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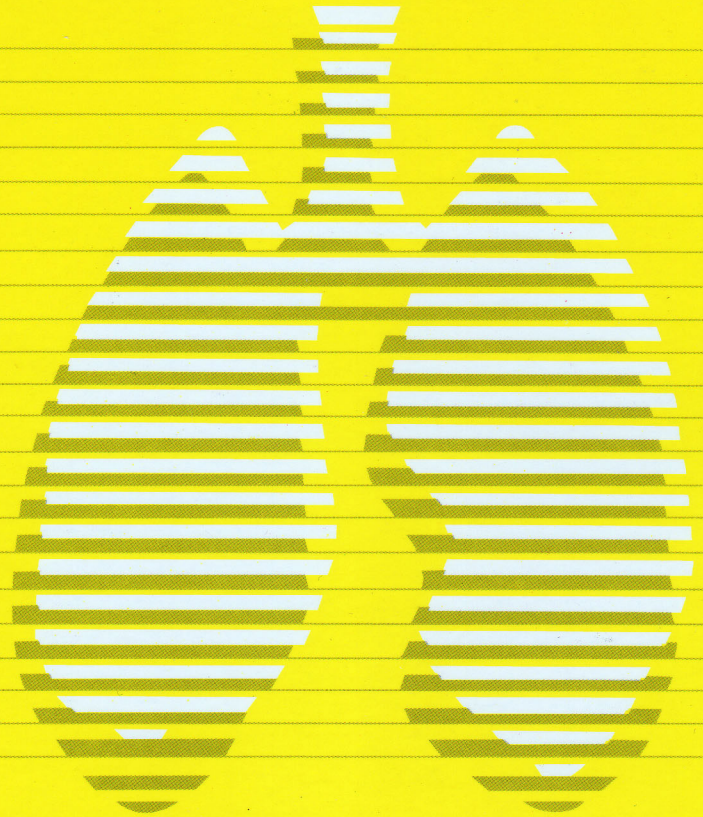

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Orginial Article

Case Reports

Increased Risk of Sleep Apnea in Taiwanese Patients with Chronic Obstructive Pulmonary Disease

Chia-Yu Kuo*, Ming-Ju Tsai*,**, Jui-Ying Lee***, Chau-Chyun Sheu*,**, Jen-Yu Hung*,**, Inn-Wen Chong*,**

Objective: The potential association between chronic obstructive pulmonary disease (COPD) and sleep apnea has been previously studied; however, the study results are contradictory. Therefore, we designed a nationwide population-based cohort study to determine the association between COPD and sleep apnea in Taiwan.

Methods: Using the Taiwan National Health Insurance Research Database, adult patients with a diagnosis of COPD were enrolled; those with a sleep apnea diagnosis prior to their COPD onset were excluded. The date of each patient's first COPD diagnosis was defined as the index date. Each COPD patient was matched with 5 randomly selected control subjects without a COPD diagnosis. The control subjects were assigned the same index dates as their corresponding COPD patient, and we ensured that they had no sleep apnea diagnosis prior to their index date.

Results: A total of 35,095 COPD patients were matched with 175,475 control subjects. The incidence rate of sleep apnea was significantly higher among the COPD patients than among the control subjects (0.5 vs. 1.0 per 1,000 patient-years; $p<0.0001$). Multivariable Cox regression analysis revealed COPD to be a significant risk factor for sleep apnea ($p<0.0001$). Factors associated with incident sleep apnea among COPD patients in this study included male, resident of northern Taiwan, higher income, heart disease, connective tissue disease and cancer.

Conclusion: COPD patients had a significantly higher risk of developing sleep apnea than non-COPD patients. When caring for patients with COPD in any context, clinicians need to pay special attention to the risk of incident sleep apnea, especially among male patients, and those with heart disease, connective tissue disease and cancer. ***(Thorac Med 2019; 34: 178-189)***

Key words: sleep apnea, sleep disordered breathing, chronic obstructive pulmonary disease

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease that is characterized by persistent airflow limitation associated with enhanced chronic airway inflammation [1]. As a patient's airflow limitation increases, that person usually experiences productive cough, disabling dyspnea and impaired gas exchange with hypercapnia and hypoxemia; this results in a decreased quality of life and an increase in morbidities and mortality [2-3]. Major treatment strategies have focused on symptom control and the prevention of acute exacerbations [2]. Many COPD patients experience nocturnal symptoms, and as a result, they often have significantly worse sleep quality than healthy individuals [3-5]. Nocturnal cough and wheezing have been reported in 53% of COPD patients, which can make it difficult for them to fall asleep and stay asleep; 23% of patients described excessive daytime sleepiness [1,3].

Sleep apnea (SA) is a sleep disorder characterized by repeated pauses in breathing during sleep, which leads to fragmented sleep and decreases the body's oxyhemoglobin saturation [6]. Obstructive SA (OSA), which has an estimated prevalence of 10-20% in the general population, makes up >90% of SA cases [7]. It is characterized by repeated episodes of breathing cessation or marked airflow reduction due to increased upper airway resistance [8]. Risk factors for SA include male gender, age, obesity, and upper airway diseases, such as rhinitis [9]. Over the past few decades, SA has been found to be associated with a variety of neurocognitive dysfunctions, behavioral disorders and cardiovascular diseases, which may increase the mortality rates of these patients [10-12]. Timely diagnosis and appropriate treatment of SA are essential due to the cardiovascular comorbidities and risk of sudden death [13].

COPD and OSA are both obstructive disorders of the airway, and the potential association between them has been previously discussed. However, this association remains unclear and is still debated. We therefore performed a nationwide population-based cohort study to determine the association between COPD and SA in Taiwan.

Methods

Data sources

Taiwan's National Health Insurance (NHI) has covered ambulatory care, hospital inpatient care, dental services and prescription drugs in Taiwan since March 1995. The NHI coverage rate was 96.16% of the whole population (about 23 million people) in 2000 and rose to 99% by the end of 2004 [14]. The NHI medical reimbursement claims database is managed by the National Health Research Institute. The dataset used for the current study was the Longitudinal Health Insurance Database 2005 (LHID2005), a cohort of 1 million randomly selected individuals enrolled in the NHI system before the end of 2000; it includes reimbursement information up to the end of 2013 [15]. Patient identification numbers were encrypted for confidentiality. The present study protocol was approved by the Kaohsiung Medical University Hospital Institutional Review Board (KMUH-IRB-EXEMPT-20130034 and KMUH-IRB-EXEMPT-20140002).

COPD cohort

A total of 62,290 patients with COPD were identified using the algorithm presented in Figure 1. Initially, 86,720 patients with a COPD

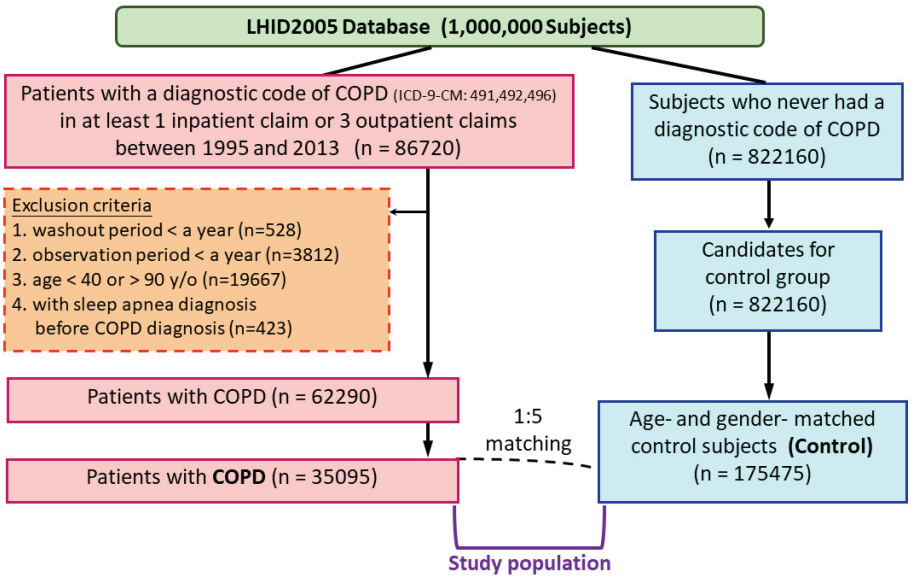

Fig. 1. Algorithm for identifying the study population. COPD: chronic obstructive pulmonary disease; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification.

diagnosis on at least 1 inpatient claim or 3 outpatient claims between 1995 and 2013 were identified. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 491, 492 and 496 were used for diagnosis of COPD [16-18]. Patients with washout periods (from NHI enrollment to the index date) of less than 1 year were excluded to ensure newly diagnosed COPD and those with less than a 1-year follow-up were also excluded. Patients who were less than 40 years old or over 90 years old on the index date, and those with a diagnosis of SA before the index date were excluded. ICD-9-CM codes 780.51, 780.53 and 780.57 were used for a diagnosis of SA [19-21].

Each patient was followed from the date of their initial COPD diagnosis, defined as the index date, to the time of development of SA, the end of the study period, or the termination of their records because of death or withdrawal from the insurance program, whichever came first.

Control cohort

For each patient with COPD, 5 age- and gender-matched control subjects were randomly selected. The control subjects were given the same index date as their corresponding COPD patient. During the matching process, the exclusion criteria used for the COPD patients were also applied to the control subjects to ensure washout periods and follow-up periods that were long enough, and the absence of any SA diagnosis before the index date. Following this, 175,475 control subjects were matched with 35,095 COPD patients. As with the COPD patients, the control subjects were followed from the index date to the development of SA, the end of the study period, or termination of the records because of death or withdrawal from the insurance program, whichever came first.

Comorbidities

The presence of any comorbidity was identified by a diagnostic code before the index

date, and was further confirmed by the presence of any corresponding codes in at least 3 ambulatory claims or a single inpatient claim. A modified Charlson Comorbidity Index (mCCI) score was calculated by excluding chronic pulmonary disease from the original CCI score.

Statistical analysis

The demographic data, comorbidities and mCCI scores of the COPD patients and control subjects were compared using Pearson's χ^2 test for categorical variables and Student's t test for continuous variables, as appropriate. The SA incidences were compared, and stratified analyses, which classified the subjects by sex, age group or the presence of comorbidities, were used. The SA incidence rate was calculated as the number of SA cases that developed during the follow-up period, divided by the total number of person-years. The SA incidence rates among the COPD patients and control subjects were further compared by calculating the incidence rate ratio (IRR), which was defined as the ratio of SA incidence among COPD patients and control subjects. The 95% confidence intervals (CIs) for the IRRs were estimated under the assumption that the observed number of SA cases followed a Poisson probability distribution. Stratified analyses, classifying the subjects by sex, age group, area of residence, income level, and the presence of comorbidities, were also performed. The adjusted IRRs were obtained using multivariable analyses adjusted for sex, age, area of residence, income, and the presence of various comorbidities. The cumulative incidence of SA was calculated and compared using the Kaplan-Meier method and log-rank test. To further assess the effect of COPD on the incidence of SA and the factors associated with incident SA in COPD patients, multivariable Cox proportional hazards regression analysis was performed with adjustments for age, gender and comorbidities, and the hazard ratios (HRs) were calculated.

Data extraction, analysis, linkage, and processing, and all statistical analyses were performed using the SAS system (version 9.4 for Windows, SAS Institute Inc., Cary, NC, USA). A 2-sided p value of <0.05 was considered to indicate a statistically significant difference.

Results

In all, 35,095 COPD patients were matched with 175,475 control subjects. The baseline characteristics of the COPD cohort and the control group are listed in Table 1. The mean age in both groups was 56.6 years. The COPD cohort had a significantly higher rate of comorbidities, including heart disease, peripheral vascular disease, major neurological disorders, connective tissue disease, peptic ulcers, liver disease, diabetes mellitus, renal disease and cancer.

The cumulative incidence of SA was significantly higher in the COPD patients than in the control subjects ($p<0.0001$; Figure 2). In addition, the incidence rate of SA was significantly higher among the individual COPD patients than among their 5 corresponding control subjects (1.0 vs. 0.5 per 1,000 patient-years; adjusted IRR [95% CI]: 1.5 [1.5-1.6], $p<0.0001$; Table 2). In the stratified analyses, a significantly higher SA incidence rate was observed among the COPD patients across the majority of strata, including male and female subjects, residents of northern Taiwan or other areas, patients with a lower or higher income and patients with or without comorbidities. However, when the study population was stratified by age, a significantly increased SA incidence rate

Table 1. Baseline Characteristics of the Study Cohorts

Characteristics	Control	COPD patients	*p*-value
N	175,475	35,095	
Male, n (%)	87,865 (50%)	17,573 (50%)	
Age (years), mean ± SD	56.6 ± 11.1	56.6 ± 11.1	0.8639
Age (years), n (%)			0.8522
≤50	63,057 (36%)	12,557 (36%)	
>50	112,418 (64%)	22,538 (64%)	
Area of residence			<0.0001
Northern Taiwan	39,800 (23%)	7577 (22%)	
Other areas	135,675 (77%)	27,518 (78%)	
Monthly income (NT$), median (IQR)	21,900 (1007-33,300)	21,900 (1099-31,800)	<0.0001
Monthly income (NT$), n (%)			0.0173
≤ 24,000	119,437 (68%)	24,115 (69%)	
> 24,000	56,038 (32%)	10,980 (31%)	
Wash-out period (years), median (IQR)	9.1 (5.5-12.9)	9.3 (5.6-13)	0.0002
Follow-up period (years), median (IQR)	8.8 (5.1-12.6)	8.8 (5-12.7)	0.5187
Modified CCI score, mean ± SD	0.8 ± 1.5	1.3 ± 1.8	<0.0001
Modified CCI score, n (%)			<0.0001
= 0	113,116 (64%)	16,315 (46%)	
= 1	30,819 (18%)	8209 (23%)	
≥ 2	31,540 (18%)	10,571 (30%)	
Underlying diseases, n (%)			
Heart disease	4349 (2%)	1928 (5%)	<0.0001
Peripheral vascular disease	1917 (1%)	617 (2%)	<0.0001
Major neurological disorder	12,993 (7%)	4668 (13%)	<0.0001
Connective tissue disease	2258 (1%)	845 (2%)	<0.0001
Peptic ulcer disease	29,965 (17%)	10,263 (29%)	<0.0001
Liver disease	18,177 (10%)	6178 (18%)	<0.0001
Diabetes mellitus	19,997 (11%)	5617 (16%)	<0.0001
Renal disease	4880 (3%)	1598 (5%)	<0.0001
Cancer	7099 (4%)	2091 (6%)	<0.0001

SA: sleep apnea; IQR: interquartile range; CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease.

was observed only in COPD patients aged ≤50 years (adjusted IRR [95% CI]: 2.3 [2.2-2.4], $p<0.0001$); COPD did not appear to be significantly associated with the SA incidence rate in patients aged >50 years (adjusted IRR [95% CI]: 1.1 [1.0-1.1], $p=0.0726$). In the multivariable Cox regression analysis, COPD remained a significant risk factor for the development of SA after adjusting for age, sex, area of residence, income level and comorbidities (adjusted

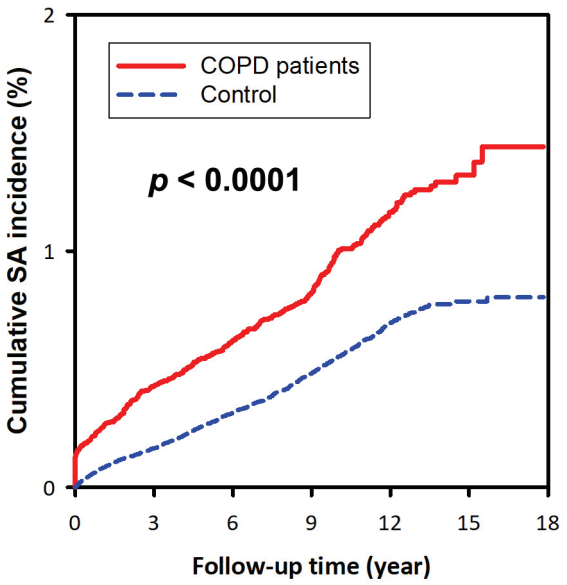

Fig. 2. Cumulative incidences of sleep apnea. The blue dashed lines and red lines show the cumulative sleep apnea (SA) incidence rate for the control cohort and the COPD cohort, respectively. The cumulative SA incidence was significantly higher in the COPD cohort than in the control cohort. SA: sleep apnea; COPD: chronic obstructive pulmonary disease.

HR [95% CI]: 1.6 [1.4-1.8], p<0.0001).

Factors associated with SA development in COPD patients were further investigated (i.e., "COPD-SA overlap syndrome"), using multivariable Cox proportional hazards regression analyses. For the COPD patients, independent factors associated with incident SA included male sex (HR [95% CI]: 3.6 [2.7-4.7]), residency in northern Taiwan (HR [95% CI]: 1.4 [1.1-1.8]), higher income (HR [95% CI]: 1.6 [1.3-2.0]), heart disease (HR [95% CI]: 2.1 [1.4-3.3]), connective tissue disease (HR [95% CI]: 1.4 [1.1-1.9]) and cancer (HR [95% CI]: 3.6 [2.7-4.7]; Table 3).

Discussion

In the present population-based cohort study, a significantly higher incidence rate of SA was observed in COPD patients than in the control subjects. However, for subjects aged >50 years, COPD was not significantly associated with an increased SA incidence rate after adjusting for sex, area of residence, income and comorbidities. Among the COPD patients, male sex, residency in northern Taiwan, higher income, heart disease, connective tissue disease, and cancer were all associated with a significantly increased incidence of COPD-SA overlap syndrome.

The association between COPD and SA has been previously discussed in the literature, as both COPD and SA are associated with airflow limitation; however, study results have been inconsistent. In a previous population-based study enrolling 676 subjects in Warsaw, Poland, no association was observed between COPD and OSA [22]. A study carried out in the US revealed no significant association between mild COPD and SA [23]. Another study from the US showed a high prevalence of OSA in 54 patients with moderate-to-severe COPD; however, this study did not compare COPD patients with healthy subjects [24]. An Israeli study using an insurance database showed a significantly higher COPD prevalence in OSA patients than in control subjects [25]. However, a community-based cross-sectional study enrolling 853 older men revealed a significantly lower prevalence of SA in patients with obstructive airway disease (either COPD or asthma) compared to those without obstructive airway disease [26]. In the current study, the incidence rate of SA was significantly higher in COPD patients than among the corresponding control subjects.

The predictors of COPD-SA overlap syndrome have also been discussed in previous studies. A study from Switzerland reported that body mass index (BMI) and smoking history

Table 2. Incidence Rate of Sleep Apnea after the Index Date in Each Group

	Control				COPD patients				Crude	Adjusted
	N	SA	PY	IR	N	SA	PY	IR	IRR [95% CI]	IRR [95% CI]
Whole study population	175,475	842	1,535,425.1	0.5	35,095	304	307,668.2	1.0	1.8 [1.7-1.9] ***	1.5 [1.5-1.6] ***
Stratified analyses										
Sex										
Female	87,610	199	821,927.6	0.2	17,522	69	164,279.1	0.4	1.7 [1.6-1.8] ***	1.3 [1.2-1.3] ***
Male	87,865	643	713,497.5	0.9	17,573	235	143,389.1	1.6	1.8 [1.7-1.9] ***	1.6 [1.5-1.7] ***
Age										
≤50	112,418	301	883,464.6	0.3	22,538	166	176,497.8	0.9	2.8 [2.6-2.9] ***	2.3 [2.2-2.4] ***
>50	63,057	541	651,960.5	0.8	12,557	138	131,170.5	1.1	1.3 [1.2-1.3] ***	1.1 [1.0-1.1]
Area of residence										
Northern Taiwan	39,800	271	431,026.3	0.6	7577	99	82,530.0	1.2	1.9 [1.8-2.0] ***	1.7 [1.5-1.8] ***
Other areas	135,675	571	1,104,398.8	0.5	27,518	205	225,138.2	0.9	1.8 [1.7-1.8] ***	1.4 [1.4-1.5] ***
Monthly income										
≤NT$24,000	119,437	354	1,002,990.7	0.4	24,115	155	201,708.9	0.8	2.2 [2.1-2.3] ***	1.7 [1.6-1.7] ***
>NT$24,000	56,038	488	532,434.4	0.9	10,980	149	105,959.3	1.4	1.5 [1.4-1.6] ***	1.4 [1.3-1.5] ***
Comorbidity										
No (mCCI score = 0)	113,116	556	1,114,765.5	0.5	16,315	131	169,018.7	0.8	1.6 [1.5-1.6] ***	1.4 [1.3-1.5] ***
Yes (mCCI score ≥ 1)	62,359	286	420,659.6	0.7	18,780	173	138,649.6	1.2	1.8 [1.7-1.9] ***	1.6 [1.5-1.7] ***

The adjusted IRRs were calculated by multivariable analyses adjusting for sex, age, area of residence, income and the presence of various comorbidities (except for the variables used for stratification).

*p<0.05; **p<0.01; ***p<0.0001

mCCI: Modified Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; N: number of patients; SA: number of patients developing sleep apnea; PY: total patient-years; IR: incidence rate, expressed as SA incidence per 1,000 patient-years; IRR: incidence rate ratio; CI: confidence interval.

were predictors of COPD-SA overlap syndrome [27]. In a community-based cross-sectional study from Korea, BMI was associated with a decreased risk of COPD in moderate-to-severe OSA patients; however, male sex and age were associated with an increased risk of COPD in mild OSA patients [26]. In the current study, factors predicting the development of COPD-SA overlap syndrome in COPD patients included male sex, residency in northern Taiwan, a higher income, heart disease, connective tissue disease, and cancer.

Male sex is traditionally considered a risk factor for both SA and C. In Taiwan, as in many Asian countries, smoking has traditionally been a behavior undertaken by males, and most male COPD patients continue to smoke despite being informed of the negative health effects [3,28]. Therefore, in addition to the genetic factor, cigarette smoking (which may narrow the upper airway via mucosal inflammation) may predispose male patients to SA [29-30]. Compared to individuals with a lower income, patients with a higher income may be more aware of their health status and are therefore more likely to seek medical advice. In addition, patients in northern Taiwan have better access to medical resources than individuals in

Table 3. Multivariable Cox Regression Analysis of Factors Contributing to Sleep Apnea in COPD Patients

	HR [95% CI]	*P* value
Male vs. Female	3.6 [2.7-4.7]	<0.0001
Age >50 vs. Age ≤50	1.0 [0.8-1.3]	0.9713
Area of residence (northern Taiwan vs. other areas)	1.4 [1.1-1.8]	0.0052
Higher income (>NT$24,000) vs. Lower income (≤NT$24,000)	1.6 [1.3-2.0]	<0.0001
Presence of underlying diseases:		
Heart disease	2.1 [1.4-3.3]	0.0009
Peripheral vascular disease	1.3 [0.5-3.2]	0.5647
Major neurological disorder	1.0 [0.7-1.5]	0.8431
Chronic pulmonary disease	0.7 [0.3-2.0]	0.5556
Connective tissue disease	1.4 [1.1-1.9]	0.0047
Peptic ulcer disease	1.2 [0.9-1.6]	0.1445
Liver disease	1.2 [0.9-1.7]	0.3066
Diabetes mellitus	1.0 [0.6-1.8]	0.9844
Renal disease	0.6 [0.3-1.2]	0.1225
Cancer	3.6 [2.7-4.7]	<0.0001

HR: hazard ratio; CI: confidence interval; COPD: chronic obstructive pulmonary disease.

other areas. Since health awareness and medical accessibility might influence the likelihood of a diagnosis of SA, higher income level and residency in northern Taiwan were found to be independent factors associated with incident SA in COPD patients. We believe that the observed lower incidence of SA in COPD patients with a lower income level and residency in areas other than northern Taiwan might result from underdiagnosis of SA due to lower health awareness and less access to medical care. Cardiovascular disease is a common comorbidity of COPD, and could be related to the increased systemic inflammation observed in COPD patients. Heart disease, with impaired heart function, may alter the loop gain of breath control and predispose patients to the development of SA. Several clinical features of connective tissue disease, such as rheumatoid arthritis, have been recognized as risk factors for SA; these clinical features include micrognathia, cervical spine pathology, temporomandibular joint involvement, cricoarytenoid joint involvement and obesity [31]. Patients with severe SA have been reported to have an increased risk of incident cancer [32], suggesting that cancer might share some pathophysiological pathways with SA. It is therefore not surprising that cancer was a risk factor for the development of SA in COPD patients in the present study.

Patients with both COPD and SA have more profound oxygen desaturation during sleep and greater sleep perturbation than those with a single disease [23]. The pathophysiological alterations observed in COPD and SA share some common features and have intimate interactions, in which one may accentuate the other [3]. First, increased resistance in various levels of the airway might affect other areas. Increased upper airway resistance, which is classically

seen in SA, may have an impact on thoracic physiology and reduce the effectiveness of gas exchange distal to the site of airway narrowing. Cigarette smoking, the major cause of COPD, may cause chronic rhinitis and pharyngeal mucosal inflammation, leading to crowding of the upper airway, which may predispose patients to SA [29-30]. Second, thoracic and diaphragmatic structures, as well as the ventilatory function during sleep, are altered in both COPD and SA patients. Ventilation is generally reduced by about 40% during rapid eye movement (REM) sleep, and this may be accentuated in COPD patients [33]. Diaphragmatic flattening, which is related to hyperinflation, also leads to diminished excursion and efficiency and can result in an increased dependence on compensatory mechanisms with accessory muscle use. While skeletal muscle atonia occurs during REM sleep, accessory muscle weakness and reduced function of the diaphragm may combine and lead to impaired ventilation and a struggle to overcome obstructions in the airway [3]. Third, the response of the central respiratory drive to hypercapnia and hypoxemia is greatly blunted in COPD [34]. This may contribute to the profound oxygen desaturation observed in COPD patients during sleep, and may aggravate the incidence and severity of both COPD and SA. Fourth, repeated and prolonged nocturnal hypoxemia, which occurs in patients with both COPD and SA, may increase the risk of developing cardiovascular diseases, such as pulmonary hypertension and recurrent cardiac arrhythmia [35-36].

The present study does have some limitations. First, diagnostic codes were used to identify diseases in the database, and this may have led to some inaccuracies. However, the methods we used to identify COPD, SA and many other comorbidities in the NHI Research Database (NHIRD) have been adopted in many studies, and have been previously validated. Second, the NHIRD did not provide detailed information on the severity of COPD, environmental factors, occupation, smoking history, family history, alcohol consumption, abdominal adiposity indices (such as waist circumference or waist-to-height ratio), BMI, diet preference and physical activity. A number of clinical results, including serum laboratory data, polysomnography, pulmonary function tests, and imaging results of the patients were also unavailable as part of the NHIRD. Therefore, controlling for these potentially confounding factors was not possible in the current study. However, stratified analyses were performed and adjustments were made for many important covariates, including age, sex, income level, residential area, and comorbidities, which could minimize the influence of these confounders. To confirm the findings of the current study, further clinical studies collecting data on more clinical variables are needed.

In conclusion, the current study found that patients with COPD have a significantly higher risk of developing SA than those without COPD. Therefore, while caring for patients with COPD, clinicians should be alert to the symptoms and signs of SA, especially among male patients, and those with heart disease, connective tissue diseases or cancer.

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台灣肺阻塞的病人有較高睡眠呼吸中止症的風險

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目的：肺阻塞（COPD）和睡眠呼吸中止症（SA）兩者之間的關係一直有所爭議。因此，我們進行了一個以全國性的人口為基礎的研究來探討 COPD 與 SA 間的關聯性。

方法：從台灣全民健康保險研究資料庫中，我們收錄了成人 COPD 的病人，並排除了在診斷 COPD 前即確診 SA 的病人。以病人第一次診斷 COPD 的日期為指標日期。每個 COPD 患者與 5 個隨機選擇之無 COPD 診斷的對照者配對。對照組在指標日期前確定沒有 SA 的診斷。

結果：本研究共收錄 35,095 位 COPD 患者與 175,475 位對照者進行分析。SA 在 COPD 的病人比起對照組有較高的發生率。以多變項 Cox 迴歸分析校正後，COPD 仍然是發生 SA 的獨立危險因子。在 COPD 的病人當中，男性、居住於北台灣、較高收入、合併心血管疾病、結締組織疾病及癌症與較高的 SA 發生率有關。

結論：COPD 病人有明顯較高的風險罹患 SA。因此，臨床醫師針對 COPD 的病人需花費更多的注意力在 SA 的發生，尤其是針對男性、居住於北台灣、較高收入、合併心血管疾病、結締組織疾病及癌症的病人。*(胸腔醫學 **2019; 34: 178-189**)*

關鍵詞：睡眠呼吸中止，睡眠呼吸障礙，肺阻塞

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Uncommon Metastasis from Lung Cancer: A Case Series and Literature Review

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The most common sites of lung cancer metastasis include the brain, bone, liver, adrenal glands, contralateral lung, and distant lymph nodes. Metastasis of lung cancer to other organs is relatively rare and may not be identified by routine chest computed tomography for lung cancer staging or by checking tumor markers.

We report 3 cases of advanced lung carcinoma with uncommon metastasis at a southern medical center in Taiwan. These uncommon distal metastases included ovary metastasis, intestinal metastasis, and kidney metastasis. All of the metastases were adenocarcinomas. One presented as abdominal pain, the second as flank pain, and the third as an abdominal mass.

Lung cancer patients with uncommon metastases are rare, and the prognosis of this group is relatively poor, according to the literature review. When a patient presents with atypical symptoms including abdominal pain or flank pain, additional images should be taken to identify whether there is an uncommon metastasis. Local treatment and re-biopsy may be beneficial for these patients. ***(Thorac Med 2019; 34: 190-196)***

Key words: lung cancer, uncommon metastasis, ovary metastasis, intestine metastasis, kidney metastasis

Background

Metastatic spread of cancer to distant organs is the major cause of cancer-related death. More than half of lung cancer patients have distant metastasis at the initial diagnosis. The major distant metastatic sites of lung cancer include the central nervous system (37%), bone (36%), liver (17%), and adrenal glands (8%) [1]. Although the majority of distant metastases can be diagnosed based on regular imaging studies, including computed tomography (CT) of the chest, magnetic resonance imaging (MRI) of the brain, and whole body bone scans, 5% of patients still have rare metastatic sites that cannot be diagnosed using the above imaging modalities [1-3]. We herein report 3 cases of uncommon metastasis from lung cancer along with a literature review.

Case 1

A 50-year-old male came to our hospital

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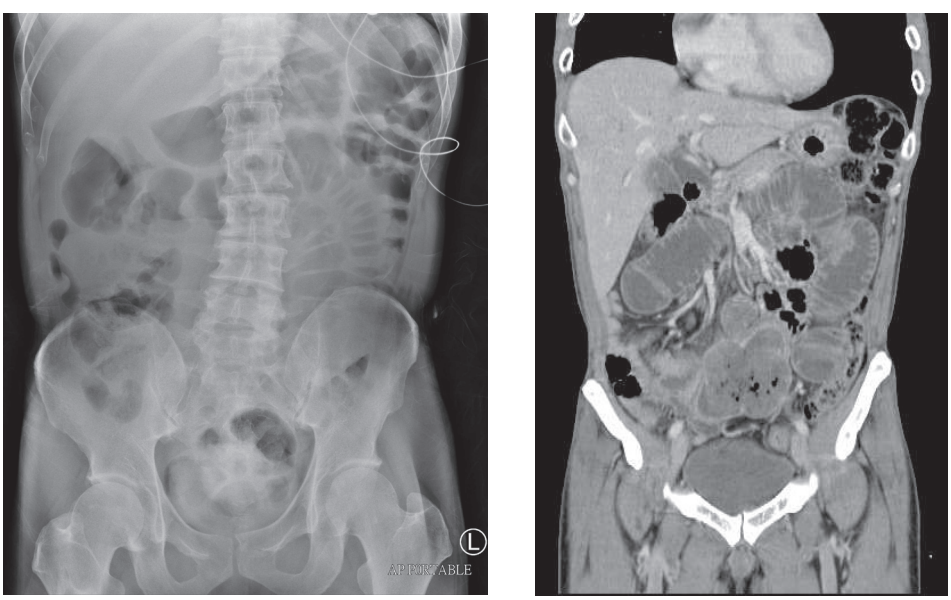
with the chief complaint of a change in bowel habits and body weight loss for 4 months. He had a history of smoking 30 packs of cigarettes per year. The abdominal CT accidentally revealed a right lower cavitation lung lesion and focal irregular wall thickening of the jejunum. CT of the chest showed suspected right lower lung cancer with mediastinal lymphadenopathy, preliminary stage IIIA (T2bN2M0). A CT-guided biopsy was performed, and the pathological report showed adenocarcinoma. During admission, the abdominal pain became aggravated, and repeated abdominal CTs revealed an enlarged jejunal mass with an obstructive ileus (Figure 1). The patient then underwent an operation for excision of a small bowel tumor; the pathology of the jejunal mass revealed adenocarcinoma, compatible with a pulmonary origin. Epidermal growth factor receptor (EGFR) mutation analysis showed no mutation. The final staging was T2bN2M1b, stage IV, and chemotherapy was indicated. However, the patient refused to undergo further treatment.

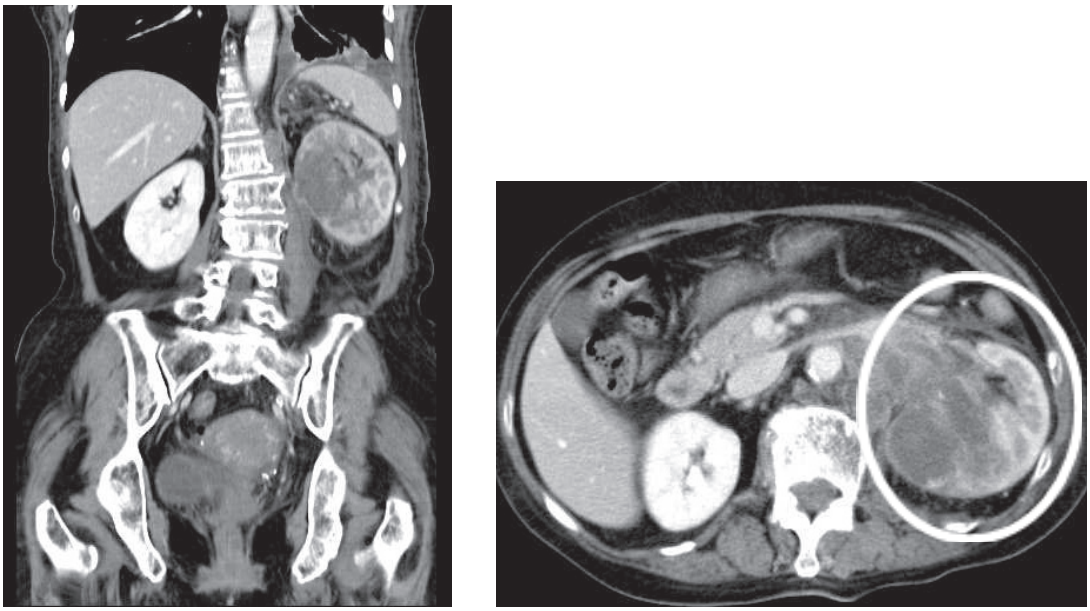
Case 2

A 67-year-old female came to our hospital with the chief complaint of sudden onset of left upper limb weakness. MRI of the brain revealed a tumor at the right frontal lobe, suspected to be metastatic cancer. The chest plain film revealed a left lower lung mass. CT of the chest showed a left lower lung tumor with chest wall involvement and mediastinal lymphadenopathy. The pathology showed adenocarcinoma, and EGFR mutation analysis showed L858R. Thus, the patient received EGFR-TKI and local palliative radiotherapy for symptomatic brain metastasis. Two months later, the lung tumor had shrunk significantly. However, left waist pain developed. CT of the abdomen revealed an infiltrative left renal mass with para-aortic and retrocrural lymphadenopathy (Figure 2). A CT-guided para-aortic lymph node biopsy revealed metastatic adenocarcinoma, compatible with



(A) (B)

Fig. 1. KUB showed ileus (A), and abdominal CT revealed progression of a jejunal mass with an obstructive ileus (B)



(A) (B)

Fig. 2. CT of the abdomen revealed an infiltrative left renal mass with para-aortic and retrocrural lymphadenopathy (A) and (B)

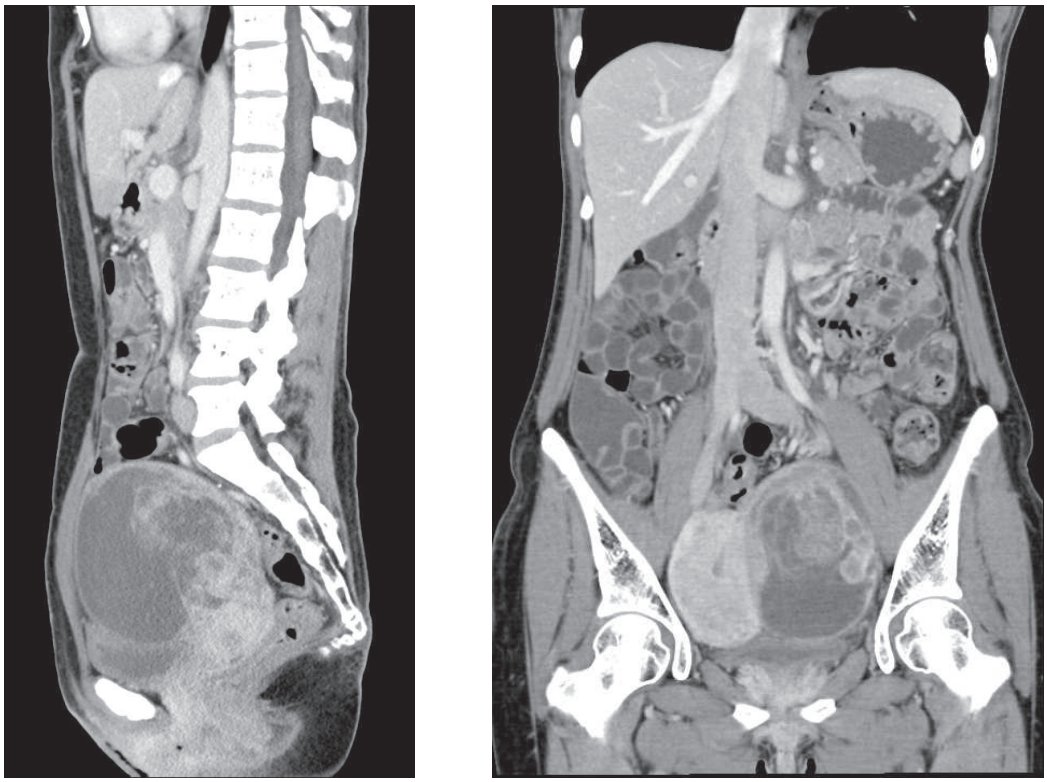
lung origin. After discussion with the family, the patient was given palliative care due to the poor performance status.

Case 3

A 44-year-old female came to our hospital with the chief complaint of chronic cough for 1 and a half years. She also complained of having had low back pain and shortness of breath for 3 months. CT of the chest showed a right middle lung tumor with mediastinal lymphadenopathy. MRI of the brain also revealed a metastatic tumor. A CT-guided biopsy was performed and revealed adenocarcinoma. The EGFR mutation test showed an exon 19 deletion, and afatinib was prescribed for disease control. Follow-up imaging of the chest revealed partial regression. However, 1 year later, abdominal pain developed with an enlarged lower abdominal mass (Figure 3). After discussion with a radiologist and gynecologist, a left ovarian tumor was suspected, and debulking surgery was performed. The pathology report showed metastatic adenocarcinoma, compatible with lung origin. The EGFR test showed a T790M mutation. She then received osimertinib as sequential treatment, and the disease was controlled for more than 1 year.

Discussion

Approximately 5% of lung cancer patients have metastatic sites other than the brain, bone, liver, and adrenal glands; this is referred to as uncommon metastases [1-3]. In our case series, we reported 3 patients with uncommon metastatic sites, including the intestine, kidney, and ovary. A previous retrospective study in China documented the incidence of uncommon metastatic sites, including the kidney (0.87%), peritoneum (0.84%), spleen (0.66%), pancreas (0.59%), and intestine (0.24%), in non-small cell lung cancer [3]. Patients in our case series all had rare metastatic sites.



(A) (B)

Fig. 3. Abdominal CT showed a left ovarian tumor. (A) and (B)

According to autopsy data from patients with lung cancer in 3 retrospective studies, 2 in America and 1 in Denmark, the pooled prevalence of intestinal metastasis was 7.1% (77/1072) [4-6]. In another retrospective study from China, the incidence of intestinal metastasis was only 0.24%. The differences between autopsy data and clinical data indicate that the rate of intestinal metastasis may be higher because most patients are asymptomatic [3]. A review of 57 case reports and 3 retrospective studies found that symptoms, including intestinal perforation (46%), gastrointestinal bleeding (14%), and obstruction (35%) in 100 cases of lung cancer with intestinal metastasis presented only when a metastatic lesion became too large. The pathological reports for these 100 cases showed mostly large cell lung cancer (32%), followed by squamous cell lung cancer (27%) and adenocarcinoma (23%) [7].

Renal involvement in lung cancer is also rare. In a review of 35 case reports of renal metastasis from lung cancer in the English literature [8], pathology reports indicated predominantly squamous cell carcinoma (15/35), and only 1 case of adenocarcinoma. Most patients (27/35, 77%) were diagnosed with renal involvement after documentation of lung cancer. Although most patients had symptoms of hematuria (29/35, 82%) and pain (27/35, 77%), 13 cases (37%) were asymptomatic.

In the literature review, we found similar data for ovary involvement in lung cancer: primary lung cancer was identified in 4 of 915 cases (0.4%) with metastatic ovary tumors [9-12]. In patients with lung cancer, only 36 cases

with ovary metastasis were found [13-15]; most (19/36, 52%) were diagnosed as having ovary involvement after documentation of lung cancer. Most patients had pathological reports indicating small cell lung cancer (14/36, 39%), followed by adenocarcinoma (13/36, 36%), large cell carcinoma (5/36, 14%), and squamous cell carcinoma (1/36, 0.03%). The most common clinical presentations were abdominal pain and pelvic masses, but most patients were asymptomatic.

Patients with uncommon metastasis have been found to have poor prognoses. A retrospective study found median overall survival (mOS) to be significantly shorter for patients with uncommon metastases than for those with common metastases (mOS 13.0 months [95% CI: 10.1-15.9] versus 18.3 months [17.4-19.2], $P<0.01$) [3]. However, additional survival benefits were found for those receiving additional local therapy, compared to those receiving systemic therapy alone (mOS: 12.5 months [95% CI: 4.5-20.5] versus 7.4 months [95% CI: 5.2-9.6], $P<0.01$) [3]. In the AURA 3 study, use of osimertinib, compared to chemotherapy, led to significant improvements in progression-free survival in patients presenting T790M as a resistance mechanism [16]. In our case series, we also had a patient with disease progression secondary to an emerging T790M mutation. She subsequently achieved disease control with osimertinib usage. Re-biopsy for a resistance mechanism, in order to choose an optimal sequential treatment, is very important for lung cancer patients.

Conclusion

According to the literature review, lung cancer patients with metastatic sites other than the brain, bone, liver, and adrenal glands are rare, and the prognosis is relatively poor. When patients present with atypical symptoms, additional examinations should be arranged to identify possible uncommon metastases. Local treatment may be beneficial, but re-biopsy for resistance mechanisms is more important for optimal sequential treatment.

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肺癌的少見遠端轉移：病例系列報告及文獻探討

吳昱蔚　阮筠婷*　陳建維　蘇柏嵐　林建中

肺癌常見的遠端轉移包含腦部、骨頭、肝臟、腎上腺、淋巴結，而其他器官的轉移相對來說少見，並且無法藉由常規的胸部斷層掃描或腫瘤指數察覺。

在此我們提出三位在南台灣醫學中心被診斷肺腺癌的個案，分別有卵巢、小腸、腎臟的轉移。兩位以疼痛來表現，另一位則是發現腹部的腫塊。

經文獻回顧，這些少見的轉移預後較差，當病人有不典型的症狀時，可能需要更進一步的影像檢查。
*(胸腔醫學 **2019; 34: 190-196**)*

關鍵詞：肺癌，遠端轉移，卵巢轉移，小腸轉移，腎臟轉移

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Afatinib-Related Severe Pneumonitis in a Patient with HIV under Anti-Retroviral Therapy: A Case Report

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Afatinib, a second-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), improved progression-free survival and time-to-treatment failure as a first-line treatment in non-small cell lung cancer (NSCLC) patients. Use of combination antiretroviral therapy (cART) for human immunodeficiency virus (HIV) infection poses a potential risk of drug-drug interaction in HIV-infected patients simultaneously receiving EGFR-TKI treatment for NSCLC. EGFR-TKI-related pneumonitis is known as a serious drug toxicity. Previous research on EGFR-TKI-related pneumonitis mainly focused on gefitinib and erlotinib. We presented the first case of afatinib-related severe pneumonitis in a patient with NSCLC and HIV under cART. This study emphasizes the critical issue of drug-drug interaction between cART and afatinib. The patient's severe drug-related pneumonitis resolved after steroid pulse therapy. ***(Thorac Med 2019; 34: 197-204)***

Key words: drug-related pneumonitis, human immunodeficiency virus (HIV), afatinib, EGFR-TKI, tyrosine kinase inhibitor (TKI), NSCLC

Introduction

In the era of combination antiretroviral therapy (cART), human immunodeficiency virus (HIV) infection has become a chronic disease. According to the Taiwan Centers for Disease Control, there are about 31,000 HIV-infected patients in Taiwan, and more than 80% of them are using cART [1]. HIV-infected patients are also known to have an increased risk of lung cancer due to either higher smoking rates or immunosuppression and the inflammation process [2]. Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) is the first-line treatment of choice for patients with non-small cell lung cancer (NSCLC) harboring EGFR mutations [3]. Afatinib, a second-generation EGFR-TKI, improved progression-free survival (PFS) and time-to-treatment failure (TTF) of NSCLC patients [4-5]. The drug-drug interaction between cART and TKIs could pose a potential problem when physicians treat patients with coexisting HIV and lung cancer [6]. Here, we report a case of afatinib-related pneumonitis in a patient with HIV infection and newly diagnosed EGFR mutation-positive NSCLC.

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Case Report

A 68-year-old man was referred to our department for newly developed massive right pleural effusion (Figure 1A). The patient was a never-smoker and had human immunodeficiency virus (HIV) infection under cART with lamivudine + zidovudine (Combivir®) and atazanavir (Reyataz®) for 20 years, and psoriatic arthritis with rheumatoid arthritis, which was refractory to disease-modifying anti-rheumatic drugs (DMARDs), under treatment with adalimumab for 9 years. Adalimumab treatment was held after pleural effusion was discovered. Pleural effusion examination revealed a brownish lymphocyte-predominant exudate (white blood cell count: 1,520/cumm, neutrophil/lymphocyte: 25%/61%, lactic dehydrogenase: 575 U/L). Contrast-enhanced chest computed tomography (CT) revealed a mass in the right upper lobe with multiple lung-to-lung metastases, bone metastases, and mediastinal metastatic lymphadenopathies, after his pleural effusion was drained out by pigtail thoracostomy. Stage IV lung cancer was the most likely scenario (Figure 2A and Figure 2D). Cell-block analysis of the pleural effusion revealed adenocarcinoma with positive thyroid transcription factor-1 staining. However, the tumor cells of the cell-block specimen were insufficient for an EGFR mutation test. Brain magnetic resonance imaging revealed diffuse brain metastases. Whole body bone scan showed multiple bony metastases. Blood testing revealed a CD4 count of 866/cumm, and an HIV viral load was undetectable. EGFR mutation analysis of plasma cell-free DNA revealed an exon 21 L858R mutation that was EGFR-TKI-sensitive. The patient then received targeted therapy with afatinib, a second-generation EGFR-TKI, at 40 mg per day for lung adenocarcinoma with an EGFR-TKI sensitizing mutation. On the third day after afatinib use, diarrhea developed, but resolved with the use of loperamide. He was then discharged from the hospital.

On the 13th day after the administration of afatinib, the patient started to have intermittent fever and dyspnea. He came back to our emergency department on the next day with fever (39.3°C), tachycardia (126 beats per minute) and tachypnea (30 cycles per minute). Chest roentgenogram revealed diffuse bilateral ground-glass opacities (Figure 1B). After admission to the respiratory critical care unit (RCU), his oxygen saturation was 75% using a non-rebreathing mask. He was then put on mechanical ventilator support after intubation with an endotracheal tube. A blood test revealed leukocytosis (11,100/cumm, seg/lym: 67.9/17.9%), elevated CRP (14.07 mg/dl), elevated d-dimer (15.52 ug/mL), and elevated lactic acid (24 mg/dl), but normal troponin-I. Chest CT showed no evidence of pulmonary embolism, regression of the lung tumor, mediastinal lymph nodes or lung-to-lung metastasis, but newly developed ground glass opacity/consolidation in left upper lobe and right lower lobe (Figure 2B and Figure 2E) was seen. Antimicrobial therapy with meropenem, linezolid, anidulafungin, and trimethoprim/sulfamethoxazole was initiated empirically. Methylprednisolone 1.5 mg/kg/day was also prescribed for suspected drug-induced pneumonitis. On the next day, his CD4 count decreased to 107/cumm. The specialist in infectious disease suggested continuing cART. Diagnostic bronchoalveolar lavage (BAL) with a nasogastric tube was performed on the third day after RCU admission. Cytomegalovirus (CMV) polymerase chain reaction, Grocott-Gomori's methenamine silver stain and toluidine blue

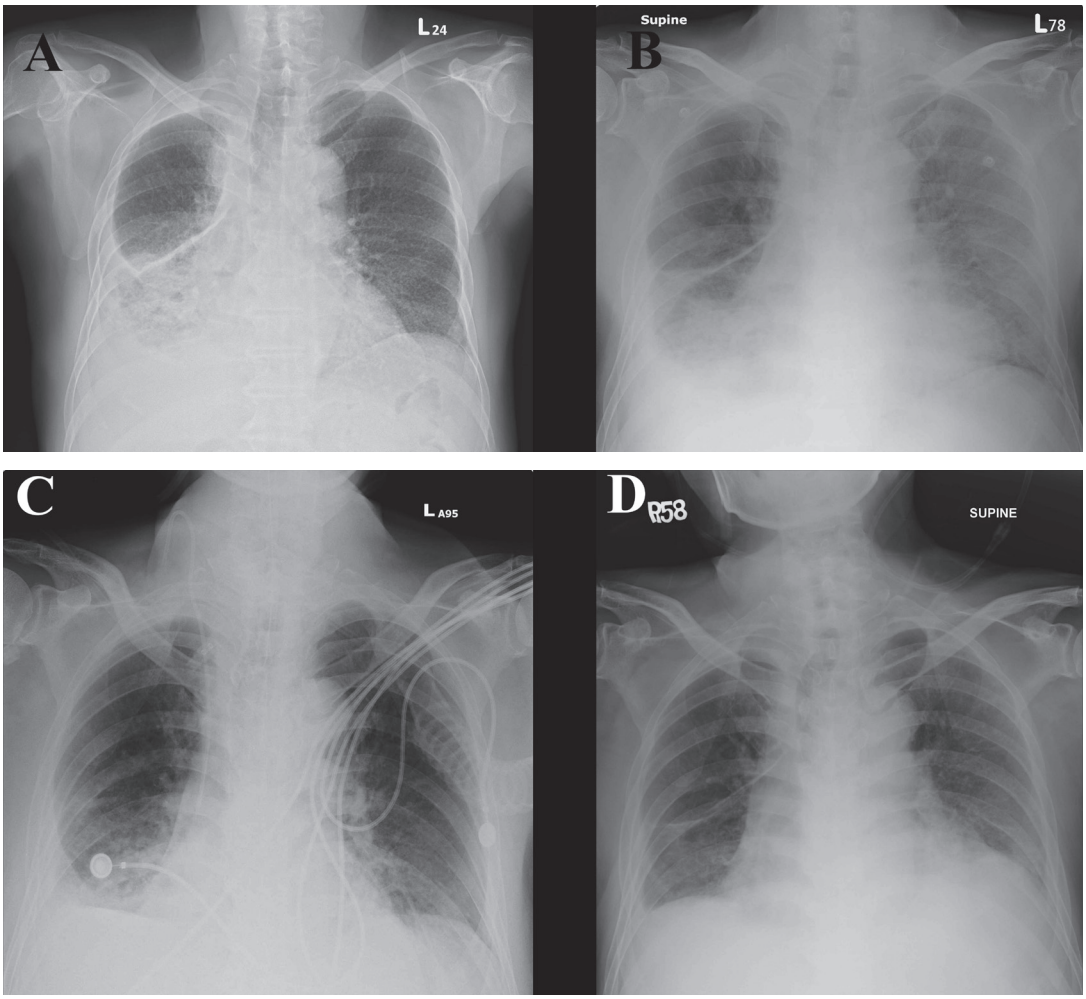

Fig. 1. Serial chest roentgenograms

A: Right pleural effusion and tumor at the right upper lobe on day 0 before afatinib administration; B: Tumor regression but ground glass opacity at the bilateral lung fields in the emergency room on day 14, C: Pneumonitis improved after pulse therapy on day 5 after RCU admission; D: No evidence of recurrent pneumonitis in the general ward (day 56 after pneumonitis).

O stain of the BAL fluid all revealed negative findings, so CMV pneumonia and *Pneumocystis jiroveci* pneumonia (PJP) were unlikely. Steroid pulse therapy with methylprednisolone 500 mg/day was given for 3 days for drug-related pneumonitis. His chest roentgenogram improved (Figure 1C), FiO_2 was tapered to 30%, and the CD4 count increased to 158/cumm. Steroid therapy was tapered, and the antibiotic regimen was shifted to levofloxacin, based on the culture report. The patient was successfully extubated on day 11 after RCU admission. He was then transferred to the ward and steroid was tapered to methylprednisolone 16 mg per day.

In the ward, the follow-up chest CT scan showed tumor regression (Figure 2C and Figure 2F). Because of the patient's poor physical condition, including being bed-ridden for 1 month due to severe pneumonitis and a poor immune status, chemotherapy was not favored. After re-

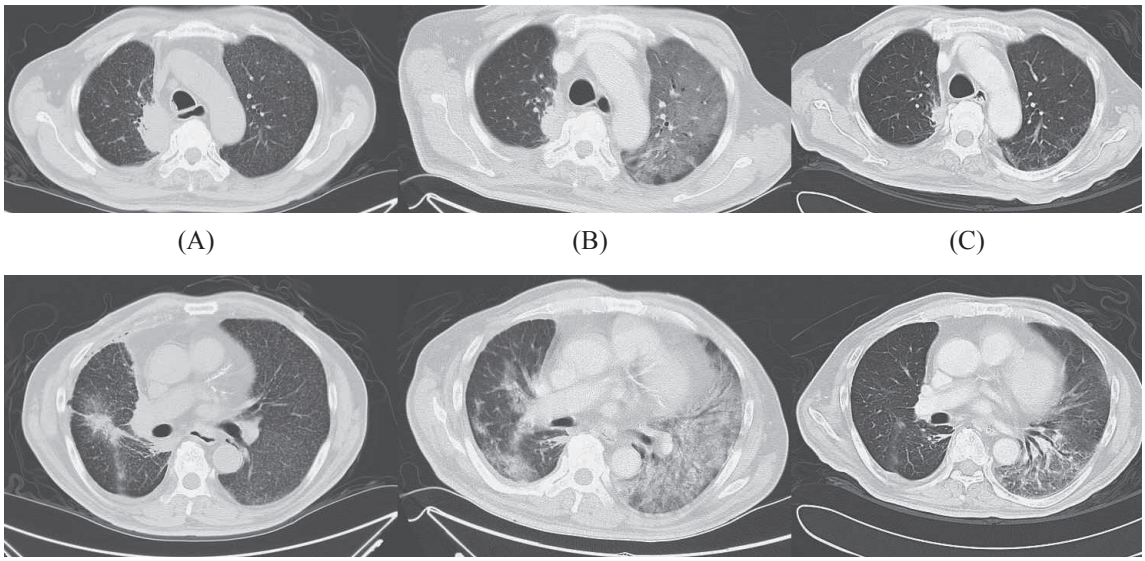

Fig. 2. Serial chest computed tomography
A&D: Baseline chest computed tomography (CT) revealed tumor in the right upper lobe and pleural seeding in the right major fissure; B&E: Diffuse ground glass opacity on day 14 after afatinib treatment at the emergency room; C&F: Regression of the tumor and pneumonitis in the chest CT on day 18 after pneumonitis developed in the ward.

covery from pneumonitis, we decided to rechallenge an EGFR-TKI. Despite the patient's clinical efficacy, re-use of afatinib was not indicated due to recent severe drug-related pneumonitis. Osimertinib, a third-generation EGFR-TKI, was initiated at 80 mg every other day. Chest roentgenogram showed no recurrent pneumonitis 1 month after osimertinib treatment (Figure 1D).

Discussion

To our knowledge, this is the first case report of EGFR-TKI pneumonitis in a patient with lung cancer and co-existing HIV infection. The drug-drug interactions between EGFR-TKI and cART might have played a role in the development of EGFR-TKI pneumonitis. The patient was treated with steroid therapy, and another EGFR-TKI was rechallenged.

Pneumonitis is known as a severe adverse effect of EGFR-TKI treatment for NSCLC, at an incidence of 1.12% in patients without prior exposure to EGFR-TKI and 1.13% in an EGFR-TKI retreatment group [7]. Onset is usually within 90 days [8], with 0.6% having high-grade pneumonitis and a 0.20% mortality rate [7]. Interstitial lung disease (ILD) or ILD-like symptoms, such as lung infiltration, pneumonitis, acute respiratory distress syndrome or allergic alveolitis, developed in 1.6% of 4,257 afatinib recipients [9]. In the LUX-lung 3 study of afatinib as first-line therapy for patients with EGFR-sensitive NSCLC, the incidence of grade ≥3 ILD was 1.3%, with a 1% fatal event rate in the afatinib-treated group [4]; in the LUX-lung 6 with a similar study setting, only 1 patient had grade 4 pneumonitis in the afatinib group (N=242) [5]. The diagnosis is usually based on several criteria: (1) A history of drug exposure with correct identification of the drug, its dose,

and duration of administration. (2) Clinical, imaging and histopathological patterns that are consistent with previous reports on the same drug. (3) Exclusion of other lung diseases. (4) Improvement following discontinuation of the suspected drug. (5) Recurrence of symptoms on rechallenge [10]. BAL was performed with our patient to exclude the possibility of infection; the cytology of the BAL fluid might yield lymphocytosis [10-12].

The mechanism of EGFR-TKI pneumonitis is not fully understood, but EGFR-TKI might interfere with type 2 pneumocytes and alveolar wall repair. A case report by Tsubata *et al*. suggested pneumonitis might be related to elevated drug concentrations [13]. While elevated drug concentrations were a potential cause of ILD, the drug-drug interactions of the antiretroviral drugs should be reviewed. The backbones of cART are nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Cytochrome P450 (CYP450), a superfamily of hemoproteins, are enzymes involving drug metabolism, and CYP450, family 3, subfamily A, polypeptide 4 (CYP3A4) is the most common and versatile one. NNRTIs are CYP3A4 inducers and PIs are CYP3A4 inhibitors [6]. Our patient was using lamivudine, zidovudine, and atazanavir. Both lamivudine and zidovudine are NRTIs, not a substrate, inducer or inhibitor of CYP3A4. Atazanavir, a PI, is metabolized via CYP3A4 and a CYP3A4 inhibitor. Both erlotinib and gefitinib are metabolized via CYP3A4, and the drug concentration might be elevated when they are co-administered with CYP3A4 inhibitors [14-15]. However, CYP3A4 inhibitor and inducer do not affect afatinib metabolism [16]. Afatinib was administered to our patient to minimize the risk of drug-drug interactions with regard to the CYP3A4 pathway. However, some PIs are p-glycoprotein (P-gp) inhibitors. One report revealed that ritonavir, a PI and also a P-gp inhibitor, will increase the bioavailability of afatinib about 11~48% (AUC0-∞) [16]. Our patient was using atazanavir, which is both a CYP3A4 inhibitor and a P-gp inhibitor [17]. Use of afatinib cannot entirely avoid drug-drug interactions, and afatinib bioavailability may be affected by atazanavir. Although the drug concentrations of afatinib and its metabolite were not checked in our patient, the presumed cause of pneumonitis may be related to relatively high drug concentrations. A lower starting dose of afatinib (e.g., 30 mg per day) may be considered in NSCLC patients with HIV under cART therapy due to a concern for drug-drug interaction.

The standard treatment for EGFR-TKI pneumonitis is to withhold EGFR-TKI during the assessment of patients with suspected pneumonitis and to discontinue EGFR-TKI in patients with confirmed ILD. In a literature review, high-dose corticosteroid therapy (prednisolone ≥0.5 mg/kg/day) or pulse therapy (methylprednisolone ≥500 mg/day for 3 days) were administered with an improvement in ILD [18-20]. We administered pulse therapy with methylprednisolone 500 mg/day for 3 days for the present patient.

In clinical trial settings, rechallenge is not allowed [21]. However, in a literature review, rechallenge never produced recurrence when combined with concurrent steroid therapy, but recurrence could be observed without steroid use [22]. Kashiwabara and colleagues retrospectively surveyed 196 patients who had received EGFR-TKI, and found that 17 developed ILD and 4 of them died due to chemotherapy-related causes. Five of the 13 patients who recovered

from ILD received EGFR-TKI rechallenge with concurrent oral administration of prednisolone 0.5 mg/kg, and all of the 5 patients achieved a partial response [23]. Rechallenge would be an option for patients who cannot receive chemotherapy. The other available EGFR-TKIs in our hospital, including gefitinib, erlotinib, and osimertinib, are metabolized by CYP3A4 and are substrates of P-gp [24]. The patient's condition was similar to that with the 3 other EGFR-TKIs, so he underwent EGFR-TKI rechallenge under close monitoring. Osimertinib was administered due to its better efficacy and fewer side effects compared to gefitinib and erlotinib, as shown in the FLUARA study [25]. There is no clear evidence to guide the dosage of osimertinib after EGFR-TKI pneumonitis. However, several case reports suggested reducing the osimertinib dosage to 40 mg once daily [26-28]. A case report described a successful introduction of osimertinib at 80 mg every other day, which was then returned to a standard dose after 2 weeks [29]. The osimertinib 40 mg tablet was not available in our hospital, so the patient received osimertinib 80 mg every other day without recurrent pneumonitis, as in the previous case report.

Conclusion

We presented the first case of TKI afatinib-related severe pneumonitis in a patient with HIV under cART. Drug-drug interaction of EGFR-TKIs and antiretroviral drugs might potentially affect the drug concentration of the EGFR-TKI, leading to drug-related pneumonitis that is severe, but manageable. Physicians should be aware of this rare side effect of EGFR-TKIs and monitor this pulmonary toxicity closely in this patient population.

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雞尾酒療法下人體免疫不全病毒感染者的 Afatinib 相關重症肺炎：病例報告

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Afatinib 為二代 EGFR-TKI，已被證實對有 EGFR 突變的非小細胞肺癌有療效。人類免疫不全病毒感染的患者是肺癌的高風險族群，而此類患者使用的抗病毒藥物雞尾酒療法會產生的藥物交互作用。使用 EGFR-TKI 治療肺癌，有 1% 的機率會產生嚴重的藥物引起的間質性肺炎。過去關於 EGFR-TKI 藥物引起的間質性肺炎病例報告都著眼於 gefitinib 或 erlotinib，尚未有人分享過發生於人類免疫不全病毒感染的患者的間質性肺炎。因此，我們提出第一位同時使用 afatinib 及雞尾酒療法後發生間質性肺炎的人類免疫不全病毒感染的肺癌患者，在經過類固醇脈衝治療後恢復的案例。*(胸腔醫學 **2019; 34: 197-204**)*

關鍵詞：藥物相關肺炎，人體免疫不全病毒，妥復克（afatinib），EGFR-TKI，TKI，非小細胞肺癌

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Hemodynamic Instability Caused by Cardiac Metastases of Non-small Cell Lung Cancer – Case Studies

Chia-I Shen*, Chi-Lu Chiang*,***, Bo-Wei Hu*, Yuan-Hung Wu**, Chao-Hua Chiu*,***, Yuh-Min Chen*,***, Yu-Chin Lee*,****

The incidence of cardiac metastases is 9.1% in oncologic patients, and lung cancer is the leading source. Most patients are asymptomatic, and if symptoms exist, they may mimic cardiovascular diseases. Hemodynamic instability is often life-threatening. Here, we report 2 rare cases of fatal cardiac metastases in patients with non-small cell lung cancer with hemodynamic instability. With the advances in clinical treatment and prolonged survival, the incidence of cardiac metastases is increasing. Physicians should be alert that new cardiac symptoms in patients with known malignancy can be caused by cardiac metastases. Although limited, some data shows early detection and multidisciplinary management in selected patients may improve the outcome. ***(Thorac Med 2019; 34: 205-212)***

Key words: non-small cell lung cancer (NSCLC), cardiac metastases (CM)

Introduction

Cardiac metastases are more common than physicians previously recognized. Primary cardiac tumors are infrequent, with an incidence of less than 0.1% in the general population [1]. However, secondary metastatic tumors are reported to have a more than 9.1% occurrence in oncologic patients [2]. Due to the prolonged life expectancy of cancer patients and improved clinical modalities, the incidence of cardiac metastases is increasing [3].

Lung cancer is the leading cause of cardiac metastases, and adenocarcinoma accounts for most cases [1,4]. The clinical symptoms and signs depend on the location of the cardiac tumors. Most patients are asymptomatic. Some patients may have dyspnea, chest tightness, palpitations and clinical manifestations that mimic cardiovascular diseases. Life-threatening emergencies such as cardiac tamponade and myocardial ischemia require early detection and have a poor prognosis [2].

Here, we report 2 rare cases of fatal cardiac metastases from non-small cell lung cancer (NSCLC) and serial hemodynamic change. We

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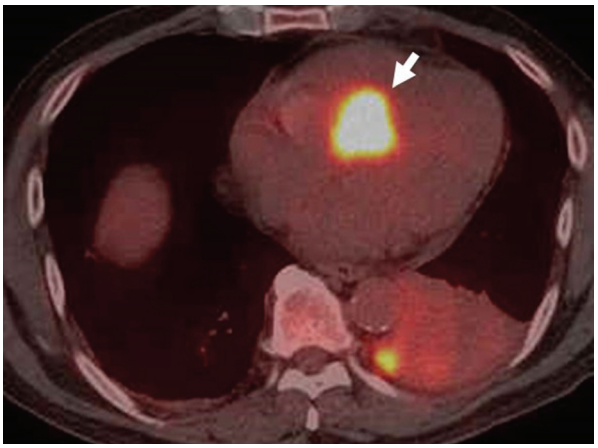

Fig. 1. PET/CT revealed a mass lesion at the interventricular septum at ainitial diagnosis.

hope to increase clinical awareness of cardiac metastases and recommend multidisciplinary management in selected patients.

Case 1

A 66-year-old male, a heavy smoker, presented with stage IV(M1b) squamous cell carcinoma of the lung. At the initial diagnosis, chest computed tomography (CT) revealed a low-density mass at the interventricular septum and the anterior wall of the left ventricle (Figure 1, Figure 2a). A mass on the right side of the ventricular septum, 4×2.5 cm in size, was noted on the echocardiogram (Figure 2b). The patient had no palpitation or chest discomfort at that time. 24-hour-Holter monitoring was arranged and no arrhythmia episodes were reported. The patient was given chemotherapy with cisplatin (60 mg/m^2) combined with gemcitabine (1,000 mg/m^2) as first-line treatment. However, an episode of syncope was noted after just 2 courses of systemic treatment. Follow-up CT and echocardiogram showed an increase in the size of the heart tumor within 2 months (Figure 2c, 2d). Holter monitoring reported 27 episodes of a long pause due to the high degree of a complete atrioventricular block (Figure 3). Pacemaker implantation was not suggested because of the patient's limited life expectancy. The patient was informed of the possibility of symptomatic relief with palliative radiotherapy, as reported in the literature. After discussion, the patient asked for hospice care. Progressive bradycardia and frequent syncope were noted, and he died 3 months after diagnosis.

Case 2

A 76-year-old never-smoker presented with stage IIB squamous cell carcinoma of the lung. The main lesion was located at the right middle lobe, with the pathology report revealing pericardium invasion. However, the patient refused further chemotherapy after lobectomy, and was then placed under regular follow-up. Seven months later, the patient mentioned chest tightness and dyspnea on exertion. Chest CT showed pericardial and epicardial metastasis with an invasion of the right ventricle and encasement of the left anterior descending coronary artery (Figure 4a, 4c). Echocardiogram revealed a large infiltrative mass at the apical wall, 2.1×3.4 cm in size (Figure 4b, 4d). Systemic treatment with chemotherapy was started, but the patient could tolerate only oral vinorelbine (60 mg/m^2) due to frequent neutropenia. Chest tightness aggregated, and serial EKG showed ST-segment elevation, suspected due to the progression of tumor encasement (Figure 5). The patient then decided to receive supportive care only, and died 3 months after cardiac metastases.

Discussion

With the advances in clinical treatment and improved survival, cardiac metastases are be-

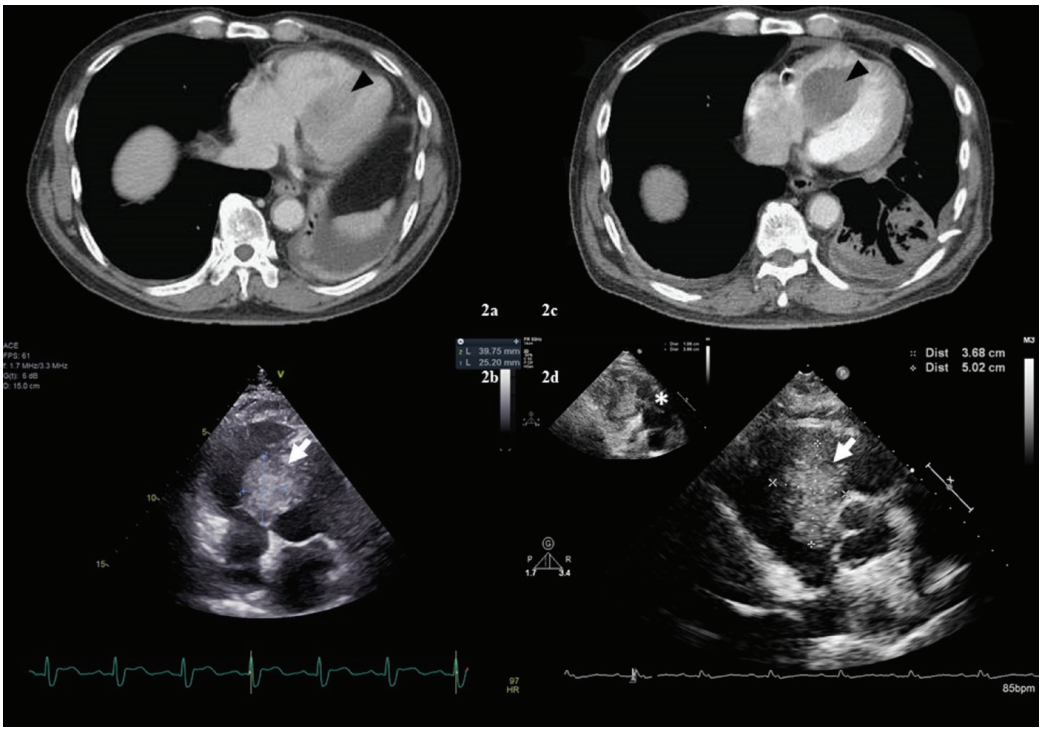

Fig. 2. (a) A low-density mass at the interventricular septum and the anterior wall of the left ventricle (arrowhead). (b) A mass on the right side of the ventricular septum, 4x2.5 cm in size (arrow). (c) Chest CT scan 2 months later revealed tumor progression (arrowhead). (d) Echocardiogram showed tumor progression with extension to the tricuspid valve 2 months later (arrow and *).

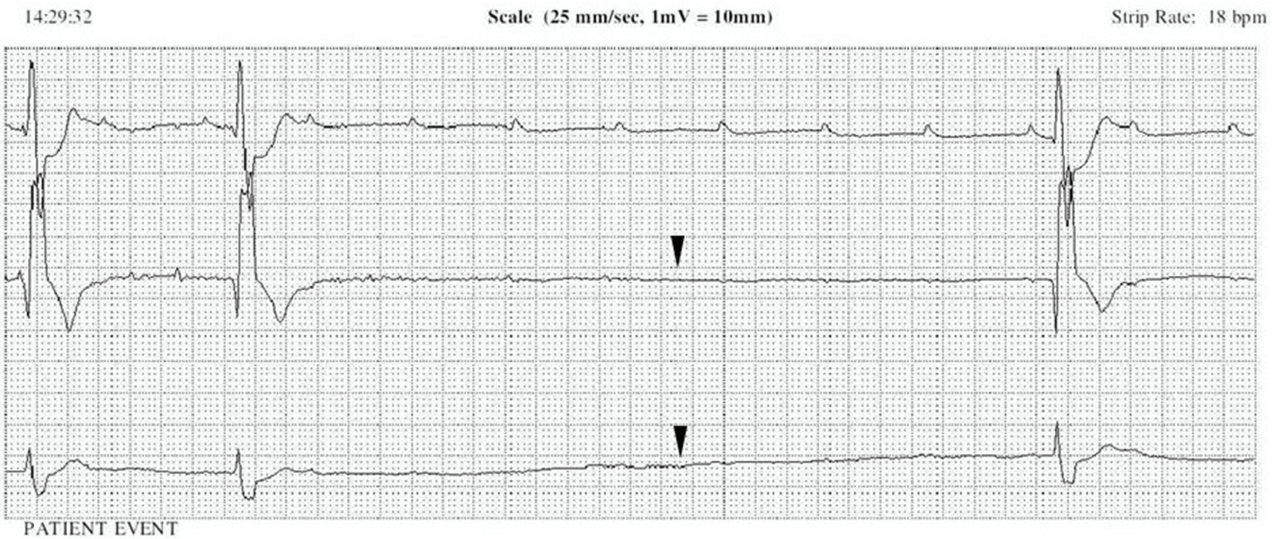

Fig. 3. Holter monitoring reported 27 episodes of a long pause due to the high degree of complete atrioventricular block.

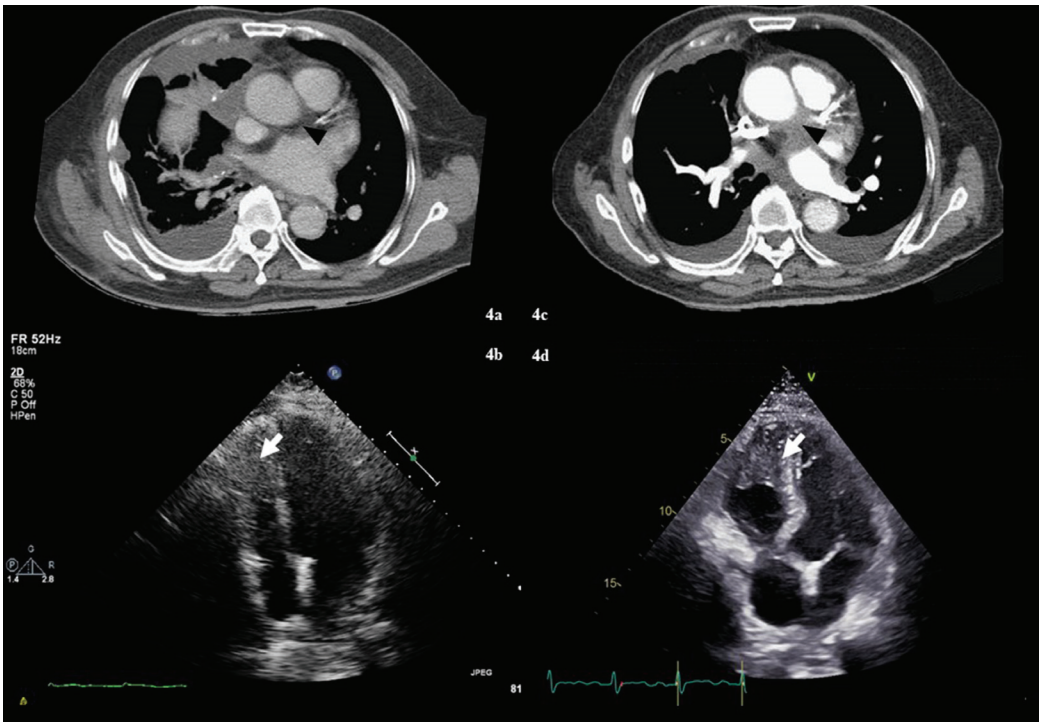

Fig. 4. (a, c) Chest CT showed progression of pericardial and epicardial metastasis with an invasion of the right ventricle and encasement of the left anterior descending coronary artery 7 months later (arrowhead). (b, d) Echocardiogram revealed progression of the infiltrative mass at the apical wall, 2.1x3.4 cm in size, 7 months later (arrow).

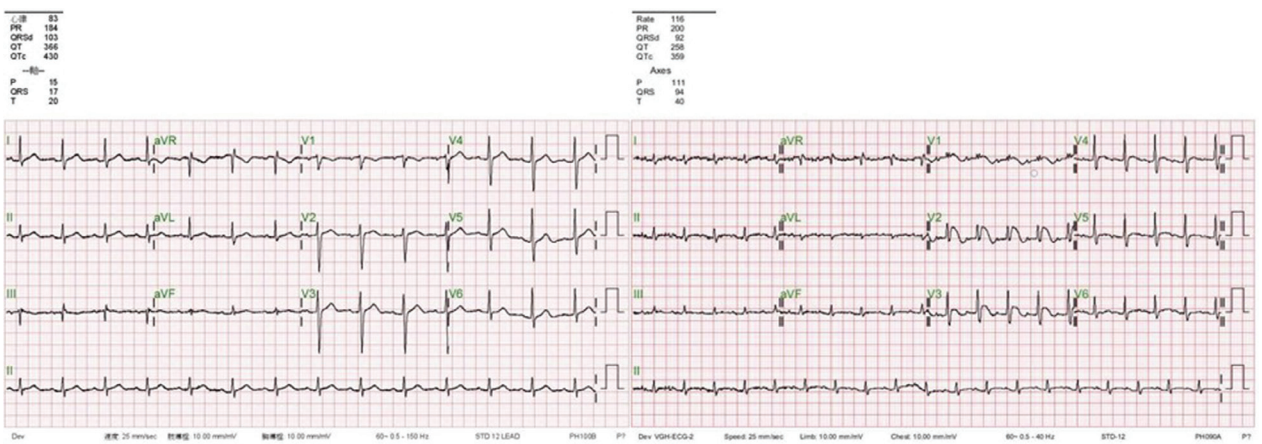

Fig. 5. Serial EKG showed ST-segment elevation.

coming more and more common [3]. Most patients with cardiac metastases have a poor prognosis [5-6]. However, better resolution imaging modalities and the concept of early intervention may affect the clinical outcome of selected patients [4]. Here, we reported 2 rare cases of hemodynamic instability caused by myocardial metastasis related to NSCLC. The patients died

quickly after the diagnosis of cardiac metastasis, despite medical treatment.

The tumor spreads to the heart via 4 routes: hematogenous spread, lymphatic spread, transvenous extension and direct invasion [1,7]. Metastases via the hematogenous route often involves invasion of the myocardium or endocardium [2]. Lymphatic spread leads to pericardial and epicardial tumor involvement [8]. Different tumor locations and disease burdens can present different clinical manifestations. Pericardium invasion is the most common type of heart involvement, accounting for over 64% of cardiac metastases. Epicardial or myocardial invasion is the second most common type of cardiac metastasis [9]. Tumors involving the epicardium or myocardium may disrupt the conduction system and affect coronary artery blood supply. Dysrhythmia and myocardial dysfunction are fatal, and are challenging for clinicians [1,10]. Endocardial metastases comprise less than 3% of cardiac metastases and are reported as the cause of cardiogenic shock due to ventricular outflow obstruction [9]. Myocardial metastases can involve any of the heart chambers, without preference. However, endocardium metastases tend to be located in the right ventricle or atrium. It is assumed that the right side of the heart has a slower blood flow and lower intraventricular pressure. Besides, malignancy from blood circulation enters the right atrium first [1]. For lung cancer patients, lymphatic spread with pericardial effusion is the most common type of cardiac metastases [7]. Rapid accumulation of malignant pericardial effusion causes emergency cardiac tamponade and requires pericardiocentesis [11]. Our first patient had myocardium metastases and progression of conduction dysfunction. Hematogenous spread was the leading cause. The pathology report for the second patient revealed pericardium invasion. Metastases to the pericardium and epicardium were noted 7 months later. Direct invasion was more favored as the metastatic route.

Physicians should be aware that new cardiac symptoms in patients with known malignancy can be caused by cardiac metastases [2]. ECG and chest x-ray provide basic information. Echocardiography is the most frequently selected tool initially for cardiac metastases imaging evaluation. It reveals the extent of tumor invasion and provides an evaluation of pericardial effusion [12]. However, echocardiography has its limitations in surveying the extracardiac structure and is operator-dependent [13]. Cardiac CT can visualize the adjacent anatomy, which is underestimated by an echocardiogram. Cardiac CT can also identify coronary artery invasion. Thus, it is a better choice for myocardial invasion evaluation and radiotherapy planning [4]. However, cardiac magnetic resonance imaging (CMR) has better resolution and tissue characterization, to aid in differentiating a tumor from a thrombus. With its special sequences, CMR helps to reveal adhesion of the tumor and cardiac structures [14-15]. 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT provides a benefit in the detection of distant metastases, but may have a limited role in cardiac tumor determinations due to the background uptake of FDG in the myocardium [13,15-16] (Table 1).

Treatment for cardiac metastases depends on tumor location and symptoms. Surgical resection is an option for a limited number of patients [7]. Pericardiocentesis, catheter placement or pericardial window are treatments for pericardial effusion [11]. Implantation of a defibrillator and catheter ablation are promising treatment modalities for uncontrolled arrhythmia

Table 1. Advantages and Limitations of Imaging Modalities Used in Evaluating Cardiac Metastases

Modalities	Advantages	Limitations
Echocardiogram	● Most selected clinically ● Rapid evaluation ● Extension of tumor and pericardial effusion ● Can assess multiple cardiac diseases	● Limited acoustic windows ● Operator-dependent ● Limited evaluation of extracardiac structures
Cardiac CT	● Better spatial resolution ● Can identify tumor extension of adjacent structures ● Can identify tumor invasion of the coronary artery	● Requires a slow heart rate ● Resolution inferior to that of cardiac MR
Cardiac MR	● Better resolution than CT and echocardiogram ● Better tissue characteristics ● Can identify adhesion of tumors and structures	● Requires slow heart rate
PET/CT	● Can detect distant metastases	● FDG uptake may be non-specific

[10,17]. Case reports show the effectiveness of pacemaker implantation for managing atrioventricular block; however, there is a limited life expectancy due to systemic disease progression [18-19]. Palliative radiotherapy is potentially effective in symptom control and can improve the quality of life of selected patients regardless of histology. Ghiam *et al* reported a case series involving cardiac metastases and suggested that palliative radiotherapy should be considered, especially when patients are not suitable for systemic treatment. In cases with hemodynamic instability, there is limited data indicating palliative radiotherapy as an alternative choice. The role of local control and even tumor ablation by radiotherapy is still under investigation [20-21].

In conclusion, cardiac metastases remains a challenge in terms of detection and treatment. The prognosis is still not satisfactory. In malignant patients with a new onset of cardiovascular symptoms, cardiac metastases should be considered. Although the clinical data are limited, we believe that further imaging evaluation and multidisciplinary management may improve the outcome in selected patients.

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非小細胞肺癌心臟轉移引起之血流動力不穩－案例報告

沈佳儀 * 江起陸 *,*** 胡栢瑋 * 吳元宏 ** 邱昭華 *,*** 陳育民 *,*** 李毓芹 *,****

癌症病人心臟轉移之發生率約為 9.1%，其中肺癌是心臟轉移主因。多數病人沒有症狀，臨床表徵和心血管疾病也不好區分，血流動力學不穩則通常有致命性。隨著治療技術的進步，癌症病人存活率增加，同時心臟轉移的盛行率也增加。本文呈現兩個少見的非小細胞肺癌引起之致命性心臟轉移，試圖提高臨床醫師對於心臟轉移的警覺性。對於已知有癌症診斷的病患，任何新出現的心血管相關症狀，都可能是心臟轉移的徵兆。目前已有的資料顯示，提早偵測到心臟轉移，進而配合多專科團隊的介入，有機會提高特定族群病患的存活率。*(胸腔醫學* ***2019; 34: 205-212****)*

關鍵詞：非小細胞肺癌，心臟轉移

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Idiopathic Chronic Eosinophilic Pneumonia Successfully Treated with Corticosteroids: A Case Report

Jia-Jun Wu*, Kuo-Hsuan Hsu*,**,***

Chronic eosinophilic pneumonia (CEP) is a rare disorder, with an incidence rate of approximately 0.23 cases per 10 million persons per year; CEP primarily affects non-smoking females. The disease is cryptogenic, and is characterized by the accumulation of eosinophils in the alveola and interstitium of the lung. CEP usually manifests as a subacute clinical course, with respiratory symptoms including cough and shortness of breath. Diagnosis depends upon chest images and bronchoalveolar lavage results. The disease responds well to corticosteroid treatment. We present the case of a 55-year-old male who had complained of progressive shortness of breath for 1 month. Chest images showed bilateral consolidation in the upper lung field. The patient had been healthy prior to admission, and denied a history of exposure to drugs or allergens. He was diagnosed with CEP with eosinophilia, as evidenced by his peripheral blood (8,472/mm^3) and bronchoalveolar lavage results (eosinophils, 51%). Systemic corticosteroid was administered during admission, and his symptoms gradually improved. There was no relapse of the disease after steroid treatment was terminated. ***(Thorac Med 2019; 34: 213-220)***

Key words: chronic eosinophilic pneumonia, bronchoalveolar lavage, corticosteroid

Introduction

Chronic eosinophilic pneumonia (CEP) is an idiopathic disorder characterized by the abnormal accumulation of eosinophils in the interstitium and alveola of the lung. It has been nearly 50 years since the first case of CEP was recognized [1]. The clinical course is usually indolent, and presents with cough, dyspnea, and constitutional symptoms such as body weight loss, general weakness, and fever. Image studies, including chest radiography and chest computed tomography (CT), commonly show bilateral pulmonary infiltrates in an alveolar pattern, with a peripheral distribution and an upper lung field predominance [2-3]. Laboratory studies

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of CEP usually show peripheral blood eosinophilia [4-5]. In addition, bronchoalveolar lavage (BAL) fluid should reveal an elevated proportion of eosinophils (≥40%) to establish the diagnosis. We present a case of diagnosed CEP and include a literature review in the following article.

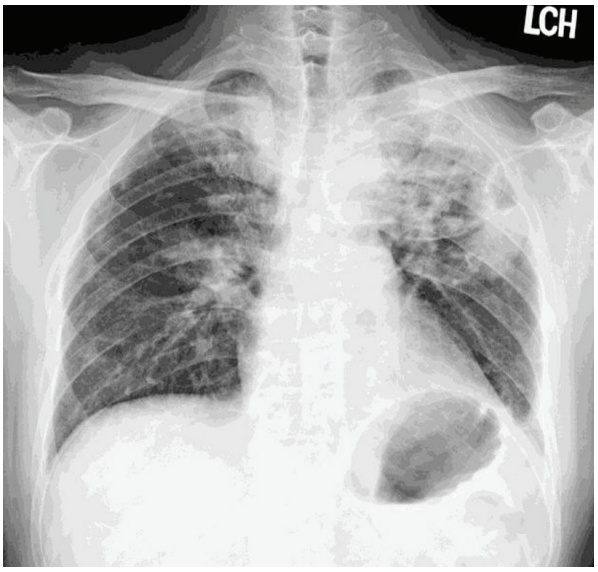
Case Report

A 55-year-old male presented to our emergency department (ED) with progressive shortness of breath. The patient had been in his usual state of health until approximately 1 month before presentation, when he developed a gradual onset of general weakness, shortness of breath, and poor appetite. The patient's shortness of breath was persistent and would be aggravated during exertion. In addition, the shortness of breath did not differ whether it was day or night, and was not related to his bodily position (i.e., standing, sitting, or lying down.). He previously had been able to comfortably hike in the mountains, but now he found it difficult to walk only a few feet. He also reported symptoms of poor appetite, night sweating and body weight loss, from 61 kg to 52 kg in 6 months. He had no previous medical history, and worked as a microchip engineer. He had smoked approximately 1 pack per year for 25 years when he was younger, but had quit 10 years prior to admission.

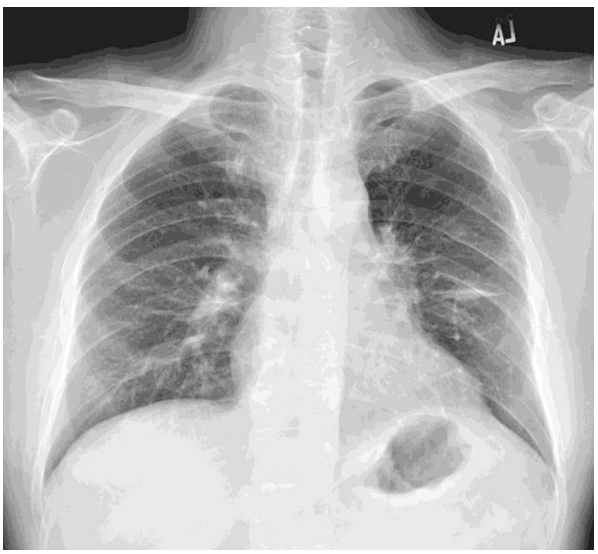
On arrival at the ED, the patient's body temperature was 38.1°C; blood pressure, 104/67 mmHg; heart rate, 106 beats per minute; respiratory rate, 18 breaths per minute; and oxygen saturation was 95% while breathing with a nasal cannula at 3 liters per minute. He appeared chronically ill and was experiencing mild tachypnea without accessory muscle retraction. Bilateral crackles were heard, but other physical examination results were normal.

Laboratory test results were notable for a white-cell count of 17,290 per cubic millimeter (reference range 4,500 to 10,500), with an eosinophil count of 8,472 per cubic millimeter (reference range 100 to 300), a high sensitivity C-reactive protein (CRP) of 10.7 mg per deciliter (reference range, <0.3 mg per deciliter), a serum sodium level of 134 mEq per liter, (reference range 137 to 153 mEq per liter), and an alanine aminotransferase of 62 U per liter (reference range, 10-50 U per liter). Other laboratory test results were normal. An electrocardiography showed sinus tachycardia. Chest radiography (Figure 1A) showed alveolar infiltrates at the bilateral upper lung fields.

The patient was admitted and underwent antibiotics treatment with both intravenous amoxicillin/clavulanate and oral erythromycin, under the impression of community-acquired pneumonia. The patient's fever subsided soon after admission. However, his symptoms of dyspnea on exertion persisted. The sputum bacterial cultures and acid-fast stains were negative. Blood culture was also negative. A follow-up chest radiography showed the progression of the bilateral upper lung consolidation. A chest CT (Figure 2) revealed multifocal consolidation in the bilateral lung, with upper lobes predominant, and involving the subpleural area. He then underwent bronchoalveolar lavage (BAL) at the apicoposterior segment of the left upper lobe, for purposes of confirming the diagnosis. The BAL fluid had a translucent appearance, with a red-cell count of 2,800 per microliter and a white-cell count of 5,029 per microliter, with 2,565 (51%) eosinophils per microliter, 2,012 (40%) neutrophils per microliter, and 402 (8%) lymphocytes per microliter.



(A)



(B)

Fig. 1. Chest X-ray of the patient during initial presentation (A), and disease resolution after 3 months of corticosteroid treatment (B).

Under the impression of CEP, intravenous methylprednisolone at 80 mg daily was administered. His clinical symptoms and chest X-ray results improved gradually, with the steroid dosage tapered to oral prednisolone at 60 mg daily after discharge. During the follow-up period, there was no relapse of respiratory symptoms, and the chest X-ray showed resolution of the pulmonary infiltrates (Figure 1B). Corticosteroid treatment was stopped after 3 months. The patient experienced no recurrence of the disease for more than 1 year after treatment.

Discussion

Epidemiology

CEP is a cryptogenic disorder. The incidence of CEP is low: it has been reported in only 0.23 cases per 10 million population per year [6]. CEP has accounted for 0-2.5% of cases of interstitial lung disease in Europe [7]; it occurs nearly twice as often in women as in men, and usually involves middle-aged individuals [4,8]. A majority of patients are nonsmokers [4,9]. Up to 50% of patients have had a previous history of asthma or atopic disease [10].

Clinical characteristics

Most patients diagnosed with CEP have a subacute clinical course. Common symptoms of CEP include dyspnea, cough, chest tightness, weight loss, and fever [4,9,11]. Classic radiological findings of CEP include bilateral peripheral alveolar infiltrates, with hilar sparing. The lesions are usually reported as having an ill-defined margin, and are predominantly located at the upper lobes. A chest CT usually discovers ground-glass opacity and consolidation involving the middle or upper lung zones. Less typical radiographic findings may include nodular infiltrates, a reverse-halo sign, or other non-specific densities [1-5,12-13].

Patients diagnosed with CEP usually manifest peripheral blood eosinophilia (≥1,000/mm^3), which accounts for 20% to 30% of the leukocyte differential [4,14]. Other laboratory abnormalities may include an elevation of both

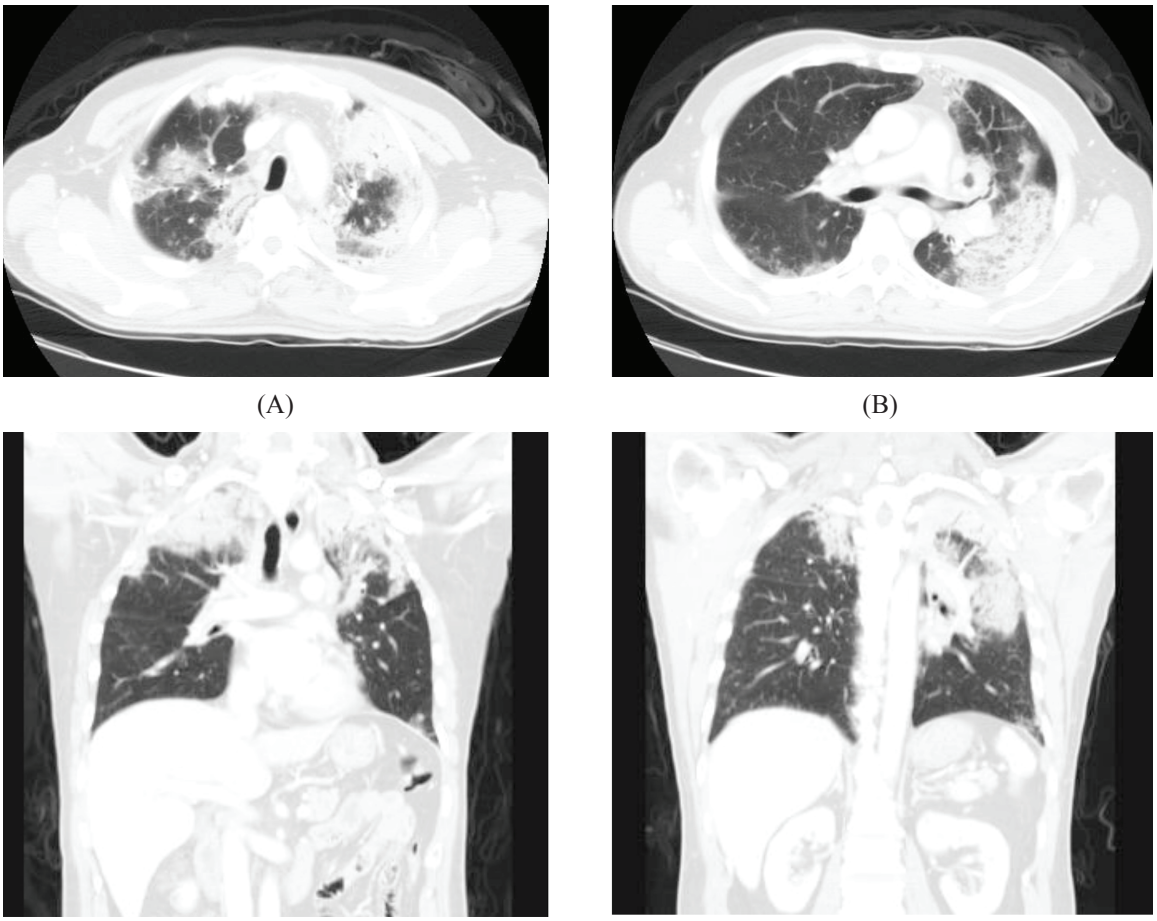


Fig. 2. Chest CT of the patient during initial presentation, including the lung window in axial (A, B), and coronal views (C, D).

the erythrocyte sedimentation rate and CRP levels [14]. BAL fluid analysis shows increased eosinophils, typically ≥40% of the white cell count differential [9,14-15].

Before initiating steroid treatment, pulmonary function tests of patients with CEP, using spirometry, can uncover a restrictive, obstructive, or normal pattern [4,9,16-17]. The diffusion capacity of the lung for carbon monoxide (D_{LCO}) usually decreases from normal. A persistent impairment in pulmonary function tests after treatment has been observed in more than 35% of patients [16-17].

The pulmonary pathology of CEP is characterized by eosinophil infiltrates of the alveolar space and interstitium [1,9]. Eosinophilic microabscesses, fibrinous exudate, or non-necrotizing non-granulomatous microangitis may also be found. Up to one-third of cases may have proliferative bronchiolitis obliterans or bronchiolitis obliterans – organizing pneumonia. Disruption of the basal lamina and intraluminal fibrosis are features of CEP that differentiate it from AEP [18].

Diagnosis

The diagnostic criteria for CEP are listed in Table 1 [5,19]. Prior to making the diagnosis

Table 1. Diagnostic Criteria for Idiopathic Chronic Eosinophilic Pneumonia

1.	Respiratory symptoms present for at least 2 to 4 weeks.
2.	Eosinophilia accounting for ≥40% of the differential count by bronchoalveolar lavage, and/or peripheral blood eosinophils ≥1,000/mm^3.
3.	Chest image showing bilateral diffuse pulmonary alveolar consolidation, and/or ground glass opacity, with/without peripheral predominance.
4.	Absence of any other known cause of eosinophilic lung disease.

All of the above criteria should be fulfilled to reach a diagnosis of ICEP.

of CEP, other known etiologies of eosinophilic lung disease, including drugs or toxin exposure, and infections from fungi or parasites, should be excluded. In cases with a typical clinical and radiological presentation, the diagnosis of CEP can be established when marked eosinophilia is noted in the BAL fluid [5,14,20]. A lung biopsy is rarely needed to confirm the diagnosis.

Differential diagnosis

The differential diagnosis of CEP includes eosinophilic or non-eosinophilic lung disease with similar clinical presentations. Acute eosinophilic lung disease (AEP) is another idiopathic eosinophilic lung disease, but usually presents with an acute onset (less than 14-31 days), while also involving more fulminant symptoms [14,20-22]. Patients with AEP also complain of cough, fever, and shortness of breath, and are more likely to develop acute respiratory failure than patients with CEP. In contrast to CEP, AEP occurs twice as often in smokers as in non-smokers, and rarely involves patients with a history of asthma [5,14]. A typical image of AEP reveals a diffuse alveolar and interstitial pattern, along with pleural effusion, while CEP usually involves the upper and middle zone lung fields, with no pleural effusion. There is no peripheral blood eosinophilia in patients with AEP, but a BAL of each showed high eosinophil counts. The pathology of AEP shows diffuse alveolar damage with eosinophil infiltrates in the alveola, interstitium, and bronchiole of the lung. Patients with AEP respond well to corticosteroids, and relapse after treatment is rare.

Other differential diagnoses include allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, and cryptogenic organizing pneumonia. In addition, eosinophilic pneumonia can be induced through exposure to drugs, toxins and radiation therapy [5]. Possible agents include nonsteroidal anti-inflammatory drugs, ethambutol, penicillin, minocycline, sulfonamides, trimethoprim-sulfamethoxazole, captopril, and G-CSF [20]. Obtaining a detailed history of the patient can help differentiate the diagnosis from CEP. Parasitic infections also cause eosinophilic pneumonia [5,20,23]. Pathogens that have been involved include *Ascaris lumbricoides*, *Toxocara canis*, *Strongyloides stercoralis*, *Wuchereria bancrofti* and *Brugia malayi*.

Treatment

Corticosteroids are the mainstay treatment for CEP. An initial treatment using 0.5-1 mg/kg/day of prednisolone orally or intravenous methylprednisolone has been suggested. A gradual tapering off of steroids can begin after the resolution of symptoms and radiographic

infiltrates, which usually occurs within 1 to 2 weeks. The total duration of any steroid treatment has varied, ranging from 8 weeks to 12 months [9,14,17,24].

Patients diagnosed with CEP usually respond well initially to corticosteroids treatment. However, a relapse of symptoms is common in approximately 50% of cases [4,24]. Maintenance treatment involving oral steroids (2.5-10 mg/day prednisone) or inhaled corticosteroids has been suggested in order to help the patient remain disease-free [16,25]. Both omazilumab and mepolizumab, the anti-IgE and anti-IL5 monoclonal antibodies, respectively, have been reported to treat CEP successfully as a steroid-sparing agent [26-27].

In conclusion, we have reported a typical case of CEP. The patient responded well to steroid treatment, which involved a 3-month course of corticosteroid treatment. Long-term follow-up to monitor any possible disease recurrence is strongly suggested.

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慢性嗜伊紅性白血球肺炎－病例報告

吳珈潤 *　徐國軒 *,**,***

慢性嗜伊紅性白血球肺炎(Chronic eosinophilic pneumonia)為一種罕見的肺部疾病。過去的文獻指出，慢性嗜伊紅性白血球肺炎的發生率約為每十萬人年有 0.23 個案例，且好發於女性及沒有吸菸史的病人。此疾病的發生原因不明，病理上可以看到肺泡以及肺間質中有嗜伊紅性白血球浸潤。慢性嗜伊紅性白血球肺炎的病程為亞急性或慢性，通常以咳嗽或喘等呼吸道症狀為表現。慢性嗜伊紅性白血球肺炎需仰賴胸腔影像檢查以及支氣管肺泡灌洗的結果來診斷，使用類固醇治療通常有良好的效果。本文案例為一 55 歲男性，因為一個月來漸進性呼吸困難至急診就醫。就醫過程胸部 X 光及電腦斷層皆有雙側上肺野浸潤，抽血以及支氣管肺泡灌洗檢查皆發現嗜伊紅性白血球升高，因此被診斷為慢性嗜伊紅性白血球肺炎。其病況在接受類固醇治療後逐漸改善，於類固醇停藥後也沒有復發的狀況。*(胸腔醫學 **2019; 34: 213-220**)*

關鍵詞：慢性嗜伊紅性白血球肺炎，支氣管肺泡灌洗，類固醇

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A Case of Pleuroparenchymal Fibroelastosis with Coexisting Features of Usual Interstitial Pneumonia

I-Hsien Lee, Min-Shu Hsieh*, Ping-Hung Kuo

Pleuroparenchymal fibroelastosis (PPFE) is a rare idiopathic interstitial pneumonitis. The diagnosis of PPFE can be based on clinical and radiological features, and pathological findings. PPFE can coexist with usual interstitial pneumonia (UIP) on both high-resolution computed tomography (HRCT) and lung biopsy. Therefore, it may cause a diagnostic dilemma in the differentiation of PPFE from idiopathic pulmonary fibrosis (IPF) with upper lung involvement. We report a 71-year-old woman suffering from progressive dyspnea and dry cough for 1 year. HRCT revealed dense pleural thickening and subpleural fibrosis and consolidations in the upper lobes. There was also diffuse subpleural reticulation and traction bronchiectasis/bronchiolectasis. She underwent surgical lung biopsy and the pathology was consistent with PPFE after elastin staining. Histological features of UIP were also found in the upper lobes. Her cough and exertional dyspnea partially improved after off-label treatment with pirfenidone. Our experience with this case suggests that PPFE patients may have HRCT and pathological features of UIP. We also reviewed the differential diagnoses of PPFE and IPF and their clinical outcomes in the literature. ***(Thorac Med 2019; 34: 221-229)***

Key words: idiopathic pulmonary fibrosis (IPF), pleuroparenchymal fibroelastosis (PPFE), usual interstitial pneumonia (UIP)

Introduction

The diagnosis of idiopathic pulmonary fibrosis (IPF) can be made by clinical evaluation and high-resolution computed tomography (HRCT) findings and through multidisciplinary discussion. Surgical lung biopsy is not recommended in patients with a typical usual interstitial pneumonia (UIP) pattern on HRCT. However, in patients that present with atypical or indeterminate HRCT features, other diagnostic modalities, including bronchoalveolar lavage cellular analysis and surgical or cryobiopsy can be used to help in the differentiation [1].

Pleuroparenchymal fibroelastosis (PPFE) is a rare and new disease entity that is characterized predominantly by upper lobe pleural and subjacent parenchymal fibrosis [1]. According to the most updated guideline on the diagnosis of IPF [2], patients with UIP on HRCT might have features of PPFE at the lung apices. However, there is no clear cut-off border for the pro-

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portions of each pattern, and these cases should be regarded as being a single UIP/IPF entity [3].

We report a PPFE patient that presented with radiological and pathological patterns suggestive of both IPF and PPFE. The final diagnosis was reached after surgical biopsy and multidisciplinary discussion. The differential diagnosis of these 2 interstitial lung diseases will also be addressed.

Case Report

A 71-year-old woman presented to our outpatient clinic with chronic cough and mild exertional dyspnea for 1 year. Her cough was usually worse at night and during winter seasons. She also noted body weight loss, from 70 kg to 65 kg in 6 months. There was no fever, purulent sputum, wheezing, stridor or orthopnea.

Her past history included diabetes mellitus, hypertension and chronic hepatitis C virus infection status post-interferon treatment. She denied cigarette smoking, and environmental or occupational exposures.

On examination, she was fully conscious. Body temperature was 36.8°C; pulse rate, 72 beats per minute; respiratory rate, 15 breaths per minute; and blood pressure, 140/84 mmHg. Pulse oxygen saturation was 95% under ambient air. Physical examination also revealed mild "Velcro" crackles at the posterior aspect of both lower lungs. The ratio of the anterior-posterior diameter to the transverse diameter of the thorax (APDT/TDT) was normal. There were no cardiac murmurs, wheezing, digital clubbing or peripheral edema. Chest radiograph (Figure 1) revealed reduced lung volumes, bilateral interstitial change, apical pleural thickening and bilateral hilar elevation. HRCT (Figure 2) showed bilateral dense pleural thickening, subpleural fibrosis and consolidations in the upper lobes. There was also diffuse subpleural reticulation and traction bronchiectasis/bronchiolectasis. In addition, mild honeycomb change was observed in the right lower lung. Both upper lobes and lower lobes were involved, but the volume reduction was more prominent at the upper lobes.

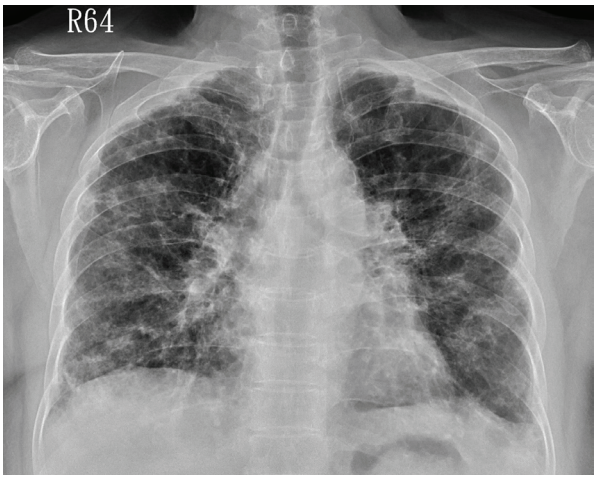

Fig. 1. Chest Radiograph. Chest radiograph showing reduced lung volumes, bilateral interstitial change, apical pleural thickening and bilateral hilar elevation.

The lung function test (Table 1) revealed a mild restrictive pattern as well as a mild impairment in diffusion capacity (DLCO). The ratio of residual volume to total lung capacity was slightly increased.

Her complete blood count and other biochemistry profiles were within normal limits. She did not have clinical features suggestive of any connective tissue diseases and the serum autoimmune profiles did not reveal significant findings. The cellular component of the bronchial alveolar lavage fluid (BALF) was macrophages: 82.6%, bronchial epithelial cells: 10.6%, neutrophils: 5.8%, and lymphocytes: 1%. The microbiology study results of the BALF were negative.

To achieve the final diagnosis, a video-

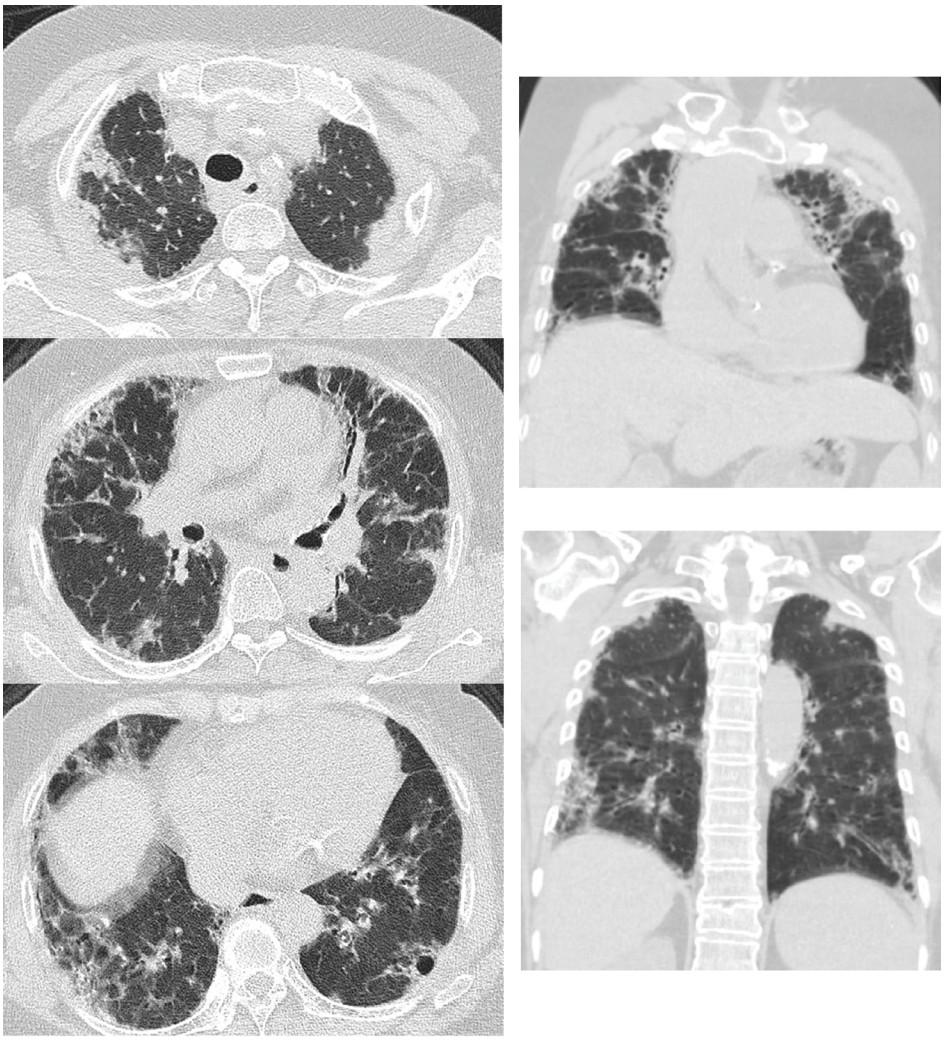

Fig. 2. HRCT. HRCT reveals dense pleural thickening and subpleural fibrosis and consolidations in the upper lobes. There is also diffuse subpleural reticulation and traction bronchiectasis/bronchiolectasis. Mild honeycombing is observed in the right lower lung.

assisted thoracoscopic surgical lung biopsy was performed at the right upper lung. Pathology (Figure 3) reported fibrosis of the pleura and underlying parenchyma. Intra-alveolar fibrosis and elastin deposition were revealed by elastic stain. Fibroblastic foci were frequently observed at the interface of the fibroelastotic zone and the adjacent lung parenchyma. The lung parenchyma away from the PPFE also showed UIP-like changes, including heterogeneous interstitial fibrosis, fibroblastic foci, and focal honeycomb change. After a multidisciplinary discussion, PPFE coexisting with UIP features was diagnosed based on the patient's clinical course, radiological features and histopathology. Administration of off-label treatment with pirfenidone partially improved her cough and exertional dyspnea. No photosensitivity or other side effects were observed.

Table 1. Serial Lung Function Testing

	At presentation	4 months later
FVC L (% of predicted)	1.5 L (82%)	1.36 L (74%)
FEV_1 L (% of predicted)	1.35 L (98%)	1.24 L (89%)
FEV_1/FVC	90%	91.2%
TLC L (% of predicted)	2.77 L (83%)	-
RV/TLC	44%	-
DLCO (ml/min/mmHg)	8.01 (53%)	8.62 (57%)

Table 2. Summary of the Differences between PPFE and IPF [6,9,11,13,16,27-28]

	PPFE	IPF
Age at diagnosis (years)	Two peaks, in the 30s and 60s	>50
Gender	Female > male	Predominantly male
Smoking	Usually non-smokers	Mainly smokers
Pneumothorax	20-80% (more common)	15-30%
BMI at diagnosis (kg/m^2)	Lower (BMI: 16-18) [7-9,15]	Higher
Ratio of anterior-posterior diameter to transverse diameter of the thorax	56-60% reduced	65% not reduced
FVC (% predicted)	63-75% [8-9,14,16,27]	70-85%
RV/TLC (% predicted)	130-150% [8-9,14,16,27]	100-110%
HRCT features		UIP pattern
Pleura changes	Pleural thickening (>4-15 mm) and subpleural fibrosis	Not striking
Histopathological features	Pleural and subpleural fibrosis, interstitial fibroelastosis, intra-alveolar fibrosis, preserved alveolar structure	Dense fibrosis with architectural distortion, fibroblast foci
Consensus of diagnostic criteria	Not established	Available
Approved therapies	Nil	nintedanib and pirfenidone
Survival	2-8 years, wide range (worse if secondary to transplant) [3,8-9,14,16,27,29]	2-5 years 3.8 years in US (>65 y/o)
Annual decline of FVC (ml/year)	270 (187-500) [8-9,14,16,27]	220 (without treatment) (with treatment)

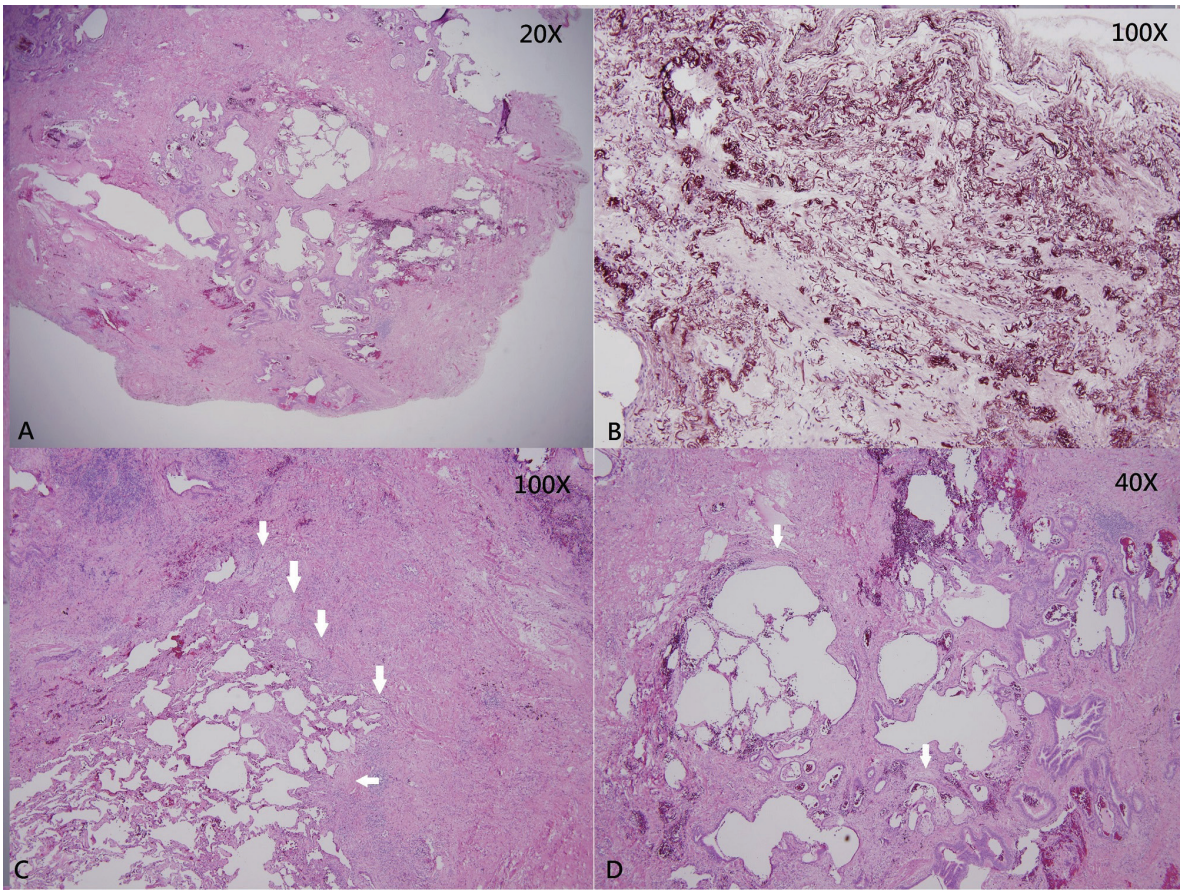

Fig. 3. Histopathology of the Right Upper Lung. (A) Lung tissue shows marked fibrosis of the pleura and subpleural lung parenchyma (hematoxylin and eosin stain, original magnification 20×). (B) Elastin deposition and intra-alveolar fibrosis are noted in the PPFE zone (orcein stain, original magnification 100×). (C) Fibroblastic foci (arrows) are frequently observed at the interface between PPFE and the adjacent lung (hematoxylin and eosin stain, original magnification 100×). (D) The lung parenchyma also shows interstitial fibrosis, fibroblastic foci (arrows), and focal honeycomb change (UIP changes) (hematoxylin and eosin stain, original magnification 40×).

Discussion

In this report, we described a case of PPFE with coexisting features of UIP. To our knowledge, this is the first case report of this rare interstitial lung disease in Taiwan.

PPFE was first reported by Frankel *et al* in 2004 in 5 patients with pulmonary fibrosis predominantly involving the upper lobes [4]. PPFE can be divided into idiopathic or secondary to lung transplantation, bone marrow transplantation, autoimmune disease, or recurrent infection, or due to family history or exposure to silicosis or asbestosis [3,5]. In 2013, PPFE was isolated from other types of idiopathic interstitial pneumonitis in the ATS/ERS guideline, due to its distinct disease entity [1].

Patients with PPFE may present with breathlessness and cough, and physical examination sometimes reveals "Velcro" crackles. Increased ratio of the anterior-posterior diameter to the transverse diameter of the thorax can be observed in some patients [6-11]. HRCT characteristics of PPFE include pleural thickening with associated subpleural fibrosis concentrated in the upper lobes, with involvement of the

lower lobes being less marked or absent [1,3]. The thickness of the apical pleura is usually more than 4-15 mm, and progression of the lesion was detected in 63% of cases [5,10,12].

The typical histopathological features of PPFE include fibrosis of the visceral pleura and subjacent intra-alveolar space area and alveolar septal elastosis, as revealed by elastin stain. The distribution of PPFE is mainly in the subpleural area with upper zone predominance, and with sparing of the parenchyma away from the pleura and lower lungs [3]. The diagnosis of PPFE relies on its special HRCT and histopathological features.

These image features of PPFE should be differentiated from other diseases and conditions such as the chronic fibrosis phase of organizing pneumonia, the fibrotic stage of sarcoidosis, hypersensitivity pneumonitis, old TB pleurisy, and apical cap [13]. PPEF can also coexist with other HRCT and pathological features, such as UIP, non-specific interstitial pneumonia, chronic hypersensitivity pneumonitis, and a combination of pulmonary fibrosis and emphysema, but the cut-off border of the proportions of each pattern is not established [3,12-15].

Around 13~75% of patients with PPFE have coexisting features of UIP on HRCT and pathological examination [3,14,16-21]. Without clear etiologies, the diagnosis of IPF can be made if the pattern is predominantly UIP. Therefore, sometimes it is difficult to differentiate between IPF and idiopathic PPFE. The differences between these 2 diseases are summarized in Table 2.

The histological criteria for diagnosing PPFE have not been established. Elastin stain can be used to reveal alveolar fibroelastosis in PPFE, but little attention has been paid to the elastin fiber in IPF in the past. In addition to the increase in collagen fibers, elastin fibers deposition also increases in IPF, and this is correlated with a worse outcome in IPF cases [22-24]. Some pathologists have suggested that elastin deposition of more than 80% in non-atelectatic alveoli was sufficient to make a diagnosis of PPFE, because conditions like apical caps or IPF with upper lung involvement may have indistinguishable pathological features [25]. The elastin score, the ratio of elastin fiber to collagen fiber proposed by Kinoshita in 2017, is higher in the upper lung of PPFE patients than in IPF patients. One study reported that the ratios of upper to lower lung elastin scores in PPFE and IPF were 1.7 and 0.9, respectively [16].

In PPFE, surgical lung biopsy is valuable for the diagnosis but should be considered carefully in patients with high surgical risks, such as those with high oxygen requirements, pulmonary hypertension, rapid disease progression, severely reduced FVC or DLCO [26]. For patients suspected of having PPFE coexistent with other interstitial lung diseases, previous studies suggest that elastin fiber quantification of both the upper and lower lung should be performed.

In conclusion, patients with PPFE can present with coexisting radiological and histopathological patterns of other interstitial lung diseases, including UIP. Our case, as presented here, can provide insights into the diagnostic dilemma and difficulties in this clinical setting. Pulmonologists and pathologists should be aware of this rare disease entity and a multidisciplinary discussion is necessary to reach a final diagnosis. More studies are needed to address the diagnostic criteria, pathogenesis, clinical course and optimal management of PPFE.

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肋膜肺實質彈性纖維增生合併尋常性間質性肺炎之影像學 / 病理學變化的個案：案例報告及文獻回顧

李奕嫻　謝明書 *　郭炳宏

肋膜肺實質彈性纖維增生是一種罕見的間質性肺病，其診斷需要參考臨床、影像學、病理的發現。在高解析度電腦斷層以及病理切片中，可與尋常性間質性肺炎同時存在，因此在鑑別肋膜肺實質彈性纖維增生以及在波及上肺野的特發性肺纖維化時可能遭遇困難。本個案為一位 72 歲女性，因漸進性乾咳及活動喘一年來就診，高解析度電腦斷層顯現尋常性間質性肺炎型態以外，也在上肺葉有肋膜增厚以及肋膜下纖維化的影像，經胸腔鏡楔形肺葉切片手術後病理診斷為肋膜肺實質彈性纖維增生但併有特發性肺纖維化的特徵，經多團隊會議討論後認為個案傾向肋膜肺實質彈性纖維增生的疾病，但仍給予 pirfenidone 藥物治療嘗試，病患症狀獲得改善。除呈現本個案診斷過程外，我們亦進行文獻回顧比較特發性肺纖維化及肋膜肺實質彈性纖維增生的差異。*(胸腔醫學 **2019; 34: 221-229**)*

關鍵詞：特發性肺纖維化，肋膜肺實質彈性纖維增生，高解析度電腦斷層

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