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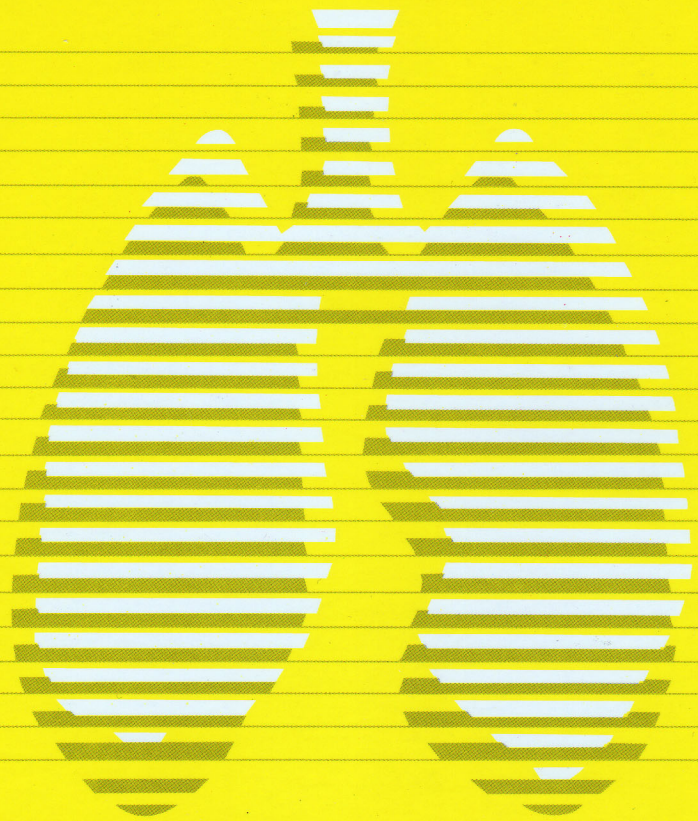

台灣胸腔暨重症加護醫學會

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Orginial Articles

Case Reports

Effects of Combined Long-Acting Beta 2-Agonists and Inhaled Corticosteroids Therapy on Lung Mechanics and Airway Secretion in Prolonged Mechanical Ventilation Patients with Chronic Obstructive Pulmonary Disease

Jiun-Long Wang*,***, Wen-Cheng Chao**,****, Sheu-Fen Lee**,
Chieh-Liang Wu**,*****

Background: To investigate the effect of combined long-acting β2 agonists (LABA)/inhaled corticosteroids (ICS) on the lung mechanics and airway secretion in prolonged mechanical ventilation (PMV) patients with chronic obstructive pulmonary disease (COPD).

Methods: Data from PMV patients receiving LABA/ICS in the respiratory care ward of Taichung Veterans General Hospital-Chiayi Branch from October 1 to December 31, 2011 were reviewed. The demographic data, nutrient parameters, and airway dynamic parameters were recorded. The weekly checked data during the 6-week period of use of LABA/LCS (4 puffs twice a day) were analyzed, including secretion quantitative grading scores, airway resistance, incidence of pneumonia, and weaning status.

Results: Nineteen male patients with a mean age of 81.1±7.6 years and duration of ventilator use of 198.7±254.9 days were enrolled. They were in a chronic wasting status with low albumin (2.8±0.5 g/dL) and body mass index (19.8±3.8) despite adequate caloric intake (1821.0±199.0 kcal). Airway secretion clearance and dynamic parameters showed impaired airway secretion clearance and increased airway resistance. After the use of LABA/ICS, airway resistance decreased by 16.3±15.2% temporally. Airway secretion quantitative scores decreased gradually and the frequency of ventilator-associated pneumonia (VAP) also significantly decreased from 0.82±0.75 to 0.56±0.55 times/month. Three patients were weaned from ventilator support for a cumulative weaning rate of 18.5%.

Conclusions: A reduction of airway resistance, airway secretion, and incidence of VAP and ventilator-dependent conditions with combined use of LABA/ICS in PMV patients with COPD was observed. However, more prospective studies are needed to validate further utilization of LABA/ICS for those patients weaning from ventilation. ***(Thorac Med 2014; 29: 323-334)***

Key words: chronic obstructive pulmonary disease (COPD), prolonged mechanical ventilation (PMV), inhaled corticosteroids (ICS), weaning

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Background

Prolonged mechanical ventilation (PMV), defined as mechanical ventilation use longer than 21 days, is a new global health system challenge because of the soaring incidence and high healthcare costs involved [1-2]. In Taiwan, the National Health Insurance (NHI) system provides comprehensive coverage for both acute and chronic respiratory healthcare services. The respiratory care ward (RCW) is a specialized and unique unit for the care of PMV patients. There are currently more than 3000 PMV patients in Taiwan, costing around 2.7 billion NT dollars each year [3-4]. The low weaning rate is a critical problem with PMV patients, in addition to the rising incidence. Weaning is difficult with PMV patients because most patients have multiple underlying disorders, including chronic obstructive pulmonary disease (COPD), cardiac disease, neurologic disease, uremia, and diabetes mellitus [5-6].

As the 5th leading cause of death in the world, affecting 65 million people and creating a tremendous economic burden, COPD is also a proven critical risk factor for PMV [7-8]. Airflow limitation and airway inflammation are key features of COPD. Current recommended medication includes long-acting β2 agonists (LABAs) as bronchodilators, coupled with inhaled corticosteroids (ICS) as anti-inflammatory agents [9]. Although combined LABA/ICS therapy has been proven to be an effective treatment for COPD, the effects of this combination therapy on PMV patients with COPD remains unknown.

This study aimed to characterize PMV patients with COPD and investigate the effect of LABA/ICS combination therapy on lung mechanics and airway section in these patients. We found that PMV patients with COPD were apparently in a cachexia state, and LABA/ICS combination may have an effect on reducing airway resistance and secretion. Thus, we observed that LABA/ICS may have some impact on facilitating weaning from the mechanical ventilator for PMV patients with COPD.

Methods

Subjects

This retrospective observational study was conducted at Taichung Veterans General Hospital-Chiayi Branch, a 600-bed hospital in southern Taiwan with a 60-bed respiratory care ward (RCW). The use of the LABA/ICS combination (Seretide 25/250 Evohaler; GlaxoSmithKline, Uxbridge, Middlesex, UK) containing salmeterol 25 mcg and fluticasone propionate 250 mcg was introduced to the RCW in September 2011. The recommended dosage was 4 puffs bid via an AeroVent collapsible holding chamber (Trudell Medical International, Canada). The LABA/ICS was an optional therapy to be used at the discretion the in-charge physicians.

All medical records of PMV patients with a history of COPD and who received inhaled LABA/ICS for at least 6 weeks were reviewed. Patients were excluded if they had any of the following conditions: (1) active infection that developed 7 days before the prescription of inhaled LABA/ICS; (2) destroyed lungs or resection of more than 2 lobes on chest X-ray (CXR); (3) motor neuron disease; (4) documented congestive heart failure (EF <30% by echocardiogram); and (5) major surgery within 30 days before the prescription of inhaled LABA/ICS.

The institutional review board of Taichung Veterans General Hospital approved the study (TCVGH IRB CE 12122).

Demographic and laboratory data before LABA/ICS

Demographic data, including age, sex, body weight, body mass index (BMI), ventilator days, and major co-morbidities were recorded. If available, the following data were also collected: white blood cell count ($10^3/\mu l$), hemoglobin (g/dL), C-reactive protein (mg/dL), albumin (g/dL), globulin (g/dL), and triacylglycerol (mg/dL) and total cholesterol (mg/dL). To characterize the PMV patients with COPD, their nutrition status was assessed using a well-established malnutrition scoring system [10-11]. Briefly, 6 parameters were selected as components of the malnutrition score: percent ideal body weight <90%, BMI <18.5 kg/m^2, serum albumin <3.5 g/dL, total lymphocyte count <1800 $cells/mm^3$, total cholesterol <90 mg/dL, and hemoglobin <12 g/dL (female) and <14 g/dL (male). Each factor was assigned a value of 1 if present or 0 if absent, and a malnutrition score (range, 0-6) was obtained by the sum of the numbers of abnormal parameters for each patient.

Primary outcome assessment: Airway secretion and dynamic airway mechanics

Based on the standard of care provided, airway secretion status, expectoration ability, and airway dynamic parameters were measured by the same qualified respiratory therapists weekly. The dynamic airway mechanics (resistance and compliance) were also recorded continuously by ventilator machine (Evita 4, Drager Medical AG & Co, Lubeck, Germany). Weaning parameters, including rapid shallow breathing index (breaths/min/L), Pi maximum (cmH_2O), and Pe maximum (cmH_2O) were measured using a Haloscale Respirometer every 2 weeks.

The secretion quantitative grading scores were defined as follows: Grade 0 for no sputum, Grade 1 for little sputum, Grade 2 for mucoid sputum, Grade 3 for little muco-purulent sputum, and Grade 4 for productive muco-purulent sputum [12]. The grading criteria of expectoration ability were as follows: Grade 0 for weak cough without airway secretion in the tube, Grade 1 for audible cough with airway secretion in the tube, and Grade 2 for strong cough with airway secretion expectorated out of the tube [13]. All the data were measured and checked by the same trained staff. Weekly secretion quantitative grading scores were recorded and data was compared with week 0 (before study enrollment).

All of the patients were ventilated with Evita 4 (Drager Medical AG & Co, Lubeck, Germany). Airway resistance and lung compliance were read directly from the display of the ventilator, according to the manufacturer's instructions and protocol. Airway resistance was also recorded and repeated weekly before and 1 hour after the use of LABA/ICS, respectively, during the study period (total of 6 weeks). Weekly data were collected and compared with week 0 (before study enrollment) within the timeframe. We used the paired t test and linear mixed effects model for repeated measurement data of dynamic airway resistance and secretion quantitative grading scores.

Secondary outcomes assessment: VAP and weaning

The secondary outcomes assessed included ventilator-associated pneumonia (VAP) and successful weaning rate. VAP was judged by the chest physician in charge. Once fever presented, we performed the fever routine: complete blood count, blood culture, sputum culture and CXR. Antibiotics were prescribed first and adjusted

based on further reports. VAP was suspected by the presence of new infiltration on CXR, use of 1 full course of antibiotics and positive culture from tracheal aspirates. The incidence of VAP in the studied patients before treatment (6 weeks prior to enrollment) and after combined use of LABA/ICS (6 weeks after enrollment) were recorded and compared. Successful weaning was defined as 5 consecutive ventilator-free days.

Statistical analysis

Data are presented as frequencies (n) or percentages (%) for categorical factors and as mean±standard deviation for continuous factors. Differences between patient sub-groups were tested by the Mann-Whitney U test for comparison between 2 groups, and Kruskal-Wallis analysis for more than 2 groups. The linear mixed effects model was introduced for repeated measurement data of dynamic airway resistance and secretion quantitative grading scores. The paired-*t* test was used to examine the incidence of VAP prior to and during the use of LABA/ICS combination therapy (total of 6 weeks). Weaning status after the use of LABA/ICS combination therapy was analyzed using the Kaplan-Meier method. Statistical significance was set at a 2-sided $p<0.05$. All data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Nineteen male patients were enrolled, including 3 who were successfully weaned from the ventilator (Figure 1). Their mean age was 81.1±7.6 years and duration of ventilator use was 198.7±254.9 days. Aside from COPD, their major co-morbidities were diabetes mellitus (47.3%) and old cerebrovascular accident

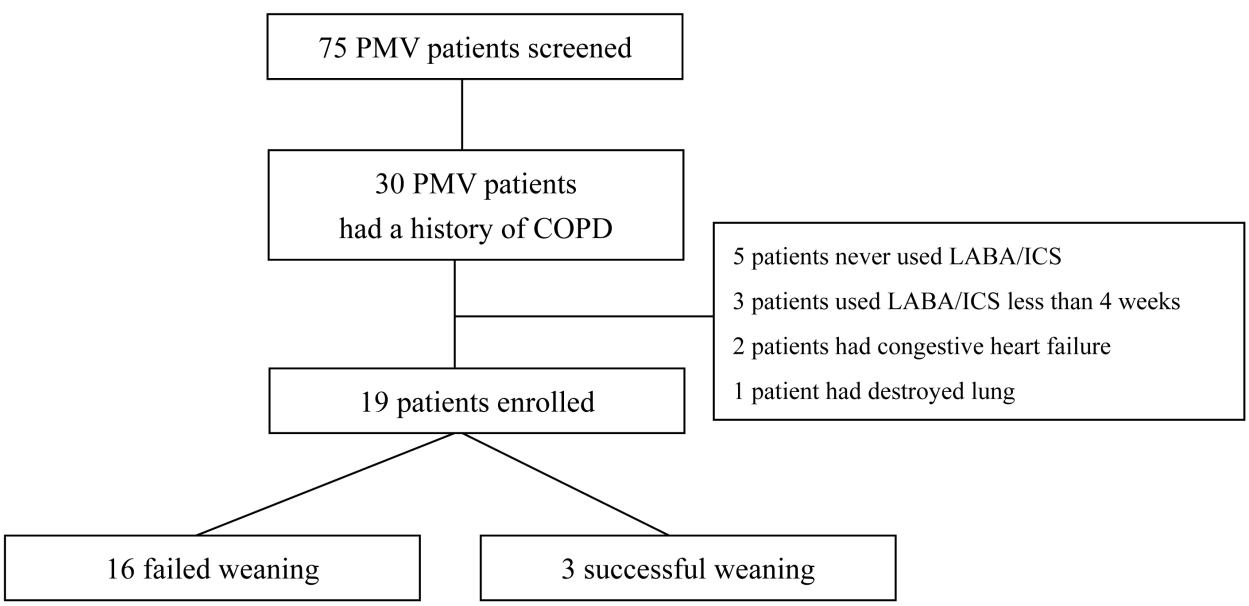

Fig. 1. Flow chart of the enrollment process

Table 1. Characteristics of Enrolled Patients (before Treatment, n=19)

Age (years)	81.1±7.6
Male %	100% (19/19)
Ventilator days	198.7±254.9
Body weight (kg)	52.3±12.0
BMI	19.8±3.8
DM/non-DM	47.3% (9/19)
HbA1C (%)	6.0±0.9
Old CVA	42.1% (8/19)
Pressure sores	0.7±1.2
Expectoration ability*	
Grade 0	0% (0/19)
Grade 1	79% (15/19)
Grade 2	21% (4/19)
White blood cell count (10^3/μl)	12300±4203
Hemoglobin (g/dL)	9.6±1.8
Albumin (g/dL)	2.9±0.5
Globulin (g/dL)	3.4±0.7
Triacylglycerol (mg/dL)	91.0±63.3
Total cholesterol (mg/dL)	125.2±31.5
C-reactive protein (mg/dL)	6.8±6.0
Feeding calories (kcal)	1821.0±199.0
Malnutrition score**	
1	0% (0/19)
2	5.3% (1/19)
3	31.6% (6/19)
4	26.3% (5/19)
5	31.6% (6/19)
6	5.3% (1/19)

Abbreviations: BMI, body mass index; DM, diabetes mellitus; CVA, cerebral vascular accident; HbA1c, hemoglobin A1c; NA, not applicable

Note: Data represented mean±SD

*Grade 0: weak cough, no airway secretion in the tube; Grade 1: audible cough, airway secretion in the tube; Grade 2: strong cough, airway secretion expectorated out from the tube

**Six parameters were selected as the components of the malnutrition score: percent ideal body weight <90%, body mass index <18.5 kg/m^2, serum albumin <3.5 g/dL, total lymphocyte count <1800 cells/mm^3, total cholesterol <90 mg/dL, and hemoglobin <12 g/dL (female) and <14 g/dL (male)

(42.1%) (Table 1). All of the enrolled patients were male, which was not surprising because only 5% of females in Taiwan have a smoking history, the most important factor for COPD, and the study hospital was a veterans' general hospital. The demographic data in this study were consistent with those from the national representative PMV dataset in Taiwan [3].

Malnutrition was a major problem among COPD patients and was correlated with mortalities and morbidities [14-15]. The study patients were in a cachexia state, with low albumin (2.8±0.5 g/dL) and low BMI (19.8±3.8). Using the malnutrition scoring system to further quantify their status, 63% (12/19) of the patients were severely malnourished, with malnutrition scores ≥4.

Airway secretion and dynamic mechanics parameters

Airway secretion clearance parameters among the study patients showed that both expectoration ability and secretion quantitative grading score were poor. Around 80% (15/19) had Grade 1 expectoration ability, which meant that they could expectorate secretion to the tracheostomy tube only, but not out of the tube (Table 1). Using baseline secretion quantitative grading scoring, 74% (14/19) had Grade 2 or 3 secretions, representing mucoid or muco-purulent sputum, and 26% (5/19) had Grade 4 secretions with abundant muco-purulent sputum (Table 2).

The airway dynamic data further confirmed that the enrolled COPD patients had high airway resistance and low Pe maximum. The measured airway resistance was 18.3±10.6 cmH_2O/L/sec (reference range, 1-6 cmH_2O/L/sec), while Pe maximum was 20.8±6.9 cmH_2O (reference range, 30-40 cmH_2O). However, the

Table 2. Characteristics before and after the Use of LABA/ICS

	Before***	After****	*p* value
Laboratory data			
White blood cell count (10^3/μl)	12300±4203	11400±4580	0.208
Hemoglobin (g/dL)	9.63±1.78	9.55±1.68	0.779
Albumin (g/dL)	2.85±0.52	2.86±0.54	0.876
Secretion characteristics*			0.005**
Grade 0	0% (0/19)	0% (0/17)	
Grade 1	0% (0/19)	24% (4/17)	
Grade 2	32% (6/19)	53% (9/17)	
Grade 3	42% (8/19)	18% (3/17)	
Grade 4	26% (5/19)	6% (1/17)	
Airway dynamics			
Airway resistance (cmH_2O/L/sec)	17.9±11.6	17.6±7.1	0.859
Lung compliance (mL/cmH_2O)	33.1±12.9	34.4±13.0	0.508
Rapid shallow index	116.0±46.2	112.5±34.0	0.759
Pi maximum (cmH_2O)	16.3±8.3	15.8±6.6	0.785
Pe maximum (cmH_2O)	21.7±7.8	20.6±6.8	0.532

*Grade 0: No sputum; Grade 1: little sputum; Grade 2: mucoid sputum; Grade 3: muco-purulent sputum; Grade 4: productive muco-purulent sputum

**Wilcoxon signed-ranks test

***Before: data collected at initial enrollment (before treatment)

****After: data collected after 6 weeks of LABA/ICS combination treatment

dynamic lung compliance and Pi maximum were relatively within normal limits (Table 2). The airway dynamic data suggested that the major problem among these patients was airflow limitation rather than lung parenchyma or respiratory drive problems. These data collectively demonstrated that airflow limitation and impaired airway secretion clearance were both essential problems among the enrolled patients.

The bronchodilator effect of LABA/ICS combination therapy

A previous study reported the bronchodilatation effect of inhaled LABA (salmeterol) in ventilated COPD patients and that the effect peaked within 30 minutes and lasted for 12 hours [16]. Thus, airway dynamic resistance before and 1 hour after the use of LABA/ICS combination therapy was determined. After each use of LABA/ICS, airway resistance decreased by 16.3±15.2% temporally (Figure 2). Although there was no significant statistical power because of the high variation, the trend of declining resistance after each use of LABA/ICS was consistent from week 1 to week 6.

Evaluation of the long-term effect of LABA/ICS combination therapy on secretion clearance among the enrolled patients showed that airway secretion quantitative grading scores decreased gradually and reached statistical significance

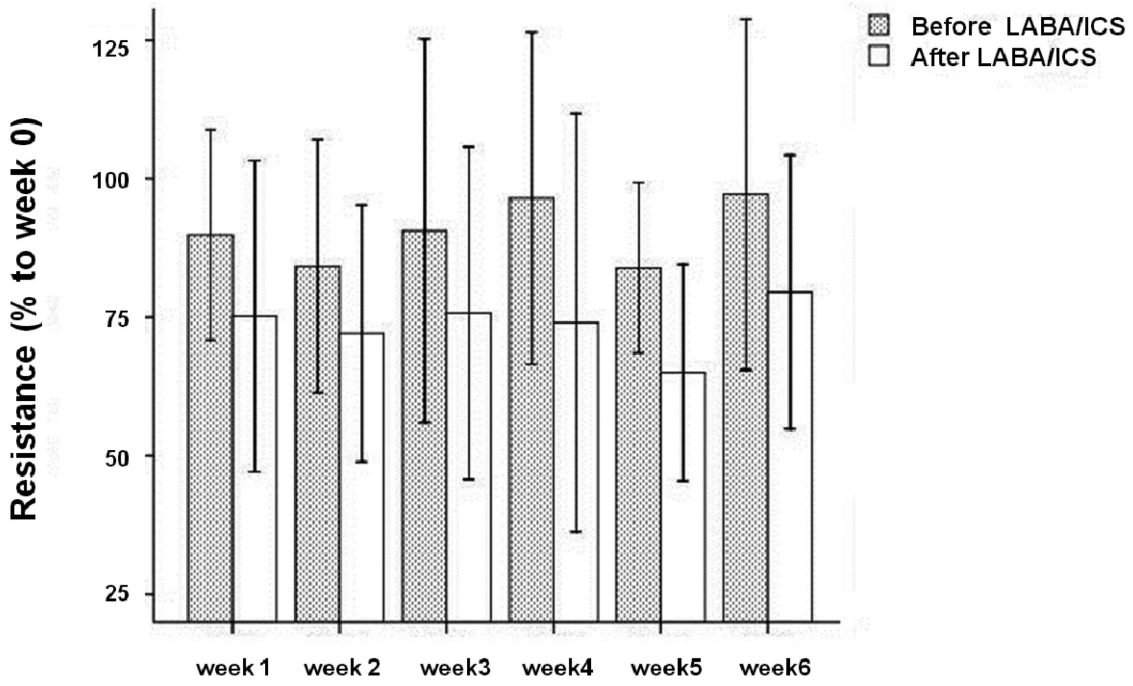

Fig. 2. Dynamic airway resistance change checked weekly, before and 1 hour after use of the LABA/ICS combination, respectively, during the 6-week period.

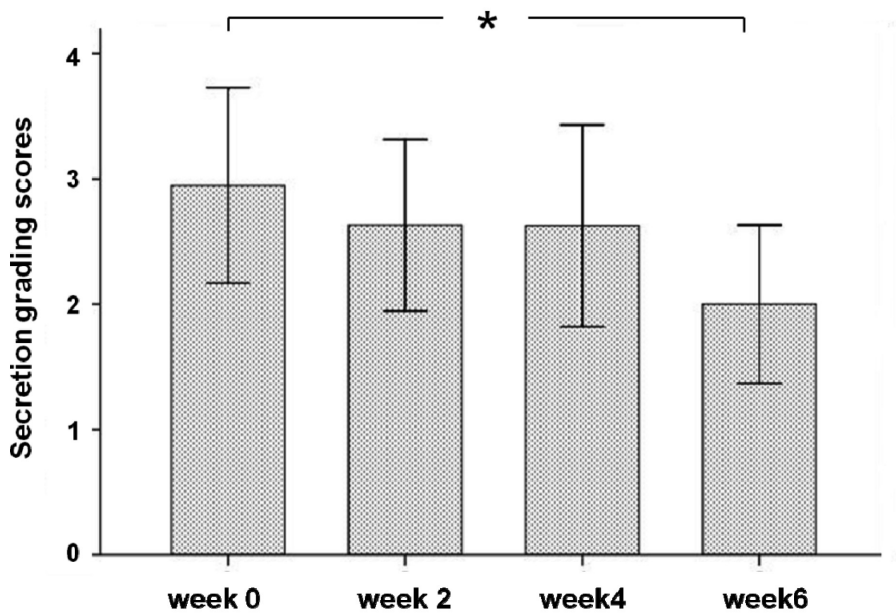

Fig. 3. Secretion quantitative grading scores during the period of combined LABA/ICS use (*p<0.05) week 0, week 2, week 4, week 6.

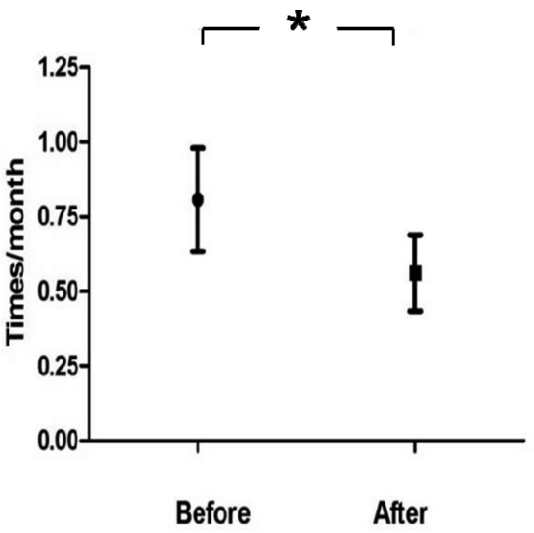

Fig. 4. Incidence of ventilator-associated pneumonia at 2 time periods during our study (*p<0.05). Before: Time period (6 weeks before enrollment). After: Time period (during 6-week use of LABA/ICS combination after enrollment).

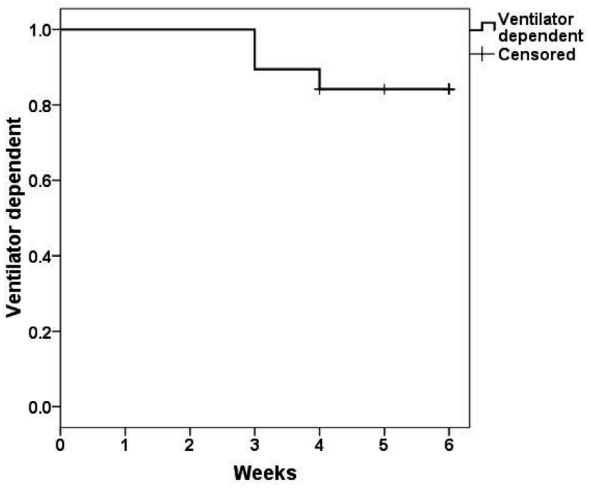

Fig. 5. Cumulative ventilator dependence probability during the period of LABA/ICS combination treatment.

compared to the secretion grades between week 0 and week 6 (Figure 3), suggesting that the use of the LABA/ICS combination may improve airflow limitation and secretion clearance in COPD patients in PMV.

The salvage effect of LABA/ICS on VAP incidence and weaning

There were controversial results regarding the use of ICS in inducing pneumonia in COPD patients [17]. Comparison of the VAP incidence 6 weeks before and after the use of LABA/ICS revealed that the incidence of VAP decreased from 0.82±0.75 times/month to 0.56±0.55 times/month (Figure 4). After LABA/ICS, 3 patients were successfully weaned, for a cumulative weaning rate 18.5%. This was higher than the 5% average weaning rate among RCWs in Taiwan (Figure 5).

Discussion

To date, this is the first study to explore the use of LABA/ICS in PMV patients with COPD. The patients were older, predominantly male, and poorly nourished. Even with mechanical ventilator support, they still suffered high airway resistance and much airway secretion. The use of LABA/ICS reduces airway resistance, airway secretion, and the incidence of VAP. It also saved some patients from further mechanical ventilator support.

PMV is less widely studied in the world because of the expensive healthcare cost [1]. In Taiwan, the NHI, established in 1995 with 99% coverage of the residents of Taiwan, offers comprehensive payment for both acute and chronic respiratory healthcare services. However, PMV cases have increased at a strikingly high rate, from 9,296 in 1998 to 21,818 in 2004 and 30,000 in 2008 [3-4]. It is estimated that in Taiwan, an adult person who lives to the age of 85 years has a 10-15% chance of being put on PMV, which is approximately 4-to-5 times higher than in the United States. Given the resource-intensiveness of PMV, the increased

financial burden is a crucial threat to the sustainability of the NHI system in Taiwan. Although not as severe or extensively studied as in Taiwan, the increase in PMV cases in many countries also has become a new health threat [2,17-18]. Therefore, there is a critical need to decrease the number of PMV cases both in Taiwan and in the world.

Not only do patients with COPD account for 23.2% of PMV cases in Taiwan, but perhaps due to their old age, they also suffer from other major diseases like urinary tract infection (29%) and other respiratory diseases such as pneumonia (26%), that contribute to their low weaning rate. This low weaning rate is an important factor in the increasing number of PMV cases in Taiwan. The overall weaning rate is only 5-10% among PMV patients using mechanical ventilation for more than 42 days [3,19].

COPD has traditionally been considered a lung disease with airflow limitation and obstruction, which subsequently leads to secretion accumulation and infection. The use of inhaled LABA in COPD patients with mechanical ventilation has been clearly demonstrated to contribute to 15-20% of improvement in airway resistance lasting for around 8 hours [16]. The LABA/ICS combination is a well-known effective treatment for COPD, but the effects on PMV patients with COPD have not been well studied. The findings here show obvious bronchodilatation after LABA/ICS administration, but the effect was temporary because airway resistance was similar before administration of LABA/ICS each week (Figure 2). As such, LABA/ICS exerts a significant but short-term bronchodilator effect on PMV patients with COPD.

The cumulative effect of LABA/ICS decreased the amount of airway secretion within a timeframe, from week 1 to week 6 (Figure 3). The significant decrease in the amount of airway secretions suggests that LABA/ICS exerts anti-inflammatory effects on the airways, and then decreases the amount of secretions. It also implies that combined LABA/ICS has a cumulative effect on down-regulating airway inflammation in PMV patients with COPD.

VAP is common in PMV patients. The incidence of VAP during LABA/ICS therapy is less than that before LABA/ICS. A previous study reported that LABA/ICS increases the risk of pneumonia in stable COPD patients [20-22]. However, our results were completely different from those in the above study. Moreover, LABA/ICS has been shown to significantly reduce airway secretions, which may be helpful in maintaining airway hygiene. Thus, it may decrease the incidence of pneumonia.

Increasing the dosage of inhaled agents for patients on mechanical ventilation has been suggested before, due to drug deposition in the circuits of the ventilator. The present study used the Seretide 250 Evohaler 4 puffs twice a day, and each puff contained salmeterol 25 mcg and fluticasone 250 mcg. A previous study reported the efficacy of salmeterol 25 mcg 4 puffs twice a day in COPD patients on mechanical ventilation [16,23]. Higher doses have been proposed to achieve an adequate anti-inflammatory effect, but some studies showed that high-dose ICS might be associated with pneumonia and tuberculosis [24-26]. In the present study, salmeterol 25 mcg/fluticasone 250 mcg 4 puffs twice a day decreased the rate of VAP. With this dosage, LABA/ICS exerted both bronchodilatation and anti-inflammation effects. This dosage can therefore be applied safely and effectively with COPD patients in PMV, although the optimal dose has yet to be determined.

This study has some limitations. First, it is a retrospective study and lacks comparable patients who did not use the LABA/ICS combination. However, the challenge of a prospective study is the involvement of the ethical issue and the medical fees in the RCW units under Taiwan's NHI system. Second, the sample size was relatively small, which precluded multivariable analyses. Third, the measurement of respiratory mechanical parameters should be done in a fully sedated status with the same constant flow. Airway secretion should be assessed with more objective methods and a double-blind control design. Finally, the concept of the clinical pulmonary infection score (CPIS) for VAP management and evaluation should be introduced in the clinical setting.

Conclusions

PMV patients with COPD have a tremendous public and economic impact on Taiwan. This is also a unique phenomenon in clinical practice. In this study, we elucidated the pulmonary cachexia of these patients and observed that the combined use of LABA/ICS may decrease airway resistance and secretion amounts, and have some impact on the incidence of VAP. However, more prospective studies are needed to validate the further effects of LABA/ICS on PMV patients with COPD weaning from the ventilator.

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評估使用長效乙二型擴張劑（LABA）及吸入性類固醇（ICS）合併吸入劑對於長期呼吸器依賴的慢性阻塞性肺病患者在肺部機械力學及痰液量的影響

王俊隆 *,*** 趙文震 **,**** 李淑芬 ** 吳杰亮 **,*****

前言：評估使用長效乙二型擴張劑（LABA）及吸入性類固醇（ICS）合併吸入劑對於長期呼吸器依賴的慢性阻塞性肺病患者在肺部機械力學及痰液量的影響。

方法：我們回溯性的從 2011 年 10 月 01 日至 2011 年 12 月 31 日期間，針對於台中榮民總醫院嘉義分院呼吸照護病房長期呼吸器依賴的慢性阻塞性肺病患者，接受長效乙二型擴張劑（LABA）及吸入性類固醇（ICS）合併吸入劑的案例做病歷資料回顧。我們收集並記錄個案相關的流行病學情形，營養參數及呼吸道動力參數。收案個案給予每天兩次、每次四噴的長效乙二型擴張劑（LABA）及吸入性類固醇（ICS）合併吸入劑，為期六週的藥物使用。收案期間，每週都會定期分析相關指標及參數（痰液分泌量化指數、呼吸道阻力指數、肺炎發生率及呼吸器脫離情形）。

結果：經篩選後符合收案條件的共 19 位男性病患。平均年齡為 81.1±7.6 歲，使用呼吸器的平均時間為 198.7±254.9 天。每天維持足夠的灌食熱量（1821.0±199.0 大卡路里），檢測其營養狀況皆呈現慢性耗損情形：低白蛋白（albumin: 2.9±0.5 g/dL）及低身體質量指數（BMI: 19.8±3.8)。病患大多呈現氣道痰液清除能力較差且合併較高的呼吸道阻力。經由使用長效乙二型擴張劑（LABA）及吸入性類固醇（ICS）合併吸入劑後發現呼吸道阻力可下降達 16.3±15.2% 嗅液分泌量化指數也明顯改善 呼吸器相關肺炎（VAP）發生次數從每月 0.82±0.75 次減為 0.56±0.55 次。最後有 3 位病患成功脫離呼吸器(平均脫離率為 18.5%)。

結論：從我們的研究觀察發現，使用長效乙二型擴張劑（LABA）及吸入性類固醇（ICS）合併吸入劑對於長期呼吸器依賴的慢性阻塞性肺病患者可以降低呼吸道阻力，減少痰液分泌量及有較低呼吸器相關肺炎（VAP）發生的機會，關於協助脫離呼吸器，需要更多大型的研究來進一步佐證。*(胸腔醫學* ***2014; 29: 323-334)***

關鍵詞：慢性阻塞性肺病，長期呼吸器依賴，吸入性類固醇，脫離呼吸器

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Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI)-Related Severe Interstitial Lung Disease in Taiwanese Patients with Non-Small Cell Lung Cancer

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Background: It has been shown in recent years that epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), whether gefitinib or erlotinib, can provide significant benefit to patients with advanced non-small cell lung cancer (NSCLC). A major concern with EGFR-TKI treatment is the development of interstitial lung disease (ILD). The incidence and clinical characteristics of ILD associated with EGFR-TKIs in Taiwanese patients are less well defined.

Methods: Patients with advanced NSCLC in Taipei Veterans' General Hospital were screened and those who had received an EGFR-TKI were enrolled in this study. Their clinical information, including medical records and chest images, was reviewed. The diagnosis of EGFR-TKI-related ILD was confirmed by 2 pulmonologists in accordance with previously published criteria. Association between ILD development and clinical factors was evaluated.

Results: From February 2008 to July 2012, 1212 patients who received an EGFR-TKI as single therapy for NSCLC were screened. Patients who developed severe ILD and needed hospitalization (NCI CTC grade 3-5) were included. Nine of the 1212 patients (0.7%) were diagnosed as having severe EGFR-TKI-related ILD. The median time interval from EGFR-TKI use to onset of ILD was 31 days (range: 10-75 days). The most common symptom of EGFR-TKI-related ILD was dyspnea (88.9%). The most common radiological manifestation was bilateral ground glass opacity, which was noted in 5 patients (55.6%). Six of the 9 patients (67%) died due to ILD.

Conclusion: EGFR-TKIs, both gefitinib and erlotinib, may cause fatal ILD in Taiwanese NSCLC patients. Physicians should be aware of this rare side effect of EGFR-TKIs and monitor this pulmonary toxicity closely. ***(Thorac Med 2014; 29: 335-343)***

Key words: non-small cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitor, interstitial lung disease

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Introduction

Non-small cell lung cancer (NSCLC) is a major cause of cancer death. In patients with advanced NSCLC, systemic chemotherapies have been the main therapeutic option [1]. However, in recent years, it has been shown that epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), either gefitinib or erlotinib, can provide significant benefit to these patients [2-3]. Patients with sensitive EGFR mutations who received EGFR-TKI treatment had longer progression-free survival and better quality of life than with standard chemotherapy [2,4].

A major concern with EGFR-TKI treatment is the development of interstitial lung disease (ILD), which was first reported by Inoue *et al*. in 2003 [5]. Although rare, this is a potentially fatal complication during treatment. The incidence of ILD in patients receiving gefitinib has varied among studies, and was reported as 1% outside Japan and 3-4% among Japanese patients [6-8]. The exact mechanism is not clear yet. Old age, male gender, smoking history, preexisting ILD and poor performance status are risk factors for the development of gefitinib-induced ILD [6-7,9]. Although studies have been relatively scarce, the frequency of ILD in patients receiving either erlotinib or gefitinib has been similar [10-11].

The incidence and clinical characteristics of ILD associated with EGFR-TKIs in Taiwanese patients are less well defined. A case series study reported that 4 of 69 NSCLC patients (5.8%) developed ILD during gefitinib treatment, and there was no mortality [12]. A multi-institute retrospective study showed the incidence of ILD in patients receiving gefitinib was 2.3% and the mortality rate was 40% [13]. The frequency of ILD among Taiwanese patients who received erlotinib is not known. In this study, we examined the incidence and clinical characteristics of ILD in Taiwanese patients with NSCLC who were treated with gefitinib or erlotinib monotherapy in a single institute.

Methods

Study population and definition of ILD

Between February 2008 and July 2012, patients aged more than 18 years with cytologically or pathologically proven NSCLC at Taipei Veterans General Hospital were screened for eligibility for inclusion in this study. The NSCLC patients who had received an EGFR-TKI were enrolled into this study. The clinical information, including medical records and chest images, were reviewed. The diagnosis of EGFR-TKI-related ILD was confirmed by 2 pulmonologists using previously published criteria [6-7]: a clinical syndrome composite of the acute onset of respiratory symptoms associated with interstitial pulmonary infiltrates on a chest roentgenogram or computed tomography scan; exclusion of pulmonary infection, lymphangitis carcinomatosis and radiation pneumonitis. ILD was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. This study was approved by the Institutional Review Board in Taipei Veterans' General Hospital (2013-02-023BC).

Clinical data

The following demographic and clinical data of the patients were reviewed from medical records: age, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status, histology type, clinical staging and duration of EGFR-TKI treatment. The

symptoms and duration from EGFR-TKI administration to ILD were recorded. The patients were followed until death or October 31, 2012.

Statistical analysis

Association between ILD development and clinical factors was analyzed by chi-square test and Fisher's exact test. Statistical analysis was performed using SPSS statistics 17.0 (SPSS Inc., Chicago, IL).

Results

Patient Characteristics

From February 2008 to July 2012, a total of 1212 patients who received an EGFR-TKI as single therapy for NSCLC were screened. Patients who developed severe ILD and needed hospitalization (NCI CTC grade 3-5) were included. Nine of the 1212 patients (0.7%) were diagnosed as having severe EGFR-TKI-related ILD (Table 1). The median age of the patients with ILD was 61.0 years and 6 were male (66.7%). The histologic type was adenocarcinoma in 7 (77.8%) and the most common stage of lung cancer at diagnosis was stage IV (Table 2). As for the timing of EGFR-TKI therapy, 3 patients were in first-line therapy; 3 had had 1 previous chemotherapy, and 3 used TKI after second-line chemotherapy.

Clinical manifestations and prognosis of ILD

The median time interval from EGFR-TKI use to onset of ILD was 31 days (range: 10-75 days). The most common symptom of EGFR-TKI-related ILD was dyspnea (88.9%). The most common radiological manifestation was bilateral ground glass opacity, which was noted in 5 patients (55.6%). All patients discontinued their EGFR-TKI immediately, once ILD was

Table 1. Demographic and Clinical Characteristics of the Total Patients

		Total	ILD (%)	*p* value
	(n)	1212	9(0.7)	
EGFR-TKI				
	Iressa	561	4 (0.7)	0.517
	Tarceva	651	5 (0.8)	
Gender				
	Male	643	6 (0.9)	0.514
	Female	569	3 (0.5)	
Smoking				
	Ever	455	5 (1.1)	0.309
	Never	757	4 (0.5)	
Histology				
	Adenocarcinoma	1091	7 (6.4%)	---
	Squamous cell carcinoma	63	0	
	NSCLC	47	2 (4.3%)	

Table 2. Clinical and Demographic Characteristics of the 9 Patients with ILD

Patient No.	Age	Gender	Smoking	Histology	Stage	ECOG PS	Preexist PF	Prior chemotherapy	Length of treatment (days)	Radiological findings	Response to steroid	ILD- related death
Gefitinib												
1	70	M	Never	Adeno	IV	2	Yes	No	36	Bilateral GGO	No	Yes
2	67	M	Ever	Adeno	IV	0	No	Yes	75	Bilateral interstitial infiltration	No	Yes
3	57	F	Never	Adeno	IV	0	No	Yes	31	Unilateral GGO and consolidation	No	Yes
4	43	F	Never	Adeno	IV	1	No	No	17	Bilateral GGO	Yes	No
Erlotinib												
1	57	M	Ever	Adeno	IV	1	No	Yes	21	Bilateral GGO	No	Yes
2	77	M	Ever	NSCLC	IV	3	No	Yes	10	Bilateral GGO	No	Yes
3*	83	F	Never	Adeno	IV	4	No	No	49	Bilateral GGO	Yes	--
4	51	M	Ever	NSCLC	IIIb	1	No	Yes	19	Bilateral GGO and consolidation	No	Yes
5	47	M	Ever	Adeno	IIIb	1	No	Yes	42	Unilateral consolidation	Yes	No

ILD, interstitial lung disease; PS, performance status; PF, pulmonary fibrosis; NSCLC, non-small cell lung cancer; GGO, ground glass opacity

*This case is demonstrated in Figure 2.

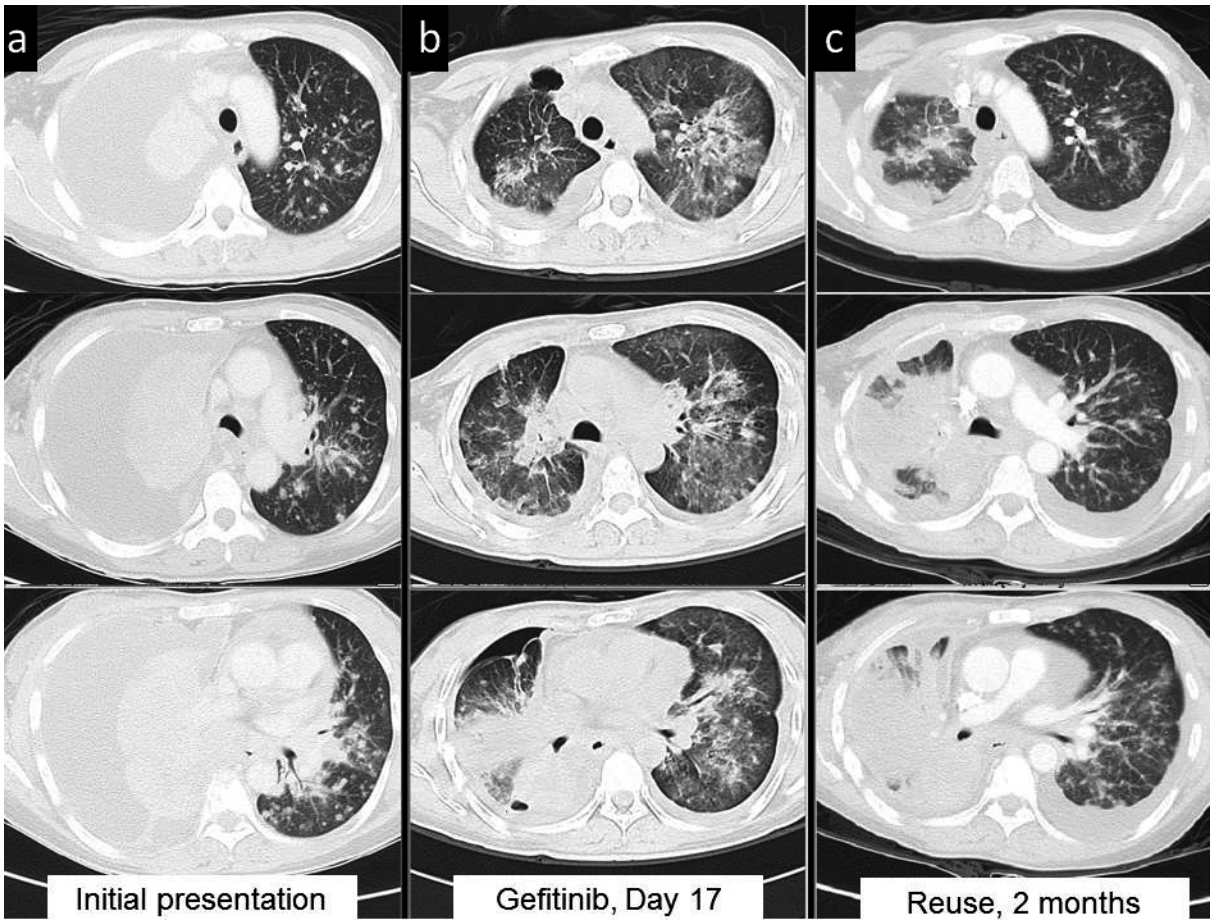
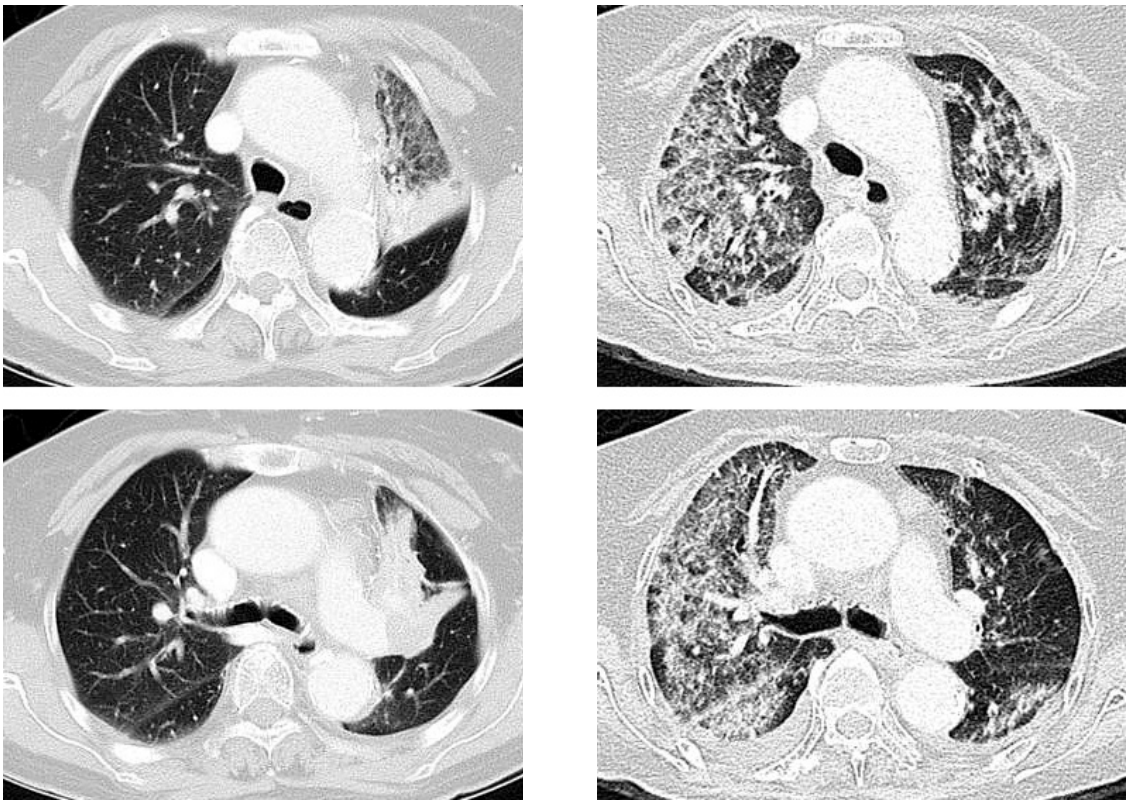


Fig. 1. A patient with advanced lung adenocarcinoma developed ILD after 17 days of gefitinib treatment (a,b). We then discontinued gefitinib and prescribed steroid. Half-dose gefitinib was rechallenged after pneumonitis resolved. CT scan 2 months later showed stable disease and no recurrence of ILD. (c)

suspected, and 8 patients (88.9%) received systemic steroids. Six of the 9 patients (67%) died due to ILD. Two of the survivors re-challenged the same EGFR-TKI (1 with gefitinib, 1 with erlotinib) for disease control after ILD subsided, which resulted in disease control without recurrence of ILD.

Discussion

Nine patients in this study (0.7%) developed severe ILD during EGFR-TKI treatment. The incidence rate was relatively low compared to previous Taiwanese studies, and was similar to the global incidence [8,12-13]. However, the 67% mortality in our study was higher than in previous studies (0% in Shih *et al* and 40% in Chang *et al*) [12-13]. This may be related to patient selection, in that only those patients with grade 3 or above interstitial pneumonitis were included in our study. Also, our study period was relatively later than that of previous Taiwanese studies (2002-2003 in Shih *et al* and 2004-2009 in Chang *et al*). We found that the incidence rate of ILD in Japan also seemed to decline, from 5.4% in 2003-2004 to 1% in 2008



(a) (b)

Fig. 2. A patient with left upper lobe lung adenocarcinoma before (a) and after (b) 49 days of erlotinib treatment. Note the regression of the tumor and development of ILD.

[9-10]. Physician's awareness of this rare side effect of EGFR-TKIs may have contributed to this finding.

The results of univariate analysis in our study showed no clinical factor was significant in the development of severe ILD. A study by Hotta *et al*. showed that despite the statistical insignificance, patients receiving erlotinib developed less ILD than those taking gefitinib [10]. Another study compared adverse events of erlotinib and gefitinib that occurred in Japanese patients, and found the incidence of pneumonitis did not differ between the 2 groups [11]. Our study showed a similar incidence of ILD in Taiwanese NSCLC patients treated with either erlotinib or gefitinib. Clinical physicians in Taiwan should monitor this rare side effect no matter which EGFR-TKI is used.

Discontinuance of EGFR-TKI is mandated when ILD is suspected clinically. When the clinical condition improves, physicians may hesitate to reuse the drug for fear of ILD recurrence, but this may hamper patients from benefiting from the efficacy of EGFR-TKIs, especially those patients with EGFR-sensitizing mutations. In our study, 2 patients were given the same EGFR-TKI after their ILD subsided and disease control was obtained (Figure 1). Successful gefitinib retreatment after gefitinib-related ILD has been reported in the past [14-

15]. Patients in our study received retreatment with EGFR-TKI at a reduced dosage initially and were monitored closely for the recurrence of ILD. This may be a reasonable approach when trying to find a balance between toxicity and treatment efficacy.

There are several limitations in our study. First, this was a retrospective study and only those patients with severe pneumonitis requiring admission were included. Therefore, the incidence of EGFR-TKIs-related ILD may be underestimated. Second, the diagnosis of ILD in our study was based on clinical history and chest images, and no case was proved by pathology. In fact, pathological diagnosis of EGFR-TKIs-related ILD is difficult because the respiratory distress may progress rapidly, before invasive diagnostic procedures can be performed. Third, the dosage of steroid and EGFR-TKI retreatment were based on the judgment of the clinical physician, without a protocol. Large prospective studies may be needed to verify the incidence and management of EGFR-TKI-related ILD in Taiwanese NSCLC patients.

Conclusion

The incidence of severe interstitial pneumonitis following EGFR-TKI use in our study was low (<1%), but it carried a high mortality rate (67%). No significant risk factor was found for the development of severe ILD. Both gefitinib and erlotinib, individually, may cause fatal ILD in Taiwanese NSCLC patients. Physicians should be aware of this rare side effect of EGFR-TKIs and monitor this pulmonary toxicity closely.

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非小細胞肺癌患者使用表皮生長因子受體激酶抑制劑後發生嚴重間質性肺炎之研究

江起陸 * 邱昭華 *,**,*** 李毓芹 *,** 蔡俊明 *,** 吳杰鴻 *,**

前言：非小細胞肺癌是國人因癌症死亡最重要的原因之一。表皮生長因子受體激酶抑制劑的發現對晚期非小細胞肺癌的患者提供相當大的幫助；但其最嚴重的副作用為間質性肺炎。雖然罕見，但據國內外文獻指出具有高死亡率。國內目前對於表皮生長因子受體激酶抑制劑引起之間質性肺炎，其發生率及臨床特徵仍無深入研究。

方法：以回溯性病例研究方法，搜集台北榮民總醫院過去病理或細胞學診斷為非小細胞肺癌的病患，其於表皮生長因子受體激酶抑制劑治療期間發生嚴重間質性肺炎之機率及臨床表現。

結果：於 2008 年二月至 2012 年七月間，篩選本院 1212 位使用表皮生長因子受體激酶抑制劑的非小細胞肺癌病患，找出治療期間發生嚴重間質性肺炎而需要住院治療的患者。其中 9 位（0.7%）被診斷為表皮生長因子受體激酶抑制劑引起之間質性肺炎，服藥至發生間質性肺炎的時間之中位數為 31 天（10-75 天）。在這九位患者中，最常見的臨床症狀為喘（88.9%），最常見的影像學變化為雙側毛玻璃狀病變（55.6%），其中六位病人因間質性肺炎死亡，死亡率為 67%。

結論：雖然罕見，表皮生長因子受體激酶抑制劑在國人仍可造成致命之間質性肺炎。臨床醫師在開立此藥時應密切監測和注意。*(胸腔醫學 **2014; 29: 335-343**)*

關鍵詞：非小細胞肺癌，表皮生長因子受體激酶抑制劑，間質性肺炎

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索取抽印本請聯絡：吳杰鴻醫師，台北榮民總醫院　胸腔部　胸腔腫瘤科，台北市北投區石牌路二段 201 號

Primary Pulmonary Synovial Sarcoma: A Case Report and Literature Review

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Primary synovial sarcoma in the lung is a very rare disease. Herein, we presented a 59-year-old female with the symptoms of chest tightness, exertional dyspnea and hemoptysis. CXR and chest CT showed a primary tumor located at the right lower lobe with invasion into the right middle lobe. Curative operation with bilobectomy was performed and monophasic synovial sarcoma was suspected by histology and immunohistochemical stains. The tumor was then confirmed by reverse transcription-PCR analysis to be a SYT-SSX2 fusion type. After 7 months of follow-up, local recurrence was noted. The patient was lost to follow-up thereafter and died 2 months later due to sepsis. ***(Thorac Med 2014; 29: 344-350)***

Key words: lung tumor, synovial sarcoma, SYT-SSX fusion type

Introduction

Synovial sarcoma is the 4th most common soft tissue sarcoma and accounts for about 10% of all soft tissue sarcoma. Its origin is still unclear. Most patients are 20-40 years old and present with a deep soft tissue mass in their lower extremities. There is no predilection for sex. The soft tissue mass has also been identified in the head and neck, thorax (including the lung, mediastium and pericardium), abdominal wall, and peritoneal cavity. Primary pulmonary synovial sarcoma is a rare primary lung tumor. Herein, we present the case of a patient with the initial presentation of chest tightness, dyspnea on exertion and hemoptysis.

Case Presentation

This 59-year-old female was a non-smoker and had hypertension with regular medical control. She had intermittent right-side chest pain with radiation to her right shoulder for 6 months, but she ignored these symptoms. She came to our hospital due to progressive exertional dyspnea and hemoptysis for 3 months. Physical examination was unremarkable except decreased breathing sounds in the right lower lung. Chest roentgenogram revealed a radiopaque lesion in the right lower lung field with a blurred border on the right side of the heart and blurred diaphragm border; a right-side blunt costophrenic angle was also noted

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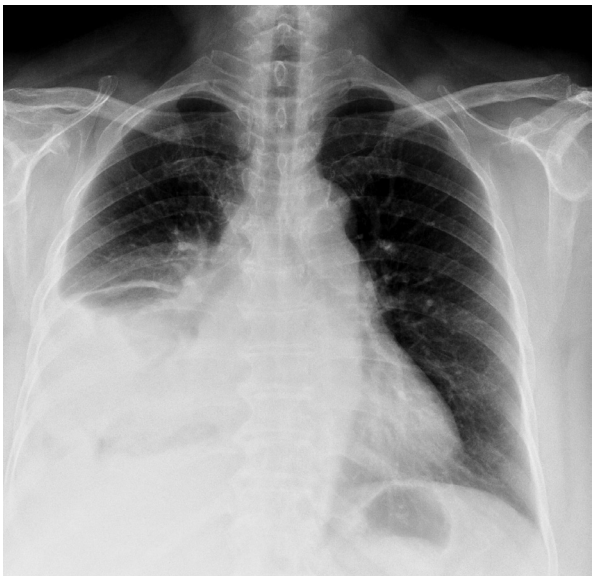
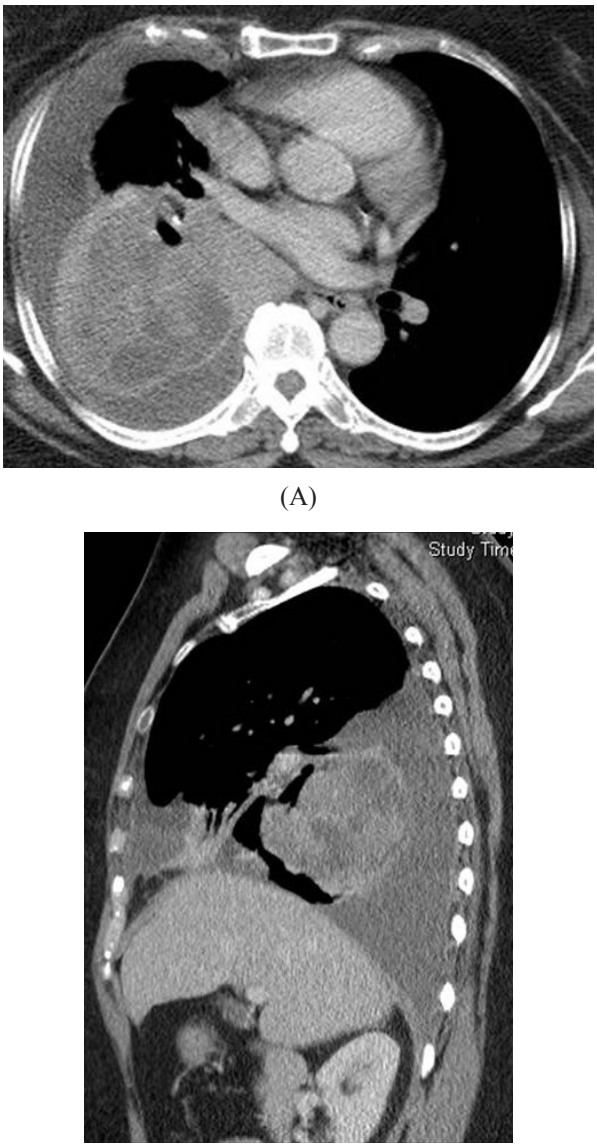


Fig. 1. Radiopaque lesion in the right lower lung field, with a positive silhouette sign at the border of the right side of the heart and the right side of the diaphragm. A right-side blunt costophrenic angle was also noted.

(Figure 1). Chest ultrasound revealed right-side massive pleural effusion. Thoracentesis revealed serosanguinous pleural fluid, analysis of which showed lymphocyte-predominant exudate. Chest computed tomography (CT) showed a heterogeneous enhanced mass lesion in the right lower lung and massive pleural effusion (Figure 2). Lung cancer was suspected at first. CT-guided biopsy was subsequently performed, with the preliminary pathological report of inflammatory myofibroblastic tumor. Exploratory thoracotomy was performed and located a huge tumor with a maximal diameter of 12 cm almost completely occupying the right lower lung; straw-colored pleural effusion was also noted. The tumor had invaded the right inferior pulmonary veins, right lower lobe bronchus and middle lobe bronchus; a bilobectomy was then performed. Macroscopic pathology reported a huge whitish soft mass measuring 13 × 12 × 10 cm in size occupying the lung parenchyma; no



(A)

(B)

Fig. 2. A heterogeneous enhanced mass at the right lower lung field with massive pleural effusion. (A) Axial view; (B) Sagittal view.

obvious capsule formation nor calcified lesion was noted (Figure 3). The histology revealed dense proliferative spindle cells with vascular channels formation (Figure 4). Immunohistochemical stains revealed a typical pattern of synovial sarcoma with focal positive of cytokeratin (Figure 5A) and negative of vimentin, BCL-

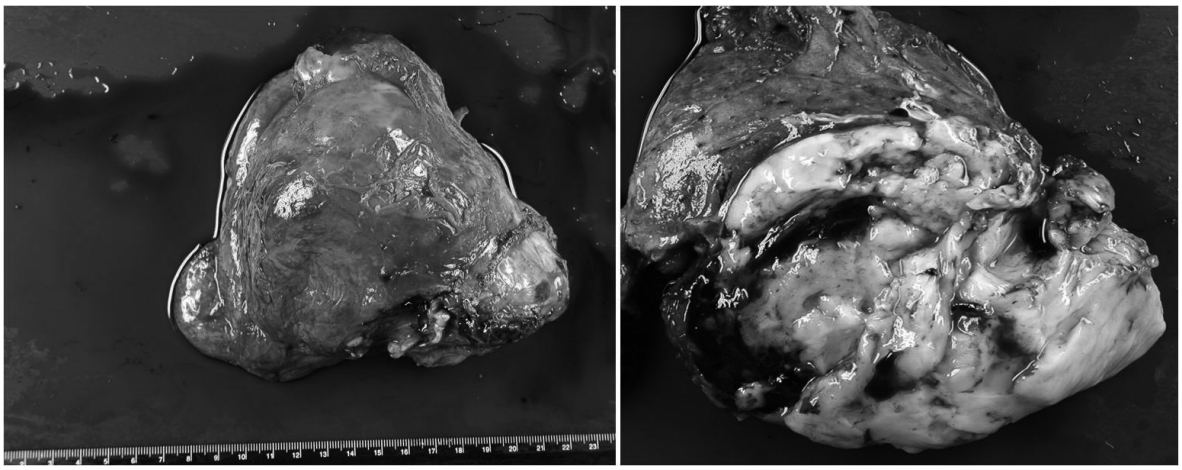


Fig. 3. A whitish tumor without capsule, measuring 13 × 12 × 10 cm in size, occupied the lung parenchyma.

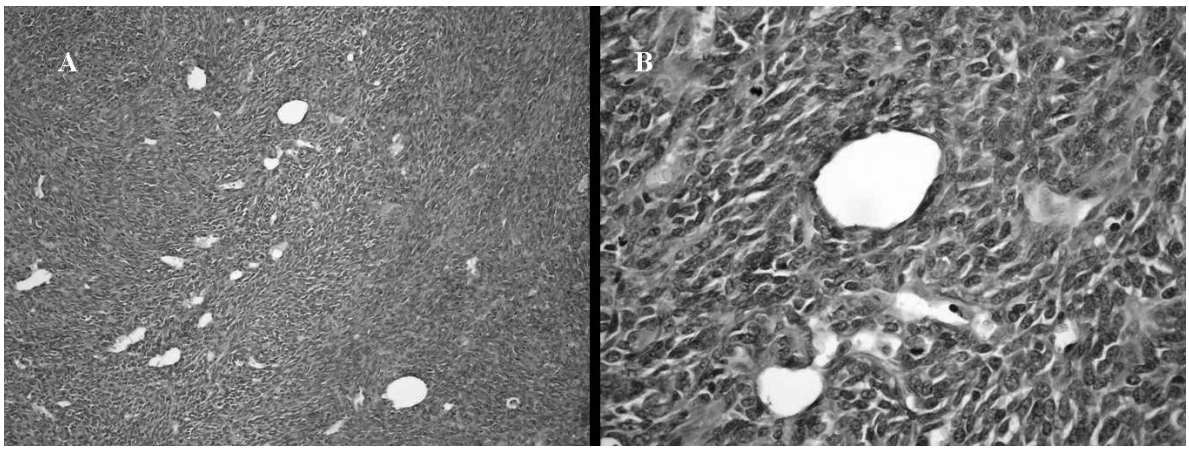


Fig. 4. The histology of the patient. (A) In the low power field (10 × 10), the main tumor was composed of dense proliferative spindle cells. (B) In the high power field (40 × 10), there was vascular channels formation that mimicked a hemangiopericytoma pattern, and accompanying focal necrosis and frequent mitosis.

2, and CD34 (Figure 5B,C,D). Reverse transcription-polymerase chain reaction (RT-PCR) confirmed this patient had a SYT-SSX2 fusion-type tumor. Primary pulmonary monophasic synovial sarcoma was diagnosed based on the histology and immunohistochemical stains. After the operation, no subsequent chemotherapy was arranged. After 7 months of follow-up, chest CT revealed local recurrence. The patient was not seen again until 2 months later when she was brought to hospital due to urosepsis. She died of profound shock with multiple organ failure.

Discussion

Synovial sarcoma is divided into 3 histological subtypes: biphasic, monophasic, and poorly differentiated. Biphasic synovial sarcoma is the classic histology pattern and has 2 components:

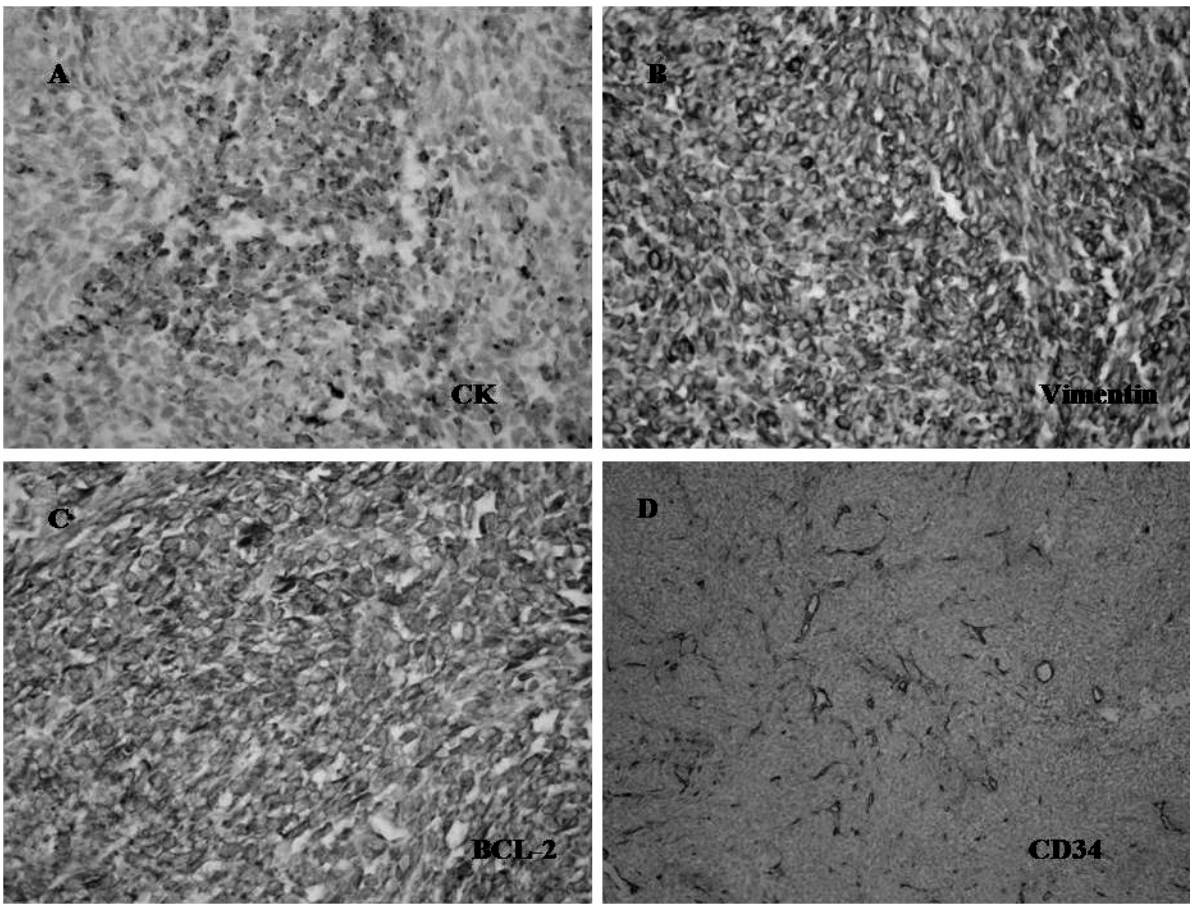


Fig. 5. Immunohistochemical stains of the patient: (A) Focally positive cytokeratin; (B) Diffusely positive vimentin; (C) Diffusely positive BCL-2; (D) The stromal cells were negative for CD34 uptake.

background spindle cells and epithelial components with glandular features. Background spindle cells without epithelial components are typical for monophasic synovial sarcoma. The diagnosis depends on the clinical history, histology and immunohistochemical stains. However, the differential diagnosis of monophasic synovial sarcoma is problematic, because many sarcomas or sarcomatoid carcinomas, including fibrosarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, hemangioperictoma, and spindle cell carcinoma, mimic the feature of background spindle cells without epithelial components.

Synovial sarcoma is characterized by the cytogenetic feature of t(X;18)(p11;q11). This translocation results from the fusion of the SYT gene on chromosome 18 to either the SSX1 or SSX2 gene on chromosome X, and is very specific for synovial sarcoma, with sensitivity greater than 95% [1]. This cytogenetic feature can be detected by either fluorescence in situ hybridization (FISH) or RT-PCR analysis. Although very useful in diagnosis, routine use of this cytogenetic feature for diagnosis is not suggested [2]. The impact of the SYT-SSX fusion type on the prognosis of synovial sarcoma has not been consistent in previous studies [3-

7]. In a retrospective analysis of 271 synovial sarcoma patients, Gronchi et al. found that only 2 factors influence disease-specific survival and metastasis-free survival: tumor size >5 cm and high-grade histological characteristics [6].

Primary sarcomas of the lung are rare, and most are the metastases of a primary tumor from elsewhere. Primary pulmonary sarcoma accounts for less than 0.5% of pulmonary tumors [8]. Etienne-Mastroianni *et al*. collected 12 cases of primary pulmonary sarcomas [9], and found the most common type was leiomyosarcoma (58%). Synovial sarcoma accounts for only 16.6% of primary pulmonary sarcomas [9]. The natural course of synovial sarcoma is poor, with a 5-year mortality rate of 25% [10]. Hartel *et al*. retrospectively collected 60 cases of primary pulmonary and mediastinal synovial sarcoma (58% from the lung, 42% from the mediastinum/pleura) and found that 46% of patients died of disease within 5 years after diagnosis [11]; this showed the primary pulmonary and mediastinal types were more aggressive than soft tissue synovial sarcoma. In the Hartel study, 67% of patients with SYT-SSX1 fusion type died of disease within 5 years, compared to 33% of patients with the SYT-SSX2 fusion type [11].

The cornerstone of treatment for synovial sarcoma is complete surgical resection with a clear margin of 1-3 cm [12]. Adjuvant radiotherapy is recommended for patients with a tumor size >5 cm [13]. Synovial sarcoma has been regarded as a particularly chemosensitive soft tissue sarcoma. Although significant improvement in survival with ifosphamide-based chemotherapy has been observed in previous studies [14-16], there has been no randomized control or case-control study of chemotherapy in primary pulmonary synovial sarcoma.

In conclusion, we presented a rare case of primary pulmonary synovial sarcoma of the lung, monophasic and SYT-SSX2 fusion type, involving the right middle lobe and lower lobe that was surgically resected. The diagnosis of synovial sarcoma usually can be made based on the clinical information and histology with immunohistochemical stains, but cytogenetic analysis of SYT-SSX translocation is very helpful in equivocal cases or when tumors are found in unusual sites (such as the lung). The major prognostic parameters of synovial sarcoma are tumor size (>5 cm) and high-grade histology. Treatment for pulmonary synovial sarcoma depends on complete surgical resection with subsequent radiotherapy and ifosfamide-based adjuvant chemotherapy, especially in high-risk patients.

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原發性肺滑膜肉瘤：病例報告

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原發性滑膜肉瘤在肺部是相當罕見的腫瘤，我們報導了一位 59 歲女性，因為胸悶及活動性呼吸喘及咳血來求診，胸部 CXR 及電腦斷層顯示腫瘤位於右下肺，經手術切除之後病理報告為單相滑膜肉瘤，且確診為滑膜肉瘤 SYT-SSX 第二型。術後七個月胸部電腦斷層發現腫瘤局部復發，但病人拒絕進一步治療與追蹤，病人於兩個月之後死於敗血性休克。*(胸腔醫學 **2014; 29: 344-350**)*

關鍵詞：肺腫瘤，滑膜肉瘤，SYT-SSX

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Pulmonary Cryptococcosis Mimicking Malignancy in Cancer Patients Diagnosed by Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration: Two Case Reports

Yi-Cheng Shen*, Chih-Yen Tu*,**, Wei-Chih Liao*, Chia-Hung Chen*, Chuen-Ming Shih*, Wu-Huei Hsu*

In cancer patients, pulmonary nodules are often considered a metastatic disease or primary lung tumor. We report the cases of a 43-year-old woman with breast cancer and a 56-year-old man with early-stage lung adenocarcinoma, both of whom presented with asymptomatic pulmonary nodules. A presumptive diagnosis of pulmonary metastasis or tumor relapse was made, and they underwent endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) to establish the diagnosis of cryptococcal infection. Antifungal therapy was prescribed subsequently, and full recovery followed. We demonstrate the importance of differentiating between pulmonary cryptococcal infection and metastasis in cancer patients, and the safety and efficacy of TBNA in the diagnosis of pulmonary cryptococcosis. ***(Thorac Med 2014; 29: 351-357)***

Key words: pulmonary cryptococcosis, endobronchial ultrasound-guided transbronchial needle aspiration

Introduction

Pulmonary cryptococcosis is an uncommon fungal infection in patients with malignancy [1-2]. It is caused by inhalation of spores from *C. neoformans*, with effects ranging from primary infectious lesions in the peripheral lung to diffuse pulmonary infiltration that may lead to systemic dissemination with cerebral and meningeal involvement. Primary infectious lesions often manifest as pulmonary nodule(s) that may be difficult to distinguish from primary or metastatic lung cancer. We describe 2 rare cases of asymptomatic pulmonary cryptococcosis diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), 1 in a patient with breast cancer and the other in a patient with early-stage lung adenocarcinoma. Correct diagnosis and treatment resulted in a favorable outcome.

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Case Report

Case 1

A 43-year-old woman with right breast cancer and right axillary lymph node metastasis had undergone a modified radical mastectomy 8 years prior to this presentation. Pathological examination revealed invasive ductal carcinoma, and the oncology work-up revealed T2N1M0, grade II, stage IIb disease. The tumor expressed estrogen and progesterone receptors without HER-2/neu overexpression. The patient received adjuvant chemotherapy and hormone therapy for 3 years post-surgery. However, there was local recurrence at the right chest wall, so wide excision was performed. The pathological examination revealed breast cancer recurrence. The patient then received 6 cycles of salvage chemotherapy with paclitaxel and gemcitabine plus radiotherapy, and had a good response. The patient received gosereline (a luteinizing hormone-releasing hormone analogue) monthly for 3 years after the chemoradiotherapy. There was no tumor recurrence until February 2013, when follow-up chest computed tomography (CT) (Figure 1) revealed several nodules in the right lower lung. The patient did not have fever, cough, or chest pain. Laboratory exams and tumor markers (carcinoembryonic antigen (CEA), cancer antigen 15-3) were all within normal limits. Ultrasonography of the breast and whole body bone scan revealed no evidence of recurrence. She subsequently underwent EBUS-TBNA (real-time convex probe EBUS-TBNA) for the parabronchial pulmonary nodule (Figure 2). The pathology (Figure 3A) revealed a background of chronic granulomatous inflammation with numerous yeast-like micro-organisms. Special staining with Grocott's methenamine silver (Figure 3B) confirmed cryptococcal infection. The fungal culture of dull, creamy, and butyrous colonies confirmed *C. neoformans*. Later, the serology test for cryptococcal antigen was found to be positive, with a titer of 1:32. The patient was treated with fluconazole for 6 months, and the follow-up chest CT revealed diminished right lower lobe nodular opacity (Figure 4).

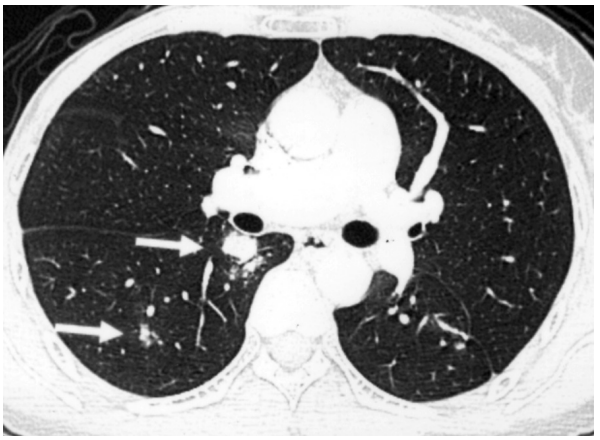

Fig. 1. Computed tomography revealed several nodules (white arrow) in the RLL.

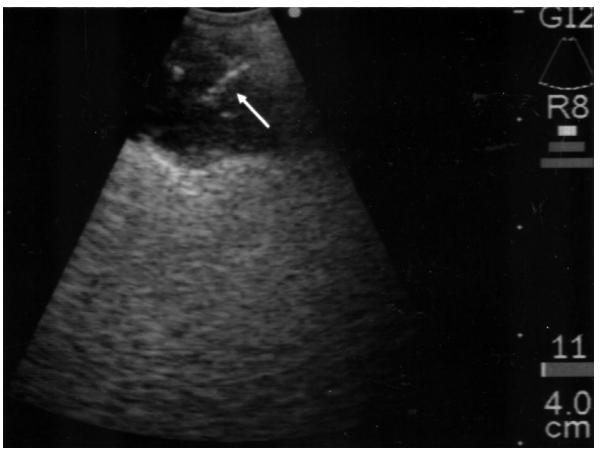

Fig. 2. Real-time convex probe EBUS-TBNA revealed the hyperchoic needle (white arrow) within the parabronchial pulmonary nodule.

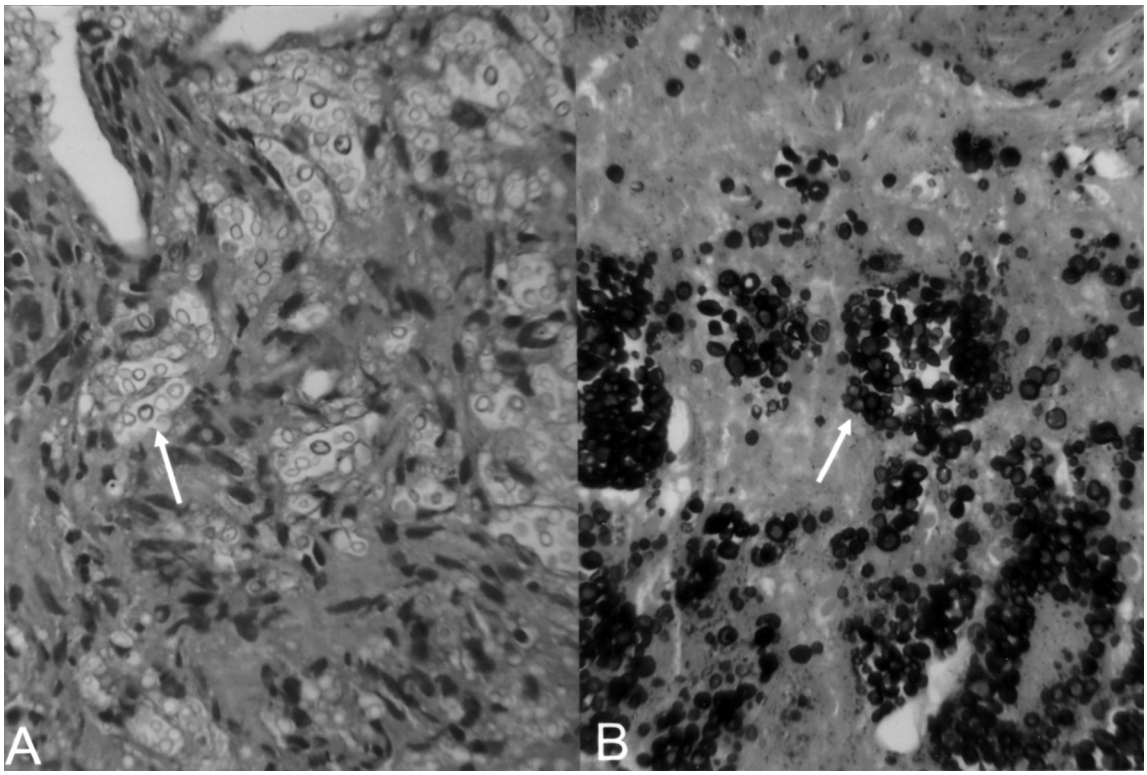

Fig. 3. Cryptococcus (white arrow) with histopathological staining using: (A) H.E stain (x400). (B) Grocott's methenamine silver (x400).

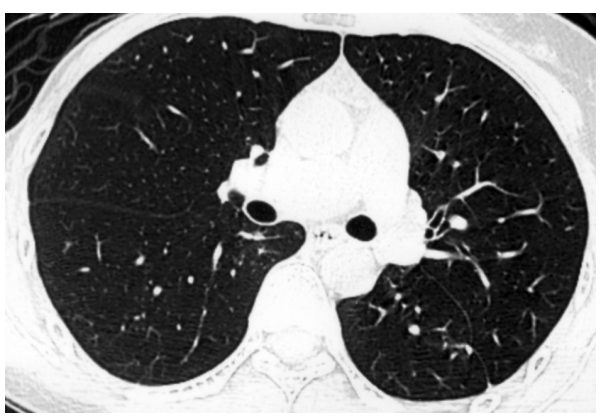

Fig. 4. Chest CT after fluconazole treatment revealed diminished right lower lobe nodular opacity.

Case 2

A 57-year-old man with right lower lung adenocarcinoma (pT1aN0M0, stage Ia) had undergone right lower lobectomy in July 2007. No tumor recurrence was found until July 2011, when his CT exam revealed a pulmonary nodule (2.6 × 2.3 cm in size) in the right para-bronchial region (Figure 5). The patient was asymptomatic, and the CEA level was within normal limits. The possibility of lung cancer recurrence was considered. Therefore, we performed an EBUS-TBNA (radial probe EBUS-TBNA) of the right parabronchial nodule (Figure 6), and the cytology of the TBNA specimen revealed many yeast-form fungi encapsulated within epithelioid cells (Figure 7). The serology test for Cryptococcus antigen was positive, with a titer of 1:8. The patient received antifungal therapy with fluconazole (400 mg per day orally) for 3 months. The serum Cryptococcus antigen titer

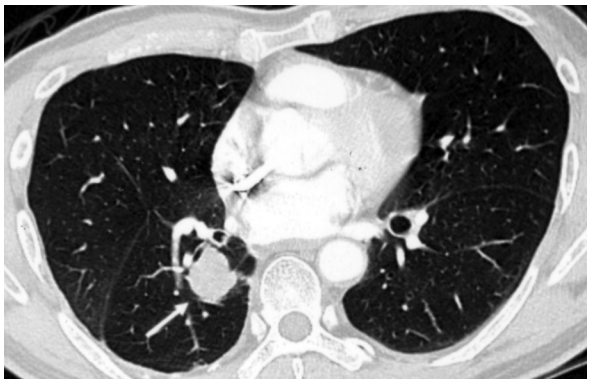

Fig. 5. Chest CT revealed a lung nodule (white arrow) in the right parabronchial region.

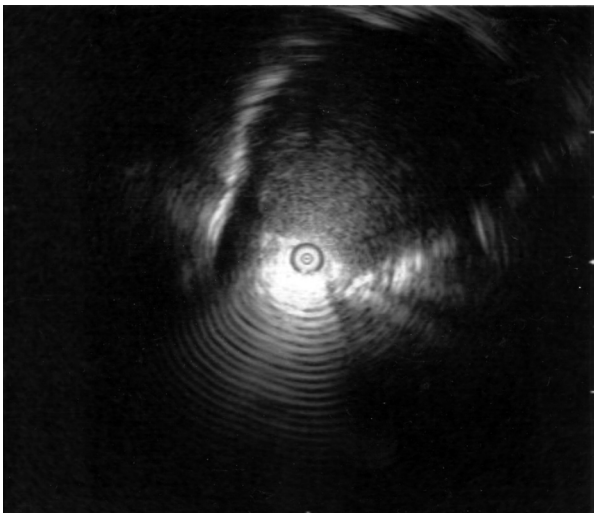

Fig. 6. Radial EBUS image of the parabronchial pulmonary nodule.

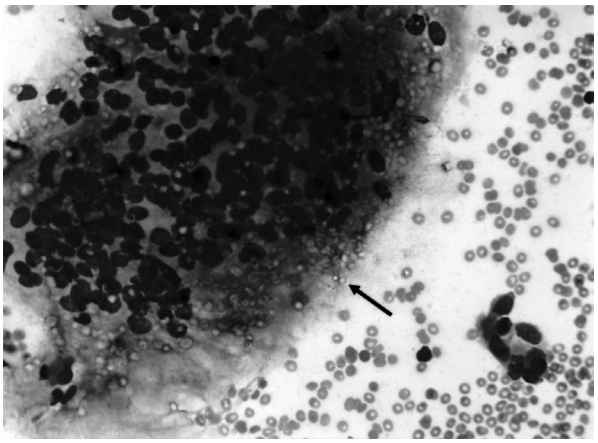

Fig. 7. Cytology of the EBUS-TBNA specimen showing encapsulated forms of Cryptococcus (arrow) using Liu stain (x400).

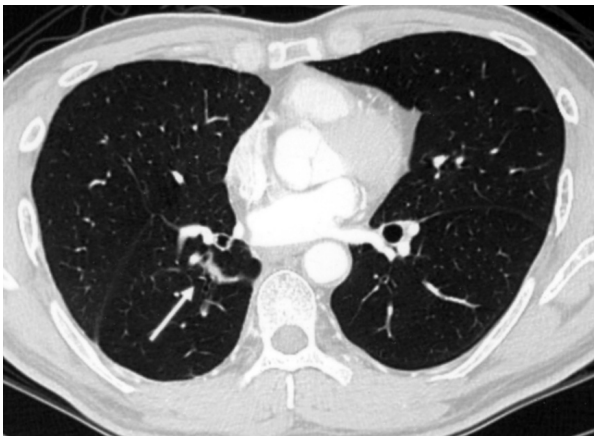

Fig. 8. Chest CT after fluconazole treatment revealed lung nodule shrinkage to a fibrotic band (white arrow).

decreased to zero after 3 months' treatment and the follow-up chest CT of the pulmonary nodule in October 2010 showed it had shrunk to a fibrotic band (Figure 8).

Discussion

Differentiating between a benign lesion and primary tumor or metastasis in patients with pulmonary nodules is crucial for clinicians, but is difficult in some patients such as those with cancer. Surgical resection is the only recommended treatment for early-stage non-small cell lung cancer. Cancer patients with multiple pulmonary nodules may be regarded as having metastatic disease and may be treated immediately with chemotherapy. However, according to the literature, nearly half of the pulmonary nodules identified in patients with extrapulmonary cancers were malignant [3]. Thus, it is important that a biopsy be performed for definite diagnosis and correct management.

Cryptococcosis is often found in the lungs of immunocompromised hosts, but is occasionally found in immunocompetent hosts [4]. HIV infection is a well-documented major risk factor for Cryptococcus infection. Approximately one-third of immunocompetent patients with Cryptococcus infection are asymptomatic, and for the others, the most common symptoms are cough, dyspnea, and fever [5]. In asymptomatic patients, the pulmonary infection is usually discovered incidentally following chest radiography. Radiography patterns of pulmonary cryptococcosis include interstitial infiltrates and alveolar infiltrates in immunocompromised hosts, and solitary or multiple nodular shadows in immunocompetent hosts [6]. In immunocompetent patients with pulmonary Cryptococcus infection, subsequent dissemination to the central nervous system is infrequent after appropriate treatment [7]. Lumbar puncture is not always necessary for an immunocompetent patient with pulmonary cryptococcosis; the exception is patients whose clinical condition worsens, those who present with neurologic signs of disease progression, or those with a high serum Cryptococcus antigen titer (>1:250) in the initial work-up. None of these findings was observed in our patients; hence, lumbar puncture was not performed.

EBUS-TBNA has emerged as an important diagnostic imaging modality, and TBNA has proved to be a valuable tool in the diagnosis and non-surgical staging of bronchogenic carcinoma. Both radial and convex probe EBUS-TBNA can allow determination of a more precise location [8]. Convex probe real-time EBUS-TBNA has been shown to have a higher diagnostic yield in mediastinal staging than radial probe EBUS-TBNA [9]. Although EBUS images show target lesions beyond the airway, needle penetration of the target lesion cannot be proved by radial probe EBUS-TBNA. To confirm whether the target lesion was aspirated, rapid on-site evaluation (ROSE) is needed immediately after aspiration [10]. The use of ROSE in radial probe EBUS-TBNA contributes to the improvement of the diagnostic yield. The number of aspirations with a cytology needle should be at least 3 for each target lesion in radial probe EBUS-TBNA to increase the diagnostic rate, if ROSE is unavailable [11]. Endoscopic ultrasound can identify lymph nodes as small as 3 mm, particularly in the celiac, subcarinal, and aorto-pulmonary areas [12]. Real-time convex probe EBUS-TBNA is a valuable diagnostic tool for differential diagnosis of lymph nodes from lung cancer [13], sarcoidosis [14] and tuberculosis [15]. Pulmonary cryptococcosis in a lung lesion can be diagnosed by radial probe EBUS with transbronchial biopsy. However, radial probe EBUS with TBNA can improve the sensitivity of the diagnosis [16]. Concurrent diagnoses of patients with pulmonary cryptococcal isolates are common, especially patients with HIV infection [17]. It has been shown that EBUS-TBNA has a 97% accuracy rate for tissue confirmation, and should be the test of choice, especially for evaluating patients with posterior mediastinal lymphadenopathy [18-19]. We suggest that such patients undergo EBUS-TBNA for tissue diagnosis since this procedure is safe and less invasive.

Conclusion

We presented the cases of 2 cancer patients with pulmonary nodules who underwent mini-invasive EBUS-TBNA to confirm the diagnosis of Cryptococcus infection. Differentiating between pulmonary Cryptococcus infection and

metastasis in cancer patients is important for determining the correct management. TBNA is a useful and safe means of diagnosing the etiology of these pulmonary nodules and can provide a rapid diagnosis of pulmonary Cryptococcus infection.

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模仿惡性腫瘤之肺隱球菌於癌症病人經支氣管內視鏡超音波導引細針抽吸術診斷

沈宜成 * 涂智彥 *,** 廖偉志 * 陳家弘 * 施純明 * 徐武輝 *

在癌症患者中，肺結節常常被認為是轉移性惡性腫瘤或原發性肺腫瘤。我們在此報告兩位案例，一位為 43 歲女性病患患有乳腺癌，和一位 56 歲男性病患患有早期肺腺癌，他們的表現皆為沒有症狀的肺部結節。初步懷疑診斷為肺部轉移或腫瘤復發，他們接受微創診斷方法的支氣管內視鏡超音波導引細針抽吸術（EBUS-TBNA）確定肺隱球菌感染的診斷。隨後，接受抗黴菌藥物的治療，患者恢復良好。我們証明在癌症患者區別肺隱球菌感染或癌症肺部轉移，並因此接受正確治療的重要性，以及利用支氣管內視鏡超音波導引細針抽吸術診斷肺隱球菌感染確實是安全及有效。*(胸腔醫學 **2014; 29: 351-357**)*

關鍵詞：肺隱球菌，支氣管內視鏡超音波，支氣管內視鏡超音波導引細針抽吸術

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Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) – A Case Report

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Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare pulmonary condition presenting with cough, wheezing, and obstructive ventilatory defect. The pathogenesis of the disease is diffuse hyperplasia or dysplasia of pulmonary neuroendocrine cells, multiple carcinoid tumorlets, and peribronchiolar fibrosis causing small airway obliteration. Herein, we present the case of a 70-year-old patient with this rare condition who had been treated for asthma for years, and who had a left lower lung tumor noted during follow-up chest radiography. Chest computed tomography showed a mosaic pattern of the lung parenchyma and multiple lung nodules. The pathological diagnosis of DIPNECH was made after a surgical resection of the lung nodules. The patient's symptoms remained stable with inhaled corticosteroid and bronchodilator use. ***(Thorac Med 2014; 29: 358-364)***

Key words: diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, neuroendocrine cells, tumorlets, carcinoid, lung neoplasm

Introduction

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare condition that has been defined by the World Health Organization as a precursor to pulmonary carcinoid tumor [1]. Typical symptoms and signs include cough, wheezing, and obstructive ventilatory defect. Herein, we present the case of a typical patient with this rare condition who had been treated for asthma for years and later received the diagnosis of DIPNECH after a surgical resection for lung tumors.

Case Report

A 70-year-old woman presented to our institution with incidental findings of lung tumors. She had had asthma since childhood and during the past decade, she received treatment with inhaled corticosteroid and long-acting beta agonist at another institution, and her symptoms were under control. An annual chest radiograph checkup revealed a well-defined round nodule

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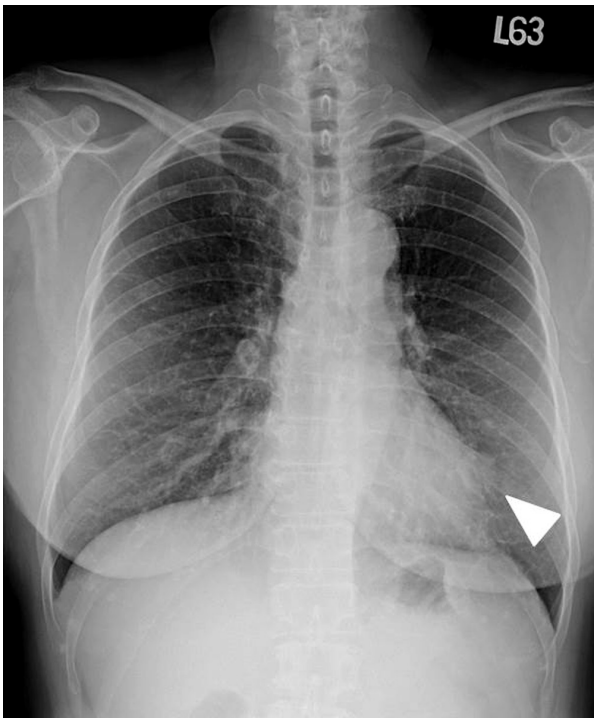
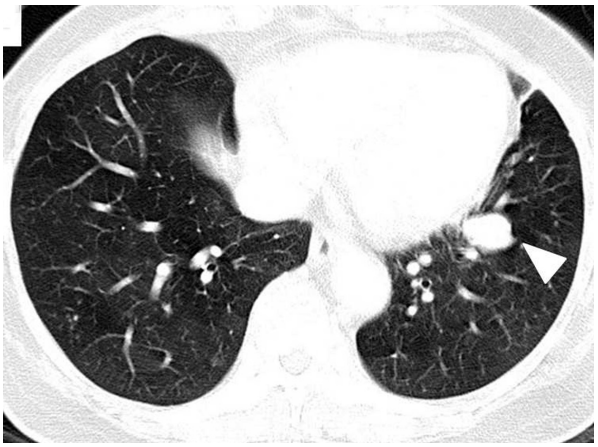


(A)



(B)

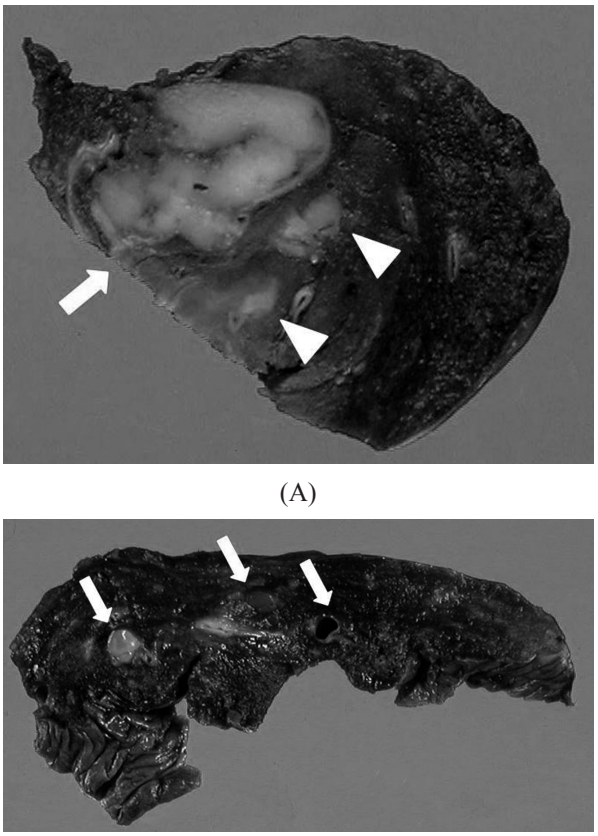
Fig. 1. (A) Plain radiograph of the chest showed a well-defined round nodule in the left lower lung field (arrowhead); (B) Computed tomography demonstrated a mosaic pattern of the lung parenchyma and a lung tumor at the left lower lobe (arrowhead).

in the left lower lung field (Figure 1A). The lesion was seen to increase in size during a 9-month follow-up, so she was then referred to our institution.

Her past history included cervical cancer in situ which was treated with total hysterectomy, hypertension, and breast mammoplasty for cosmetic purposes. Her family history was unremarkable. She was non-alcoholic and never smoked. Lab tests including complete blood count and biochemistry panels showed mild polycythemia with a hemoglobin level of 15.2 g/dL and otherwise normal results. Physical examination revealed clear breathing sounds.

Further examination with spirometry showed normal FVC (2.4L, 117% predicted) and FEV1 (1.72L, 109.1% predicted), and the FEV1/FVC percentage was 71.7%. A thoracic computed tomography (CT) scan (Figure 1B) showed multiple small, well-defined nodules in both lung fields, with the largest nodule located at the left lower lobe and measuring 1.7 cm. Mosaic and ground glass attenuation were also seen in the bilateral lung parenchyma.

A video-assisted thoracoscopic surgical lung biopsy was performed. Two firm tumors at the left lower lobe were resected with wedge resection (Figure 2A). The lung parenchyma also showed many dilated bronchioles filled with mucus plugs (Figure 2B). Frozen pathology reported a nodular neoplasm composed of round cells in solid nests, suggesting carcinoid tumor. Formal pathology examination revealed round to spindle cells arranged in nests or a trabecular pattern, with no necrosis and a low mitotic count (<2/10 high power field). The Ki-67 proliferative index was less than 1%. The immunohistochemistry stains of chromogranin A and synaptophysin were positive (Figure 3A); immunohistochemistry staining was also positive for CD56, and weakly positive for TTF-1. More sections from the lung parenchyma revealed more than 20 tumorlets and multiple foci of neuroendocrine cell hyperplasia (Figure



(A)

(B)

Fig. 2. (A) Gross picture in this section shows a carcinoid tumor (arrow) and 2 tumorlets (arrowheads). (B) Gross picture of the lung parenchyma showing dilated small bronchioles, with some filled with mucus plugs (arrows).

3B-D). These findings were consistent with DIPNECH. The patient was discharged after an uneventful postoperative course. The hormone profile of the patient was checked for possible hormone hypersecretion. Growth hormone was 0.075 nanograms per milliliter (reference range, 0 to 8), and insulin-like growth factor was 139 nanograms per milliliter (reference range, 46 to 195 for age 70). The adrenal corticotropic hormone and cortisol levels were 20.7 picograms per milliliter and 11.6 micrograms per deciliter, respectively. The intact parathyroid hormone was 37.3 picograms per milliliter (reference range, 15 to 68.3). No hormone hypersecretion was identified.

Discussion

DIPNECH is a rare condition that was first described as a distinct entity in 1992 by Aguayo, *et al* [2]. That series reported 6 patients with diffuse hyperplasia or dysplasia of pulmonary neuroendocrine cells (PNCs), multiple carcinoid tumorlets, and peribronchiolar fibrosis causing small airway obliteration. In addition, obstructive and restrictive ventilatory defects were found in these patients, caused by mucus occlusion of the bronchus. Unlike cases of neuroendocrine-cell hyperplasia, which has been commonly reported in smokers and those living at high altitude, all patients in the case series were non-smokers. DIPNECH has been accepted as a precursor to pulmonary carcinoid tumors, and the prevalence of DIPNECH was 5.4% (3/55) among pulmonary neuroendocrine tumors [3]. The concomitant presence of adenocarcinoma inside DIPNECH foci has been reported recently [4] in 4 cases, possibly suggesting another distinct oncogenetic pathway. Secretion of neuropeptide hormones in DIPNECH has also been reported [5]. The paracrine secretion of neuroendocrine cells was postulated to be related to the development of fibrosis around tumorlets [6]. Fessler, *et al* [7] reported a case of DIPNECH with acromegaly, revealing a possible relationship with syndromes of hormone hypersecretion.

The epidemiology of DIPNECH was studied in a systematic review of available case reports, and a significant female predominance of 92% was found [8]. The mean age of the patients at diagnosis was 58 years [8]. Most patients (92%) were symptomatic and eventu-

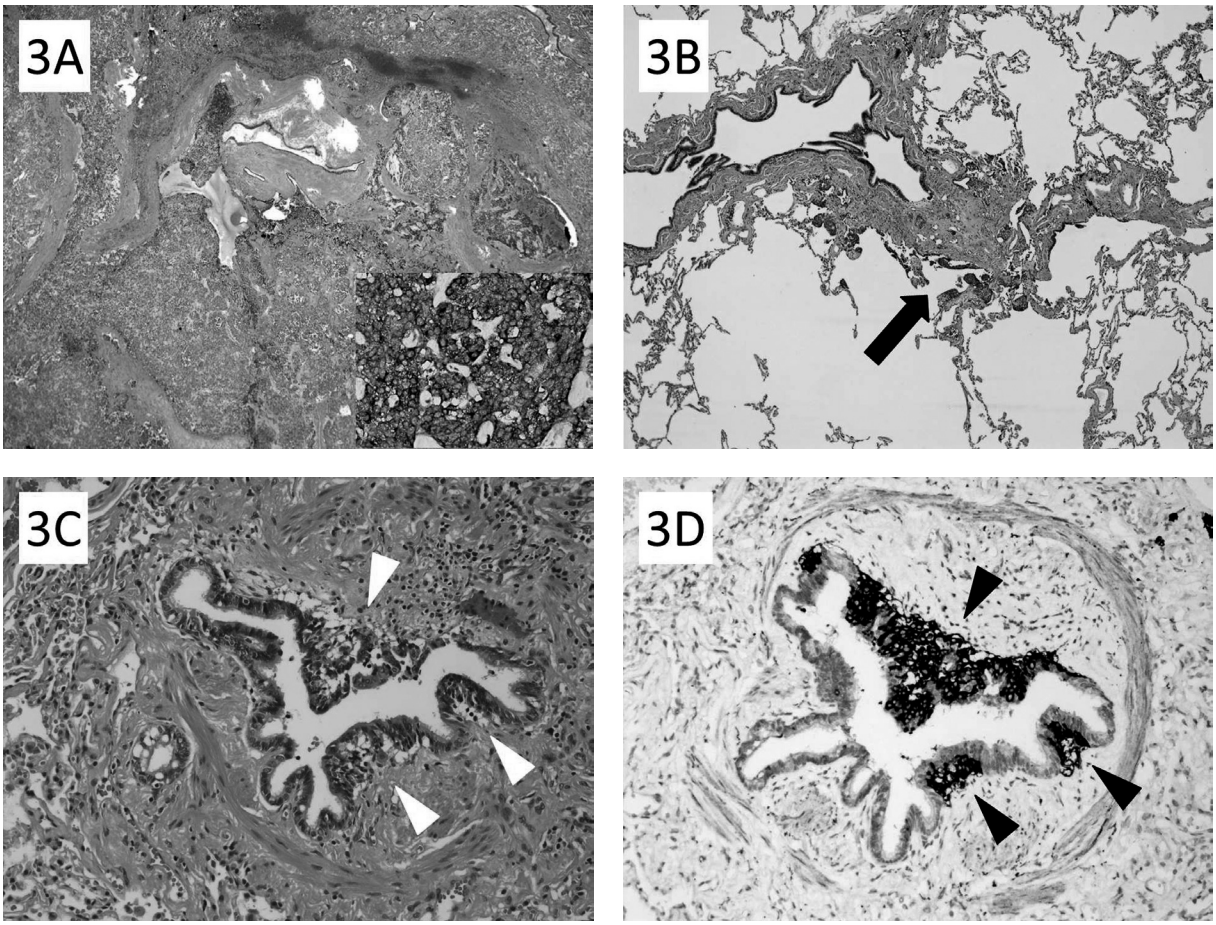


Fig. 3. (A) The large carcinoid tumor was composed of solid nests of neuroendocrine cells immunoreactive to synaptophysin (inlet). (hematoxylin and eosin stain, original magnification ×20) (B) Small tumorlet (arrow) could frequently be identified adjacent to the small bronchioles. (hematoxylin and eosin stain, original magnification ×40) (C) Neuroendocrine cell hyperplasia (arrowheads) confined within the respiratory mucosa with an intact basement membrane, which formed polyp-like cell nests protruding into the bronchiolar lumen. (hematoxylin and eosin stain, original magnification ×200) (D) Neuroendocrine cell hyperplasia (arrowheads) could be easily demonstrated by synaptophysin immunohistochemical stain. (original magnification ×200)

ally received the diagnosis of DIPNECH [8]. Although obstructive ventilatory defect was the most common abnormality in the pulmonary function tests of these patients, 17% had normal spirometry, similar to our patient. Whether this was related to the therapeutic effect of the inhaled corticosteroid and bronchodilator or a difference in bronchiolar involvement remained to be clarified. The clinical symptoms of small airway obstruction may be related to the extent of constrictive bronchiolitis and lumen narrowing.

While the plain thoracic radiograph is often normal, high-resolution CT frequently reveals multifocal bilateral pulmonary micro-nodules and areas of air trapping (mosaic pattern) related to constrictive bronchiolitis [9]. Hence, surgical biopsy with enough lung tissue remains the preferred diagnostic approach [8]. Histological examination is characterized by widespread proliferation of PNCs confined to the bronchiolar epithelium or bulging into the

lumen at a later stage [1]. As the proliferating PNCs break through the basement membrane, small aggregates (2-5 mm) of these cells and fibrous stroma form and are known as 'tumorlets' [1]. A carcinoid is defined as PNCs reaching a size of 5 mm or greater [1].

Due to the rare incidence of DIPNECH, there are very few published reports regarding long-term outcomes and treatment for the condition. The dominant neuroendocrine tumor should be resected during the diagnostic surgical procedure [10]. Nassar, *et al* [8] reported a case of DIPNECH in a patient who had been weaned from the mechanical ventilator after systemic steroid use. The case supported the hypothesis that the bronchiolar inflammatory response caused by the PNCs may be reduced by steroid. Reyes, *et al* [11] reported 2 cases that were managed with long-term beta agonists and inhaled corticosteroid, as in our case. Experience with other therapeutic agents like somatostatin analogue or interferon gamma has been reported [10]. Most of the cases with DIPNECH had a relatively stable clinical course, but a few have been reported to progress to respiratory failure [8,10]. More clinical data may be required for a better understanding of the condition and to provide evidence-based treatment for patients with DIPNECH.

In conclusion, breathlessness or an obstructive ventilatory defect associated with pulmonary micro-nodules in middle-aged women should lead to a suspicion of DIPNECH. Surgical biopsy is required for a definite diagnosis and resection of the dominant neuroendocrine tumor. Inhaled corticosteroid and bronchodilator can be considered for symptomatic control of this relatively stable disease.

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瀰漫性自發肺部神經內分泌細胞增生－病例報告

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瀰漫性自發肺部神經內分泌細胞增生是一種罕見的肺部疾病，主要臨床表現為咳嗽、呼吸哮鳴聲、以及肺功能呈現阻塞性缺損。此疾病主要的致病機轉為肺部神經內分泌細胞瀰漫性增生或異生，產生多發的類癌微瘤、以及小支氣管周邊之纖維化造成小氣道之阻塞。我們報告一位七十歲病人，之前因哮鳴症狀被診斷為氣喘。在追蹤過程中因胸部 X 光出現左下結節而進一步檢查。電腦斷層顯現肺實質有拼貼狀變化，以及多顆肺部結節。手術切除肺部結節之後，病理診斷為瀰漫性自發肺部神經內分泌細胞增生。病人之症狀在使用吸入型類固醇及支氣管擴張劑下維持穩定，持續在門診追蹤。*(胸腔醫學 **2014; 29: 358-364**)*

關鍵詞：瀰漫性自發肺部神經內分泌細胞增生，神經內分泌細胞，微瘤，類癌，肺部腫瘤

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Chylothorax after Video-Assisted Thoracoscopic Anterior Release for Severe Adolescent Idiopathic Scoliosis

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Chylothorax has been reported rarely in patients with anterior release of severe adolescent idiopathic scoliosis (AIS) using video-assisted thoracoscopic surgery (VATS). A young girl was diagnosed with chylothorax after anterior release of the spinal deformity. After medical treatment, massive chyle leakage was still noted, and 2 surgical interventions were performed to treat the complicated condition. Anatomic variation of the thoracic duct as a network was highly suspected, and tissue glue was applied for adhesion. We present this case with a discussion of treatment for complicated chylothorax after VATS correction of severe AIS. ***(Thorac Med 2014; 29: 365-370)***

Key words: chylothorax, scoliosis, video-assisted thoracoscopic surgery

Introduction

Cases of chylothorax after video-assisted thoracoscopic surgery (VATS) for release of rigid scoliosis are rare. Chylothorax can be serious and occasionally lethal due to depletion of electrolytes, dehydration, hypoproteinemia and immune derangement. It should be treated immediately. Mass ligation of the thoracic duct is the treatment of choice, but it is not always infallible. A combination of medical and surgical treatment is recommended for complicated and severe chylothorax.

Case Report

A 13-year-old girl presented with severe adolescent idiopathic scoliosis (AIS). After diagnosis, she was followed up in our orthopedic department. The triple film showed severe scoliosis with a Cobb's angle of 80 degrees (Figure 1). VATS anterior release for severe AIS of the T6-10 spine was planned, and posterior instrumentation with fusion was scheduled for 1 week after the first operation (see Figure 2 for the timetable of her clinical course). Chylothorax was suspected on postoperative day (POD) 2,

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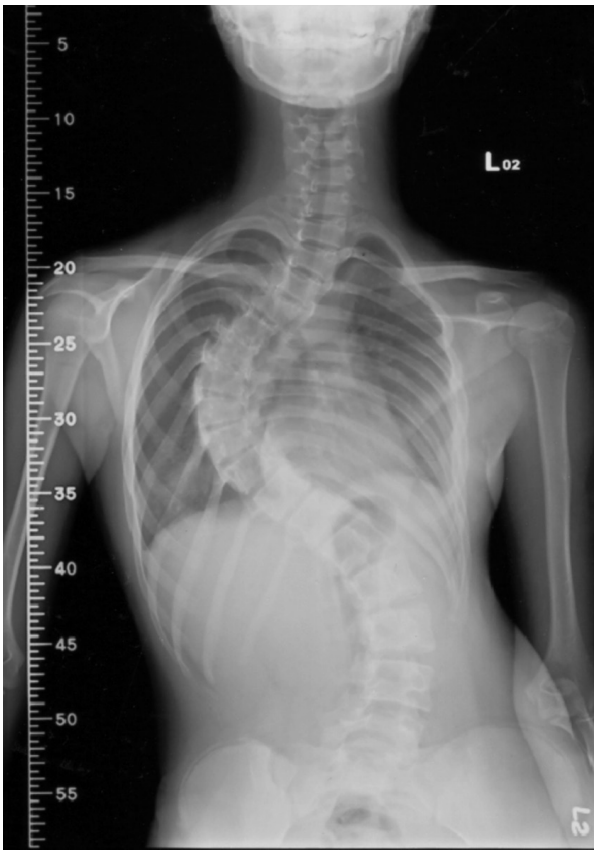

Fig. 1. A pre-operative plain film of the chest. Severe deformity of the spine was noted. Calculated Cobb's angle: 80 degrees.

due to the milky appearance of the pleural effusion from the chest tube. However, biochemical analysis revealed a triglyceride level of 68 mg/dL, and the chest x-ray (CXR) showed no fluid accumulation. The second-stage surgical intervention was performed as scheduled. The daily quantity of milky pleural effusion increased to 600-800 mL after the second surgery and biochemical analysis of the pleural effusion revealed a triglyceride concentration of 116 mg/dL, but the CXR continued to show a clear costophrenic sulcus (Figure 3). Chylothorax was diagnosed, and nothing by mouth (NPO) with total parenteral nutrition (TPN) was initiated. Octreotide was administered later, but to no effect [1]. VATS for exploration was performed on POD 25. During the operation, we drained all the effluent and tried to pinpoint the site of the thoracic duct, which was assumed to be located between the descending aorta, azygos vein and vertebral body. Surgical ligation of the thoracic duct at the T10-12 level was carried out by endo-clip application. A dry gauze was draped over the area to ensure it was dry. However, the daily volume of pleural effusion increased to 1500-2000 mL following the operation. Chest CT (Figure 4) was performed, and then an exploratory thoracotomy on POD 30. Lymph was observed to flow out from all the dissected planes of the paraspinal supradiaphragmatic region. Surgical ligation was performed again. Tissue glue (Tissucol) 4 ml was eventually applied to better seal the paraaortic area and suspicious thoracic duct site, and Surgicel was used for coverage. Tissue glue was no longer used after Surgicel coverage. A mechanical ventilator was employed for 3 days postoperatively to promote lung expansion. A fat-free diet was prescribed on POD 37. The chylothorax condition subsided, and the chest tube was removed on POD 43. The patient was discharged on POD 44. Two weeks later, CXR revealed no further pleural effusion accumulation, and the 1-year follow-up examination showed similar results.

Discussion

Chylous leaks are uncommon conditions resulting from leakage of intestinal lymph (chyle) outside the lymphatic system. Dorr *et al*. [2], in a case series, reported the reasons for this, including surgery or trauma in 101 patients (49.8%), various medical conditions in 89 (43.8%), and unknown in 13 (6.4%). It has been reported to occur at a rate of 0.42% for all

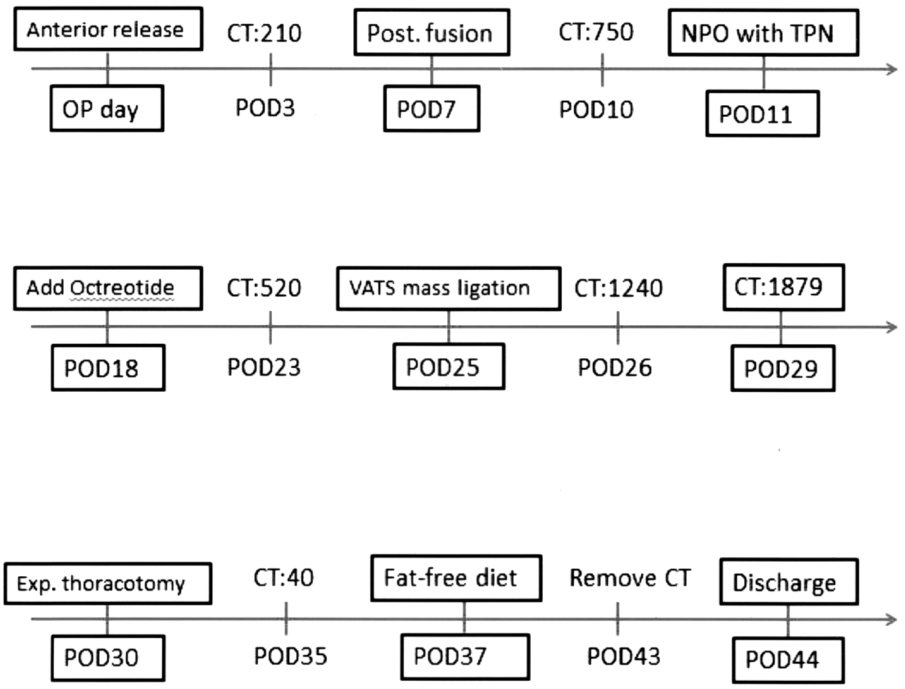

Fig. 2. Timetable of the clinical course of this patient.

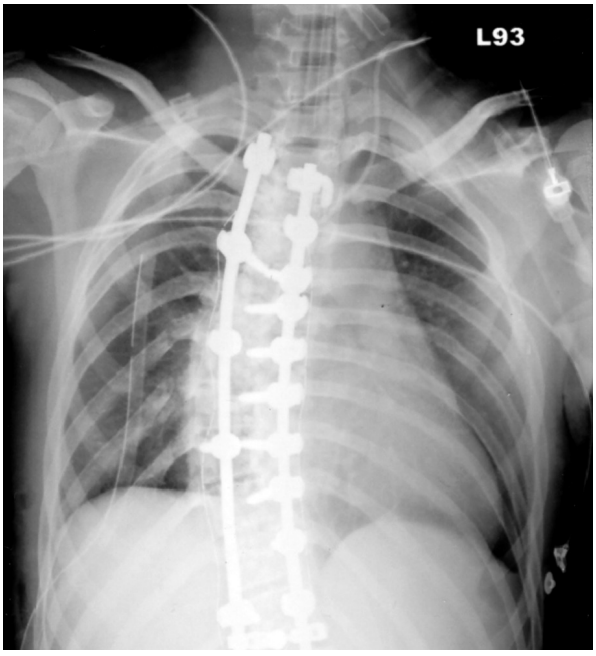

Fig. 3. After corrective surgery of the spine, a milky-appearing pleural effusion was drained from the chest tube. No fluid accumulation was noted in the postoperative AP X-ray.

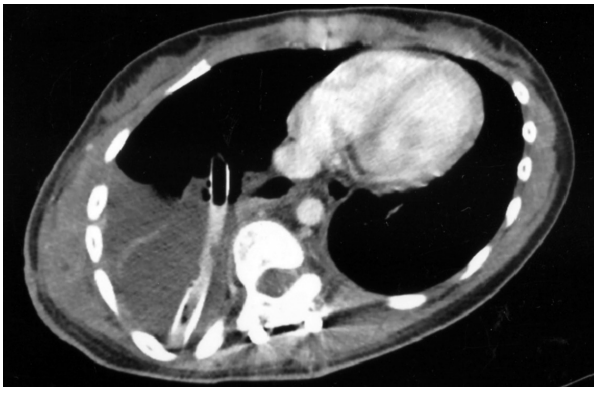

Fig. 4. Postoperative CT of the chest presented a massive accumulated volume of complex septated pleural effusion, even after chest tube drainage.

general thoracic surgical procedures. Esophagectomy (29 patients, 3.9%) and surgery for congenital heart disease (28 patients) were the most common causes of chylothorax. It seems that surgery-related chylothorax is not unusual.

Non-traumatic chylous leaks are rare, and can be caused by any disease process that results in lymphatic occlusion, such as malignancy (lymphoma), lymph vessel disease (Gorham disease, lymphangiomatosis), systemic disease (sarcoidosis, Behcet disease), and congenital malformation [3].

The thoracic duct carries 1-2 liters of lymphatic fluid a day; 80% of this fluid comes from intestinal and hepatic lymphatic ducts. The amount of flow in the thoracic duct fluctuates significantly with a patient's diet, and the flow increases significantly immediately after a meal, due to absorption of fluids and nutrients by intestinal lymphatic ducts. The thoracic duct drains lymph and chyle from the entire body, except the right hemithorax, right head and neck, and right arm.

The anatomy of the thoracic duct has been well described in anatomy texts [4]. Anatomic variation of the thoracic duct has been found in nearly half of the cases studied. A postmortem study by Kausel *et al*. [5] divided the thoracic duct into 5 types based on morphology (single, double, and multiple trunks) and the location of its outflow; the fifth type in the Kausel classification schema, a plexiform variation, is of importance to the operator performing surgical ligation because of the difficulty in identifying the main trunk of the thoracic duct. By employing a semiquantitative transport index, a 92% sensitivity and nearly 100% specificity can be achieved in diagnosing lymphedema [6]. Since lymphoscintigraphy is a functional study, we performed lymphangiography before exploratory thoracotomy. However, we still could not identify a significant source of chyle leakage or the location of the thoracic duct, based on the examination. To the best of our knowledge, there is no evidence that lymphangiography before mass ligation can be helpful. However, it may be an examination of choice for these patients. In the event of variations, further preoperative examination, such as lymphangiography or intervention requiring pleurodesis or pleurectomy, would be necessary during the operation.

In patients with a spinal deformity, the thoracic duct can be difficult to identify. Nakai and Zielke [7] reported postoperative chylothorax in 6 of 2000 (0.3%) spinal deformity operations. With the development of minimally invasive intervention, VATS has become the treatment of choice for rigid scoliosis. However, complications after the application of VATS for spinal deformity, including intercostal neuralgia, lung atelectasis, pleural epidural bleeding, diaphragm penetration, transient paraparesis, and massive myocardial infarction, have been reported in the literature [8]. Huang *et al*. [9] suggested extending the portal incisions by 2-3 cm for variable instrument angulation, and the use of flexible trocars was suggested to avoid or decrease the rate of complications after spinal corrective surgery.

Chylothorax after spinal surgery is difficult to avoid completely, and it is also difficult to treat. Conservative treatment was applied initially in our patients, including dietary modification, TPN and repeated thoracocentasis. Browse and coworkers suggested exploring the chest and ligating the thoracic duct if there was no reduction in drainage [10]. Mass ligation of the thoracic duct is a popular method for surgical repair, and pleurodesis or pleurectomy is also recommended. Maldonado *et al*. [11] reviewed 74 adult patients at a single institution. The initial treatment approach was nonsurgical for most patients, but a surgical procedure (pleurodesis, thoracic duct ligation, and/or surgical repair) was eventually performed for more

than half of the patients (59%). In our case, we assumed a plexiform variation existed, or the thoracic duct was like a network before adolescence due to lymph leakage from multiple sites. Tissue glue was applied for pleural adhesion, and it was effective. However, the anatomy of the thoracic duct of adolescents with severe spinal deformity must be further studied. Chylothorax is a rare and difficult complication after surgery to correct a spinal deformity, and composite management of chylothorax may be necessary.

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胸腔內視鏡手術矯正嚴重青少年原因不明型脊椎側彎術後之乳糜胸

曾彥強 * 謝致政 *,** 陳仁偉 *** 奉季光 ***

在經胸腔內視鏡手術矯正嚴重青少年原因不明型脊椎側彎，術後併發乳糜胸是非常稀少的。本文將簡述一名十三歲女性病人，在診斷為青少年原因不明型脊椎側彎後，接受胸腔內視鏡矯正手術，術後併發乳糜胸之治療過程。我們初始以飲食控制及藥物治療為主，然而大量乳糜滲漏的情況沒有改善。於是我們選擇以手術治療。在接受胸腔內視鏡胸管結紮手術後，大量淋巴液滲漏依舊，最後病人接受開胸探查，發現於右側橫膈上胸壁淋巴液到處滲漏。我們以組織凝膠行肋膜沾黏術後，終於止住滲漏。我們將陳述這個病例並且討論其治療方式及文獻回顧。*(胸腔醫學 **2014; 29: 365-370**)*

關鍵詞：乳糜胸，脊椎側彎，胸腔內視鏡手術

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Pulmonary Benign Metastasizing Leiomyoma: A Case Report and Review of the Literature

I-Hung Chen, Yau-Lin Wang, Shih-Tien Hsu*, Jeng-Yuan Hsu, Jeng-Sen Tseng

Benign metastasizing leiomyoma (BML) is a rare disease characterized by growth of uterine leiomyoma tissue at distant sites. Most reported cases are those of women of reproductive age with a surgical history of hysterectomy or myomectomy. The lung is the most commonly involved site and patients are usually asymptomatic. Herein, we reported the case of a 51-year-old woman with pulmonary nodules incidentally found after uterine myomectomy. The tumor consisted of estrogen and progesterone receptor-positive smooth muscle cells, similar to those in the patient's resected uterine leiomyoma. She received gonadotropin-releasing hormone receptor agonist therapy for 6 months, and the size and number of the pulmonary lesions stabilized at 16 months after diagnosis. In conclusion, BML usually presents as an incidentaloma of the lung in asymptomatic women who have a uterine leiomyoma history. Its growth can be suppressed by hormonal therapy. ***(Thorac Med 2014; 29: 371-376)***

Key words: uterine leiomyoma, lung metastasis, gonadotropin-releasing hormone receptor agonist

Introduction

Benign metastasizing leiomyoma (BML) is a rare disease, with approximately 100 cases reported in the literature [1]. It is characterized by growth of uterine leiomyoma tissue at distant sites [2]. In most cases, there is a previous history of hysterectomy or myomectomy [3]. The lung is the most commonly involved site and patients are usually asymptomatic [4]. Treatment options include careful observation, hormonal therapy, and surgical intervention [3]. Herein, we present a case of pulmonary BML and discuss its management.

Case Report

A 51-year-old woman, gravida 2, para 2, presented to our gynecological outpatient clinic with lower abdominal tenderness; she had no dyspnea, cough, or other respiratory symptoms. Gynecological ultrasound revealed a uterine mass that measured 12×10×8 cm. No lymphadenopathy at the neck or inguinal area was detected. Further physical examination was unremarkable. She had a history of uterine leio-

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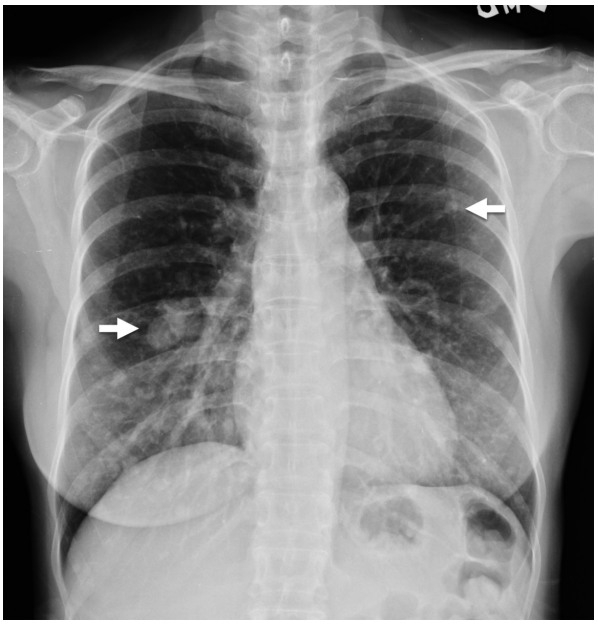
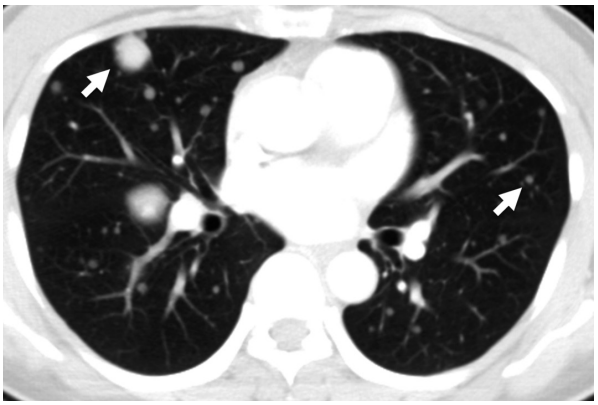


(A)



(B)

Fig. 1. Chest radiograph (A) and computed tomography (B) scan revealed multiple well-circumscribed nodules of variable size in both lungs (arrows).

myoma previously treated with myomectomy when she was 44 years old, but no other medical problems.

She was admitted to our institution for elective myomectomy. The pre-operative chest roentgenogram showed multiple pulmonary nodules in both lungs (Figure 1A). After myomectomy, she was referred to the chest medicine division for further evaluation. Chest computed tomography (CT) showed multiple well-defined nodular lesions of variable size in both lungs (Figure 1B).

Metastatic lung disease was suspected, so we checked her serum tumor markers. The levels of alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), cancer antigen 15-3 (CA15-3), and cancer antigen 125 (CA-125) were all within normal limits. We also arranged a cervical cytological Papanicolaou smear, mammography, fecal occult blood test, abdominal sonography, whole body bone scan and brain CT as part of a comprehensive tumor survey. No other focus of malignancy was identified. We then arranged CT-guided pulmonary nodule biopsy.

In gross appearance, the specimen was tan and soft. The microscopic exam revealed pulmonary tissue consisting of bland-looking spindle cells with eosinophilic cytoplasm arranged in intersecting fascicles (Figure 2A). No significant tumor necrosis, cellular atypia or increased mitotic activity was noted (1 in 20 high power fields). Immunohistochemical stains were positive for smooth muscle actin (Figure 2B), desmin, estrogen receptors (ER) and progesterone receptors (PR). These findings were consistent with resected uterine leiomyoma. The diagnosis was pulmonary BML.

The patient was followed up at our gynecological outpatient clinic and received hormone therapy with the gonadotropin-releasing hormone receptor agonist leuprorelin 3.75 mg monthly for 6 months. She entered menopause after 6 doses of leuprorelin and received no other medical or surgical intervention thereafter. Chest CT performed at about 16 months after diagnosis revealed the size and number of

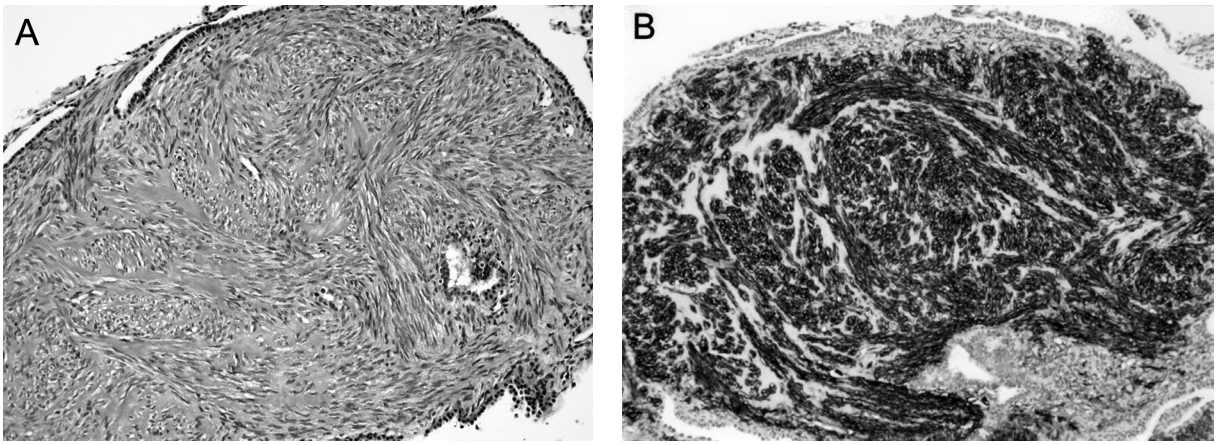


Fig. 2. Pathology of computed tomography-guided biopsy of a lung nodule: H&E stain (A), Immunohistochemical stain for smooth muscle actin (B). (Magnification 200x)

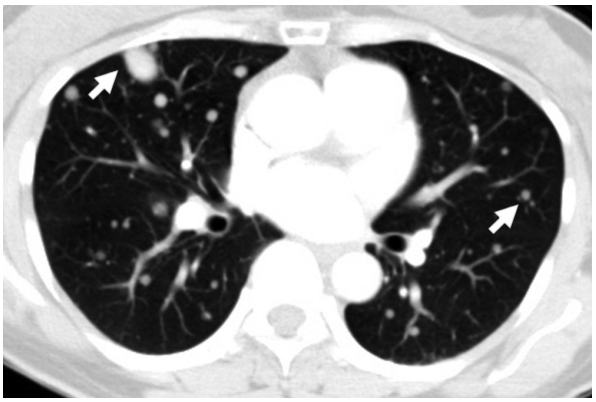


Fig. 3. Follow-up computed tomography scan 16 months after diagnosis revealed stable numbers and sizes of BML lesions (arrow).

nodular lesions were stabilized (Figure 3). The patient was doing well as of this writing.

Discussion

Steiner first described BML in 1939, reporting a 36-year-old woman who died of cor pulmonale arising secondarily to multiple pulmonary metastases from benign uterine leiomyomas [2].

Most reported cases are of women of reproductive age with a surgical history of hysterectomy or myomectomy. Abramson et al. reported that the average age of patients with BML is 48 years, with the period from hysterectomy to nodule detection varying from 3 months to 26 years [4]. Although most of these patients were asymptomatic, presenting symptoms such as dyspnea, dry cough, or chest pain have been reported [5]. In rare cases, BMLs may cause debilitating symptoms and even life-threatening complications [2]. The lung is the most common site of involvement [6], with extrapulmonary lesions reported in the lymph nodes, deep soft tissues, omentum and mesentery, bone, spine, skull base, and heart.

Typical radiological findings include well-circumscribed solitary or multiple pulmonary nodules, ranging in size from a few millimeters to several centimeters in diameter [7]. Horstmann et al. found multiple nodules in 87% of their cases (70% bilateral nodules and 17% unilateral nodules), and 13% had a solitary nodule [8]. There are some case reports of BML manifesting as cavity pulmonary nodules [9] or presenting a miliary pattern [10]. Lesions are

not enhanced in post-contrast images and show no significant metabolic activity on 18-fluorodeoxyglucose positron emission tomography (FDG-PET) [11]. The differential diagnosis of this condition includes metastatic malignancy, collagen-vascular disease, and infectious or non-infectious inflammatory granulomas.

The nature and etiology of BML are still controversial. BML consists of well-differentiated, benign-appearing smooth muscle cells that lack mitotic figures, anaplasia, necrosis, or vascular invasion [1]. Although BML has benign histological features, its metastatic behavior suggests its malignant potential. It has been suggested that BML represents a low-grade, slow-growing leiomyosarcoma, owing to the monoclonal origin of both uterine and pulmonary tumors [12-13]. However, recent advances in cytogenetic analysis and microRNAs (miRNAs) regulation studies suggest BML is a genetically distinct entity, which likely originates from a biologically distinct subset of uterine leiomyomas and has a different miRNA expression profile than malignant leiomyosarcoma [14-15].

Optimal therapy for BML has not been established. Reported treatment modalities include careful observation, surgical resection, hysterectomy and bilateral oophorectomy, progestins, aromatase inhibitors and medical castration using gonadotropin hormone-releasing analogs [5]. Several reports have described the effect of anti-hormonal therapy [16-17]. Surgical intervention may play a role in symptom relief or provide a precise histological diagnosis. The rationale for hormonal manipulation is that BML mainly affects sexually mature women when the hormonal effects are at a maximal level and these tumors have positive immunoreactivity for ER and PR. The clinical course of BML is usually indolent. Spontaneous tumor regression has been reported with alteration in the hormonal milieu, as occurs in pregnancy, the postpartum period, and with menopause [8]. Thus, the aforementioned treatments may not always be indicated and careful observation should be considered in most cases.

In conclusion, BML is a rare condition that should be considered in asymptomatic women of reproductive age with a history of uterine leiomyoma who present with multiple pulmonary nodules of the lung.

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肺部良性轉移性平滑肌瘤病例報告及文獻回顧

陳易宏　王耀麟　許世典*　許正園　曾政森

肺部良性轉移性平滑肌瘤是一種相當少見的腫瘤。曾經因為子宮平滑肌瘤而接受過子宮切除手術或肌瘤切除手術的婦女最常受到侵犯。本病例為一位 51 歲女性，於胸部 X 光意外發現雙側肺葉多發性節結。病理組織切片證實為良性平滑肌瘤。嗣後患者接受長效型性腺釋放激素促效劑治療 6 個月，腫瘤大小 16 個月後皆維持穩定。此類患者若無症狀且已停經，可以小心觀察。若未停經則可考慮接受賀爾蒙治療。長效型性腺釋放激素促效劑因施打方便且副作用較小，較多醫師選用。*(胸腔醫學 **2014; 29: 371-376**)*

關鍵詞：子宮平滑肌瘤，肺部轉移，性腺釋放激素促效劑

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Small Cell Lung Cancer with Paraneoplastic Dermatomyositis: A Case Report

Sheng-Hua Su, Pen-Fang Yeh, Agatha Te*, Wei-Kang Kwang**

The association of dermatomyositis (DM) with malignancies is well known, and has a frequency of about 6-45% [1-9]. Patients with DM have a 31-fold increased risk of lung cancer compared to the general population [7], with small cell lung cancer (SCLC) being the most common type [9-10]. We report a 66-year-old man diagnosed as having SCLC with DM. He had typical cutaneous manifestations of DM accompanied with symmetric proximal muscle weakness, an elevated creatine kinase level, and myositis features present on electromyography. Skin biopsies were consistent with DM, and bronchoscopic biopsy confirmed the diagnosis of SCLC. The signs and symptoms of DM showed improvement after chemotherapy with cisplatin and etoposide. This case report emphasizes the need for intensive screening for cancer in patients with DM. ***(Thorac Med 2014; 29: 377-383)***

Key words: dermatomyositis, small cell lung cancer

Introduction

Dermatomyositis (DM) is an idopathic inflammatory myopathy, with characteristic cutaneous manifestations and proximal muscle myopathy. The association of malignancies with DM has been extensively reported in the literatures. Cancer diagnosis can precede, coincide with, or follow the DM diagnosis. DM may present as a paraneoplastic process, and the disappearance of skin rash and muscle weakness has been noted after treatment for cancer.

Case Report

A 66- year-old male, a chronic smoker and retired coal-miner, was admitted to our hospital because of severe productive cough for 2 weeks, followed by progressive shortness of breath for about 1 week. He was an outpatient at our chest clinic due to pneumoconiosis and chronic obstructive pulmonary disease, receiving an annual chest X-ray. Three weeks before admission, erythematous maculopapular skin rashes erupted on his neck, elbows, knees, eyelids, and hands. The skin lesions gradually became more prominent and spread extensively, and were later accompanied with bilateral upper

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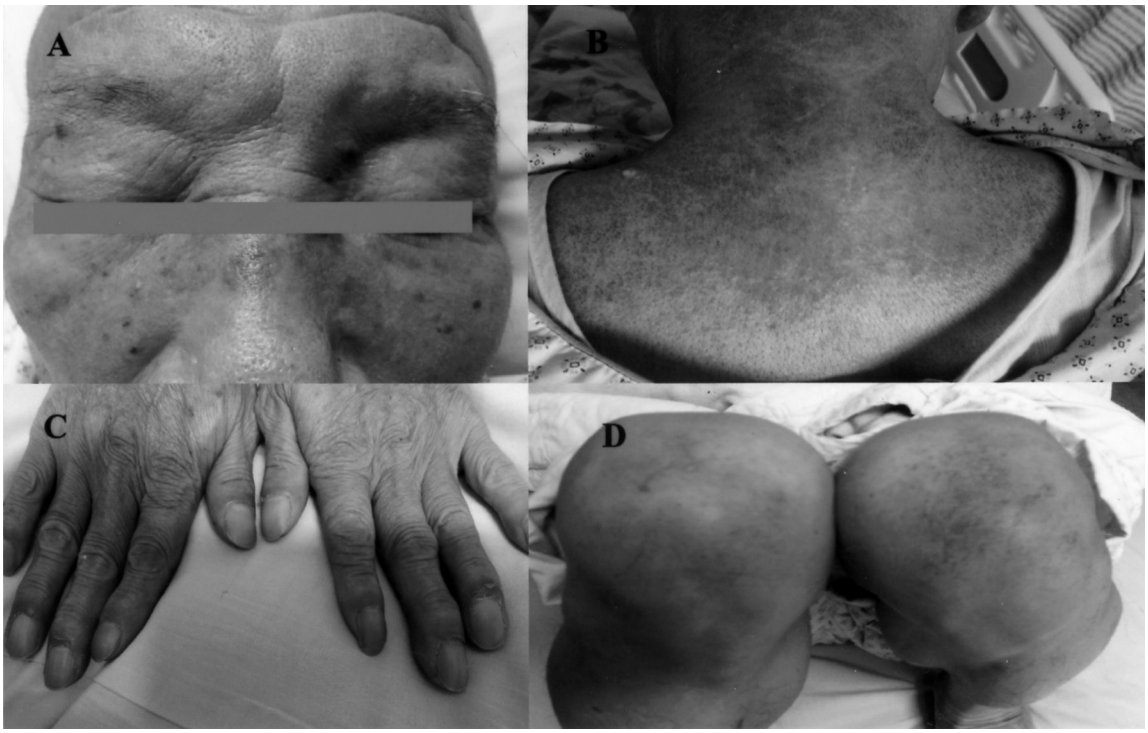

Fig. 1. Cutaneous manifestations of our patient that were consistent with DM; (A) Heliotrope rash on the upper eyelids, (B) Shawl sign on the neck, (C) (D) Gottron papules on the knuckles and knees

and lower limbs soreness and weakness.

Physical examination on admission revealed maculopapular skin rashes on the malar and frontal region of the patient's face, and on his neck, shoulders and chest . There were scaly erythematous papules on the knuckles, elbows, and knees, and purple disoloration of the upper eyelids (Figure 1). He also had symmetric proximal muscles weakness. The blood test showed an elevated creatine phosphokinase level of 965 IU/L (normal: 49-397 IU/L) and a carcinoembryonic antigen level of 10.1 ng/ml (normal ≤5.5 ng/ml in smoker). Chest X-ray revealed soft tissue density in the left hilar area and a patchy consolidation in the left lower lung field (Figure 2), which were not present in the previous chest X-ray. Based on the above symptoms and signs, lung cancer with DM was

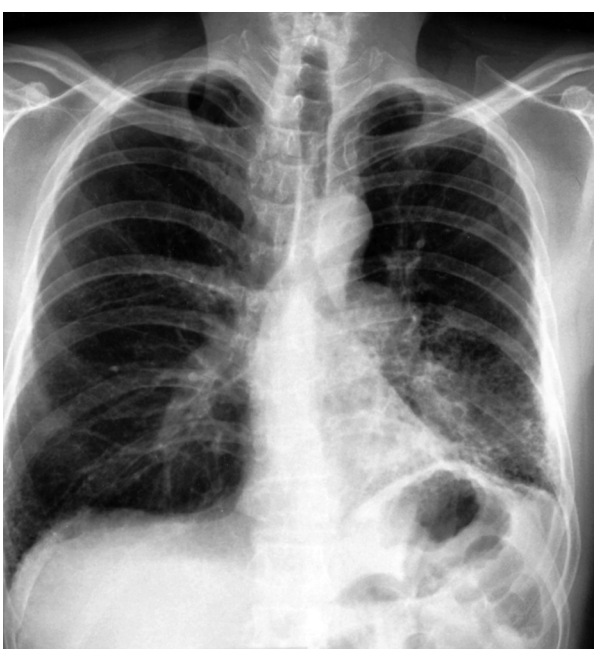

Fig. 2. Chest X-ray revealed soft tissue density in the left hilar area and patchy consolidation at the left lower lung field

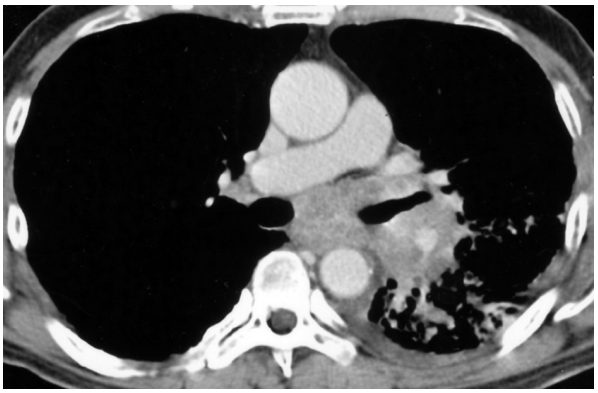

Fig. 3. Chest CT showed an irregular soft tissue mass at the left hilar area with encasement of the left main bronchus and invasion to the mediastinum and mediastinal lymphadenopathy.

considered.

Chest computed tomography (CT) showed an irregular soft tissue mass in the left hilar area with encasement of the left main bronchus and invasion to the mediastinum with mediastinal lymphadenopathy (Figure 3). Electromyography showed increased fibrillation waves in the proximal limbs muscles. Skin biopsy of the right arm and posterior neck region on the 5th hospital day revealed interface dermatitis with increased dermal mucin deposition, which was compatible with DM (Figure 4). Fiberoptic bronchoscopy revealed tumor infiltration with total occlusion of the left segmental bronchus B9+10, extending to the left main bronchus and left upper lobe. Bronchial biopsy of the left lower lobe confirmed small cell carcinoma.

The diagnosis of small cell lung cancer (SCLC) (T4N3M0), stage IIIB with a performance status (PS) of 1, along with DM was confirmed. The patient completed 6 courses of chemotherapy with a regimen of cisplatin + etoposide, after which the skin lesions and proximal muscle weakness showed improvement, indicating a para-neoplastic process. He also received radiotherapy to the mediastinum and left lower lung, but was complicated with radiation pneumonitis. Thereafter, his general condition

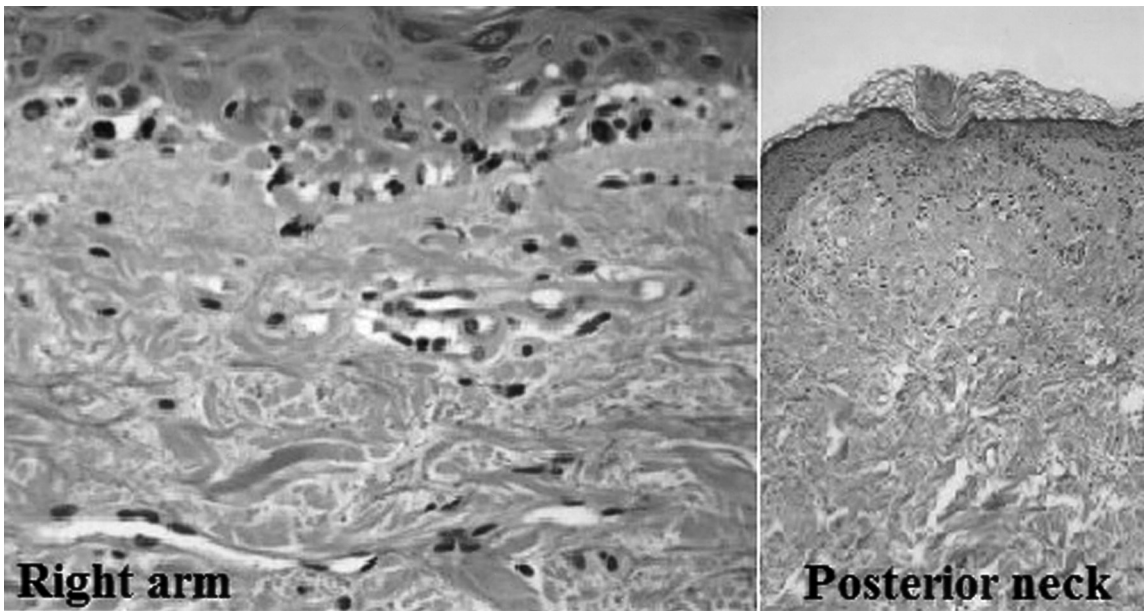

Fig. 4. Skin biopsy of the right arm and posterior neck region revealed basal vacuolation and mild perivascular lymphocyte infiltrates in the dermis with increased dermal mucin deposition, compatible with dermatomyositis.

Table 1. Diagnostic Criteria of Dermatomyositis (by Peter & Bohan)

1. Symmetrical proximal muscle weakness
2. Elevation of serum skeletal muscle enzymes
3. Characteristic electromyographic pattern
4. Muscle biopsy: evidence of myositis
5. Typical skin rash of dermatomyositis
Dermatomyositis is defined as definite (5 plus any 3 of criteria 1-4), probable (5 plus any 2 of criteria 1-4), or possible (5 plus any 1 of criteria 1-4).

deteriorated to a PS of 3, and he finally opted for supportive hospice management.

Discussion

DM is an idiopathic inflammatory myopathy, characterized by typical cutaneous manifestations and proximal muscle myopathy. It is a microangiopathy affecting skin and muscle; activation and deposition of complements cause lysis of endomysial capillaries and muscle ischemia.

DM is identified by characteristic rashes accompanying or, more commonly, preceding muscle weakness. Interstitial pulmonary disease, dysphagia, and polyarthritis are also common. Typical cutaneous skin manifestations include a heliotrope rash (blue-purple discoloration) on the upper eyelids, an erythematous rash on the face, neck, and anterior chest (V sign) or back and shoulders (shawl sign), and erythematous to violaceous papules at the extensor aspects of the metacarpophalangeal and interphalangeal joints (Gottron's papules) and the elbows, knees and ankles (Gottron's sign). Muscle weakness may vary from mild to severe, leading to quadriparesis. Our patient manifested the above typical cutaneous manifestations consistent with DM.

Most DM patients have elevated serum creatine kinase, lactate dehydrogenase, adolases and aminotransferases. About half of the patients may have positive antinuclear antibodies. Myositis specific antibodies are autoantibodies to aminoacyl-transfer (t)RNA synthetases (antisynthetase antibodies), including anti-Jo-1 which occurs in less than 25% of patients. Anti-Mi2 autoantibodies may also be present. However, data on these autoantibodies were unavailable in our case.

Electromyography proved the myositis of our patient, but was not diagnostic for DM, as similar changes are found in other diseases. Skin biopsy usually demonstrates basal vacuolation, and perivascular lymphocytic infiltrates in the dermis, known as interface dermatitis. Muscle biopsy is characterized by perimysial and perivascular inflammation with B cells and CD4 T cells, and complements deposition in vessels.

The widely accepted diagnostic criteria for DM, were proposed by Peter and Bohan in 1975 and still remains the "gold standard" for clinical studies (Table 1). Our case fulfilled the criteria for a definite diagnosis of DM.

The association between DM and malignancy has been reported extensively in the literatures. The first case report was published in 1916 and subsequent studies have consistently confirmed the increased risk of malignancy in

the setting of DM, a risk that is substantially greater than with other inflammatory myopathies. The reported frequency of malignancy in DM is about 6-45% [1-9].

Diagnosis of DM is associated with a 3-fold higher risk of any neoplasm (ovary, lung, pancreas, stomach, colorectal cancer or non-Hodgkin lymphoma) [1,4] and most cancer cases were detected within 1 year after the diagnosis of DM [9-10]. Patients with malignancy-associated DM were more frequently male and over the age of 45, and less likely to have interstitial lung disease [5,9].

Asian patients with DM tended to have cancers of the nasopharynx and lung, followed by breast and hematologic malignancies [6-8]. A population-based study [7] conducted in Taiwan, found that patients with DM had a 10-fold increased risk of cancer, with a 31-fold increased risk of lung cancer compared to the general population. Not only did patients with DM have an increased risk of lung cancer (standardized incidence rate 5.9) [4], but they were associated with all histological types of lung cancer. The most frequent type was SCLC, followed by squamous cell carcinoma; adenocarcinoma was relatively rare [9-10].

The underlying mechanism of the association between DM and malignancies remains undetermined. The widely accepted hypothetical "cross-over" model explains cross-over immunity for the development of cancer associated myositis [15-16]. Myositis-specific autoantigens were expressed in both tumor cells and undifferentiated myoblasts, leading to anti-tumor immunity. Subsequent muscle damage and regeneration reactivate the anti-tumor response, resulting in crossover immunity between tumor cells and myofibroblasts. Another possibility is that myositis consists of a paraneoplastic syndrome mediated by circulating immune complexes induced by the underlying malignancy.

DM appears as a paraneoplastic syndrome in some cases; ovary, lung and colorectal cancers are the ones most frequently involved. DM improves with cancer treatment, and there is a recurrence of muscle weakness when the tumor relapses, thus suggesting a paraneoplastic nature [1,4]. Our patient with DM also presented with a paraneoplastic phenomenon that improved with lung cancer treatment.

Conclusion

DM is associated with malignancy and may present as a paraneoplastic process. Therefore, cancer screening is recommended for patients who manifest signs and symptoms of DM.

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小細胞肺癌合併肌皮炎之病例報告

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有關皮肌炎（Dermatomyositis）與惡性腫瘤的相關性是眾所已知的，惡性腫瘤的平均發生率約佔6-45%。在皮肌炎患者中肺癌的風險相對比一般人群高出 31 倍，以小細胞肺癌（Small cell lung cancer）是最常見的類型。我們提出一名 66 歲男性罹患小細胞肺癌並併有皮肌炎。個案有皮肌炎的典型皮膚表現並伴有對稱的近端肌肉無力的症狀，肌酸激酶指標升高，與肌電圖檢查發現肌炎的表現。皮膚切片檢查的檢體與皮肌炎是一致的。從支氣管鏡病理切片檢體發現為小細胞肺癌。皮肌炎的症狀和徵象在使用阿樂癌（cisplatin）+ 滅必（etoposide）治化療後改善。故在皮肌炎的患者可積極的做癌症篩檢。*(胸腔醫學 **2014; 29: 377-383**)*

關鍵詞：皮肌炎，小細胞肺癌

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Castleman's Disease Presenting as a Mediastinal Hypervascular Tumor: A Case Report and Literature Review

Chih-Wei Wu, Pao-Shu Wu*, Yuh-Min Chen

Castleman's disease is a rare lymphoproliferative disease, and comprises a unicentric type and multicentric type. Unicentric Castleman's disease (UCD) usually presents as a solitary hypervascular tumor. In patients with multicentric Castleman's disease (MCD), the radiologic findings include mediastinal lymphadenopathy and pulmonary parenchymal infiltrates. In this report, we present the case of a 47-year-old man with blood-tinged sputum for 1 month. A series of image studies showed a solitary hypervascular tumor located at the posterior mediastinum. The initial differential diagnoses included lung cancer, neurogenic tumor, and pseudoaneurysm of the intercostal artery. After discussion with the surgeon, the patient underwent an operation for complete tumor resection. The pathologic report was hyaline vascular-type Castleman's disease. The patient did not receive steroid or chemotherapy postoperatively, and there was no sign of recurrence at the 2-year follow-up. Physicians should take Castleman's disease into consideration in their clinical practice when a solitary hypervascular tumor is present. ***(Thorac Med 2014; 29: 384-390)***

Key words: Castleman's disease, hypervascular tumor

Introduction

Castleman's disease, also known as angiofollicular lymph node hyperplasia, was first described in 1954 by Dr. Castleman [1]. It is a rare non-neoplastic lymphoproliferative disorder. Castleman's disease can be categorized histopathologically into a hyaline vascular type, plasma cell type and mixed type [2]. In clinical terms, Castleman's disease can be divided into 2 groups, unicentric (UCD) and multicentric (MCD). The 2 clinical types have different prognoses. UCD has an excellent outcome and can be cured with surgery. MCD is associated with systemic involvements, sepsis and malignant transformation [3]. UCD most commonly presents as a solitary hypervascular tumor and should be differentiated from sarcoma, thymoma, and lung cancer. MCD has typical radiologic findings of mediastinal and hilar lymphadenopathy, and mimics lymphoma, metastatic lymphadenopathy, and disseminated infection.

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The "gold standard" of diagnoses is biopsy. We present herein the case of a patient with Castleman's disease mimicking a mediastinal hypervascular tumor.

Clinical Course

A 47-year-old man suffered from cough with blood-tinged sputum for 1 month. He was a never-smoker. There was no significant drug history or past medical history. At first, he visited a local medical department, where chest X-ray revealed abnormal findings. He called at our outpatient clinic, where a left lung peri-hilar mass lesion was seen on chest X-ray images; lung cancer or mediastinal malignancy could not be excluded (Figure 1). On admission, the laboratory test findings, including normal blood cell counts and carcinoembryonic antigen (CEA) level, were unremarkable. The electrocardiogram and echocardiogram were normal. Physical examination revealed a well-nourished man without lymphadenopathy or organomegaly.

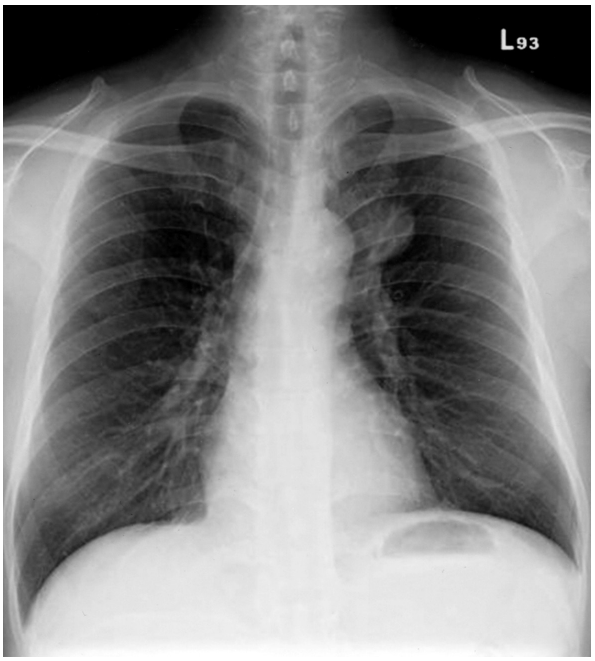

Fig. 1. Chest X-ray shows a soft tissue dense opacity, measuring about 3 cm in length at the left peri-hilar region.

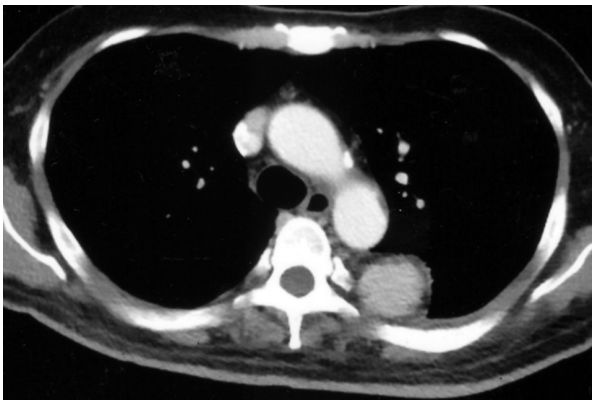

Fig. 2. CT scan shows a 3.2 × 3.0 cm contrast-enhanced soft tissue mass in the left lower lung, abutting the posterior mediastinum without bony destruction.

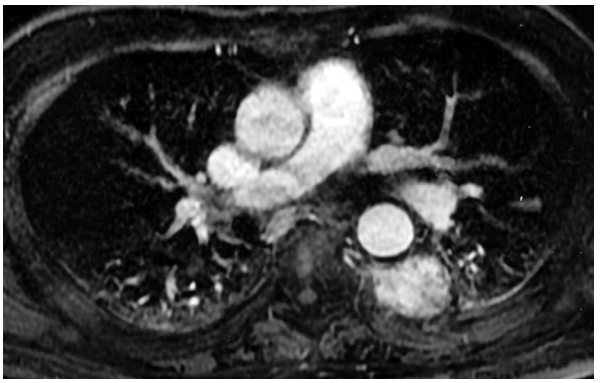

Fig. 3. Thoracic T1-weighted MRI after gadolinium infusion shows a high-signal tumor about 3.3 × 2.8 × 2.8 cm near the left para-aortic region between the level of T5 and T6. Communication with the left 6th intercostal artery could not be ruled out.

Chest CT examination was arranged for further investigation and revealed a 3.2 × 3 cm hyper-enhanced soft tissue mass in the left lower lung field near the posterior mediastinum, without bony invasion (Figure 2); thus, vascular lesion or malignancy with hypervascularity was highly suspected. Thoracic MRI and angiog-

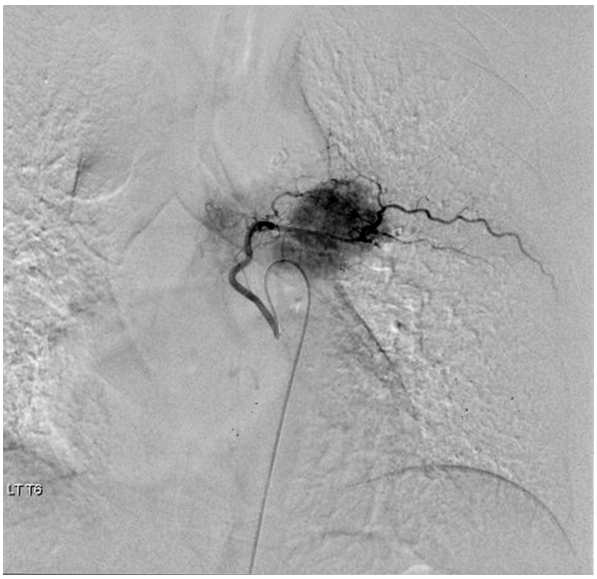

Fig. 4. Thoracic angiography shows a 3 cm hypervascular lesion at the left para-aortic region with an arterial feeder from the left T6 intercostal artery.

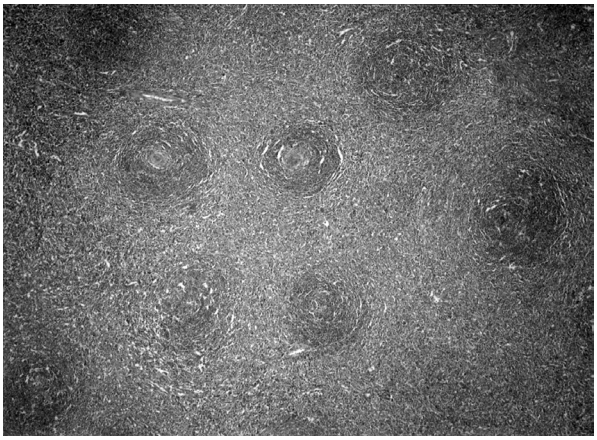

Fig. 5. Numerous follicles with regressed germinal centers in the lymph node. Proliferation of venules with hyalinized walls is seen in the inter-follicular space.

raphy were suggested by the radiologist. The patient underwent both examinations and the reports suggested the presence of a hypervascular tumor with feeding artery from the left 6th intercostal artery or an intercostal artery pseudoaneurysm (Figure 3,4).

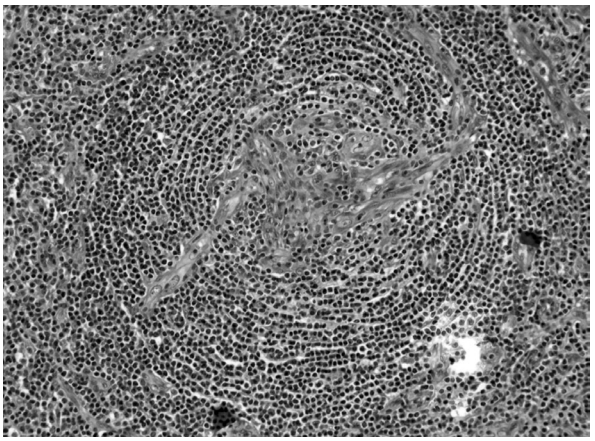

Fig. 6. In a high power field, the regressed germinal center is surrounded by concentrically arranged mantle zone lymphocytes, creating an "onion skin" appearance. Also note the hyalinized, sclerotic vessel radially traversing into the germinal center, creating a "lollipop" appearance.

As a result of the above findings, appropriate surgical excision was arranged in consultation with a cardiovascular surgeon and a chest surgeon. During operation, a solid chest wall tumor was found. It was connected to the chest wall by a stalk containing a feeding artery. The tumor was excised and the feeding artery was ligated. The pathology report confirmed a lymph node origin of the tumor without evidence of malignancy. The microscopic finding was numerous small follicular centers with prominent hyalinized central vessels, surrounded by concentric layers of small lymphocytes (Figure 5,6). The picture was compatible with the hyaline vascular type of Castleman's disease.

The postoperative course was smooth. Cough with blood-tinged sputum subsided gradually. Post-operation, the patient did not receive steroid, radiotherapy or chemotherapy. Two years after the operation, there were no signs of recurrence. The patient received regular outpatient follow-up.

Discussion

Castleman's disease is a rare lymphoproliferative disorder with unknown etiology. Many possible origins have been proposed, such as immunocompromised states, chronic inflammation, and autoimmune processes [4]. The disease occurs throughout the lymphatic chains of the body, including nodal or non-nodal organs such as the lung or pancreas. Approximately 70% of all cases of Castleman's disease occur in the chest, 15% in the neck, and 15% in the abdomen and pelvis [5].

Castleman's disease is divided into a hyaline vascular type, plasma cell type and mixed type. The hyaline vascular type is the most common, and is characterized by prominent follicles, marked vascular proliferation with thick and hyalinized walls and hyalinization of germinal centers. The concentric layering of peripheral lymphocytes creates the "onion-skin" appearance. A hyalinized capillary may frequently penetrate a follicle and make the follicle look like a lollipop under the microscope. The plasma cell type shows follicular hyperplasia with large germinal centers and marked plasmacytosis in interfollicular areas, without hyaline vascular changes. The mixed type combines features of the hyaline vascular and plasma cell types. Histological examination of the affected lymph node is the "gold standard" of diagnosis [2]. The hyaline vascular type accounts for about 90% of UCD. The remaining 10% is plasma cell type. UCD is not associated with human herpes virus-8 infection [3].

Most patients with UCD are young and asymptomatic. They are often diagnosed incidentally and in their 3rd or 4th decade of life. The incidence is equal in both sexes. About 50% of the plasma cell type has systemic manifestations, such as an elevated erythrocyte sedimentation rate, anemia, and hypergammaglobulinemia [3].

UCD most commonly presents as a solitary hypervascular thoracic tumor. Both chest CT and MRI typically show a contrast hyperenhancing tumor [6-7]. There are many case reports of UCD with diverse images mimicking thymoma, lymphoma, schwannoma, pancreatic tumor, renal artery pseudoaneurysm, and others. Due to the hypervascular images of our case, pseudo-aneurysm was 1 of the differential diagnoses. Thus, a cardiovascular surgeon was consulted preoperatively for possible vascular surgery. There are only 3 case reports of UCD mimicking pseudoaneurysm in the literature. The primary lesion sites are the renal artery, axillary artery and coronary artery [8-10].

Surgical excision is curative in UCD and the associated symptoms will also resolve. If complete resection is not feasible, partially resected UCD provides a favorable outcome, and the remaining lesions are stable and asymptomatic for years [5]. If resection is not possible, radiotherapy results in a 40% rate of complete remission [11]. Chemotherapy is usually unnecessary for UCD.

MCD was first introduced in a case report in 1978 [12]. It is typically the plasma cell type of Castleman's disease [13], and is usually associated with human herpes virus-8 infection, especially in human immunodeficiency virus-infected patients [14-15].

In terms of clinical features, patients with MCD usually present in their 5th and 6th decades of life. The symptoms, including fever, body weight loss, fatigue, and night sweats, are common but non-specific, and are suggestive of an inflammatory illness. More than 90% of patients are symptomatic. Patients with MCD almost

always have peripheral lymphadenopathy. The laboratory findings include anemia, elevated erythrocyte sedimentation rate, hepatosplenomegaly, hypoalbuminemia and hypergammaglobulinemia [3]. MCD was reported to have the potential of malignant transformation, for example, to Kaposi sarcoma [5] and lymphoma [14,16].

The radiologic characteristics of MCD include bilateral hilar and mediastinal lymphadenopathy, diffuse abdominal lymphadenopathy, and hepatosplenomegaly. Pulmonary parenchymal involvements are diverse, and include subpleural nodules, ground glass opacities, patchy areas of consolidation and peribronchovascular thickening. Pleural effusion or ascites may also be present [6].

There is no effective treatment for MCD at this time. Most regimens are palliative with variable responses. The traditional therapies include steroid and chemotherapy. Neutralizing antibodies against interleukin-6 and rituximab (the monoclonal anti-CD20 antibody) recently have shown promising clinical efficacy [17-18]. There is no role for surgical resection [5]. The prognosis of MCD is poor. The median survival is 26 to 30 months in HIV-negative MCD [15,19]. In HIV-positive MCD, the median survival is shorter.

Castleman's disease is a great mimicker. UCD usually presents as a solitary hypervascular tumor. It can simulate a mediastinal tumor, intra-abdominal neoplasm, or pseudoaneurysm. Our reported patient had UCD presenting with a pulmonary neoplasm-like lesion that mimicked a hypervascular lesion on detailed imaging examinations. Physicians should consider UCD as a differential diagnosis when caring for patients with a thoracic hypervascular nodular or mass lesion.

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卡斯曼病以縱膈腔的單一高血管性腫瘤來表現：病例報告

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卡斯曼病是一種罕見的淋巴細胞增生性疾病。臨床上，它區分為兩種表現型：單中心型與多中心型。單中心型的卡斯曼病通常以單獨一顆的高血管性腫瘤來表現。多中心型的卡斯曼病，影像學上的表現主要是縱膈腔淋巴腺腫大及肺部的浸潤。在本篇個案報告中，一位 47 歲的男性病患因為咳嗽合併血絲痰一個月來求診。一系列的影像學檢查發現一顆位於後縱膈腔的高血管性腫瘤。一開始我們的鑑別診斷包含肺癌、神經性腫瘤及肋間動脈的血管瘤等。經與外科醫師討論後，病患接受了手術切除，病理報告為透明性血管型的卡斯曼病。術後此病患沒接受類固醇治療或化學治療。經過兩年的追蹤，沒有復發的證據。在臨床實務上，對於單一顆高血管性的腫瘤，醫師應該把卡斯曼病列入鑑別診斷中。*(胸腔醫學 **2014; 29: 384-390**)*

關鍵詞：卡斯曼病，高血管性腫瘤

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