and that the rate of decline in FEV_1 can be used as a surrogate of disease progression [4-6]. However, FEV_1 does not adequately reflect all aspects of the disease in our clinical practice. For example, the change in FEV_1 does not correlate with health status [7], and the FEV_1 level poorly correlates with the dyspnea scale [8]. The degree of dyspnea is also superior to FEV_1 in association with health-status scores [9] and the risk of death [1]. Therefore, a multidimensional grading system called the BODE index, including the body-mass index (B), the degree of airflow obstruction (O), dyspnea (D), and exercise capacity (E, measured with the 6-minute walking test), was developed for systemic evaluation of COPD severity [10]. Current investigations also support the BODE index as a better measure than FEV_1 in predicting all-cause mortality among patients with COPD [10].

The 2013 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline update, first announced at the 2011 Asia-Pacific Society of Respirology annual international meeting, regarded FEV_1 as an unreliable marker of breathlessness, exercise limitation, and health status impairment, and suggested integrating FEV_1, symptom scoring, and future risk of acute exacerbation into a stratification of COPD severity [11]. Whether such an assessment is useful in predicting mortality risk or exercise capacity remains unclear. This study aimed to compare the difference in the mortality rate and 6-minute walking distance (6MWD) between corresponding COPD stages using the old and new GOLD guidelines, in the hope of providing clinical evidence for better evaluation of COPD.

Methods

This study was approved by the institutional review board of Chang Gung Memorial Hospital (IRB number: 94-319). Funds were also provided by Chang Gung Memorial Hospital (CMRPG840421). The aim of the study was to compare the differences in the 6MWD and mortality using the new and old GOLD stages. Between April 2005 and July 2006, a cohort of COPD patients with wide-ranging symptom severity was enrolled from the outpatient clinic of the Division of Pulmonary Medicine in Chang Gung Memorial Hospital-Kaohsiung Medical Center, a 2300-bed facility that serves as a primary care and tertiary referral center in Taiwan. These patients underwent spirometry and lung volume measurements according to the recommendations of the American Thoracic Society and other standard references [12]. The inclusion criteria for COPD patients were as follows: more than 40 years old, a smoking history of more than 10 pack-years, a ratio of post-bronchodilator FEV_1 to forced vital capacity less than 0.7, and poor reversibility with inhaled bronchodilator (increase in FEV_1 less than 200 ml and 12% of pre-bronchodilator level) [1]. The old GOLD classification was used following the 2010 GOLD guideline update, and the new classification referred to the 2013 GOLD update [11]. All COPD patients were in stable condition, which was defined as no exacerbation for more than 6 weeks. Patients who experienced an exacerbation of COPD (e.g., fever, increased purulent sputum, or dyspnea) or who were hospitalized for any reason in the most recent 6 weeks were excluded from this study. Other comorbidities with probable correlation to airflow limitation, such as pulmonary tuberculosis, bronchial asthma, bronchiectasis, and

heart failure, were excluded.

After enrollment, the patients received follow-up every 3 months for 2 years, and data were recorded at the same time. Basic characteristics (Table 1), including BODE index and spirometry results, were collected at the initial presentation. Data collections at follow-up were not unified, and were dependent on clinical requirements for disease evaluation. If a patient were lost to follow-up, the research assistant would make contact with the patient or his/her family members and acquire information about any mortality by telephone interview. The 6MWD was used to evaluate exercise capacity, and all-cause mortality during the follow-up period was used as the outcome measure separately.

Table 1. Basic Clinical Characteristics of the 114 Patients with Stable Chronic Obstructive Pulmonary Disease

Characteristic	Mean ± SD
Age (yr)	69.6 ± 10.3
Male (%)	111/114 (97.4)
Smoking history (pack-yr)	57.6 ± 31.9
Current smoking status (%)	37/114 (32.5)
Body-mass index (BMI)[§]	23.5 ± 3.6
FVC (% of predicted value)	71.6 ± 19.2
FEV_1/FVC (%)	54.0 ± 11.5
FEV_1 (% of predicted value)	53.2 ± 21.4
Old GOLD stage I/II/III/IV	17//37/49/11
mMRC dyspnea scale[‡] Scale 0/1/2/3/4	17/25/29/30/31
Distance walked in 6 min (meter)	402.4 ± 111.1
Frequencies of acute exacerbation/ year ≥2	29/114 (25.4%)

Abbreviations: FEV_1: forced expiratory volume in 1 s; COPD: chronic obstructive pulmonary disease; mMRC: the modified Medical Research Council; 6MWD: 6-minute walking distance

[§] Body-mass index is the weight in kilograms divided by the square of the height in meters.

[‡] Scores on the modified Medical Research Council (mMRC) dyspnea scale may range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

Statistical analyses

Continuous variables were presented as mean ± standard deviation, and categorical variables as absolute numbers and percentages. The correlation of the Modified Medical Research Council (mMRC) dyspnea scale and FEV_1 was calculated using Crosstabs and Pearson correlations. Univariate analysis was performed using Student's *t*-test for quantitative variables of normal distribution or the Chi-square test for qualitative variables. If $p<0.05$ was statistically significant in 1-way ANOVA, post hoc analysis would be performed among the subgroups using the Tukey method. Survival was estimated by the Kaplan-Meier method with a log-rank test. A 2-sided value of $p<0.05$ was considered to be statistically significant. Statistical analyses were performed using the SPSS software package (version 13.0; SPSS Inc., Chicago, IL, USA).

Results

A total of 114 clinically stable COPD patients were enrolled in this study (Table 1). The new GOLD classification included group A (29 patients, 25.4%), group B (21 patients, 21%), group C (14 patients, 12.3%), and group D (50 patients, 43.9%) (Table 2). The old GOLD classification included 17 stage I patients (14.9%), 36 stage II patients (31.6%), 50 stage III patients (43.9%), and 11 stage IV patients (9.6%). FEV_1 and mMRC scores showed a significant correlation among all patients ($p<0.001$, R=-0.55). However, disproportion between FEV_1 and mMRC dyspnea scores was noted in 35

Table 2. The New GOLD Classification Grouping Stratified by Old GOLD Stage, modified Medical Research Council (mMRC) Dyspnea Scale and Frequencies of Acute Exacerbation: Groups A; B; C; and D

Old GOLD stages	mMRC 0-1	mMRC 2-4	Exacerbation
4	C 14 (12.3%)	D 50 (43.95%)	>1
3			
2	A 29 (25.4%)	B 21 (18.4%)	<1
1			

Symptoms

patients (30.7%). In each stage and group, there was no significant difference in age, gender, BMI, and pack-years. A significant difference in the 6MWD was noted between groups A and D (461.6 vs. 362.9 meters, p=0.001) (Figure 1A), and between stages I and III (477.1 vs. 365.9 meters, p=0.001) (Figure 1B, Table 3). As for mortality risk, there was a significant linkage to the new GOLD classification (p=0.02) (Figure 2A), but not to the old GOLD classification (p=0.58) (Figure 2B).

Discussion

This study provides clinical evidence and demonstrates that the new GOLD classification is associated with exercise capacity and mortality in stable COPD patients. COPD is a complex disease, and the assessment of COPD

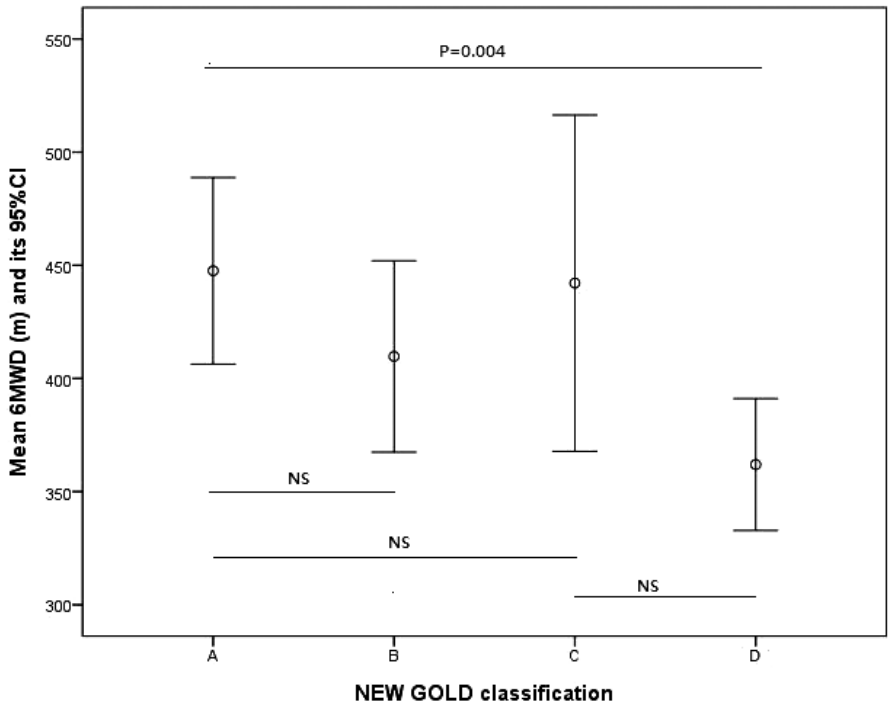

Fig. 1A. Six-minute walking distance was significantly different between groups A and D (447.5 vs. 361.9 meters, p=0.003) in the new GOLD classification.

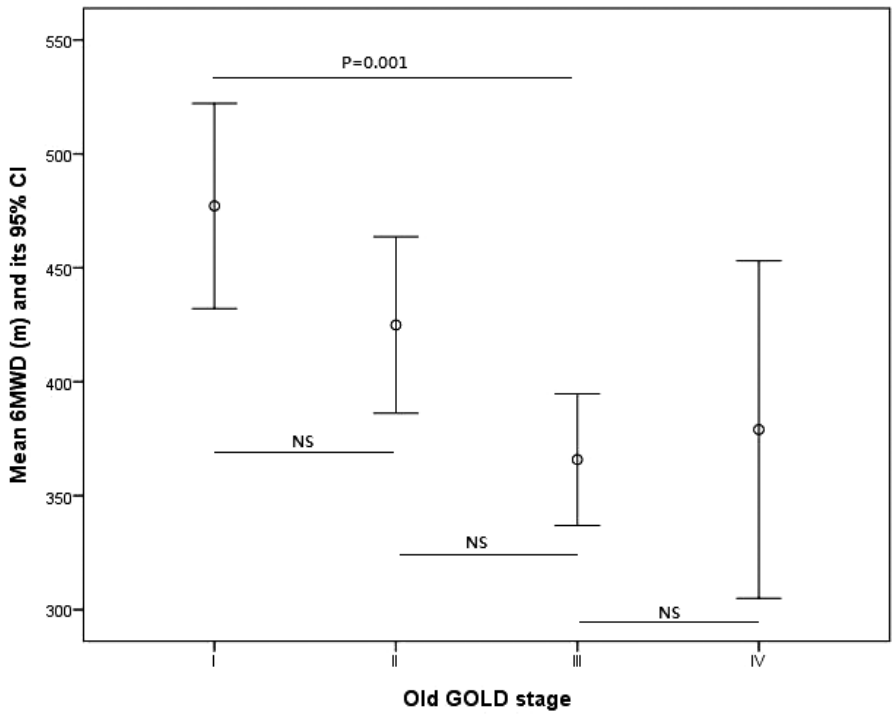

Fig. 1B. Six-minute walking distance was significantly different between stages I and III (477.1 vs. 365.9 meters, p=0.001) in the old GOLD classification.

Table 3. Six-Minute Walking Distance in the Old and New Classifications

	6MWD (m) ± SD
Old GOLD stages*	
Stage I	477.2 ± 22.2
Stage II	424.0 ± 18.6
Stage III	365.3 ± 14.7
Stage IV	379.0 ± 33.2
New GOLD classification§	
Group A	447.5 ± 20.1
Group B	409.7 ± 20.2
Group C	442.0 ± 34.4
Group D	361.9 ± 14.5

* Old GOLD stages: refer to GOLD guideline 2010 updates

§ New GOLD classification: refers to GOLD guideline 2013 updates

severity by FEV_1 alone is not enough to predict quality of life, exercise capacity, and risk of mortality. Staging by the new GOLD classification can be easily obtained with adoption of the dyspnea score, FEV_1, and the frequencies of acute exacerbation. Although it may not be the best stratification method for COPD severity, at least it is convenient to use in clinical practice and was verified for estimation of disease manifestations as well as prognosis in this study.

The 6MWD is simple to perform clinically [13], and is widely accepted as a good predictor of mortality risk among patients with other chronic diseases, including heart failure [14] and pulmonary hypertension [15]. In addition, the 6MWD has been validated as a good outcome measure after interventions, such as pulmonary rehabilitation [16]. This study showed that the 6MWD results were significantly different between groups A and D in the new classification. Group A had a higher FEV_1 and better

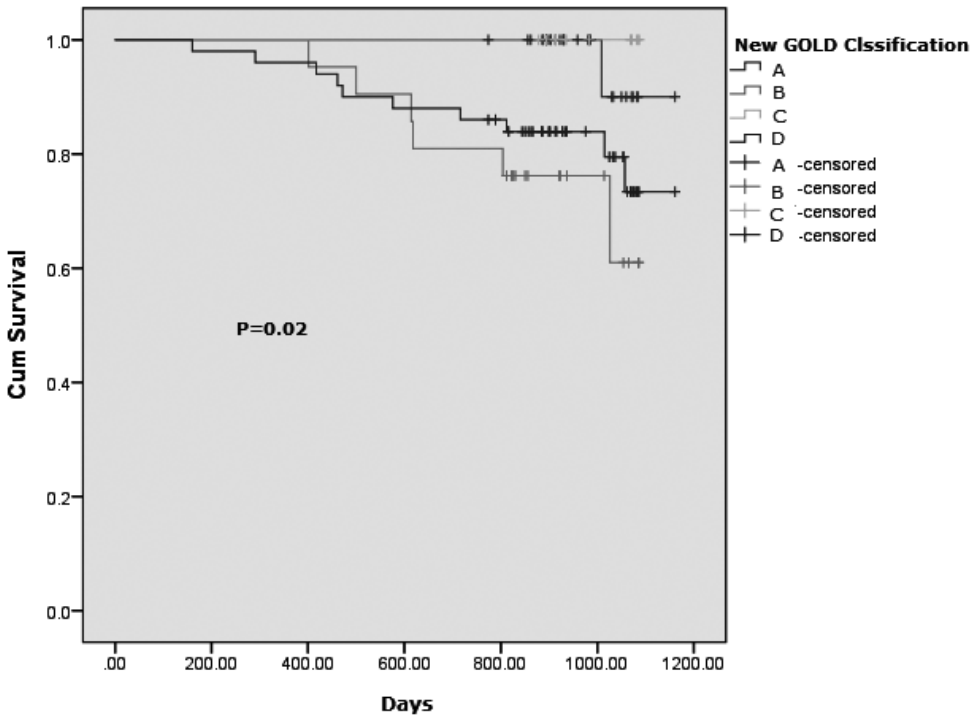

Fig. 2A. Kaplan-Meier method using the log rank test showed the new classification was associated with mortality (p=0.02) and cumulative survival differences between subgroups.

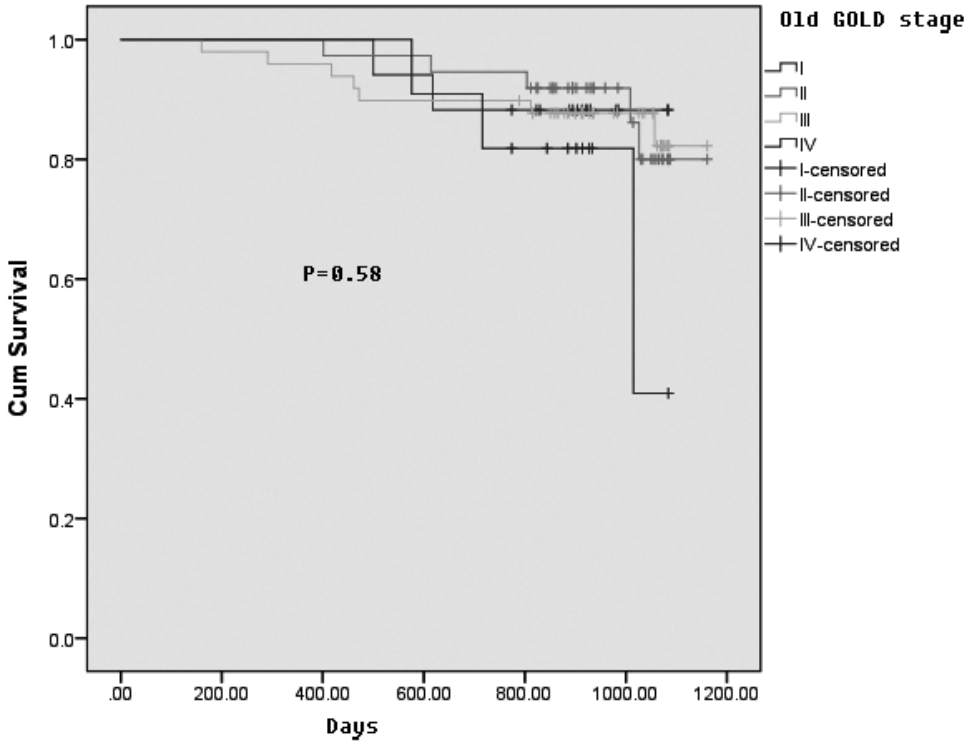

Fig. 2B. Kaplan-Meier method using the log rank test showed the old GOLD classification was not associated with mortality risk (p=0.58).

symptom score, and group D had a lower FEV_1 and worse symptom score. There is no doubt that patients in group A had a longer 6MWD than those in group D. Patients in groups B and C had reverse FEV_1 and mMRC scale levels. Thus it is still acceptable that the 6MWD may not be significantly different between the 2 groups, as seen in our study.

Although there was a significant difference in the 6MWD between stage I and stage III in the old GOLD classification, it was very difficult to explain why the 6MWD showed no significant difference between stage I and stage IV, which were the best and worst stages by definition. It could be inferred that the new GOLD classification would more reliably reflect the exercise capacity of COPD patients.

As a complex disease of heterogeneous etiologies and clinical manifestations, COPD is known for multiple factors that could be correlated with mortality risk, such as low FEV_1 [1-3], a low body-mass index [17-18], hypoxemia, hypercapnia [19-20], a short walking distance in a fixed time [21], functional breathlessness [22], comorbidities [23], frequent acute exacerbation [24-25], and a poor multidimensional index (like the BODE index [10] or the ADO score [26]). Analysis of a single factor may lead to controversial results in different studies. Combined variables usually provide useful information that can improve the comprehensiveness of the evaluation of patients with COPD, but some variables may be difficult to apply clinically due to inconvenience. Our study demonstrates that the new GOLD classification provides an easy and reliable tool to evaluate COPD severity.

In the new GOLD guideline, there are different management choices for group A to D patients, each listed as the first, second or alternative treatment. Medication selection may have been an important confounding factor for mortality risk in our study. Drug selections were generally based on the suggestions of the old GOLD guideline. Also, medication adjustments were made commonly based on identification of improvement or deterioration of the patient's condition, so it would be difficult to make a medication profile of our patients. Therefore, a summarizing of the patient's drug records was not performed in this study.

In summary, COPD is a complex disease, and the assessment of severity by FEV_1 alone is far from enough. With regard to estimation of exercise capacity and mortality risk in stable COPD patients, the newly published GOLD classification proved to be a better stratification tool than the old one in our study.

Acknowledgements

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新版 GOLD 分類（2013 版本）與運動能力及死亡率之關聯性

周柏安 * 郭乃瑛 ** 曾靜苑 ** 王金洲 *,** 秦建弘 **,***
林孟志 *,**,*** 劉世豐 *,**,***

背景：2013 年發表新版 GOLD 指引，建議合併第一秒吐氣量、症狀評分以及急性惡化頻率，以評估慢性阻塞性肺病嚴重程度，本研究針對新舊版 GOLD 指引評估疾病嚴重度，比較兩者與病人運動能力跟死亡率的關聯性。

研究方法：由 114 位病況穩定慢性阻塞性肺病病人，比較不同的嚴重度分類方法（新舊版 GOLD 指引）與六分鐘步行測試及死亡率之間的關聯。

結果：病人一開始先根據舊版 GOLD 指引分成階段 I（17 位，14.9%）、II（36 位，31.6%）、III（50 位，43.9%）以及 IV（11 位，9.6%），然後再根據新版指引重新分組為群組 A（29 位，25.4%）、B（21 位，18.4%）、C（14 位，12.3%）以及 D（50 位，43.9%），各階段及群組的病人，在年紀、性別、身體質量指數及抽菸包－年數的組成並沒有顯著的差異。六分鐘步行測試顯示群組 A 及 D（447.5 vs. 361.9 公尺，p=0.003）與階段 I 及 III（477.1 vs. 365.9 公尺，p=0.001）有明顯差異，Kaplan-Meier 統計方法顯示新版分類與病人死亡率有關連（p=0.02），但舊版的部分並沒有（p=0.58）。

結論：新版 GOLD 指引相較於舊版，更能有效預測病人的運動能力與兩年內死亡率。*（胸腔醫學 **2014; 29: 263-271**）*

關鍵詞：GOLD 分類，6 分鐘步行測試，死亡率，運動能力，慢性阻塞性肺病

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Obstructive Sleep Apnea and Risk of Gout – A Nationwide Population-Based Study

Vincent Yi-Fong Su*, Jen-Yee Hong**, Diahn-Warng Perng*

Introduction: Studies evaluating the risk of gout in patients with obstructive sleep apnea (OSA) are limited. Most of them are small in sample size, cross-sectional in design or lack appropriate controls and information associated with gout development. We designed this study to explore the risk of incident gout in adult patients with OSA.

Methods: From Jan. 1, 2000, we identified adult patients with OSA from the Taiwan National Health Insurance Research Database. A control cohort without OSA, matched for age and sex, was selected for comparison. The 2 cohorts were followed up until Dec. 31, 2008 or occurrence of gout.

Results: Of the 21,817 subjects (4,365 OSA patients vs. 17,452 matched controls), 1,111 (5.09%) suffered from gout during a mean follow-up period of 6.58 years, including 212 (4.86%) in the OSA cohort and 899 (5.15%) among the controls. Kaplan-Meier analysis revealed that there was no difference in the incidence of gout between the OSA cohort and the matched cohort (log rank test, p=0.499). After multivariate adjustment, OSA was not an independent risk factor for gout.

Conclusions: OSA did not increase the risk of future gout. ***(Thorac Med 2014; 29: 272-280)***

Key words: obstructive sleep apnea, sleep-disordered breathing, gout

Introduction

Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing, affecting 2% of women and 4% of men living in Western communities, and probably an even higher percentage of Asians [1]. This disease is characterized by repetitive complete and/or partial collapses of the upper airway during sleep, leading to intermittent hypoxemia and sleep fragmentation [2]. Furthermore, tissue hypoxia increases the catabolism of purines and leads to increased levels of uric acid in animal models [3-4]. However, there are few studies addressing the relationship between sleep-disordered breathing and gout, and most of them are small in sample size, cross-sectional in design or lack appropriate controls and information associated

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with gout development [5-9]. There has been no large-scale study addressing this issue until now. For this study, we hypothesized that OSA may predispose to the development of gout, and then conducted this nationwide population-based study to explore their relationship.

Materials and Methods

Database

For this study, we used a publicly released cohort dataset, the Longitudinal Health Insurance Database, comprised of approximately 1,000,000 randomly sampled people, and collected all the records of these individuals from 2001 to 2008. The released database has been confirmed by the National Health Research Institutes (NHRI) to be representative of the Taiwanese population and is 1 of the largest population-based databases in the world; its data has been used in many published scientific papers. The NHRI has encrypted every patient's original identifiable information in this dataset in a consistent manner, to protect their privacy and allow linkage of claims belonging to the same patient within the database.

Study sample and control

This study was approved by the institutional review board of Taipei Veterans General Hospital (VGHIRB No. 2012-09-007BC). In this retrospective cohort study, we enrolled adult patients (≥20 years old) who were newly diagnosed with OSA [*International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 780.51, 780.53, 780.57] from 2001 to 2008 as the study cohort (OSA cohort) [10]. The date of enrollment was defined as the date on which OSA was initially diagnosed. An age- and gender-matched group of subjects without OSA was randomly selected from the same datasets. The control group was selected from among those patients without OSA at a ratio of 4 controls per OSA patient. The controls were matched for each OSA patient by age and gender. For the control group, the start of follow-up was defined as the first date of clinical visit to a medical facility in the enrollment year. In both groups, subjects with a past medical history of gout (ICD-9-CM codes 274.xx) before enrollment were excluded to avoid interference from the antecedent infection.

Variables

Comorbidities associated with the development of gout, including preexisting diabetes mellitus, hypertension, hyperlipidemia, heart failure, coronary artery disease, chronic obstructive pulmonary disease (COPD), asthma, cerebrovascular disease, cancer, chronic kidney disease, alcoholism, and tuberculosis, were assessed.

Main outcome measures

The primary outcome of interest was gout (ICD-9 code 274.xx) after the initial diagnosis of OSA. All gout diagnoses included in the analysis were accompanied by prescription of anti-hyperuricemic drugs. We did not include suspected clinical diagnoses without using drugs to treat gout. All enrollees were followed from the date of enrollment until the first diagnosis of gout, or censored on the date of death, withdrawal from the national health insurance program, or until Dec. 31, 2008 if they were free of gout.

Statistical analysis

Extraction, matching and computation of

data were performed using the Perl programming language (version 5.12.2). A Microsoft SQL Server 2008 (Microsoft Corp., Redmond, WA, USA) was employed for data linkage, processing, and sampling. Statistical analysis was performed utilizing SPSS software (Version 19.0, SPSS, Inc., Chicago, IL, USA). All data were expressed as mean ± standard deviation (SD) or percentage (%) unless otherwise stated. Comparison between 2 groups was made by independent Student's *t*-test for continuous variables or Pearson's χ^2 test for categorical variables as appropriate. Survival analysis was conducted using the Kaplan-Meier method, with significance based on the log-rank test. A Cox proportional hazard model was used for multivariate adjustment. Statistical significance was inferred at a 2-sided *p* value of <0.05.

Results

We identified 5,175 patients with OSA from Jan. 1, 2001 to Dec. 31, 2008. After excluding patients aged <20 years (n=409) and those with antecedent gout (n=846), 4,365 patients with OSA (mean age 46.53±14.50 years) were included. Another 17,452 age- and sex-matched controls without OSA (mean age, 46.53±14.50 years) were selected for comparison (Figure 1) (Table 1).

During the 6.58±0.79-year follow-up period, there were fewer gout events among the OSA cohort than among the matched group [212 (4.86%) vs. 899 (5.15%)]. OSA patients had an insignificantly lower hazard for incident gout than the control group (log-rank test, *p*=0.499, Figure 2). Incidences in the OSA cohort and the control group were 7.38 and 7.83 persons per 1,000 person-years, respectively. In comparing subjects with vs. without gout, those with incident gout were older and had a higher percentage of hypertension, hyperlipidemia, heart failure, coronary artery disease, COPD, asthma, stroke, chronic renal disease and tuberculosis (Table 2). After multivariate adjustment, OSA was not an independent risk factor for gout

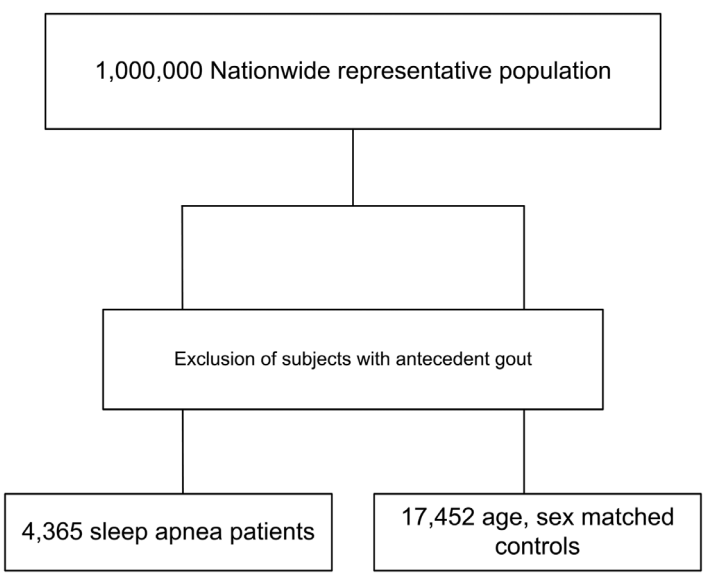

Fig. 1. Flow diagram summarizing the process of enrollment and follow-up.

Table 1. Characteristics of the Sleep Apnea Cohort and Matched Controls

Characteristics	Sleep apnea		Matched controls		*p* value
	n	%	n	%	
N	4,365		17,452		
Age (mean ± SD)	46.53±14.50		46.53±14.50		
<65 years old	3,810	87.3	15,232	87.3	1.000
≥65 years old	555	12.7	2,220	12.7	
Follow-up years (mean±SD)	6.58±0.80		6.58±0.79		0.938
Female	1,717	39.3	6,939	39.8	0.616
Male	2,648	60.7	10,513	60.2	
Comorbidities					
Diabetes mellitus	560	12.8	1,905	10.9	<0.001
Hypertension	1,339	30.7	3,714	21.3	<0.001
Hyperlipidemia	962	22.0	2,404	13.8	<0.001
Heart failure	167	3.8	350	2.0	<0.001
Coronary artery disease	736	16.9	1686	9.7	<0.001
COPD	1,276	29.2	3,181	18.2	<0.001
Asthma	508	11.6	1,193	6.8	<0.001
Stroke	198	4.5	486	2.8	<0.001
Cancer	242	5.5	652	3.7	<0.001
Chronic renal disease	240	5.5	658	3.8	<0.001
Alcoholsim	119	2.7	298	1.7	<0.001
Tuberculosis	49	1.1	165	0.9	0.303

Abbreviations: SD = standard deviation; COPD = chronic obstructive pulmonary disease.

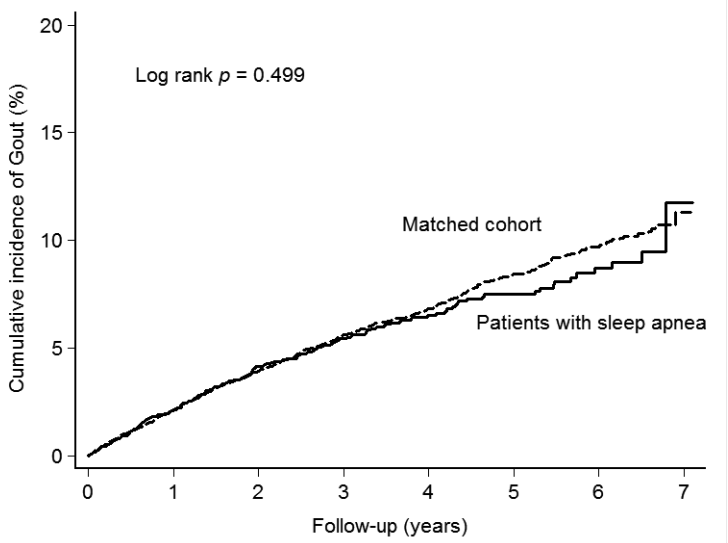

Fig. 2. Kaplan-Meier curves plotting cumulative incidences in subjects with and without sleep apnea. There was no statistically significant difference between the 2 curves (log-rank test, p=0.499).

Table 2. Characteristics of Patients with and without Gout

Characteristics	Gout				*p* value
	Yes (n=1,111)		No (n=20,706)		
	n	%	*n*	%	
Age (mean±SD)	51.33±14.92		46.27±14.43		
<65	871	78.4	18,171	87.8	<0.001
≥65	240	21.6	2,535	12.2	
Sex					
Female	368	33.1	8,288	40.0	<0.001
Male	743	66.9	12,418	60.0	
Comorbidities					
Sleep apnea	212	19.1	4,153	20.1	0.441
Diabetes mellitus	118	10.6	2,347	11.3	0.494
Hypertension	381	34.3	4,672	22.6	<0.001
Hyperlipidemia	181	16.3	3,185	15.4	0.419
Heart failure	37	3.3	480	2.3	0.038
Coronary artery disease	165	14.9	2,257	10.9	<0.001
COPD	230	20.7	4,227	20.4	0.821
Asthma	99	8.9	1,602	7.7	0.166
Stroke	39	3.5	648	3.1	0.485
Cancer	34	3.1	850	4.1	0.090
Chronic renal disease	54	4.9	844	4.1	0.213
Alcoholism	18	1.6	399	1.9	0.566
Tuberculosis	13	1.2	201	1.0	0.529

Abbreviation: SD = standard deviation; COPD = chronic obstructive pulmonary disease.

(Table 3).

Discussion

In this study, we demonstrated that OSA is not an independent risk factor for incident gout. To our knowledge, this is the largest cohort study to investigate the risk of gout among adult patients with OSA. In contrast to other published literature [5-14], this study addressed the temporal relationship between OSA and gout. All patients with gout diagnoses included in the analysis were prescribed anti-hyperuricemic drugs or non-steroidal anti-inflammatory drugs. We did not include suspected clinical diagnoses lacking confirmatory findings. Therefore, the diagnoses of OSA and gout in our research were not only reliable but also exhaustive.

One study [15] showed that subjects with OSA had significantly higher urinary uric acid excretion. After continuous positive airway pressure (CPAP) treatment, a marked reduction of urinary uric acid excretion was observed. Another case-control study [7] also indicated that CPAP treatment could reduce urinary uric acid excretion in patients with OSA. Overnight

Table 3. Predictors of Gout by Cox Proportional Hazards Regression Analysis

Variables	Unadjusted		Adjusted	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Sleep apnea	0.94 (0.81-1.09)	0.429		
Age ≥65 years old	1.07 (0.92-1.23)	0.371		
Male gender	1.76 (1.55-1.99)	<0.001	1.74 (1.53-1.98)	<0.001
Diabetes mellitus	0.55 (0.45-0.66)	<0.001	0.65 (0.53-0.79)	<0.001
Hypertension	0.94 (0.83-1.07)	0.330		
Hyperlipidemia	0.67 (0.57-0.78)	<0.001	0.82 (0.69-0.97)	0.023
Heart failure	0.89 (0.64-1.23)	0.481		
Coronary artery disease	0.82 (0.70-0.97)	0.022	1.00 (0.84-1.19)	0.981
COPD	0.70 (0.61-0.81)	<0.001	0.71 (0.59-0.86)	<0.001
Asthma	0.81 (0.66-0.99)	0.043	1.17 (0.90-1.52)	0.236
Stroke	0.69 (0.50-0.95)	0.022	0.79 (0.57-1.09)	0.146
Cancer	0.47 (0.34-0.66)	<0.001	0.52 (0.37-0.74)	<0.001
Chronic renal disease	0.75 (0.57-0.98)	0.035	0.90 (0.68-1.19)	0.466
Alcoholism	0.77 (0.49-1.23)	0.279		
Tuberculosis	0.92 (0.53-1.58)	0.756		

Abbreviations: HR = hazard ratio; CI = confidence interval; COPD = chronic obstructive pulmonary disease.
All factors with $p<0.1$ in univariate analyses were included in the Cox multivariate analysis.

increase in the urinary uric acid/creatinine ratio was considered as a marker of tissue hypoxia in patients with OSA [16]. A possible explanation for the change in urinary uric acid in patients with OSA is the cellular response to the hypoxemia, which initiates a catabolic process of adenosine triphosphate and results in the generation of excess uric acid that is fed into the blood. The second mechanism of uric acid production is hypercapnia and acidosis, which increases the likelihood of monosodium urate precipitation. An epidemiological sample study [9] indicated that individuals diagnosed with OSA had higher levels of serum uric acid than those without OSA.

A cross-sectional study [6] that enrolled 260 males found that hyperuricemia is frequent in those with OSA (56.2%), and a study [5] of 105 OSA females also found a high incidence of hyperuricemia in their subjects. These 2 small cross-sectional studies showed the association of OSA and gout. However, the result of a large cross-sectional study did not support the finding of a relationship between gout and sleep apnea. Using a validated database of general practice records from 9 practices in the UK between 2001 and 2008 [17], 1,689 individuals with gout were surveyed and each was successfully matched with 4 controls. The study found that sleep apnea was not significantly increased in the gout cases compared to the controls (0.7% vs. 0.3%, adjusted odds ratio: 1.49, 95%

CI: 0.7-3.14). Similar to our data, patients with OSA did not show a higher risk of gout development.

The abovementioned research failed to clearly demonstrate whether or not OSA patients are susceptible to gout. Our results, derived from a large-scale database, provide a closer look at this issue. We found it surprising that OSA did not confer a higher risk for gout, even within a relatively long follow-up period (6.58 years) in such a young population (aged 46.53 years on average). Although previous studies [5-6] indicated the positive relationship between OSA and gout, most were small-scale studies. The largest cross-sectional study [17] did not show a higher risk of gout development in patients with OSA. Publication bias should be considered for the inconsistent results of the abovementioned studies.

In this study, patients with cancer, COPD, diabetes mellitus and hyperlipidemia had a lower risk of gout. One possible explanation may be that weight reduction is associated with a decline in serum urate levels [18]. Cancer or COPD often results in the development of wasting and malnutrition. Two case series studies [19-20] found that glucosuria in patients with diabetes mellitus may decrease urate reabsorption and could result in hypouricemia. A possible explanation is that patients with metabolic diseases tend to eat healthier food and avoid a high-protein/fat/purine diet.

Conclusion

OSA may not be a risk factor for gout. In the future, more elaborate prospective research is needed to confirm our finding and elucidate the possible underlying mechanisms.

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阻塞性睡眠呼吸中止症與痛風風險－全國健保資料庫研究

蘇一峰 *　洪任諭 **　彭殿王 *

背景：過去研究發現阻塞性睡眠呼吸中止症（Obstructive sleep apnea, OSA）與痛風風險可能有關，但是相關研究非常侷限，大部分的研究是小型的研究、橫斷性研究，或者是缺乏對照組的研究。本研究探討 OSA 與痛風的風險。

方法：從健保資料庫百萬人抽樣檔中，從 2000 年 1 月至 2008 年 12 月，選出有 OSA 的成年患者，對照組則選配同性別與年齡的無 OSA 的成年患者，兩組患者分別追蹤到 2008 年 12 月或者痛風的發生為止。

結果：總共選取了 21,817 名的患者，其中 4,365 名 OSA 患者，17,452 名對照組患者。在平均 6.58 年追蹤時間中，1,111（5.09%）人發生痛風，OSA 組其中有 212 人發生痛風，佔 4.86%；而對照組中有 899 人發生痛風，佔 5.15%。痛風發生曲線以 Kaplan-Meier 法分析，在痛風發生率上兩組並無統計學上的差異（p=0.499），在多因子校正分析之後，OSA 不是痛風的危險因子。

結論：OSA 可能不會增加痛風的發生率。*(胸腔醫學 **2014; 29: 272-280**)*

關鍵詞：阻塞性睡眠呼吸中止症，睡眠呼吸障礙，痛風

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Anti-synthetase Syndrome Presenting as an Interstitial Lung Disease: A Case Report

Horng-Ming Yeh, Chang-Hung Chen, Wen-Hung Lee

Anti-synthetase syndrome is a serological subtype of idiopathic inflammatory myositis characterized by the production of antisynthetase antibodies and the development of dermatomyositis or polymyositis, symmetrical arthritis, interstitial lung disease, mechanic's hand, fever, and photosensitivity. It has a generally poor prognosis, mainly due to irreversibly progressive pulmonary involvement. We report the case of a 64-year-old man who presented with symmetrical upper extremity arthralgia, interstitial lung infiltrates in chest films and anti-Jo-1 antibody. Early diagnosis followed by immunosuppressive therapy is essential to prevent the development of respiratory failure in these patients. ***(Thorac Med 2014; 29: 281-286)***

Key words: polymyositis, interstitial lung disease, anti-synthetase syndrome, anti-Jo-1 antibodies

Introduction

Anti-synthetase syndrome (AS) is a rare systemic autoimmune disorder, classified as an idiopathic inflammatory myopathy [1]. It has a generally poor prognosis, mainly due to irreversibly progressive pulmonary involvement. Early diagnosis followed by immunosuppressive therapy can significantly increase both the quality of life and life expectancy of the patients. We report herein a 64-year-old man who was diagnosed with AS at an early stage, which allowed the early introduction of systemic immunosuppressive therapy.

Case Report

A 64-year-old man had been healthy, but had a history of hepatitis C and interferon therapy in the preceding 7 years. He also had gouty arthritis, hypertension and dyslipidemia with regular follow-up. In the most recent 2 weeks, he experienced symmetrical pain and swelling of the joints of the hands, wrists, elbows and shoulders, in addition to myalgia of the upper arms. Cough with mild dyspnea was also noted. Chest X-ray revealed bilateral interstitial pneumonia (Figure 1A). Fever developed after admission, and due to a suspicion of pneumonia, he was empirically treated with intravenous ceftriaxone and levofloxacin.

Physical examination revealed bibasilar

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crackles and proximal muscle weakness in the upper limbs. The laboratory evaluation was remarkable for leukocytosis of 11,450/mm^3 with an elevated segment fraction of 77% (normal, 45-75%), an elevated erythrocyte sedimentation rate of 27 mm/1 h (normal, <20 mm/1 h), elevated C-reactive protein of 1.22 (normal, <0.3 mg/dl) and creatinine kinase of 930 U/L (normal, 60-190 U/L). Urine analysis was normal, but negative serum anti-nuclear antibody (ANA) and rheumatoid factor (RF), positive anti-SS A and anti-Jo-1 antibody were noted.

The results of lung function testing were as follows: FEV_1 (forced expiratory volume in 1 second): 2.43L (83.2% predicted), FVC (forced vital capacity): 2.55L (68.4% predicted), FEV_1/FVC: 95.18% and TLC (total lung capacity): 6.4L (91.3% predicted). The results of arterial blood gas in room air were pH 7.448, $PaCO_2$ 34.5, PaO_2 64.1 mmHg, HCO_3^- 23.3 mmol/L, and PaO_2/FiO_2 64.1/0.2=320.5, and there was an alveolar arterial difference of oxygen ($AaDO_2$) of 42.5 mmHg.

High-resolution computed tomography (HRCT) of the thorax revealed a bilateral interstitial pattern, with areas of ground glass opacity, predominantly in the lower lobes (Figure 2). An extensive infectious disease evaluation for bacteria, tuberculosis, mycoplasma, and legionella was unrevealing.

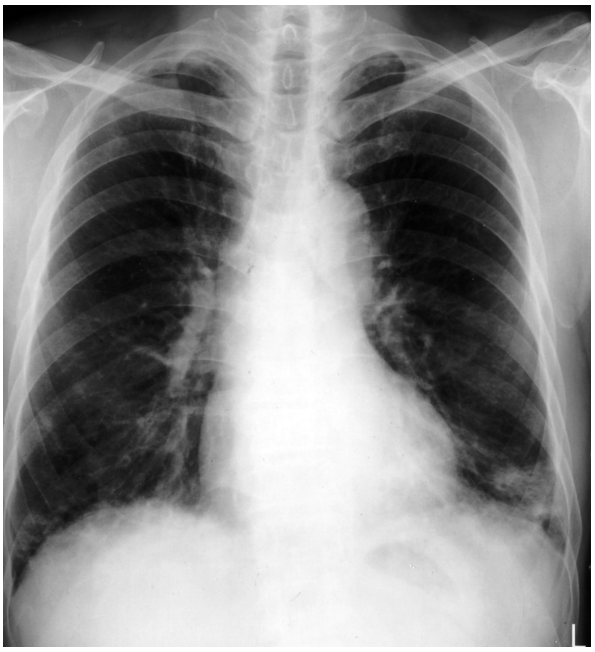
Administration of hydrocortisone sodium succinate 100 mg q6h led to a considerable improvement in muscle strength, but hemoptysis, and chest pain persisted, and chest X ray showed further deterioration (Figure 1B). Pulse therapy with intravenous methylprednisolone 1,000 mg was then initiated for 3 days. Thereafter, his fever, cough and breathing improved markedly. He was then discharged with a prednisolone starting daily dose of 60 mg, azathioprine 50 mg bid, and cyclosporin 100 mg qd. Follow-up chest X-ray 1 month after discharge (Figure 1C) showed progressive improvement.

Discussion

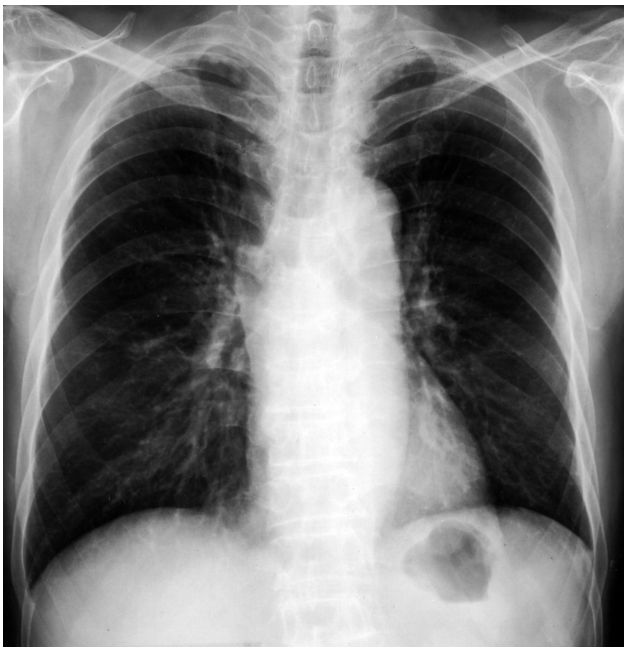
AS is a serological subtype of idiopathic inflammatory myositis that is characterized by the production of anti-synthetase antibodies and the development of dermatomyositis or polymyositis, symmetrical arthritis, interstitial lung disease (ILD), mechanic's hand, fever, Raynaud's phenomenon, and photosensitivity [1]. The autoantibodies produced in different forms of myositis can be divided into myositis-specific and myositis-associated autoantibodies. A subgroup of myositis-specific autoantibodies consists of antibodies directed against aminoacyl tRNA synthetase, i.e. the anti-synthetase antibodies. The most common of the anti-synthetase antibodies is the anti-histidyl-tRNA synthetase (anti-Jo-1) antibody [2].

It has been demonstrated that the presence of anti-synthetase antibodies is the strongest predictive factor for the development of ILD in idiopathic inflammatory myositis [3]. The coexistence of anti-SSA/Ro and anti Jo-1 seems to be related to a more severe, rather therapy-resistant and extensive pulmonary fibrosis with a higher score on HRCT, as with the patient reported herein, than anti-Jo-1 antibodies alone [4-5].

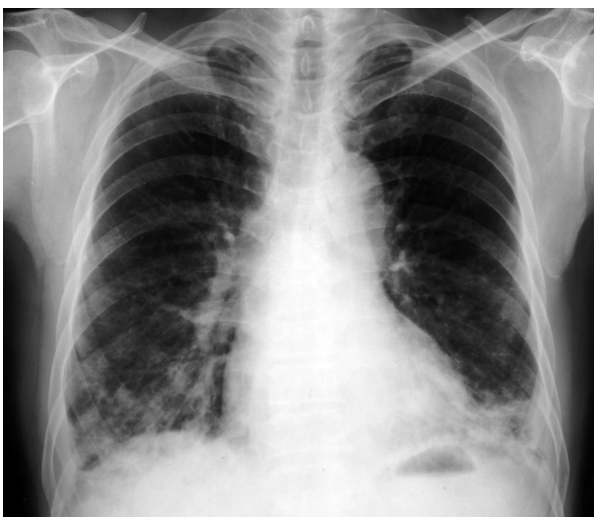
An increased $AaDO_2$ of 42.5 mmHg was noted in this patient. $AaDO_2$ levels above 32 mmHg on admission were a poor prognostic factor for ILD with dermatomyositis in 1 study [6]. $AaDO_2$ is calculated by subtracting PaO_2 from PAO_2. In certain pathologic conditions (diffusion impairment, V/Q mismatching, and shunt), the A-a gradient increases, reflecting in-



(A)



(C)



(B)

Fig. 1. Chest X ray revealed bilateral interstitial pneumonia on admission (Fig. 1A) and further deterioration (Fig. 1B) 4 days later. Follow-up chest X ray 1 month after discharge (Fig. 1C) showed progressive improvement.

adequacy of oxygen transfer [7].

The diagnosis of ILD requires differential causes, including drugs or other environmental exposures, and connective tissue disease. Therefore, most clinicians routinely do serologic testing, such as ANA, RF and other autoantibodies, in addition to detailed history-taking and physical examination at the time of diagnosis, to provide a clue as to a possible unrecognized connective tissue disease [8].

Inflammatory myositis is a rare disease entity affecting skeletal muscles and other organs, including the lungs. ILD in inflammatory myositis is increasingly recognized as a serious complication of the disease [9]. Myositis associated with ILD may present together with ILD,

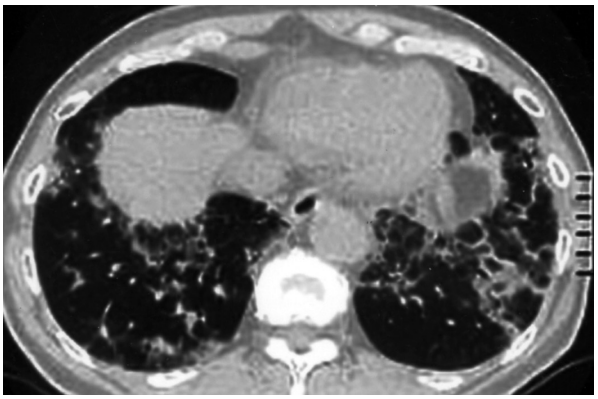


Fig. 2. High-resolution computed tomography showing a bilateral interstitial pattern, with areas of ground glass opacity, predominantly in the lower lobes.

as with the case presented herein, or precede the presentation of myositis, or at any time during the disease course [10]. Management of ILD is crucial for outcome and survival, but there are no controlled trials to support a specific treatment regimen for this kind of patient. If the onset of ILD is acute and rapidly progressive, more potent immunosuppressive therapies may be needed. Pulses of intravenous prednisolone (1 g/day for 3 days) and intravenous cyclophosphamide (750 mg) could be effective in these refractory cases [11]. In a report of 5 patients with acute and refractory ILD treated with intravenous immunoglobulins, 2 patients survived but the others died [12].

This case highlights the importance of considering a broad differential diagnosis for suspected infectious pneumonia cases that are not responding to standard antibiotic regimens. Prompt diagnosis and appropriate therapy for those cases can prevent disease progression and improve patient outcome. Thus, early clinical diagnosis and timely aggressive immunosuppressive therapy is essential to prevent the development of severe respiratory failure and pulmonary hypertension [13].

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抗合成酶症候群以間質性肺病來表現：個案報告

葉宏明　陳長宏　李文宏

抗合成酶症候群是發炎性肌炎的一種亞型，特點在於發炎性肌炎或皮肌炎合併對稱性關節炎、間質性肺病、技工手、發燒、光過敏和血中測得抗合成酶，通常會因為肺部病變不可逆性進展而預後不佳。我們在此報告一位 64 歲男性，以兩手關節炎，胸部 X 光出現間質性肺病和抗 Jo-1 抗體來表現。早期診斷可以提早施用免疫抑制劑而得到較佳之預後。*(胸腔醫學* ***2014; 29: 281-286)***

關鍵詞：多發性肌炎，間質性肺病，抗合成酶症候群，抗 Jo-1 抗體

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Bronchiolitis Obliterans-Organizing Pneumonia – A Rare Presentation of Rheumatoid Arthritis with Lung Involvement: A Case Report and Literature Review

Chuan-Hung Kao, Su-Lin Peng, Han-Yu Chang

There are several manifestations of rheumatoid arthritis (RA) with lung involvement, including bronchiolitis obliterans-organizing pneumonia (BOOP). Diagnosis is usually difficult and open or thoracoscopic lung biopsy is often required. Herein, we report the case of a woman with rheumatoid arthritis who presented with dyspnea and cough. Chest X-ray (CXR) revealed abnormal infiltration and the clinical symptoms did not improve after antibiotics treatment. After thoracoscopic lung biopsy, BOOP was confirmed. Her symptoms and images improved with steroid treatment. ***(Thorac Med 2014; 29: 287-291)***

Key words: rheumatoid arthritis, bronchiolitis obliterans-organizing pneumonia, interstitial lung disease

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease, primarily involving the joints. Pulmonary abnormalities are common in patients with RA, but may not result in significant symptoms. There are several different manifestations, such as usual interstitial pneumonia, nonspecific interstitial pneumonia [1], organizing pneumonia [2], and pleura, chest wall, and pulmonary vascular disease [1]. Diagnostic confirmation of the relationship between RA and lung manifestations is usually difficult, due to multiple impacting factors such as drugs and infection. Biopsy is often needed, and more commonly an open or thoracoscopic lung biopsy [3]. Lung biopsy can provide a specific diagnosis, identify a more treatable process and predict the likelihood of response to therapy [4]. In our case, we treated the patient as having pneumonia initially. However, her symptoms and chest X-ray (CXR) did not improve. After chest computed tomography (CT), bronchiolitis obliterans-organizing pneumonia (BOOP) was suspected, and was confirmed by VATS biopsy.

Case Report

A 74-year-old woman had a history of RA for 10 years. She received regular follow-ups at our outpatient department. Her rheumatoid factor was 230 IU/ml in May 2013. One week be-

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fore admission, she suffered from fever off and on. Accompanying symptoms included general malaise, poor appetite, cough and mild dyspnea. She was admitted to our chest ward for further survey. Laboratory data revealed white blood cells 7300/μL, adequate renal and liver function, and elevated C-reactive protein (133.1 mg/L). CXR showed bilateral interstitial infiltration (Figure 1). Chest CT showed ground glass opacity and consolidation at the peripheral area (Figure 2). We prescribed antibiotics, including ampicillin/sulbactam, azithromycin, and oseltamivir. Bronchoscope was also performed and the lavage routine showed lymphocytes: 8%, neutrophils: 30%, monocytes: 32%, and eosinophils: 0% with negative culture results. Her symptoms and CXR did not improve. Lung biopsy under video-assisted thoracic surgery (VATS) was performed and the pathology revealed characteristic fibroblastic plugs (Masson bodies) filling some air spaces, foamy histiocytes with scattered, distributed giant cells, a few neutrophils, and thickening of the alveolar septa. The mucin, GMS and acid-fast stains revealed no specific pathogen (Figure 3). The result was consistent with interstitial lung disease with BOOP.

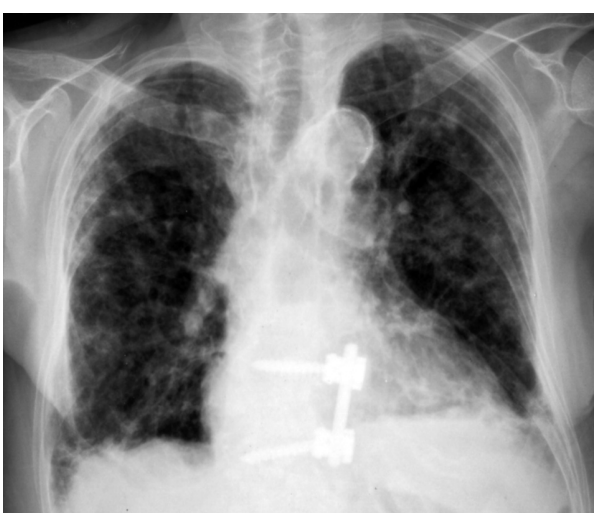

Fig. 1. CXR shows bilateral interstitial infiltration.

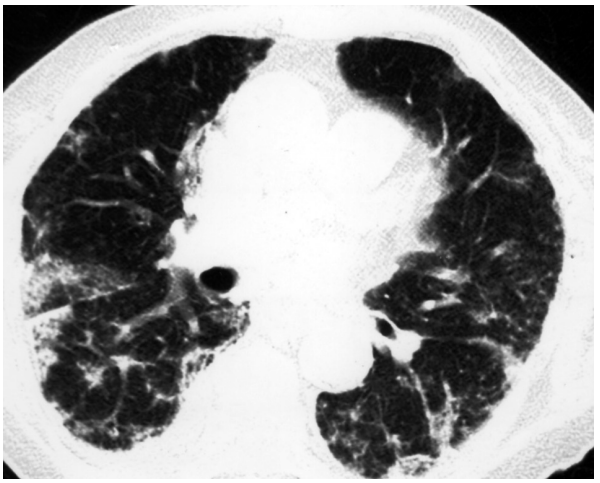

Fig. 2. Chest computed tomography (CT) shows ground glass opacity and consolidation at the peripheral area.

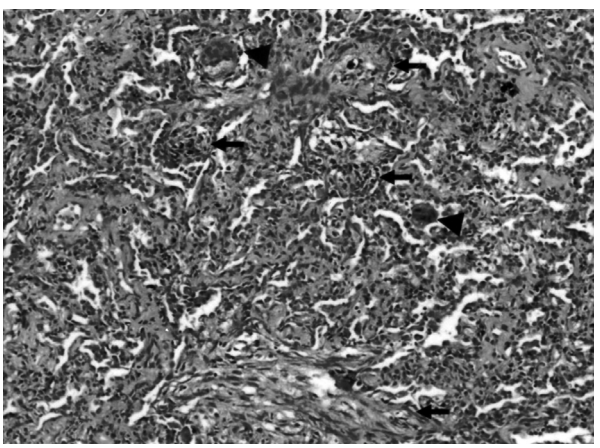

Fig. 3. In the low-power view, there were Masson bodies (arrow) and a scattered distribution of multinucleated giant cells (arrowhead).

After the pathology result, we gave the patient prednisolone at the dosage of 1 mg/kg/day. Two months later, CXR showed resolving infiltration (Figure 4). Her airway symptoms also improved.

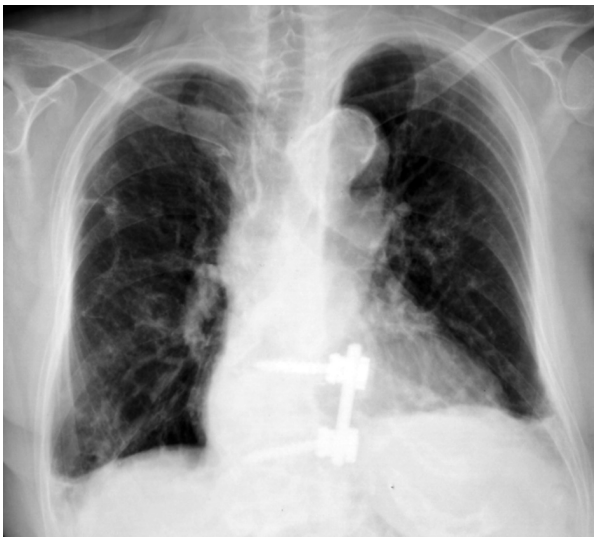

Fig. 4. CXR shows infiltration in significant resolution 2 months after steroid treatment.

Discussion

BOOP, also call cryptogenic organizing pneumonia, is a type of diffuse interstitial lung disease that affects the distal bronchioles, respiratory bronchioles, alveolar ducts, and alveolar walls [5]. The histopathologic features of BOOP are excessive proliferation of granulation tissue consisting of loose collagen-embedded fibroblasts and myofibroblasts involving alveolar ducts and alveoli with or without bronchiolar intraluminal polyps [6]. "Masson body" is a pathological term to describe these findings [7].

When lung biopsy confirms the diagnosis of BOOP, we must determine whether the disease is cryptogenic or secondary to another process. Differentiating cryptogenic organizing pneumonia (COP) from secondary organizing pneumonia is difficult based on radiologic or pathologic findings alone. A careful review of the patient's history, physical examination, medication usage, potential exposures, and underlying diseases is needed. Secondary causes of BOOP include organizing diffuse alveolar damage, diffuse alveolar hemorrhage, drugs (e.g., amiodarone, cocaine), infections (e.g., mycoplasma, virus, *Pneumocystis jirovecii*, bacterial), connective tissue diseases, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, and aspiration [8]. In our case, RA was thought to be the cause of BOOP after reviewing the patient's history.

The role of flexible bronchoscopy is mainly to obtain bronchoalveolar lavage (BAL) samples to evaluate for infection, hemorrhage, and malignancy. BAL findings of BOOP typically include increases in lymphocytes (20-40%), neutrophils (5-10%), and eosinophils (5-25%), with the level of lymphocytes being higher than that of eosinophils [9]. The "mixed pattern" of increased cellularity is thought to be characteristic, although not diagnostic of BOOP [5]. Transbronchial biopsy is an important method we often use with bronchoscopy. Its role in patients with suspected BOOP is to identify other disease processes. The small size of transbronchial lung biopsies is often inadequate for definitive confirmation of BOOP and exclusion of other concomitant processes. Reliance on small transbronchial biopsies increases the likelihood of missing the primary diagnosis [10]. In our case, BAL revealed lymphocytes: 8%, neutrophils: 30%, monocytes: 32%, and eosinophils: 0%, which was compatible with a mixed cellular pattern. After VATS biopsy, BOOP was confirmed.

For patients with gradually worsening disease, initial therapy with systemic steroid is suggested [11]. The dose is usually prednisone of 0.75 to 1 mg/kg per day, based on ideal body weight [12]. The duration of steroid use is about 3 to 6 months if the patient remains stable or is improving. Routine CXR follow-up and moni-

toring should be performed during steroid treatment. In our case, we prescribed prednisolone 1 mg/kg/day. Her symptoms improved and CXR 2 months later showed the infiltration was in significant resolution.

Use of steroid is considered clinically for patients presenting with BOOP. However, the confirmation of BOOP should be established by biopsy result. Steroids are prescribed after pathology is available, as in our patient. However, is there a possibility of steroid treatment before the biopsy result is known, if BOOP is suspected? Since the side effects of steroid might be severe and relatively inappropriate in patients with severe sepsis, the decision-making should be individualized and based on the hemodynamic conditions. This issue warrants further investigation in the future.

Conclusion

Herein, we reported a case of RA with lung involvement. After VATS biopsy, BOOP was confirmed, and after steroid treatment, the symptoms and CXR showed improvement. Pulmonary manifestations in patients with RA are variable and difficult to diagnose. VATS biopsy is often needed. Steroid treatment usually yields dramatic improvement in patients with BOOP. Finally, we should keep in mind the diagnosis of BOOP when pneumonia treatment fails in patients with RA.

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阻塞性細支氣管炎合併器質化肺炎—類風溼性關節炎的罕見肺部表現：病例報告及文獻回顧

高傳紘　彭淑玲　張漢煜

類風溼性關節炎有各種不同的肺部表現，這些表現在臨床上症狀上不具特異性，如阻塞性細支氣管炎合併器質化肺炎，常常需要靠開胸或胸腔鏡手術切片才能診斷。在此，我們報告一個類風溼性關節炎的病人，臨床上的表現是咳嗽跟喘，影像學檢查有毛玻璃狀陰影及肺泡型變化，抗生素治療無效後，經過胸腔鏡手術，證實是阻塞性細支氣管炎合併器質化肺炎。經過類固醇治療後，症狀及影像學上皆獲得改善。*(胸腔醫學 **2014; 29: 287-291**)*

關鍵詞：類風濕性關節炎，阻塞性細支氣管炎合併器質化肺炎，間質性肺疾

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Primary Carcinoid Tumor of the Parietal Pleura – Case Report

Jian-Sheng Liu*, Chih-Yen Tu*,**, Chia-Hung Chen*, Pin-Ru Chen***, Guan-Chin Tseng****

Carcinoids are neuroendocrine tumors that primarily affect the gastrointestinal tract, lungs, and bronchi. They are considered benign with slow growth, but can be malignant in a substantial percentage of patients (metastasizing to the liver, bones, skin, etc). Primary bronchopulmonary carcinoids constitute 1% to 5% of resected lung cancers and about 25% of all carcinoids. The most commonly reported location for pulmonary carcinoid tumors is the major bronchi. There are very few reports of primary pleural carcinoids. We present an extremely rare case of primary pleural carcinoid tumor in a 24-year-old male. He was found incidentally to have a right pleural mass and underwent thoracoscopy with pleural tumor excision. Histological immunohistochemical analysis confirmed the diagnosis of typical carcinoid tumor in the pleura without extrapleural invasion or distant metastasis. The patient received local radiotherapy as adjuvant treatment after surgical intervention. To date, the patient has not exhibited evidence of local recurrence or metastasis. ***(Thorac Med 2014; 29: 292-297)***

Key words: carcinoid, malignancy, lung cancer, pleura, neuroendocrine

Introduction

Carcinoid tumors are typically classified as neuroendocrine neoplasms [1]. Carcinoid tumors of the lung are relatively rare, comprising 1% to 5% of lung cancers [2]. These tumors range from relatively indolent typical carcinoids to intermediately aggressive atypical carcinoids. Typical carcinoids represent 80-90% of pulmonary carcinoids and are most frequently diagnosed in the 5th and 6th decades of life, but can occur at any age. Atypical carcinoid (AC) neoplasms possess more malignant potential than typical carcinoids (TC), with a greater propensity to nodal and distant metastases [3]. The most commonly reported location for pulmonary carcinoid tumors is the major bronchi, and up to 68% of these tumors are found in the mainstem and lobar bronchi. Only 10% to 20% of carcinoid tumors are found in the lung

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periphery, and these are often identified as coin lesions or solitary pulmonary nodules in imaging studies [4]. Since symptomatic patients are more likely to undergo diagnostic evaluation, pulmonary carcinoid tumors are overrepresented in published series [1-2]. Pleural carcinoid tumors are extremely rare; only a few cases have been previously reported. Herein, we describe the case of a young male with a TC tumor in the parietal pleura that was treated using aggressive surgical intervention and adjuvant radiotherapy. To date, the patient has not exhibited signs of recurrence.

Case Report

A 24-year-old male was referred to our hospital with an abnormal chest X-ray shadow in October 2011 (Figure 1). He had an unremarkable medical and family history and was a nonsmoker. Computed tomography (CT) imaging of the chest revealed a mass (4×3×1.5 cm) in the right pleura (Figure 2). Ultrasound-guided pleural biopsy showed chronic pleurisy characterized by increased lymphoplasma cell infiltration. We performed video-assisted thoracic surgery to remove the tumor, which was connected to the right anterior parietal pleura with a short pedicle, and completed full resection within the safety margin using endoscopic electrocautery (Figure 3). Histological examination revealed the tumor consisted of oval tumor cells with fine chromatin and abundant granular cytoplasm in a trabecular or insular pattern with scanty mitotic

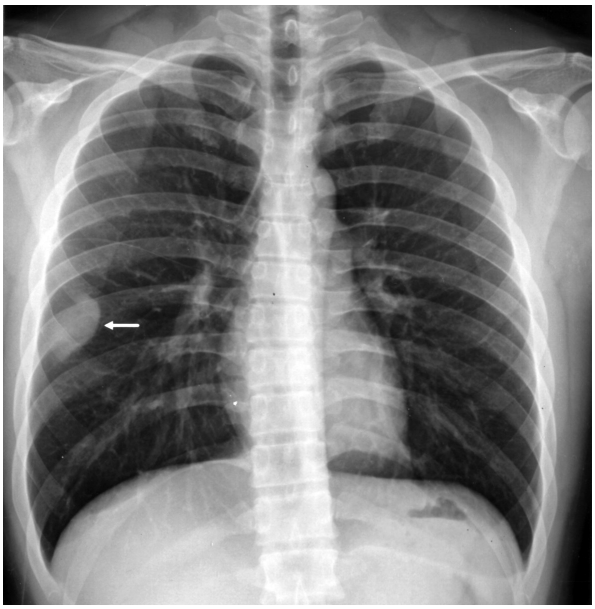

Fig. 1. Chest radiograph revealed a tumor in the right lower lung (arrow).

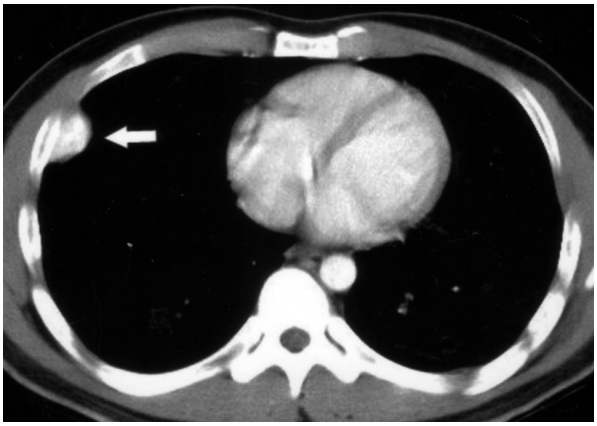

Fig. 2. Chest CT image showing a mass (4×3×1.5 cm) in the right pleura (arrow).

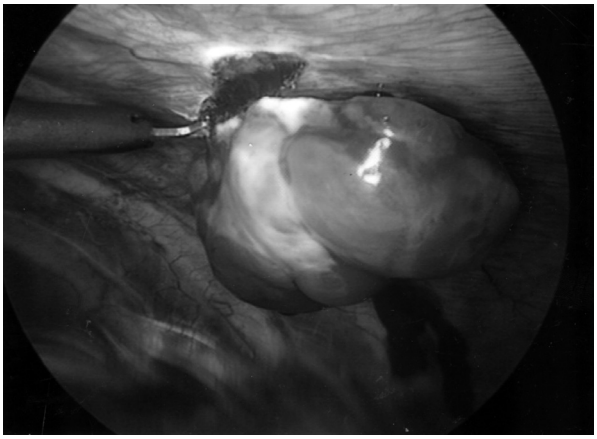

Fig. 3. Video-assisted thoracoscopy reveals a tumor beneath the parietal pleura.

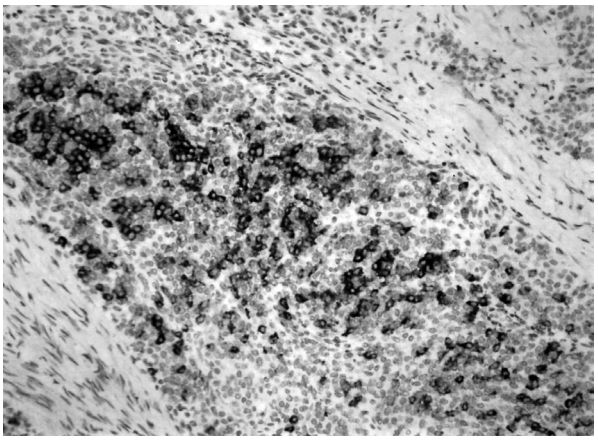

Fig. 4. Immunohistochemical staining reveals the presence of numerous endocrine cells with synaptophysin reactivity, original magnification 200x.

figures (less than 1/10 HPF). No signs of necrosis were found. Immunohistochemical staining of the pleural tumor revealed that it was reactive to synaptophysin, S-100, and vimentin, but negative for TTF-1, cytokeratin, CK5/6, calretinin, and CD34. The immunohistochemical and pathological features of the tumor indicated a TC tumor (Figure 4). Additional radiotherapy was performed after surgical intervention with no complications, and to date there has been no recurrence of the tumor.

Discussion

Carcinoids are the most frequently occurring neuroendocrine tumors and have long been thought to be mostly benign [5]. They are an uncommon malignancy that can arise in a wide range of tissues that harbor neuroendocrine cells. The bronchopulmonary system is the second most common location for primary carcinoid tumors, after the gastrointestinal system [6]. Pulmonary carcinoids are morphologically similar to carcinoma but have a much better prognosis. Around 25% of all carcinoid tumors originate in the cells of the respiratory tract [1-2]. Although rare when compared with non-small cell lung cancer, carcinoid tumors are the second most common primary malignant pulmonary neoplasm in adults.

Two radiographic patterns of carcinoid tumors have been described: central and peripheral. Central lesions involve or are directly adjacent to primary or segmental bronchi [7]. Peripheral lesions arise at or are distal to the subsegmental bronchi [8]. The most common symptoms include coughing, hemoptysis, wheezing, and pneumonia as a result of central airway involvement. Rare associations with pulmonary carcinoid tumors include carcinoid syndrome. Since symptomatic patients are more likely to undergo diagnostic evaluation, there is a predilection for pulmonary carcinoid tumors to be overrepresented in published series.

The case presented here is unusual in that the carcinoid tumor presented as a pleural mass. Previously described peripheral carcinoid tumors were all surrounded by lung parenchyma, and were peripheral lung nodules or masses [9]. In the present case, the lesion was not surrounded by lung parenchyma, and no endobronchial component could be identified. The appearance was highly suggestive of a pleural tumor. The most common neoplasms of the pleura are mesothelioma or metastatic disease -- primary benign pleural tumors are uncommon [10]. The presentation of a carcinoid tumor as a pleural mass is rare. Pleural carcinoid tumors may originate as tumors that have arisen from a peripheral portion of the tracheobronchial tree, invaded the pleural surface and encased the lung [11].

A pulmonary carcinoid tumor is classified as typical or atypical, depending on the mitotic activity and presence of necrosis. A typical

carcinoid (TC) is defined as a carcinoid tumor with fewer than 2 mitoses per 2 mm^2 and without necrosis. In contrast, an atypical carcinoid (AC) is defined as a carcinoid tumor with 2 to 10 mitoses per 2 mm^2 and/or foci of necrosis. TC tumors represent 80-90% of pulmonary carcinoids and are most frequently diagnosed in the 5^{th} and 6^{th} decades of life, but can occur at any age. AC neoplasms possess more malignant potential than TC, with a greater propensity for nodal and distant metastases. The prognosis of a TC is excellent. The 5-year and 10-year survival rates are 90-98% and 35-59%, respectively [12]. There has been only 1 published case of a primary pleural carcinoid tumor, that of an AC tumor of the parietal pleura [13]. The present case is that of a primary TC tumor. It was suggested that the clinical course and prognosis of a TC would be better than of an atypical pulmonary carcinoid tumor.

Carcinoid tumors are characterized by growth patterns that suggest neuroendocrine differentiation, such as organoid, trabecular, insular, palisading, ribbon, rosette-like, or similar arrangements. Carcinoid tumors are generally identifiable in cytological specimens. The tumor cells are uniform and polygonal with finely eosinophilic cytoplasm nuclei with a fine granular chromatin pattern ("salt and pepper" morphology), inconspicuous nucleoli, and a scant to moderate amount of cytoplasm [12]. Immunoreactivity of carcinoid for chromogranin, synaptophysin, S-100 protein, Leu-7 (CD57) and N-CAM (CD56) is typically present [12].

Surgery remains the treatment of choice currently and the only curative option for patients with typical and atypical pulmonary carcinoid tumors. Aggressive surgical intervention is justified for patients with a good performance status given the generally good survival data and lack of effective alternative treatments. Additional treatments currently under investigation include chemotherapy and radiation, particularly for patients diagnosed with unresectable or metastatic disease at the time of initial presentation [14-16]. Radiotherapy alone has been gaining attention as an adjuvant therapy in patients with carcinoid tumors; however, randomized studies are limited by the relative rarity of carcinoid tumors.

In conclusion, primary pleural TC tumors are extremely rare. To the best of our knowledge, there are no similar previous reports of this nature. Carcinoids, or well-differentiated neuroendocrine pulmonary tumors, represent an uncommon malignancy with limited medical therapeutic options. Given the indolent nature of this disease, aggressive local modalities of care, including surgery and radiotherapy, are recommended.

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原發性體側肋膜類癌

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類癌是神經內分泌腫瘤，大多數的類癌發生於腸胃道及呼吸道。它們被認為是良性的並且增長緩慢的，但也有相當比例的患者是惡性的（轉移至肝臟，骨骼，皮膚等器官）。原發性支氣管肺類癌約占已切除的肺癌的 1% to 5%；約占所有類癌的 25%。最常被報告的支氣管肺類癌的位置是支氣管。只有極少數的原發性肋膜類癌被報告過。我們提出一個極為罕見的原發性肋膜類癌案例發生在一個 24 歲的男子。他意外發現有一個腫塊位於右側肋膜，並經胸腔鏡進行腫瘤切除。組織學檢查，包括免疫染色檢查診斷為典型的原發性肋膜類癌。並沒有證據表明肋膜外浸潤或遠處轉移。隨後給予術後輔助放射治療。在隨後的追蹤到目前為止，他並沒有證據表示有局部復發或轉移。*(胸腔醫學 **2014; 29: 292-297**)*

關鍵詞：類癌，惡性，肺癌，肋膜，神經內分泌

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Avoiding Possible Misdiagnosis of Malignant Pleural Epithelioid Mesothelioma: A Case Report and Literature Review

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Distinguishing malignant pleural epithelioid mesothelioma from metastatic adenocarcinoma is difficult using histological features alone. We report the case of a 72-year-old woman with occupational exposure to asbestos for more than 30 years presenting right chest pain for 6 months. Chest computed tomography (CT) detected multiple nodules and masses, pleural thickening, focal calcified plaques and mild loculated pleural effusion in the right hemithorax. CT-guided biopsy of the right pleural mass, without immunohistochemical staining, revealed adenocarcinoma, moderately differentiated. After discussion with the pathologists, further immunohistochemical staining was performed. The final report was suggestive of malignant pleural epithelioid mesothelioma. ***(Thorac Med 2014; 29: 298-303)***

Key words: malignant pleural epithelioid mesothelioma, lung adenocarcinoma, immunohistochemistry stains, diagnosis

Introduction

Malignant pleural mesothelioma (MPM) is an insidious malignancy with a poor prognosis. Most patients were exposed occupationally to asbestos or asbestos-containing products in their early life. MPM can be difficult to diagnose, and is often misdiagnosed initially. An accurate diagnosis is based on histopathological examination of the tissue, and proper epidemiological records are important for appropriate treatment. The diagnosis of epithelioid mesothelioma always requires evaluation of immunohistochemistry stains, or even electron microscopy. Herein, we present the case of a patient with malignant pleural epithelioid mesothelioma who was misdiagnosed initially as having adenocarcinoma of the lung. This case may serve as a reminder to clinicians and pathologists of the possible occurrence of this preventable misdiagnosis.

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Case Report

A 72-year-old non-smoking female, who had been exposed occupationally to asbestos (a shipyard worker) for more than 30 years, had the symptoms of right pleuritic pain, chest tightness, shortness of breath and non-productive cough for 6 months. She then sought medical help at a hospital. Her chest radiograph (Figure 1) revealed right pleural thickening and loculated pleural effusion. Chest computed tomography (CT) findings included multiple nodules and masses, pleural thickening, focal calcified plaques and mild loculated pleural effusion in the right hemi-thorax (Figure 2A). No malignant cells were found in the cytology examination via thoracentesis of the pleural effusion. The subsequent CT-guided biopsy (Figure 2B) of the right pleural mass revealed adenocarcinoma, moderately differentiated with cytokeratin-7 (CK7) positive, and thyroid transcription factor-1 (TTF-1) negative. No apparent signs of malignancy were found in the magnetic resonance imaging (MRI) of the brain. One week later, her daughter brought her to our hospital for a second opinion.

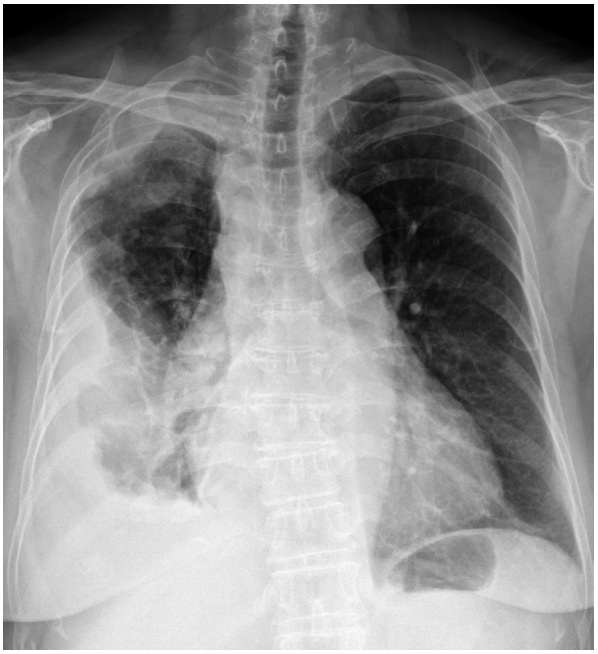
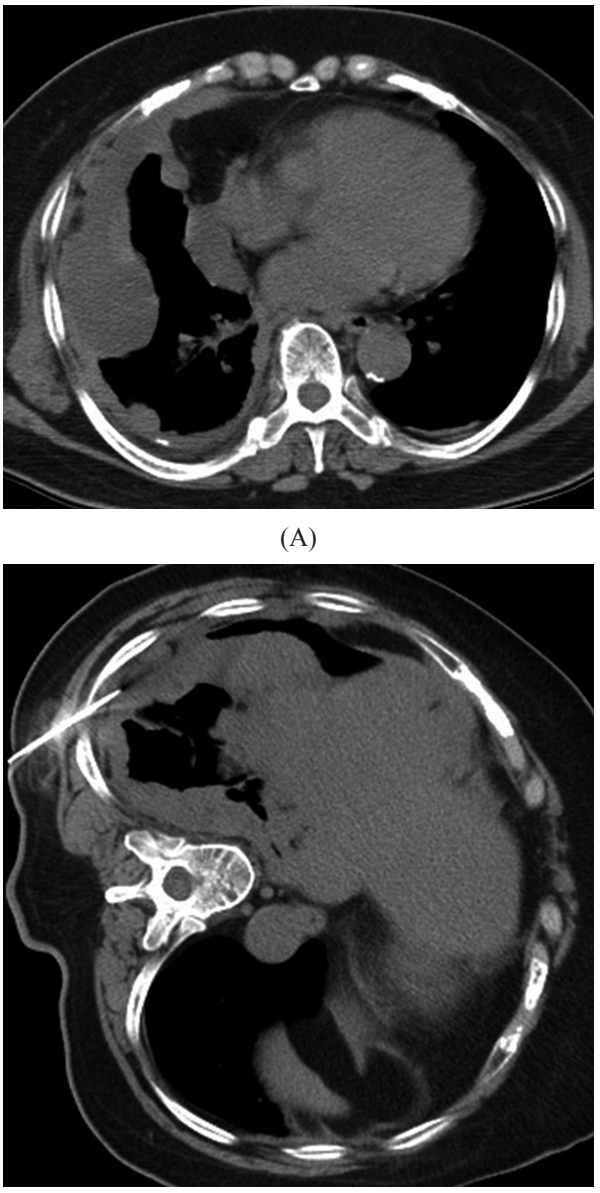


Fig. 1. Chest radiography revealed right pleural thickening and loculated pleural effusion.



(A)

(B)

Fig. 2. A, Chest computed tomography detected multiple nodules and masses, pleural thickening, focal calcified plaques and mild loculated pleural effusion in the right hemi-thorax. B, CT-guided biopsy.

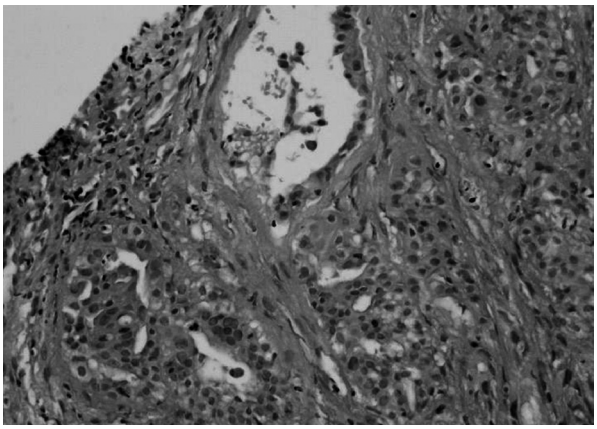
We reviewed her history and examinations. Laboratory tests indicated a hemoglobin (Hb) level of 9.4 g/dl (normal range for women: 11.3-15.3 g/dl), platelet count of 509,000/cumm (normal range: 120,000-400,000), carcinoembryonic antigen (CEA) level of 1.09 ng/ml (normal range: <5.0 ng/ml), cytokeratin fragment 21-1 (CYFRA 21-1) level of 56.6 ng/ml (normal range: <16.3 ng/ml), and a ferritin level of 570.4 ng/ml (normal range for women: 10-130 ng/ml). The mesothelin biomarker level in the pleural fluid or serum was absent. Based on the history of exposure to asbestos and the findings in the previous CT examination, MPM was highly suspected. The tissue obtained via CT-guided biopsy in the previous hospital was sent to our pathologists for further immunohistochemistry stain evaluations. The histological picture of the tumor (Figure 3A) included positive calretinin (Figure 3B), focally weakly positive mesothelin (Figure 3C), negative TTF-1 (Figure 3D), and focally positive cytokeratin-18 (CK-18) (Figure 3E). The impression was malignant epithelioid mesothelioma, based on the clinical, histopathological, and immunohistochemistry stain findings. Positron emission tomography-CT (PET-CT) scanning was suggested for precise staging, but she did not continue follow-up for personal reasons.

Discussion

MPM is considered to be an uncommon malignancy. Long-term occupational exposure to asbestos fibers and asbestos-containing products have been found to be harmful and cause fibrosis and malignancy. The latent period in the development of mesothelioma may up to 30 or 40 years once exposure to asbestos occurs [1]. In many developed countries, the use of asbestos has been reduced by “asbestos bans”. The number of cases may gradually reach a plateau by the year 2020 in the United States and Western Europe [2]. However, carbon nanotubes, which are similar to asbestos fibers, have been used widely in applications in electronics and medicine [3]. The potential carcinogenicity of carbon nanotubes, especially with regard to the pleural tissue, is of particular concern [4].

Most patients present with a gradual onset of nonspecific symptoms, such as non-pleuritic chest pain or dyspnea. Other less common symptoms are cough, fever, chills, sweats, and fatigue [5]. Symptoms may last for months or longer before diagnosis. Positive physical examination findings are related to the presence of a pleural effusion or mass. Abnormal laboratory findings are nonspecific, and include anemia and thrombocytosis. Thrombocytosis caused by tumor via interleukin-6 (IL-6) possibly augurs a poor prognosis [6]. The typical chest radiograph shows a unilateral pleural abnormality with a large amount of pleural effusion, especially right-sided. The most common finding in CT is a rind-like extension of a tumor on the pleural surfaces. Others include pleural plaques and/or calcifications, and pleural thickening with pleural-based multiple nodules [7]. PET-CT scanning may be useful to distinguish MPM from benign mesothelial disease [8]. Thoracentesis for cytology and closed pleural biopsy are often unable to provide enough tissue for diagnosis and distinguishing mesothelioma from other tumors, but CT-guided biopsy and video-assisted thoracoscopic biopsy can provide enough tissue and lead to a definitive diagnosis.

Pathologists have difficulty differentiating mesothelioma from metastatic adenocarcinoma. Several malignancies, such as metastatic involvement of the pleura, sarcoma, malignant fi-



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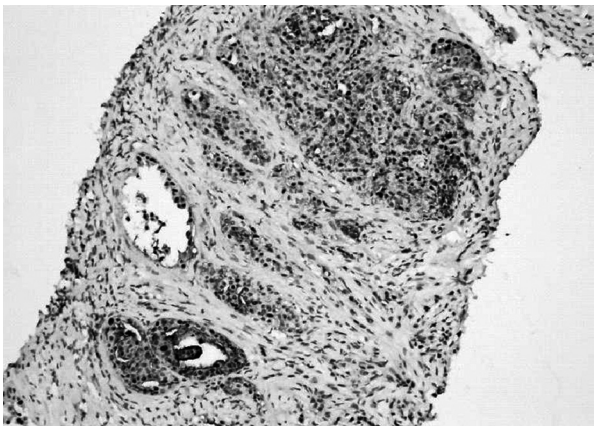

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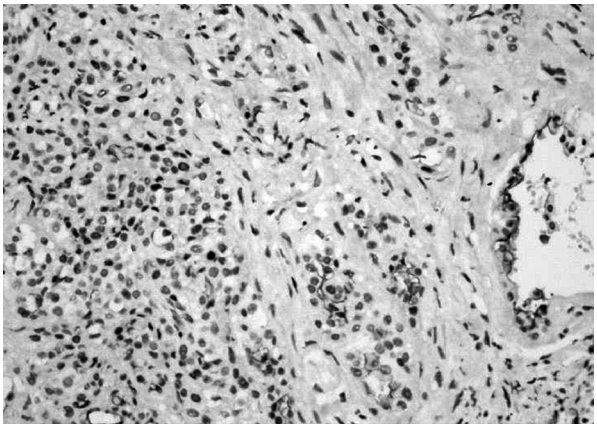

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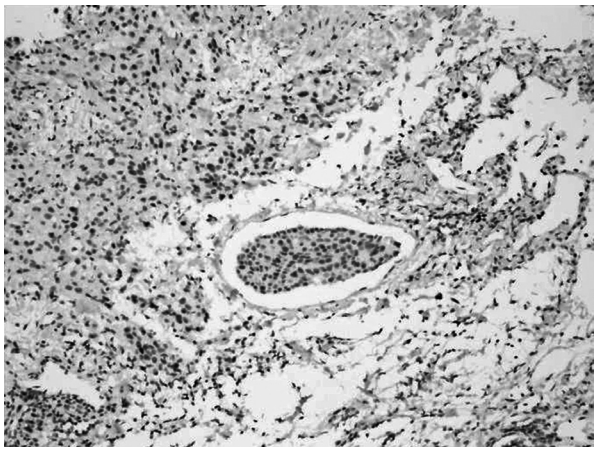

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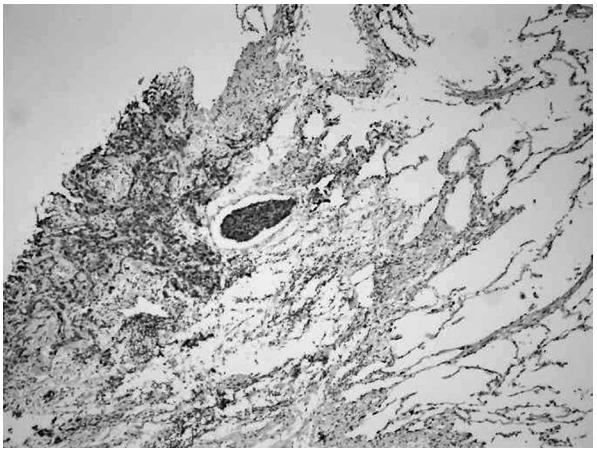

(E)

Fig. 3. A, Histological picture. B, Positive calretinin. C, Focally weakly positive mesothelin. D, Negative thyroid transcription factor-1. E, Focally positive cytokeratin-18.

brous histiocytoma, sarcomatoid carcinoma and synovial sarcoma, can be extremely difficult to distinguish from MPM grossly and histologically. Epithelioid mesothelioma and adenocarcinoma share multiple histological features [9]. Pathologists seek information about the history of asbestos exposure and the biologic behavior of the tumor from both radiographic and intra-

operative observations. They need larger specimens to perform multiple immunohistochemical staining. There is no single marker available that provides acceptable sensitivity and specificity for malignant mesothelioma. Some determinate immunohistochemistry stains are not performed due to insufficient specimens, and more importantly, financial concerns. But a panel of markers has sensitivity or specificity greater than 80% to distinguish whether the tumor is epithelioid, sarcomatoid, or poorly differentiated [9]. Antibodies suitable for immunohistochemistry have increased in number and include affirmative mesothelioma markers, so immunohistochemistry has largely replaced electron microscopy in its traditional use as the "gold standard" for diagnosing MPM. Electron microscopy can be useful occasionally in establishing the diagnosis of epithelioid mesothelioma when immunohistochemistry stain results are equivocal [10].

Concern should be raised if immunohistochemistry stains for MPM are not shown in the pathologic report of a patient with suspected MPM based on occupational history, and radiographic and intraoperative findings. In this way, a delayed diagnosis may be prevented.

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避免誤診惡性肋膜間質上皮細胞瘤：病例報告與文獻回顧

李羽仁　彭萬誠 *　簡志峰 *　劉崢偉　蘇文麟 **

惡性肋膜間質上皮細胞瘤與肺腺癌在初步的組織病理切片中，兩者很難區分，我們的案例報告是一個 72 歲女性，曾在造船廠工作，暴露在石棉環境超過 30 年，最近 6 個月開始出現右側胸痛現象。胸部電腦斷層發現右側肋膜不規則增厚，有多發性結節與硬塊併鈣化點，且存在腔室化肋膜積液。經電腦斷層導引切片後，初步病理報告為轉移性中度分化的肺癌，但並未對惡性肋膜間質細胞瘤作相關的免疫組織化學染色，因病史與影像學報告均高度懷疑惡性肋膜間質細胞瘤的可能性，於是病理科做進一步的免疫組織化學染色，最後確定診斷是惡性肋膜間質上皮細胞瘤。*(胸腔醫學 **2014; 29: 298-303**)*

關鍵詞：惡性肋膜間質上皮細胞瘤，肺腺癌，免疫組織化學染色，診斷

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Epidermal Growth Factor Receptor Tests for Differentiation of the Origin of Metastatic Adenocarcinoma of Mediastinal Lymph Nodes with an Unknown Primary Site

Ying-Chieh Chen, Chia-Hsin Liu, Cherng-Lih Perng*,**, Yao-Feng Li***, Shan-Yueh Chang, Chih-Feng Chian

Metastatic adenocarcinoma of mediastinal lymph nodes with an unknown origin is rare. We report a 62-year-old male with a mediastinal mass that grew from 1.9 to 5.1 cm in 2 years. The patient underwent mediastinoscopic tumor biopsy, and the pathological exam disclosed metastatic adenocarcinoma. The patient was diagnosed as having metastatic mediastinal adenocarcinoma of unknown origin after extensive examinations. His disease was hypothesized as adenocarcinoma of the lung with mediastinal lymph node metastasis of cT0N2M0 stage IIIA. Chemotherapy with a regimen of cisplatin and vinorelbine plus thoracic radiation therapy was administered; however, these treatments were terminated after 2 courses of chemotherapy because of intolerable side effects. The patient received gefitinib as a second-line treatment, although direct sequencing of a tumor sample revealed the presence of the wild-type epidermal growth factor receptor (*EGFR*) gene. Subsequent examinations revealed that the mass lesion had disappeared with gefitinib treatment. The patient discontinued gefitinib after 1 year of treatment and remained in complete remission 36 months thereafter. An exon 19 deletion in *EGFR* was confirmed by real-time polymerase chain reaction (real-time PCR) of the mediastinal lymph node. ***(Thorac Med 2014; 29: 304-309)***

Key words: adenocarcinoma, mediastinal lymph node, epidermal growth factor receptor, gefitinib

Introduction

The clinical presentations of metastatic adenocarcinoma with an unknown primary site depend on the sites of metastatic tumor involvement, which are frequently multiple and often

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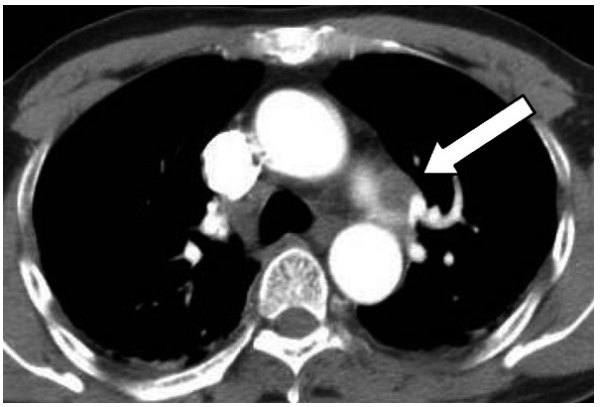
involve the liver, lungs, lymph nodes, and bones. The most frequently identified primary sites of this type of cancer are the lung, pancreas, hepatobiliary tree, and kidney, which together account for approximately two-thirds of cases; however, the origin of the disease remains unknown in 20-30% of patients [1]. Molecular tumor profiling can be used to predict the origin of the tissue of a tumor based on the detection of site-specific gene expression profiles [2]. Moreover, epidermal growth factor receptor (*EGFR*) gene mutation tests may play a pivotal role in differentiating an origin from the lung. We describe a case of metastatic adenocarcinoma of mediastinal lymph nodes with an unknown primary site. A lung origin was supported by evidence of good clinical response to gefitinib and an *EGFR* exon 19 deletion, as assessed using real-time polymerase chain reaction (PCR) of the mediastinal lymph node.

Case Report

A 62-year-old man (a nonsmoker) presented with intermittent chest tightness of 3 months' duration in December 2007. Computed tomography (CT) of the chest revealed a nodule of 1.9 cm in the mediastinum (Figure 1A). The patient refused further surgical intervention. He visited another hospital in August 2009 because of a dry cough and hoarseness lasting more than 6 months, which were associated with a loss of body weight of 2 kg within 3 months. CT of the chest showed a mediastinal tumor, 5.1 cm in size, with no lesion in the lung parenchyma (Figure 1B). Laboratory data revealed a carcinoembryonic antigen (CEA) level of 30.77 ng/mL and a carbohydrate antigen 19-9 (CA 19-9) level of 1090 U/mL. The patient underwent mediastinoscopy with tumor biopsy, leading to



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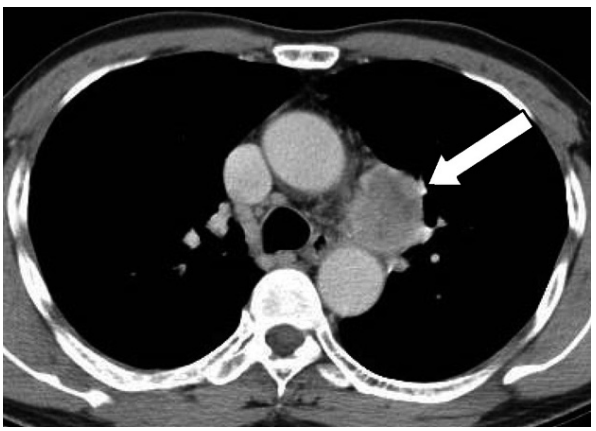

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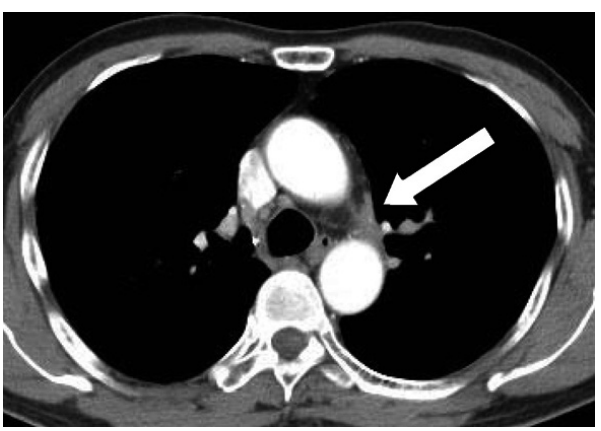
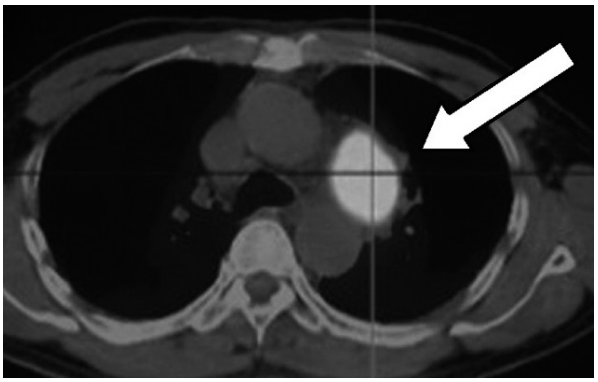


(C)

Fig. 1.
A, CT scan of the chest in December 2007 showed a focally circumscribed soft-tissue nodule, 1.9 cm in size. (white arrow)
B, By August 2009, the soft-tissue mass had grown to 5.1 cm in size. (white arrow)
C, By October 2012, after 12 months on single-agent gefitinib, the mass had completed remission and remained stable. (white arrow)
CT, computed tomography.



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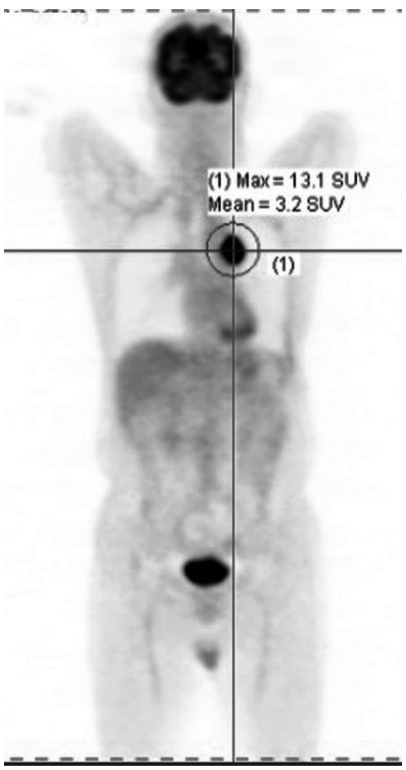

(B)

Fig. 2. Whole-body fluorodeoxyglucose-PET image demonstrating high uptake in the mediastinal lymph node. (white arrow)

a pathological diagnosis of metastatic adenocarcinoma of the mediastinal lymph nodes. Immunohistochemistry (IHC) staining was positive for CEA and cytokeratin 7, but negative for thyroid transcription factor-1 (TTF-1). The patient was referred back to our hospital for determination of the origin of the primary tumor. Panendoscopy, colonoscopy, CT of the abdomen, and even CT-supported positron emission tomography (PET) were arranged to search for a possible primary carcinoma; however, only a soft-tissue mass in the mediastinum with increased 18F-fluorodeoxyglucose uptake was found (Figure 2). An *EGFR* gene mutation test that was performed via direct sequencing to detect exons 18, 19, 20, and 21 revealed the presence of wild-type *EGFR*.

In consideration of the patent's clinical course for almost 2 years, he was assumed to have adenocarcinoma of the lung of cTxN2M0 stage IIIA. Definite chemoradiation therapy with cisplatin (80 mg/m^2, day 1), pulse vinorelbine (25 mg/m^2, day1 and day 8) and thoracic radiation therapy with a total dose of 64.35 Gy over 6 weeks was planned. The patient received only 2 courses of chemotherapy and radiation therapy (total dose of 17.55 Gy) because of persistent grade 3 tinnitus of the left ear and granulocytopenia that required subcutaneous injection of recombinant human granulocyte colony-stimulating factor. The patient received gefitinib therapy (250 mg daily) for an initial 6 months, which was tapered to every other day for another 6 months at his own cost (starting in December 2009). He subsequently, quit gefitinib treatment for financial reasons.

After discontinuation of gefitinib therapy, the patient underwent CT of the chest every 3 months as regular follow up of his disease. He remained disease-free and in complete remission for a total of 36 months, as of this writing (Figure 1C). An exon 19 deletion of *EGFR* was confirmed via real-time PCR (QIAGEN EGFR Pyro Kit) of the mediastinal lymph node in October 2012.

Discussion

Metastatic adenocarcinoma with an unknown primary site is a metastatic tumor with a site of primary origin that cannot be identified based on clinical history, complete physical examination, routine laboratory tests, imaging and radiometabolic techniques, and careful review of histological specimens [3]. In our case, metastatic adenocarcinoma with an unknown primary site was suspected by the absence of primary malignancy, despite extensive examinations. We assumed that the primary site was the lung for 2 reasons. First, although IHC staining of TTF-1 in this case was negative, carcinoma metastases from the lung could not be excluded completely because the positive rate of TTF-1 in lung cancer is 64-68% [4-5]. Second, a primary malignancy from the abdomen, thyroid or gastrointestinal tract is more likely to have- an intensive clinical course within 2 years; thus, this origin was unlikely in our case. A tumor sample exon 19 deletion in *EGFR*, -confirmed via real-time PCR, supported a primary malignancy originating in the lung.

Some somatic mutations, especially those present in genes encoding tyrosine kinases, are central to the biology of specific cancers. These driving mutations lead to the production of mutated enzymes, which then serve as excellent substrates for targeted therapies. Mutant *EGFR*-dependent adenocarcinoma of the lung is an example [6]. Treatment with EGFR tyrosine kinase inhibitors leads to rapid and durable clinical responses in patients with lung cancer with an activating *EGFR* mutation. Direct sequencing is a commonly used methodology. The main disadvantages of this method are its low sensitivity (20-50%) and the significant risk of contamination involved in handling post-PCR products [7]. Angulo et al. reported that the real-time PCR method had higher sensitivity and a lower limit of detection than direct sequencing [8]. The frequency of *EGFR* mutations in pulmonary adenocarcinoma is significantly higher in nonsmoking Asian individuals (30-50%) than in non-Asian populations (10%) [9]. In the present case, an *EGFR* mutation was not found using a direct sequencing method, but was detected using real-time PCR. These findings suggest that the selection of a more sensitive method for *EGFR* mutation detection is important in high-risk patients harboring an *EGFR*-activating mutation.

Radical surgical resection of thoracic lymph node carcinoma combined with either chemotherapy or radiation therapy may offer a chance of cure and may increase the disease-free interval or the survival period in patients with metastatic carcinoma of mediastinal lymph nodes of unknown origin [10]. In our unique case, we followed the treatment protocols of the National Comprehensive Cancer Network for non-small-cell lung cancer. The patient received chemoradiation therapy as first-line treatment, but switched to gefitinib because of the intolerable side effects of the chemoradiation therapy.

In conclusion, high-sensitivity tests for *EGFR* mutations are important for the management of patients with metastatic adenocarcinoma of mediastinal lymph nodes with an unknown primary site. Gefitinib is a suitable treatment for patients harboring an *EGFR*-activating mutation.

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表皮生長因子受體測試用於鑑別診斷原發部位不明之轉移性縱隔腔淋巴結腺癌

陳盈潔　劉佳鑫　彭成立 *,**　李耀豐 ***　張山岳　簡志峰

原發部位不明的轉移性縱隔腔線癌是很少見的。我們報告一個 62 歲男性的縱隔腫塊在兩年內從 1.9 公分增長至 5.1 公分。這位病患接受縱膈腔鏡腫瘤切片 病理檢查證實為轉移性腺癌。經過一系列檢查後，病患被診斷為原發部位不明的轉移性縱隔腔線癌。他的疾病分期被定為肺腺癌第三期（cT0N2M0, stage IIIA）。病患接受 cisplatin 加上 vinorelbine 組合之化學暨放射線治療，然而因為病患無法忍受其副作用，再經過兩次療程後終止治療。這位病患後來接受了 gefitinib 作為第二線治療，即使腫瘤樣本的表皮生長因子受體（EGFR）基因型經直接序列分析檢測為原株。在日後的檢驗中發現，病患接受 gefitinib 藥物治療之下，縱膈腔腫瘤消失不見。病患治療 1 年後停止 gefitinib 治療，但仍然維持在治療 36 個月後完全緩解。後續我們經即時聚合酶連鎖反應（Real-time PCR）的方式檢測，證實病患的表皮生長因子受體（EGFR）之外顯子 19 之氨基酸缺失（deletion）。*(胸腔醫學 **2014; 29: 304-309**)*

關鍵詞：腺癌，縱膈腔淋巴結，表皮生長因子受體，艾瑞莎

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Solitary Pulmonary Nodule Caused by Localized Pulmonary Infarction

Pai-Hsi Chen, Kuo-Ming Chang*

Solitary pulmonary nodules are not hard to detect with a chest radiograph, but the physician needs experience to make a precise diagnosis. A solitary pulmonary nodule was incidentally found in the left upper lobe of an asymptomatic 43-year-old male who was then referred to our chest surgery department. Various tumor work-up examinations were done, but a definite diagnosis was not obtained. The final diagnosis of pulmonary infarction was gained from wedge biopsy of the tumor using video-assisted thoracic surgery. Although the incidence of pulmonary infarction is low, it should be included in the differential diagnosis of pulmonary nodules. ***(Thorac Med 2014; 29: 310-316)***

Key words: solitary pulmonary nodule, pulmonary infarction, lung cancer, video-assisted thoracoscopic surgery

Introduction

In general, solitary pulmonary nodules can be considered benign or malignant, and the differential diagnoses are extensive. All of the pulmonary nodule work-ups are essential to reach a precise diagnosis, and are critical to perform because of the poor outcomes of malignancy. Early detection of the nodules may potentially reduce the lung cancer-specific mortality [1].

In images, pulmonary infarctions may reveal themselves as various shadows, including that of a solitary pulmonary nodule [2]. However, the presence of a solitary pulmonary nodule alone is not usually an indication for pulmonary perfusion-ventilation scan and pulmonary arteriography. We report the case of a solitary pulmonary nodule diagnosed as localized pulmonary infarction after surgical biopsy.

Case Report

In July 2009, an asymptomatic 43-year-old man was referred to the chest surgery department for the investigation of a 2.5×2.5 cm, well-defined nodule seen on chest radiograph (Figure 1) and computed tomography (CT) (Figure 2) before operation for a right total hip replacement. The past history of this patient revealed alcoholism and that he had suffered from right hip pain for half a year. Avascular necrosis (AVN) of the right femoral head was suspected

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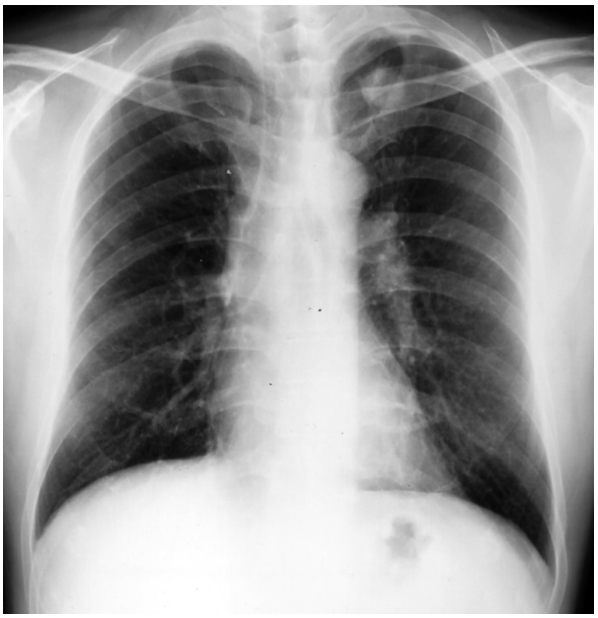

Fig. 1. A 2.5×2.5 cm well-defined and round nodular opacity at the left upper lung field

and finally confirmed after total hip replacement surgery.

In order to confirm the diagnosis of the nodule, several evaluations, including sputum culture, cytology and bronchoscopy were arranged, and all revealed negative findings. Fine needle biopsy was suggested but the patient refused the procedure.

Video-assisted thoracoscopic surgery (VATS) was performed finally under general anesthesia, with the patient in the right decubitus position and intubated with a double lumen. Wedge resection of the left upper lobe was done with stapler, and a frozen section was performed intra-operation. In gross appearance, the excised wedge of lung tissue had, at its periphery near the subpleural region, a major lesion with a light tan-white to occasionally grey solid firm nodular appearance, measuring 2.3×2.2×1.8 cm in size and possessing a small central cavity (Figure 3). In the histopathological exam, the main lesion showed a well-defined area of infarction of lung tissue, with ghost shadows of the comprising structures with consolidation but without frank lysis of the tissues or typical caseous necrosis. There was a fairly thick collar of reactive-inflammatory change around the infarcted area (Figure 4). The larger blood vessels in the infarcted lung tissue could be better

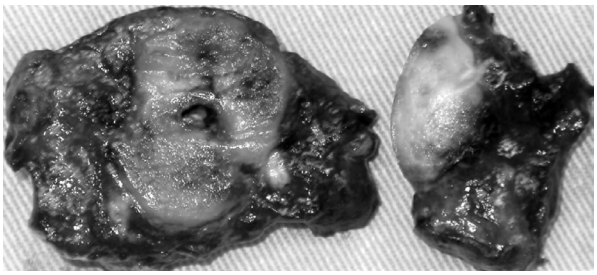

Fig. 3. Gross appearance of the pulmonary lesion

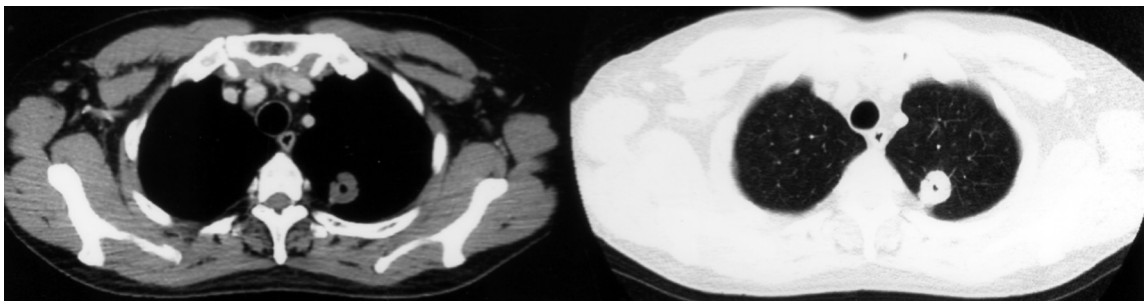

Fig. 2. One well-defined and low attenuated lesion (3 to 18HU in density after enhancement) with small central cavitation at the posterior aspect of the left upper lobe of the lung

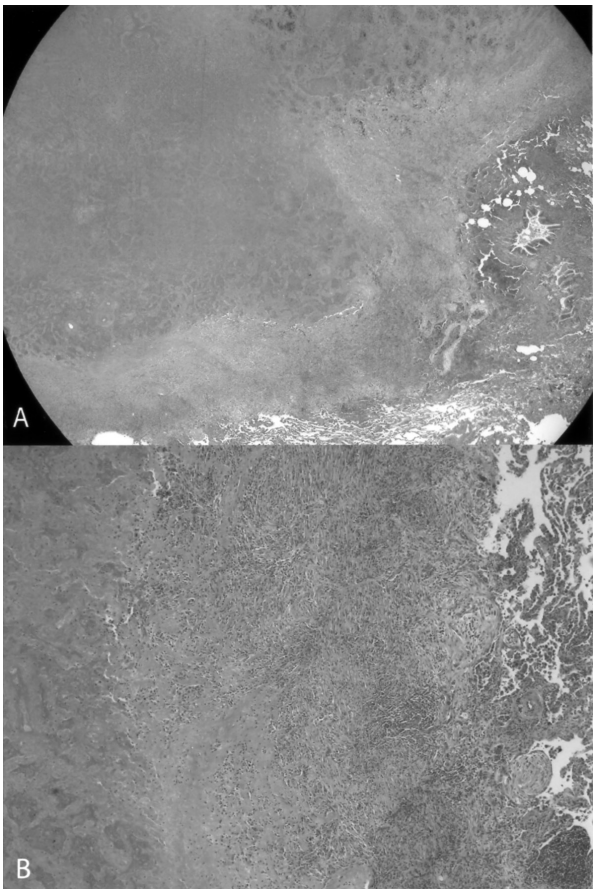

Fig. 4. Histological features of this pulmonary nodule. (A) Low-power view (infarction in the left upper field) [Hematoxylin and eosin (H&E); original magnification, x20]. (B) High-power view revealing ghost shadows of infarcted lung tissue with consolidation in the left field, a fairly thick collar of reactive-inflammatory change in the middle field, and viable lung tissue in the right field. Note the absence of caseous necrosis and granuloma in this and near all of the other sampled parts. [H&E; original magnification, x80]

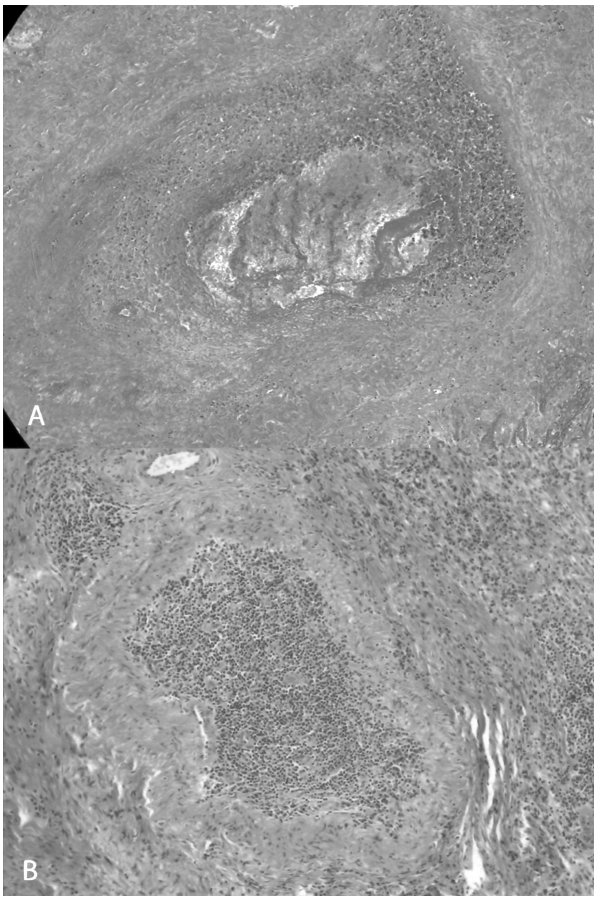

Fig. 5. Larger blood vessels in this lesion (infarcted lung tissue). (A) Necrotic debris and coagulated blood clot filling the lumen of an infarcted artery [H&E; original magnification, x100]. (B) Chronic inflammatory infiltrates and capillaries in the lumen of another blood vessel located at the periphery of the major lesion. Note the lack of inflammatory infiltrates in its muscular wall [H&E; original magnification, x200]

revealed under EVG stain and many of their lumens were filled with either necrotic debris or coagulated blood clot (Figure 5). There was no evidence of neoplasm in this lesion. The overall findings suggested organizing localized pulmonary infarction probably related to a certain focal vascular occlusive mechanism. There were no intra-operative or postoperative complications and the patient was discharged on the 7th day post-surgery.

Discussion

Pulmonary infarctions often result from pulmonary thromboembolism, heart failure, vasculitis, infection, or malignancy [3]. Due to the rarity of their occurrence, clinical physicians often do not consider this differential diagnosis. In addition, few cases of pulmonary infarctions mimicking lung cancer in the imaging examinations have been reported [4-5]. To

avoid missing a pulmonary malignancy and its poor outcome, clinical physicians try to rule out the diagnosis of pulmonary infarction as they deal with the solitary pulmonary nodule. Most cases of solitary pulmonary nodules can be diagnosed with a combination of chest radiography, chest CT, chest MRI, bronchoscopy and transthoracic needle aspiration biopsy [6]. However, some cases demand the implementation of surgical biopsy by VATS or thoracotomy [7-8]. More than 80 diseases are included in the differential diagnosis of a solitary pulmonary nodule [9]. However, the correct diagnosis usually is not reached until lung biopsy.

The appearance of pulmonary infarction in the chest plain film is not specific and the definite diagnosis is hard to confirm by a non-specific finding alone. Chest CT offers physicians more hints to help them reach a precise diagnosis. Using CT scan, Balakrishnan found pulmonary infarctions that appeared as parenchymal densities with a broad pleural base, convex borders, linear strands from the apex of the infarct toward the hilum, and low attenuation areas within the lesion in 12 patients [10]. Pulmonary infarctions, therefore, can be suspected by the presence of peripheral parenchymal opacities with characteristic CT scan findings.

Though the main causes of pulmonary cavitation are malignancy and infectious diseases, pulmonary infarction is a cause that should be considered [11]; cavitation complicates about 4-7% of pulmonary infarctions [12]. Positron emission tomography/computed tomography (PET-CT) scan is usually used in the initial and follow-up staging of lung cancer [13]. False-positive results can occur in acute inflammation or infectious conditions. Pulmonary embolisms have abnormally hypermetabolic nodules, and small occult infarctions also have hypermetabolic nodules in the peripheral lung [14].

The introduction of fine needle biopsy changed the diagnostic work-up of pulmonary nodules due to its mildly invasive characteristic, and provides a method of cytological evaluation. The diagnostic accuracy of fine needle biopsy varies in large (>1.5 cm in diameter) and small nodules (96% and 74%, respectively) [15]. But cytology revealed false-positive results for lung cancer in a patient with pulmonary infarction, due to its atypical reactive alveolar lining of type II and metaplastic cells near the infarction [16].

At present, the only certain diagnosis of the nature of the nodule is obtained by histological examination of the surgical sample [7,17]. Due to its greatly acceptable advantages, including minimized surgical trauma, shortened hospitalization period, reduced postoperative pain, and rare mortality and morbidity, VATS provides the clinician with a better way to deal with pulmonary nodules [18-20].

In our case, there were no predisposing factors of pulmonary infarction obtained from the patient's medical history and clinical presentation. The only medical history that we gained from this patient was AVN of the femoral head and alcoholism. We now know that alcohol abuse is a major causes of AVN, and that vasculitis and arterial embolism are also contributing factors [21]. In reviewing the literature, we found no studies mentioning the relationship between AVN and pulmonary infarction. In addition, microscopic examination of the patient's specimen revealed neither necrotic bone nor bone marrow tissue in the infarcted vessels. So we do not have strong evidence linking the pulmonary infarction to the AVN. The co-factors that we did not discover may have occurred before and resulted in both diseases. A discussion

of the relationship between these 2 diseases requires further retrospective review.

Conclusions

Solitary pulmonary nodule is a diagnostic challenge for clinical physicians. There are numerous common and uncommon causes of solitary pulmonary nodule.

In this context, in cases of peripheral lung nodules in subpleural regions, the possibility of pulmonary infarction should be considered despite its rarely causing solitary pulmonary nodule. Surgical removal is still the most sensitive and specific way to obtain a correct analysis of the lesion. We believe that VATS provides an easy, safe and accurate method for diagnosis and helps resolve the diagnostic doubt in patients with a high-risk of malignancy. Even though pulmonary nodule is a potentially benign pathology, one should not run the risk of losing precious time in cases of malignant disease in its early phase.

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局部性肺梗塞所導致的單一肺部結節

陳百璽　張國明 *

對臨床醫師而言，從胸部的影像學檢查去發現單一肺部結節並不困難，但是要能夠正確的診斷，卻有一定的難度。我們要報導一位無任何胸部症狀的 43 歲的男性病患，因無意間被發現左側肺部單一結節而被轉至胸腔外科做進一步的診斷治療，經由數項針對肺部結節及腫瘤的檢查，仍然無法得到確切的診斷。最終，透過胸腔鏡輔助開胸術的方式，病患接受了肺部腫瘤的切除，而得到肺部梗塞的診斷。雖然肺部梗塞的發生率很低，但仍需將其列入肺部結節的鑑別診斷之中。*(胸腔醫學 **2014; 29: 310-316**)*

關鍵詞：單一肺部結節，肺部梗塞，肺癌，胸腔鏡輔助開胸術

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Life-threatening Hypoxemia in a Young Adult: A Case Report of Idiopathic Acute Eosinophilic Pneumonia

Guan-Liang Chen, Yi-Ming Chang*, Wann-Cherng Perng, Chih-Feng Chian

Idiopathic acute eosinophilic pneumonia is a rare cause of acute respiratory failure; studies are limited to case reports, and there is no definite incidence. One study reported 18 cases among 183,000 soldiers in or near Iraq. Diagnosis would lead to a change from empirical broad-spectrum antibiotic treatment to corticosteroid therapy, but the diagnosis is always delayed until the presentation of eosinophilia. We report a 22-year-old male who developed fever and breathlessness with rapid progression to acute respiratory failure. This patient received hydrocortisone 200 mg/day 1 week before the confirmatory diagnosis, and dramatically improved to the point of extubation within 3 days. Initial radiograph and computed tomography of the chest showed multiple ground-glass opacities in the bilateral lungs. Eosinophilia (15%) developed on the 10th day, and bronchoalveolar lavage fluid revealed an elevated percentage of eosinophils (37%). No triggering agent that would have induced pulmonary eosinophilia was found in this case, so idiopathic acute eosinophilic pneumonia was diagnosed. The patient gradually recovered to normal activity within 2 weeks. No relapse of symptoms was seen up to this writing. ***(Thorac Med 2014; 29: 317-322)***

Key words: acute eosinophilic pneumonia, hypoxemia, bronchoalveolar lavage, eosinophilia, acute respiratory failure

Introduction

Idiopathic acute eosinophilic pneumonia (AEP) is a rare cause of acute respiratory failure and is a type of pulmonary eosinophilia. The differential diagnoses of pulmonary eosinophilia include helminthic or fungal infection, drug- or toxin-induced eosinophilic lung diseases, Churg-Strauss syndrome, neoplasms, and idiopathic hypereosinophilic syndrome. Many other causes of hypoxemia, such as bacterial, viral, fungal pneumonia, pulmonary embolism, or suffocation, are seen in our daily clinical practice. This diesase was first described in 1989 by Allen, *et al* [1]. The associated symptoms, like cough, fever, and breathlessness, and even acute respiratory failure, are often non-specific. The disease frequently progresses rapidly from

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mild cough to severe hypoxemia. AEP occurs in healthy individuals at any age, but the average age is 17 to 39 years [2]. It is twice as prevalent in men as in women [2]. Although many possible causes have been reported, the etiology in most cases remains unknown. We report the case of a young man who presented with severe hypoxemia and an elevated percentage of eosinophils in the serum and bronchoalveolar lavage (BAL) fluid.

Case Report

This 22-year-old male with a history of allergic rhinitis had been enlisted in the navy for months. He presented to the emergency room with shortness of breath and fever during an afternoon. His body temperature was 38.4°C, blood pressure was 109/60 mmHg, respiratory rate was 29/min, and oxygen saturation by pulse oximeter was 87% in room air. Physical examination revealed fine inspiratory crackles in the bilateral lower lobes. Skin rash, eschar, or heart murmur was not found. Laboratory data disclosed leukocytosis (27,960/uL) with an elevated percentage of neutrophils (80.2%, band forms 8.5%) and elevated CRP (13.47 mg/dL). Liver, kidney, and coagulation functioning was normal. Chest radiograph showed multiple ground-glass opacities at the bilateral lower lung field (Figure 1). Computed tomography (CT) of the chest, which was performed on the 2nd day, showed thickening of the bronchovascular bundles and interlobular septum in addition to multiple ground-glass opacities (Figure 2). Ertapenem 1 gm/day, doxycycline 100 mg/ 12 hours, and clarithromycin 500 mg/12 hours were prescribed under suspicion of pneumonia due to bacterial or atypical pathogens. However, the hypoxemia and dyspnea progressed rapidly, even with the support of bilevel positive airway pressure on the 2nd day and endotracheal intubation with mechanical ventilation on the 3rd day. In addition to progressive patchy opacities, scanty bilateral pleural effusion developed on the 5th day. Parasites were not present in the urine, stool, or sputum examinations. Testing for influenza A/B antigens and polymerase

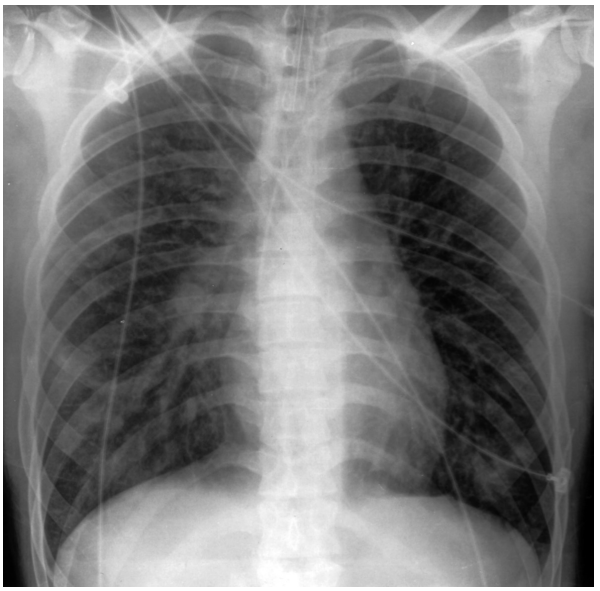

Fig. 1. Multiple patchy opacities at the bilateral lower lungs on the 3rd day.

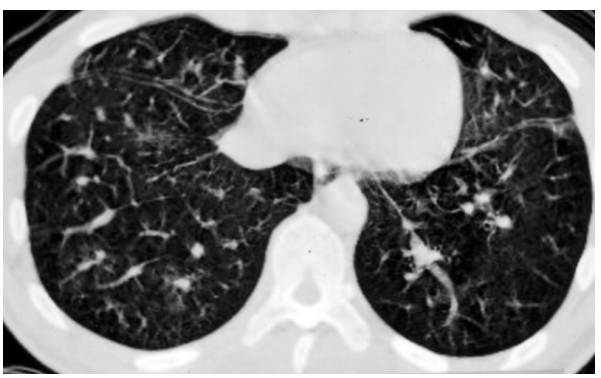

Fig. 2. Multiple ground-glass opacities and thickening of bronchovascular bundles and the interlobular septum on computed tomography of the chest.

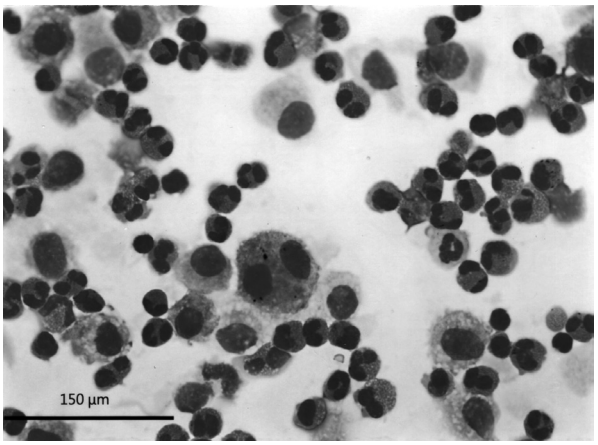

Fig. 3. Numerous eosinophils with a bi-lobed nucleus and reddish cytoplasmic granules in the BAL fluid.

chain reaction for herpes simplex virus, cytomegalovirus, and *Pneumocystis jirovecii* were negative, as was testing for serum mycoplasma antigen, sputum Chlamydia antigen, and urine Legionella antigen. Abdominal sonography and echocardiogram disclosed no remarkable findings. Due to the presentation of wheezing, hydrocortisone 200 mg/day was prescribed on the 3rd day. Fever subsided soon after, and oxygenation improved gradually within 2 days, so mechanical ventilation was removed on the 5th day. Eosinophilia (15%) developed on the 10th day, and the maximal serum percentage of eosinophils was up to 23.5% on the 18th day. Owing to rapidly progressive respiratory distress and eosinophilia, BAL was performed on the 16th day. The percentage of eosinophils was 37% in the BAL fluid (Figure 3). Because of the pulmonary infiltrates, hypoxemia, and eosinophils of more than 25% in the BAL fluid, idiopathic AEP was diagnosed in this young adult. He gradually recovered to normal activity, with complete resolution on the chest radiograph within 2 weeks. No relapse of symptoms has been observed up to this writing.

Discussion

Although the etiology of AEP remains unknown, several reports have revealed some possible factors predisposing to the onset of this disease, for instance, inhaled smoke, recent onset of cigarette smoking, fine airbone dust, environmental factors, and inhalation of cocaine or heroin [3-5]. In this case, secondhand smoke, inhaled dust, or unidentified factors in the new environment may be involved. A similar report of 18 cases of AEP among 183,000 military personnel revealed possible associations with smoking and inhaled dust [5]. In a review of 83 patients, more than 60% were current smokers [2]. The pathophysiology of AEP, however, has not yet been determined. A study of 5 patients with AEP indicated that elevated interleukin-5 in the lung may initiate the recruitment of eosinophils and enhance the release of mediators, and vascular endothelial growth factor from eosinophils was demonstrated to increase the permeability of blood vessels as a result [6].

In a review of 97 patients, the common presenting symptoms and signs were temperature >100.3°F (93.9-100%), dyspnea (54-100%), cough (60-100%), and inspiratory crackles on lung auscultation (30-80%) [2]. The characteristic manifestations of this patient included nonproductive cough, dyspnea, hypoxemia, fever, duration of symptoms less than 1 month, inspiratory crackles, and pulmonary infiltrates. Acute respiratory failure also developed during the hospital course. In another case report, 63% of patients developed acute respiratory failure and required mechanical ventilation [7]. Characteristic findings of laboratory tests in AEP were also seen in this case, and included initial neutrophilic leukocytosis, and subsequent elevated eosinophil percentage. The other laboratory

tests were unremarkable. In 2007, thymus- and activation-regulated chemokine was reported as a specific marker for AEP, but this test is not widely used currently [8].

Bilateral ground-glass opacities and interlobar septal thickening are common findings on high resolution CT. Other findings include airspace consolidation, ill-defined centrilobular nodules, thickening of bronchovascular bundles, and pleural effusion [9]. In a review of 64 patients, all had bilateral pulmonary infiltrates with variation among alveolar, interstitial, and mixed patterns. Due to these non-specific findings, it is difficult to differentiate between acute respiratory distress syndrome and infectious pneumonia [2]. In this case, chest radiograph and CT offered no more useful information; therefore, definitive diagnostic procedures are still needed for the diagnosis of AEP. One study described the diagnostic criteria required for AEP, as follows: (1) acute onset of febrile respiratory manifestations <1 month in duration, (2) bilateral diffuse infiltrates on chest radiograph, (3) hypoxemia defined as PaO_2 <60 mmHg or arterial oxygen saturation <90% in room-air pulse oximetry, (4) BAL showing >25% eosinophils or eosinophilic pneumonia on lung biopsy, and (5) an absence of known causes of pulmonary eosinophilia, including drugs, toxins, and infections [5]. The authors also suggest that the diagnosis can be made with BAL eosinophilia and without lung biopsy, but the latter indeed has a role in excluding other diagnoses. In the above study, BAL was performed with the patient, and the eosinophil percentage was up to 37% in BAL fluid, much higher than the 25% reported in other cases [7]. Under a high power field, numerous bi-lobed eosinophils presented with reddish cytoplasmic granules. This less invasive procedure avoids the need for the complication of lung biopsy, which was considered as a required procedure previously [10].

Although AEP may subside spontaneously, the disease has a good response to intravenous or oral glucocorticoid therapy [11]. No clinical trial has been performed to determine the optimal dose or duration of glucocorticoid therapy. In clinical experience, the usual dose of methylprednisolone was 60 to 125 mg/6 hours in the presence of respiratory failure for 1 to 3 days. After resolution of respiratory failure, oral prednisolone 40 to 60 mg/day can be prescribed for 2 to 4 weeks, until complete recovery [11]. However, severe refractory hypoxemia could develop before the diagnosis of AEP. Extracorporeal membrane oxygenation has a bridging role before the use of glucocorticoid [12]. If the symptoms do not respond to therapy, other diagnoses should be considered. Relapse is uncommon except through re-exposure to possible triggering agents. In a case report, a cigarette smoking challenge test induced recurrence of AEP [13].

In conclusion, AEP is a rare disease, but should be considered in unexplained acute respiratory failure, especially in young adults. According to current experience, BAL, an easily performed and well-tolerated procedure, has a good diagnostic yield and safety profile, and can avoid the need of invasive transbronchial or surgical lung biopsy.

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患有危及生命之低血氧症的年輕人：急性嗜酸性白血球肺炎的病例報告

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不明原因的急性嗜酸性白血球肺炎是造成急性呼吸衰竭的疾病中一個罕見的原因，僅少數的個案報告，沒有明確的發生率，只有一篇研究報告 183,000 個在伊拉克的士兵中有發現 18 個病例。病患往往是出現了嗜酸性白血球增多症才有進一步確診，使治療從經驗性廣效抗生素治療轉變為類固醇治療。我們報告一個出現發燒和呼吸困難，且迅速進展至急性呼吸衰竭的 22 歲年輕人。病患在確診前一週接受 hydrocortisone 200 mg/day，治療後症狀獲得戲劇性的改善，且在三天內即移除氣管內管。初始的胸部 X 光片和電腦斷層顯示肺部雙側多發性毛玻璃樣斑塊陰影。出現症狀的第 10 天後發展出嗜酸性白血球增多（15%），且支氣管肺泡沖洗術發現嗜酸性白血球百分比增加（37%）。在本個案並沒有發現會造成肺嗜酸性白血球增多的誘發因子，所以診斷為原因不明的急性嗜酸性白血球肺炎。患者於二週內逐漸恢復正常功能，症狀到目前為止並未復發。*(胸腔醫學* ***2014; 29: 317-322)***

關鍵詞：急性嗜酸性白血球肺炎，低血氧，支氣肺泡沖洗術，嗜酸性白血球，急性呼吸衰竭

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