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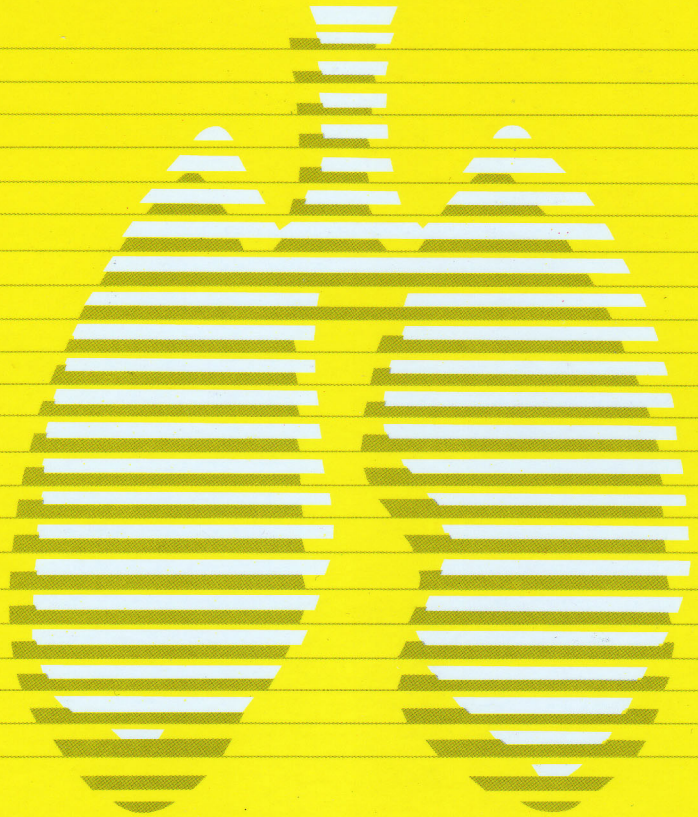

台灣胸腔暨重症加護醫學會

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原著

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Orginial Articles

Case Reports

Survival Predictors in Oldest-Old (≥85 Years Old) Patients with Acute Respiratory Distress Syndrome: A Prospective Observational Cohort Study

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Introduction: Acute respiratory distress syndrome (ARDS) is a high-mortality condition in the intensive care unit. Older patients can require more time and attention in the hospital, especially in intensive care. In this study, we focus on the oldest-old (more than 85 years old) ARDS patients, with the aim of investigating survival predictors in this group.

Patients and Methods: In this prospective observational cohort study, we focused on patients who were admitted to our hospital's intensive care units with the diagnosis of ARDS between October 2012 and May 2015. Demographic, comorbidity, severity, lung mechanics, and laboratory data and survival outcomes were collected and analyzed.

Results: A total of 463 (49%) of 945 patients with ARDS were ≥65 years old. Eighty of these elderly patients with ARDS were ≥85 years old. The overall hospital mortality rate was 60% (48/80). The hospital survivors had lower Sequential Organ Failure Assessment (SOFA) scores (7.9 vs. 9.6, p=0.021), higher platelet counts (208.7±78.2×10^3/μL vs. 141.5±80.2×10^3/μL, p<0.001), higher albumin levels (2.7±0.4 g/dL vs. 2.4±0.6 g/dL, p=0.016) and lower blood urea nitrogen levels (33.4±16.4 mg/dL vs. 52.8±38.5 mg/dL, p=0.003) than the non-survivors. Multivariate logistic regression analysis found that only albumin level (odds ratio, 0.20; 95% confidence interval, 0.05-0.88, p=0.003) was significantly and independently associated with hospital mortality.

Conclusions: The oldest-old ARDS patients had high hospital mortality, and the most important survival predictor was serum albumin level. ***(Thorac Med 2018; 33: 221-229)***

Key words: oldest-old, acute respiratory distress syndrome, SOFA score, albumin

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Introduction

Even with treatment, acute respiratory distress syndrome (ARDS) is still a high mortality condition in the intensive care unit (ICU) [1]. The LUNG SAFE study revealed a mortality rate of 40% among all patients [2]. Some predictive factors, including age, Simplified Acute Physiology Score-II, Acute Physiology and Chronic Health Evaluation II (APACHE II), underlying medical condition, oxygenation index, PaO_2/FiO_2 ratio, duration of mechanical ventilation before ARDS, mechanism of lung injury, liver cirrhosis, trauma, and right-side heart failure, have been identified in previous studies [3-4].

Older patients have been divided into 3 groups: young-old (65-74 years old), middle-old, (75-84 years old) and oldest-old (≥85 years old) [5]. These patients present a substantial challenge to the health care system [6]. The Bureau of National Health Insurance in Taiwan has reported that patients older than 65 years consume nearly 40% of total health insurance expenditures (https://www.nhi.gov.tw). The Ministry of the Interior estimates that there are 370,458 persons more than 85 years old in Taiwan as of February 2018 (http://www.ris.gov.tw). This is 1.6% of the general population. As such, the aim of this study was to investigate the survival predictors of ARDS among patients in the oldest-old (≥85 years old) age group.

Patients and Methods

Study patients and data collection

In this prospective observational cohort study, we used the Hospital Information System to screen for eligibility all of the patients who were admitted to the ICU requiring mechanical ventilation and who had available data on both PaO_2/FiO_2 ratio and chest X-ray between October 2012 and May 2015. The patients enrolled in this study were those who met the criteria of ARDS according to the Berlin definition [1]. We focused on the oldest-old patients (≥85 years old). The demographic data, ventilator setting data, laboratory data, and outcomes were obtained from the electronic medical records. The ventilator setting data and laboratory data were obtained on the day the patient was diagnosed with ARDS. The comorbidity condition was assessed using the Charlson comorbidity index [8]. The severity index, including APACHE II [9], Sequential Organ Failure Assessment (SOFA) score [10], and lung injury score [11], was obtained. Early-onset (community-acquired) ARDS is defined as ARDS that started less than or equal to 48 hours after hospital admission, and late-onset (hospital-acquired) is that which started more than 48 hours after admission [12]. The local Institutional Review Board for Human Research of the involved hospital approved this study (CGMH IRB No.102-1729B).

Managements of ARDS

The mechanical ventilator settings of the patients with ARDS included a lung protective ventilation strategy using a low tidal volume of 4-8 mL/kg of predicted body weight, and a positive end-expiratory pressure (PEEP) setting guided by the low PEEP-FiO_2 table for pressure-controlled or volume-controlled ventilation [13]. We recorded the setting data, including tidal volume, peak airway pressure (Paw), PEEP, dynamic driving pressure and fraction of inspiratory oxygen (FiO_2). The dynamic driving pressure was defined as Paw minus PEEP. Empirical antibiotics were used with all patients with evidence of infection, according to the

American Thoracic Society pneumonia guideline of 2005 [14].

Statistical analyses

SPSS version 22.0 (SPSS Inc., Chicago, IL) was used for statistical analyses and database management (SPSS Inc., Chicago, IL). Data are presented as numbers (percentages) for nominal variables, and as means ± standard deviation for continuous variables. Nominal variables were analyzed using the chi squared test, and continuous variables were analyzed with Student's *t* test. The univariate logistic regression test was used to analyze all of the factors, and the multivariate logistic regression test was used to analyze the significant predictive factors obtained from the univariate logistic regression test. We used a 2-tailed test, and the definition of significance in this study was a *p* value less than 0.05.

Results

From October 2012 to May 2015, 1,034 patients met the criteria for ARDS and were admitted to the ICUs with invasive mechanical ventilation; 945 of this group were included for analysis (Figure 1). In all, 463 (49%) patients were ≥65 years old, and 80 (8.5%) were ≥85 years. Among these 80 oldest-old patients, the hospital mortality rate was 60% (48/80). Fifty-eight patients were admitted to the medical ICU, and 22 were admitted to the surgical ICU. There was no significant difference between survivors and non-survivors in terms of gender,

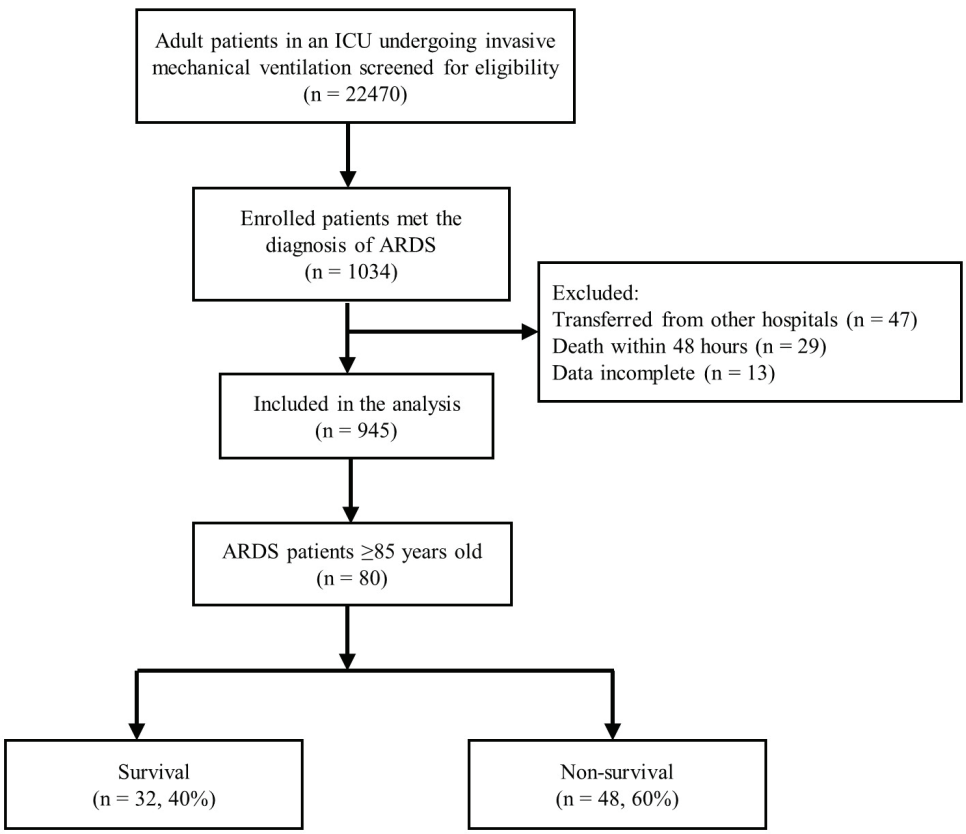

Fig. 1. Flow chart for patient enrollment in the study.
ICU: intensive care unit; ARDS: acute respiratory distress syndrome

age, body mass index (BMI), Charlson comorbidity index, APACHE II score and lung injury score, but the survivors had significantly lower SOFA scores than the non-survivors (7.9 vs. 9.6). The greatest proportion of ARDS severity among both survivors and non-survivors was moderate ARDS (46.9% and 37.5%). In terms of the distribution of severity of ARDS between the 2 groups, there was no significant difference. The proportion of severe ARDS was higher among the non-survivors than the survivors (33.3% vs. 25.0%), but without a significant difference. With regard to risk factors, pneumonia was the most common (n=34; survivors, 14; non-survivors, 20), followed by sepsis, (n=20; survivors, 8; non-survivors, 12), aspiration (n=16: survivors, 6; non-survivors, 10), major surgery (n=8; survivors, 3; non-survivors, 5), and acute pancreatitis (n=2; survivors, 1; non-survivors, 1). Septic shock was present in 15 patients when ARDS was diagnosed, and 10 of them died in the hospital. The initial respiratory parameters, such as tidal volume/predicted body weight, Paw, PEEP, PaO_2/FiO_2 ratio and dynamic driving pressure, of these 2 groups revealed no significant difference (Table 1).

A comparison of the 2 groups revealed no statistically significant differences regarding leukocytes, hemoglobin, liver enzymes and electrolytes in the baseline laboratory data. Only 3 items (platelet count, albumin and blood urea nitrogen level) showed a significant difference between the 2 groups (Table 2). Four patients had underlying liver cirrhosis in this study (Child B: 2 patients, Child A: 2 patients), but there was no significant decrease in the albumin level of these 4 patients compared to the others (2.4±0.3 vs. 2.5±0.6, p=0.678). Eleven patients had underlying chronic kidney disease, but no significant decrease in albumin level was noted in these patients (2.6±0.4 vs. 2.3±0.9, p=0.400). Furthermore, no significant difference in albumin levels was noted between early-onset and late-onset ARDS patients (2.6±0.7 vs. 2.5±0.5, p=0.372).

Univariate and multivariate logistic regression analysis were used to identify variables for hospital mortality that had significant prognostic value (Table 3). Albumin level was significantly and independently associated with hospital mortality.

Discussion

In this prospective observational cohort study, we found that oldest-old (≥85 years old) patients with ARDS had a relatively high hospital mortality rate. Hospital survivors had lower SOFA scores, higher platelet counts, higher albumin levels and lower blood urea nitrogen than non-survivors; only albumin level was significantly and independently associated with hospital mortality in these oldest-old patients with ARDS.

The overall hospital mortality rate of the oldest-old patients with ARDS was 60%, which was higher than the 40% mortality rate among the general population with ARDS, as reported in the LUNG SAFE study [2]. Age is still an important factor related to the survival outcome of patients with ARDS. Kao *et al*. [15] found the SOFA score was an independent predictor of hospital mortality in patients with ARDS and diffuse alveolar damage undergoing open lung biopsy. However, albumin level was not used as a prognostic factor in Kao's study. In the present study, the SOFA score was significantly lower among survivors than non-survivors, although it was not found to be a significant prognostic factor using multivariate logistic re-

Table 1. Demographic and Clinical Characteristics of Hospital Survivors and Non-Survivors among Oldest-Old Patients with ARDS

Variable	Total (n=80)	Survivors (n=32)	Non-survivors (n=48)	*p*
Gender (male/female)	58/22	22/10	36/12	0.540
Age (years)	87.5±2.7	87.5±2.4	87.5±2.9	1.000
BMI (kg/m^2)	22.3±3.4	22.4±3.7	22.2±3.2	0.749
Charlson comorbidity index	2.5±2.1	2.4±2.0	2.6±2.1	0.660
APACHE II score	24.6±7.2	24.8±6.6	24.4±7.6	0.825
SOFA score	8.9±3.2	7.9±2.5	9.6±3.4	0.021*
Lung injury score	2.8±0.5	2.7±0.6	2.8±0.4	0.174
Early onset/late onset	35/45	16/16	19/29	0.358
Tidal volume/PBW(ml/kgw)	8.7±3.7	9.7±5.3	8.1±1.7	0.060
Paw (cm H_2O)	27.8±5.5	27.2±6.9	28.2±4.4	0.441
PEEP (cm H_2O)	9.7±1.3	9.4±1.5	9.8±2.2	0.425
Dynamic driving pressure (cm H_2O)	18.2±5.3	17.7±6.2	18.4±4.6	0.576
PaO_2/FiO_2 ratio (mmHg)	151.1±76.6	157.8±73.9	146.6±78.8	0.525
Severity, n (%)				0.650
Mild	23(28.7)	9(28.1)	14(29.2)	
Moderate	33(41.3)	15(46.9)	18(37.5)	
Severe	24(30.0)	8(25.0)	16(33.3)	

ARDS: acute respiratory distress syndrome; BMI: body mass index; APACHE: Acute Physical and Chronic Health Evaluation; SOFA: sequential organ function assessment; Paw: peak airway pressure; PEEP: positive end-expiratory pressure; PaO_2/FiO_2: alveolar oxygen pressure/fraction of inspiratory oxygen; All values are expressed as number of patients (%) or mean ± SD.

*p-value <0.05

gression analysis.

Albumin level was the only predictor of hospital mortality for the oldest-old ARDS patients, using multivariate logistic regression analysis. Tseng *et al*. found that day 1 albumin is a predictor of 6-month life dependence (defined as Barthel's Index below or equal to 30) in patients with ARDS [16]. Hoeboer *et al*. concluded that an albumin level less than 20 g/L or that declined over a week was related to increasing severity of ARDS [17]. In patients older than 60 years, a low albumin level was related to in-hospital mortality [18]. Malnutrition is a main causes of hypoalbuminemia, and is not just a physiological process due to aging [19]. Moreover, there are several different etiologies for hypoalbuminemia, such as liver cirrhosis, hepatitis, diabetes, nephrotic syndrome, protein-losing enteropathy, infection, and sepsis, and these etiologies are also common in elderly patients [20]. However, in this study, patients with liver cirrhosis or chronic kidney disease had no significant decrease in their albumin level. Hence, malnutrition may be the most important etiology for the relationship between hypoalbuminemia and hospital mortality. In our study, the albumin level was below the normal range (2.5±0.6 g/dL vs. 3.5-5.0 g/dL), even in the survivor group (2.7±0.4 g/dL). Maybe this is a reason for a mortality rate up

Table 2. Laboratory Data of Hospital Survivors and Non-Survivors among Oldest-Old Patients with ARDS

Variable	Total (n=80)	Survivors (n=32)	Non-survivors (n=48)	*p*
Leukocytes ($\times10^3$/mL)	15.6±1.8	19.0±2.6	13.3±1.1	0.166
Hemoglobin (g/dL)	10.0±2.2	9.9±2.4	10.0±2.0	0.865
RBC (10^6/μL)	3.8±2.2	3.7±1.4	3.8±2.6	0.886
RDW (%)	16.9±3.5	16.4±3.8	17.2±3.3	0.334
Platelets ($\times10^3$/μL)	168.4±85.6	208.7±78.2	141.5±80.2	<0.001*
Albumin (g/dL)	2.5±0.6	2.7±0.4	2.4±0.6	0.016*
BUN (mg/dL)	45.2±33	33.4±16.4	52.8±38.5	0.003*
Creatinine (mg/dL)	1.8±1.4	1.5±1.4	1.9±1.4	0.245
AST (U/L)	134.1±443.7	179.8±631.3	99.5±222.2	0.527
ALT (U/L)	63.1±176.0	75.6±233.3	54.2±122.7	0.627
Bilirubin (total) (mg/dL)	1.2±3.1	1.0±1.3	1.3±3.8	0.679
Na (mEq/L)	138.8±9.7	137.9±12.1	139.4±7.7	0.506
K (mEq/L)	4.1±0.8	4.3±0.9	4.0±0.8	0.107

RBC: red blood cell count; RDW: red blood cell distribution width; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase. All values are expressed as No of patients (%) or mean ± SD.
*p-value <0.05

to 60% among these oldest-old patients with ARDS.

There are some limitations in this study. First, the patient number was small (n=80) and the study was carried out in 1 medical center only. Although the study was strengthened by its prospective, cohort, and observational design, this limitation may affect generalization of the study results and warrant external validation. Second, we concluded that the albumin level was the prognostic factor in this study, but we did not exclude patients with underlying diseases that may have caused severe hypoalbuminemia, such as liver cirrhosis or nephrotic syndrome. However, no significant decrease in the albumin level was noted in patients with underlying liver cirrhosis or chronic kidney disease.

Conclusion

For the oldest-old (≥85 years old) patients with ARDS, the hospital mortality rate was high, up to 60%, in our prospective observational cohort study. Hospital survivors had higher platelet counts, higher albumin levels and lower blood urea nitrogen levels than non-survivors. Furthermore, albumin level was significantly and independently associated with hospital mortality in these oldest-old patients with ARDS.

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Table 3. Univariate and Multivariate Logistic Regression Analyses of Clinical Variables Associated with Hospital Mortality among Oldest-Old Patients with ARDS

Parameter	Beta coefficient	Standard error	Odds ratio (95% CI)	*p*
Univariate logistic regression				
Age	0.00	0.09	1.00 (0.84-1.19)	1.00
BMI (kg/m^2)	-0.02	0.07	0.98 (0.86-1.12)	0.75
Charlson comorbidity index	0.05	0.11	1.05 (0.84-1.31)	0.66
APACHE II score	-0.01	0.03	0.99 (0.93-1.06)	0.82
SOFA score	0.18	0.08	1.20 (1.02-1.40)	0.03*
Lung injury score	0.63	0.46	1.88 (0.76-4.66)	0.17
Tidal volume/PBW (ml/kgw)	-0.20	0.12	0.82 (0.64-1.04)	0.10
Paw (cm H_2O)	0.04	0.04	1.04 (0.96-1.13)	0.40
PEEP (cm H_2O)	0.10	0.13	1.11 (0.86-1.42)	0.42
PaO_2/FiO_2 ratio (mmHg)	-0.00	0.00	1.00 (0.99-1.00)	0.52
Severity of ARDS				
Mild (reference)				
Moderate	-0.26	0.55	0.77 (0.26-2.28)	0.64
Severe	0.25	0.61	1.29 (0.39-4.24)	0.68
Leukocytes ($\times 10^3$/mL)	0.00	0.00	1.00 (1.00-1.00)	0.22
Hemoglobin (g/dL)	0.02	0.01	1.02 (0.83-1.25)	0.86
RBC ($10^6/\mu L$)	0.02	0.10	1.02 (0.82-1.25)	0.89
RDW (%)	0.07	0.08	1.07 (0.93-1.24)	0.34
Platelets ($\times 10^3/\mu L$)	-0.01	0.00	0.99 (0.98-1.00)	0.00*
Albumin (g/dL)	-1.53	0.66	0.22 (0.060-0.80)	0.02*
BUN (mg/dL)	0.03	0.01	1.03 (1.01-1.05)	0.02*
Creatinine (mg/dL)	0.21	0.18	1.23 (0.86-1.76)	0.25
AST (U/L)	0.00	0.00	1.00 (1.00-1.00)	0.54
ALT (U/L)	-0.00	0.00	1.00 (1.00-1.00)	0.63
Bilirubin (Total) (mg/dL)	0.04	0.10	1.03 (0.85-1.27)	0.68
Na (mEq/L)	0.02	0.03	1.02 (0.97-1.07)	0.50
K (mEq/L)	-0.45	0.28	0.64 (0.37-1.11)	0.11
Multivariate logistic regression				
SOFA score	-0.07	0.15	0.93 (0.69-1.25)	0.64
Platelets ($\times 10^3/\mu L$)	-0.01	0.00	0.99 (0.99-1.00)	0.12
Albumin (g/dL)	-1.60	0.75	0.20 (0.05-0.88)	0.03*
BUN (mg/dL)	0.02	0.02	1.02 (1.00-1.06)	0.11
Constant	5.28	2.61	195.5	0.04*

ARDS: acute respiratory distress syndrome; CI: confidence interval; BMI: body mass index; APACHE: Acute Physical and Chronic Health Evaluation; SOFA: sequential organ function assessment; PBW: predicted body weight; Paw: peak airway pressure; PEEP: positive end-expiratory pressure; PaO_2/FiO_2: alveolar oxygen pressure/fraction of inspiratory oxygen; RBC: red blood cell count; RDW: red blood cell distribution width; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

*p-value <0.05

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存活預測因子於急性呼吸窘迫症候群的老老人（大於 85 歲）：前瞻性觀察世代研究

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李立夫 *,*** 王九華 ***** 黃崇旂 *,*** 高國晉 *,***

背景：急性呼吸窘迫症候群在加護病房中有很高的死亡率。老年人對於醫療照護上是一項負擔，尤其在加護照護。本篇研究中，我們針對罹患急性呼吸窘迫症候群的老老人 (大於 85 歲)，研究他們的存活預測因子。

方法：在這篇前瞻性觀察世代研究中，我們蒐集 2012 年 10 月至 2015 年 5 月所有入住本院加護病房，且符合急性呼吸窘迫症候群診斷的病患，分析人口學、共病症、嚴重度指標、肺部機械特性、實驗室數據和存活預後等資料。

結果：945 位急性呼吸窘迫症候群病患中，老年人有 463 位 (49%)、大於 85 歲有 80 位，院內死亡率為 60% (48/80)。院內存活病患較院內死亡病患有較低的相繼器官衰竭評分 (7.9 vs. 9.6, p=0.021)、較高的血小板 (208.7±78.2 x 10^3/μL vs. 141.5±80.2 x 10^3/μL, p<0.001)、較高的白蛋白 (2.7±0.4 g/dL vs. 2.4±0.6 g/dL, p=0.016)、和較低的血清尿素氮 (33.4±16.4 mg/dL vs. 52.8±38.5 mg/dL, p=0.003)。於多因子羅吉氏迴歸分析中，只有白蛋白為有意義且獨立的院內死亡預測因子 (勝算比為 0.20, 95% 信賴區間為 0.05-0.88, p=0.003)。

結論：急性呼吸窘迫症候群的老老人有很高的院內死亡率，而最重要的存活預測因子是血清中白蛋白值。*(胸腔醫學 **2018; 33: 221-229**)*

關鍵詞：老老人，急性呼吸窘迫症候群，相繼器官衰竭評分，白蛋白

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Primary Pulmonary Artery Sarcoma Mimicking Pulmonary Thromboembolic Disease: A Case Report

Chih-Cheng Chen, Jih-Shuin Jerng

Primary pulmonary artery sarcoma is a rare disease entity, and patients might have the typical presentations of thromboembolic disease. We report a 50-year-old woman who presented with a 3-month history of dyspnea on exertion and chest tightness. Chest X-ray examination revealed a prominent right pulmonary trunk and a nodule at the left lower lung field; magnetic resonance imaging disclosed significant "filling defects" within bilateral pulmonary trunks. With the clinical diagnosis of pulmonary thromboembolism, she was treated with systemic anticoagulants, but the symptoms and radiographic findings progressed. Surgical biopsy of the pulmonary artery lesion revealed poorly differentiated pulmonary artery sarcoma. She died 1 year later despite treatment. Our case illustrates that pulmonary artery sarcoma should be included in the differential diagnosis of pulmonary thromboembolic disease when there is a lack of response to anticoagulation in patients with no evident risk factor for pulmonary thromboembolism, and in those with concomitant pulmonary nodules. ***(Thorac Med 2018; 33: 230-236)***

Key words: pulmonary artery sarcoma, pulmonary thromboembolism, pulmonary thromboembolic disease

Introduction

Pulmonary artery sarcoma (PAS), which was first described at autopsy by Mandelstamm in 1923 [1], is a rare disease that is often misdiagnosed as chronic pulmonary thromboembolism. Fewer than 250 patients with primary PAS have been reported as of 2009 [2]. Patients with PAS often present with dyspnea, cough, hemoptysis, or chest pain. Because these symptoms mimic pulmonary thromboembolic disease, patients are often treated with anticoagulation therapy initially, and early diagnosis requires close follow-up and clinical suspicion. Herein, we describe a case that was initially diagnosed as pulmonary thromboembolism; the correct diagnosis was established only by surgical biopsy of the pulmonary artery lesion.

Case Presentation

This 50-year-old woman was a bricklayer and reported a non-eventful past medical history and no systemic disease. She also denied

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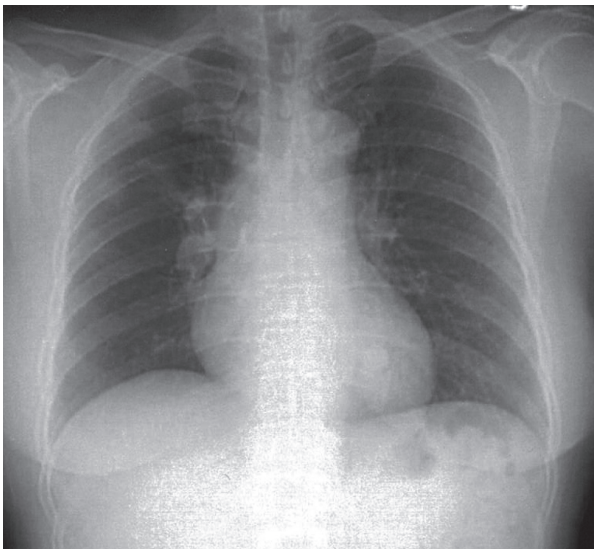
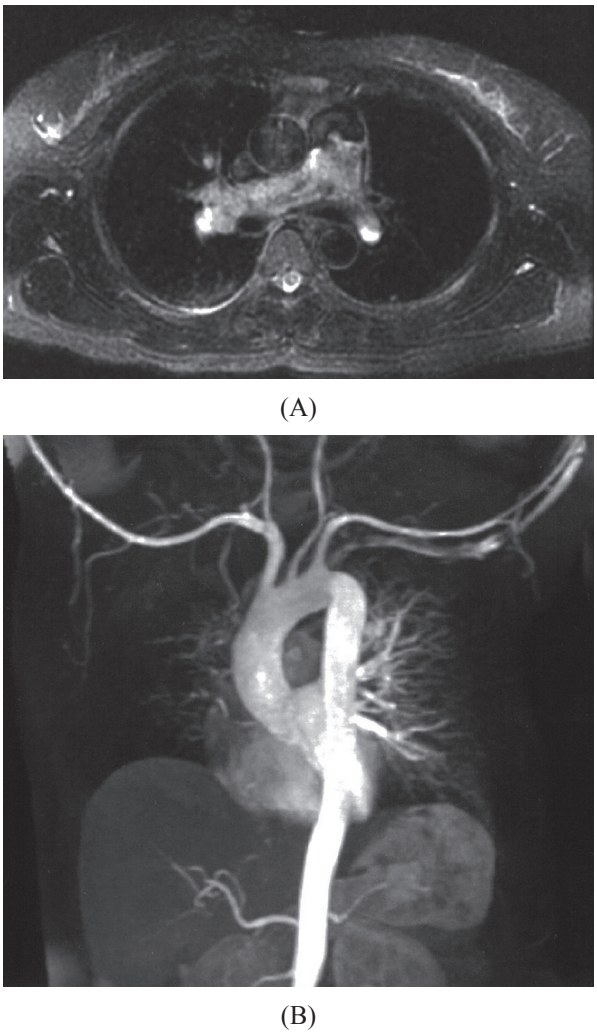


Fig. 1. Chest X-ray posterioanterior view showing an engorged right pulmonary trunk, decreased right-side lung markings, and a retrocardial nodule at the LLL field.

a smoking and drinking history. Three months prior to arrival, exertional dyspnea had gradually developed, and was alleviated partially by rest. She also had blood-tinged sputum initially, but it later resolved spontaneously. She did not have orthopnea or leg edema. Intermittent chest tightness occurred 1 month prior to arrival; it was not related to exertion but improved after the use of analgesics. During the prior 3 months, she also had non-productive cough and weight loss of 7 kg. Due to the persistent symptoms, chest X-ray exam was performed and revealed a nodular lesion at the left lower lobe (LLL) of the lung, together with a prominent right pulmonary trunk and decreased lung markings on the right side (Figure 1). Magnetic resonance imaging (MRI) showed a large "filling defect" within the pulmonary trunk and a perfusion defect of the right pulmonary vessels (Figure 2A,B), compatible with pulmonary thromboembolic disease. Laboratory data revealed an elevated D-dimer value of 1.93 ug/ml (reference range <0.55 ug/ml). Under the



(A)

(B)

Fig. 2. A. Chest MRI showed a "filling defect" at the pulmonary trunk. B. Chest MRA showed a perfusion defect of the right pulmonary vessels.

diagnosis of thromboembolic disease, treatment with low molecular weight heparin and enoxaparin 60 mg subcutaneously every 12 hours was initiated. Echocardiography showed right ventricle and right atrium dilatation with a high pressure gradient across the tricuspid valve (tricuspid regurgitation peak gradient = 85 mmHg). Workups searching for the cause of pulmonary thromboembolism, including lower-extremity duplex sonography, lupus anticoagulant titer, antithrombin III level, and protein C

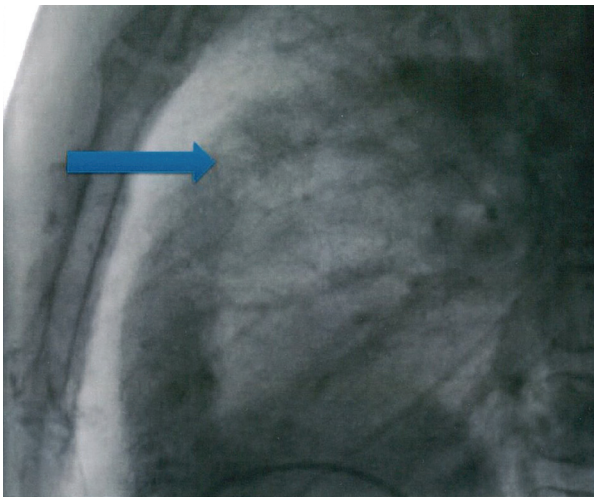
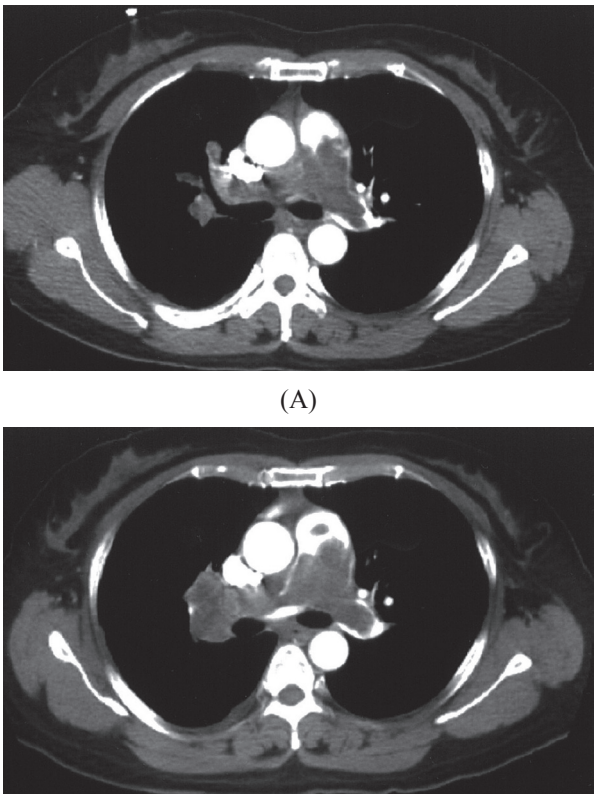


Fig. 3. Right-side catheterization revealed a protruding mass at the right pulmonary artery (arrow).



(A)

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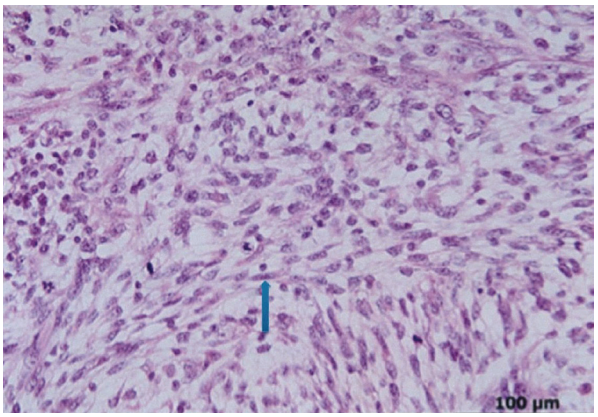
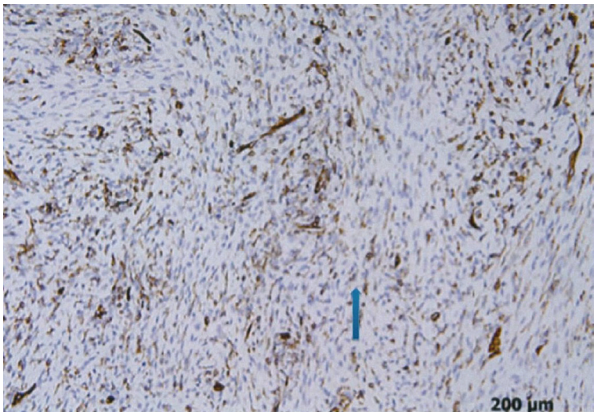
Fig. 4. A. Chest CT with contrast showed a "filling defect" at the pulmonary trunk. B. Three weeks after anticoagulation treatment, chest CT with contrast showed a mildly progressed "filling defect" at the pulmonary trunk.

and S levels, did not detect abnormal findings suggestive of deep vein thrombosis, connective tissue disease, or hypercoagulable disorders. For malignancy workups, both computed tomography (CT)-guided fine needle aspiration of the LLL nodule and endoluminal biopsy of the pulmonary trunk tumor through right-sided catheterization (Figure 3) revealed no malignant cells. Brain CT and whole body bone scan revealed no metastatic lesion.

However, her symptoms progressed even after a 3-week course of anticoagulation therapy. The follow-up chest CT showed a progressive "filling defect" (Figure 4A,B), multiple nodules in both lungs, and an increase in the size of the LLL mass. CT-guided lung nodule biopsy was considered, but the procedure was deemed too risky by the radiology staff due to the hypervascularity of the tumor and associated great vessel. After discussion with the chest surgeon, the patient underwent pulmonary trunk tumor excision and wedge resection of the right middle lobe (RML) of the lung. Pathologic studies of the pulmonary artery tumor showed a spindle cell malignancy characterized by infiltration of poorly differentiated ovoid to stellate-shaped tumor cells with a scanty to moderate amount of eosinophilic cytoplasm, nuclear atypism, brisk mitosis (15-20/10HPF), a short fascicular whirling growth pattern and multifocal necrosis with neutrophilic abscess formation in a myxoid stroma. Rich stromal vascularity with numerous branching vascular arcades, which divided the tumor cells into small lobules or nests, was noted. This tumor was focally close to the intima of the pulmonary artery. These tumor cells are focally positive for CD31 and rarely positive for CD34 (Figure 5A,B). The cells are mostly negative for cytokeratin,



(A)



(B)

Fig. 5. A. Pathology shows a spindle cell malignancy characterized by infiltration of poorly differentiated ovoid to stellate-shaped tumor cells with eosinophilic cytoplasm, nuclear atypism, and brisk mitosis (15-20/10HPF)(H&E; original magnification × 400). B. Tumor cells were focally positive for CD31 stain. (original magnification × 100)

S-100, CLA, desmin and smooth muscle actin. Similar findings were also found in the RML nodule, suggestive of metastatic sarcoma. The pathologic diagnosis of poorly differentiated intima sarcoma of the pulmonary artery with lung metastasis was then confirmed.

The patient received radiotherapy to the residual PAS tumor with a total of 2,500 cGy in 5 fractions from July 20, 2009 to July 24, 2009. Systemic chemotherapy with an IE protocol (ifosfamide 3 g/m^2 on Day 1 to Day 3; etoposide 75 mg/m^2 on Day 1 to Day 3) was given from July 27, 2009 to April 23, 2010, for a total of 12 courses. Despite the tumors appearing to respond slightly to treatment initially, the disease progressed. Even with aggressive chemotherapy, the patient finally passed away 1 year later.

Discussion

PAS is a rare tumor of the cardiovascular system, and only a few cases have been reported worldwide. The tumors tend to be rapid-growing with a very poor prognosis. Intrathoracic metastases have been reported in 50% of patients and distant metastases in 16% [6]. The age at presentation is between 45 and 55 years, with a female to male ratio of 2:1. Patients with PAS might present with a variety of cardiopulmonary symptoms, including dyspnea, cough, intermittent hemoptysis and chest pain. Because of its rarity and insidious growth, PAS is usually mistakenly diagnosed as pulmonary thromboembolism [3]. However, fever, weight loss, anemia [4], and digital clubbing [5] may be the clues for a correct diagnosis. As an initial correct diagnosis is difficult, the typical duration of symptoms before a correct diagnosis is made is 3 to 12 months. Without surgical intervention, median survival was only 1.5 months [7,12], and with surgical resection, less than half of the patients survived longer than 12 months [6].

PAS can be evaluated by CT/CT angiography scan, positron-emission tomography scan, MRI and MR angiography (MRA), and transesophageal echocardiography. The CT scan findings are nonspecific and usually are indistinguishable from thromboembolic disease of the pulmonary vessels. However, characteristic CT findings differentiating PAS from pulmonary thromboembolic diseases include contiguous heterogeneous attenuation of the mass

occupying the entire luminal diameter of the proximal or main pulmonary artery, vascular distention from tumor growth, and extravascular spread of the lesion [8]. MRI is more specific for identifying PAS because the tumor enhances with gadolinium contrast more than the thrombus [16]. Although the above diagnostic tools may be useful for differentiating tumors from thrombi [9-11], a definite diagnosis can be made only by tissue proof. Physicians should look for concomitant lung nodules, which were also found in our case, mediastinal or hilar lymph adenopathy or extravascular extension, all of which indicate a malignant etiology of the lesion rather than thromboembolic disease.

With regard to the subclassifications of PAS [2,13-14] (Table 1), Moran and colleagues [13] reported that leiomyosarcoma was associated with longer survival, and rhabdomyosarcoma had a poor prognosis. Routine immunohistochemical staining studies of the tumor cells, including cytokeratin, desmin, vimentin, and actin [13,15], are recommended for better subclassification. CD31, CD34, and Fli-1 are commonly used endothelial markers.

Chemotherapy, radiation therapy, and surgical intervention are treatment choices for malignant disease. Criteria for operation include adequate cardiopulmonary reserve, no disease outside the chest, and adequate residual lung function if lobectomy or even pneumonectomy is needed. Contrast enhanced CT scanning is needed for further surveillance of the disease. Those with an intraluminal filling defect need subsequent gadolinium-enhanced MRI to differentiate tumor from thrombus.

In conclusion, PAS should be considered in the differential diagnosis of patients with a presumptive diagnosis of pulmonary thromboembolism if a) there is a lack of response to anticoagulation b) no risk factors for pulmonary thrombi/emboli such as deep vein thrombosis can be detected and c) pulmonary nodules/metastases exist.

Table 1. Subclassifications of Primary Pulmonary Artery Sarcomas*

Undifferentiated
Rhabdomyosarcoma
Osteogenic sarcoma
Angiosarcoma
Fibrosarcoma
Malignant mesenchymoma
Myxosarcoma
Chondrosarcoma
Osteosarcoma
Malignant fibrous histiocytoma
Liposarcoma
Unclassified leiomyosarcoma

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類似肺動脈血栓栓塞性疾病的原發性肺動脈肉瘤：一個病例報告

陳志誠　鄭之勛

原發性肺動脈肉瘤是很罕見的疾病，病人經常有像肺血栓栓塞性疾病的典型表現。我們報告了一位50歲女姓，她的表現是長達三個月期間的運動喘及胸悶。胸部X光檢查發現右肺動脈幹變得很鼓且在左下肺葉有一顆結節。核磁共振掃描發現在兩側肺動脈幹有所謂“填充缺損”。臨床診斷為肺動脈血栓栓塞症，於是她開始使用抗凝血劑治療。追蹤時，其症狀及影像皆惡化。肺動脈的病灶經開刀後病理診斷為分化不良性的肺動脈肉瘤。然而即使經過開刀、電療及化療，病人仍在診斷的一年多後死亡。我們的案例闡明了：當病人沒有血栓栓塞症的危險因子，對於抗凝血劑治療沒有反應而且合併有肺結節者，肺動脈栓塞症以外的疾病像是肺動脈肉瘤一定要列入鑑別診斷。*(胸腔醫學* ***2018; 33: 230-236)***

關鍵詞：肺動脈肉瘤，肺動脈血栓栓塞症，肺動脈血栓栓塞性疾病

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Undiagnosed Pulmonary Sequestration Associated with Pleomorphic Carcinoma of the Lung: Potential Risk in Pulmonary Surgery

Tung-Ming Tsai*, Cheng-Hung How*, Yao-Hui Tseng**, Jin-Shing Chen*

Lung cancer associated with pulmonary sequestration is extremely rare; undiagnosed pulmonary sequestration with an aberrant feeding artery may be risky during surgery for lung cancer. A 43-year-old man was diagnosed with large-cell pleomorphic carcinoma of the left upper lung lobe associated with a pre-existing opacity at the left lower lung lobe. During surgery for lung cancer, it became clear that the opacity was actually a pulmonary sequestration with an engorged, aberrant feeding artery hidden in the inferior pulmonary ligament. Retrospective review of the chest computed tomography revealed that the sequestration was associated with pleural adhesions and that the feeding artery originated from the abdominal aorta, which made preoperative diagnosis of the pulmonary sequestration difficult. We suggest that during lung cancer surgery, surgeons should be aware of the possibility of undiagnosed pulmonary sequestration, to prevent massive bleeding and catastrophic complications. ***(Thorac Med 2018; 33: 237-241)***

Key words: lung cancer, pleomorphic carcinoma, pulmonary sequestration

Introduction

Pleomorphic carcinoma of the lung is a rare but aggressive malignant pulmonary disease [1]. Pulmonary sequestration is a congenital malformation, characterized by a systemic arterial blood supply and pulmonary tissues that are not directly connected to the bronchial tree. Surgery for pulmonary sequestration may cause massive bleeding if the systemic feeding artery is not carefully identified. To our knowledge, pleomorphic carcinoma of the lung associated with pulmonary sequestration has never been reported. We present a case of pleomorphic carcinoma of the lung with undiagnosed pulmonary sequestration that nearly caused massive bleeding during the surgery.

Case Report

A 43-year-old male heavy smoker presenting with a tumor in the left lung was hospital-

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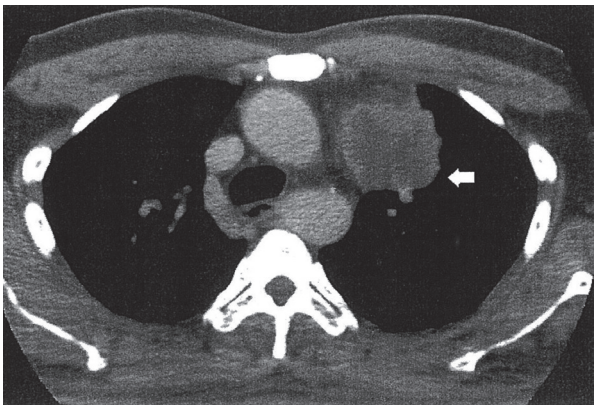
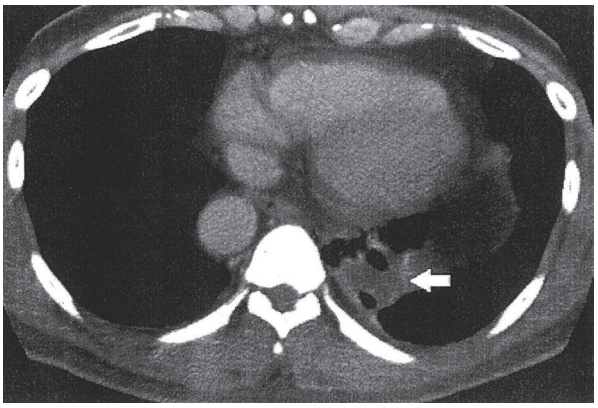
ized in May 2010. Physical examination and blood tests both yielded normal results. Chest computed tomography (CT) showed a 5.3-cm mass in the anterior segment of the left upper lobe of the lung with invasion into the upper mediastinum (Figure 1A). In addition, pulmonary atelectasis was found in the left lower lobe (Figure 1B). Echo-guided biopsy of the left upper lung tumor revealed a non-small-cell lung carcinoma. The 18-flouorodeoxyglucose (^{18}FDG) positron emission tomography (PET) showed intense FDG uptake in the left upper lobe mass, with no significant FDG uptake in the left lower lung opacity. The patient was diagnosed with locally advanced lung cancer with coexisting organizing pneumonia, so he underwent 3 cycles of neoadjuvant chemotherapy with cisplatin and docetaxel. After chemotherapy, the follow-up chest CT showed the tumor size had decreased to 4.6 cm in diameter and the patchy opacity remained unchanged.



(A)



(B)

Fig. 1. Chest computed tomography of the patient. (A) A 5.3-cm soft tissue mass (arrow) in the anterior segment of the left upper lung lobe. The tumor had invaded the ipsilateral upper mediastinum. (B) A patchy opacity (arrow) with atelectasis in the left lower lobe of the lung.

Posterolateral thoracotomy was performed in September 2010. Severe pleural adhesions were noted intraoperatively. A solid mass was found in the left upper lobe of the lung, with invasion into the left lobe of the thymus. Left upper lobectomy, partial thymectomy, and mediastinal lymph node dissection were performed. The adhesions between the left lower lung lobe and the parietal pleura, including the mediastinal pleura, were separated using electrocautery to facilitate the obliteration of the remaining pleural space. Further, a pulsating mass was felt incidentally at the lower end of the inferior pulmonary ligament. After careful dissection, an aberrant feeding artery, with a diameter of 1 cm and connected to the lower lung patch, was identified. The artery was then transected using a vascular staple, and the associated pulmonary lesion was resected. Retrospective review of the chest CT showed that the feeding artery originated from the abdominal aorta (Figure 2). Pathological exams indicated nests of residual pleomorphic carcinoma with significant post-chemotherapeutic effects in the left upper lobe and pulmonary sequestration in the left lower lobe. There was no malignancy in the lobar and mediastinal lymph nodes. The patient was uneventfully discharged 11 days after the operation; tumor recurrence and pulmonary infection were not found 4 months after surgery. Although there was no evidence of brain metastasis in the pre-operative serial brain CT

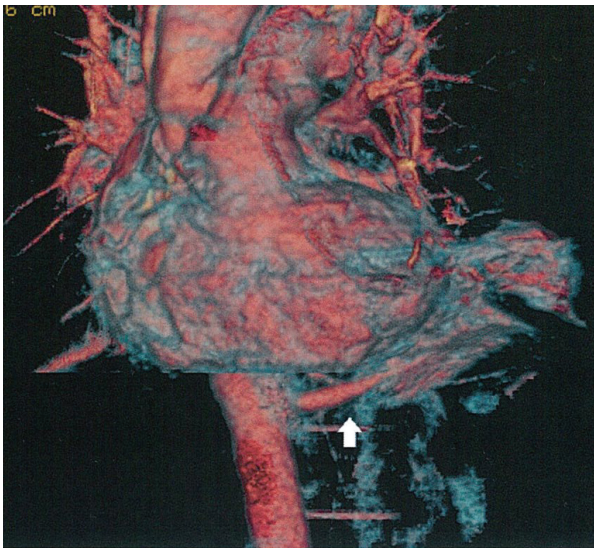


Fig. 2. Three-dimensional reconstruction showed that the feeding artery (arrow) originated from the abdominal aorta in association with the left basal lung opacity.

scan, he developed brain metastasis 5 months after the operation.

Discussion

Pulmonary pleomorphic carcinoma is a very rare but aggressive malignant disease, accounting for less than 2% of non-small-cell lung cancers [2-3]. Complete surgical resection is recommended since there is no effective chemotherapeutic regimen. Until now, only 8 cases of lung cancer associated with pulmonary sequestration have been reported, including 4 cases of squamous cell carcinoma, 3 cases of adenocarcinoma, and 1 case of carcinoid tumor [4,7]. This reported case is the first to describe the coexistence of pulmonary pleomorphic carcinoma and sequestration. The relationship between lung cancer and pulmonary sequestration is still unknown.

Pulmonary sequestration generally is diagnosed preoperatively with histories of recurrent episodes of pneumonia, chest pain, hemoptysis, or shortness of breath [5]. A definite preoperative diagnosis of pulmonary sequestration is made by the presence of an abnormal feeding artery originating from the descending aorta, noted by chest CT or magnetic resonance angiography. In our present case, the patient was asymptomatic, and enhanced thoracic CT did not show typical findings. We were completely unaware of the presence of pulmonary sequestration within the left lower lobe of the lung until we started to divide the left lower pulmonary ligament. It is well accepted that the most difficult challenge in the resection of pulmonary sequestration is the identification of the aberrant artery, which is usually hidden within the inferior pulmonary ligament. Because of inflammatory changes caused by recurrent infections, it is sometimes difficult to distinguish the aberrant artery from surrounding scarred tissues. The risk of surgical injury to an aberrant artery is very high, since usually the blood supply systemically originates from the thoracic or abdominal aorta. Kestenholz *et al*. [6] reported that even when dissection was carefully performed, vascular injury still occurred in 1 patient in a series of 14 patients undergoing pulmonary resection. In spite of modern imaging techniques, there is still a possibility that pulmonary sequestration may remain undiagnosed. Therefore, we believe that the inferior pulmonary ligament should be dissected very carefully, because of this possibility and the potential risk of systemic vascular injury.

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未確診的游離肺和多形性肺癌的關聯性：胸腔手術潛在的危險性

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肺癌合併游離肺是一個極為罕見的疾病。肺癌手術中，術前未診斷的游離肺因為有著源自於主動脈的迷動脈，將使手術的風險大大提昇。一位四十三歲的男性，經診斷為左上肺大細胞多形性癌。術前發現左下肺葉有一陰影。肺癌手術中，意外發現此陰影為一游離肺，合併有一個巨大的迷動脈。追朔評估發現，電腦斷層顯示，此一游離肺躲藏在肺部沾粘之間，同時迷動脈起源自腹部主動脈。這些因素使得術前診斷游離肺的困難度大大增加。我們建議肺癌手術中，術者應該提高警覺，注意任何術前未診斷的游離肺存在的可能性，以避免產生大量出血等合併症的產生。*(胸腔醫學 **2018; 33: 237-241**)*

關鍵詞：肺癌，多形性癌，游離肺

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Double Primary Pulmonary Adenocarcinomas with Different Morphological Subtypes and Different Anaplastic Lymphoma Kinase Expression in a 47-Year-Old Never-Smoking Woman – A Case Report

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Multiple primary lung cancer (MPLC) is a potentially curable malignancy. It is difficult to diagnose accurately, since the diagnosis depends on a histologic presentation of lung cancer, especially when these intrapulmonary nodules share the same histologic type or similar subtypes. Molecular diagnosis, such as epidermal growth factor gene mutation status, has been reported to enhance the diagnosis of MPLC. Since anaplastic lymphoma kinase (ALK) gene rearrangement is also a critical target in non-small cell lung cancer, it might be a potential tool in aiding the MPLC diagnosis. Here, we reported a 47-year-old never-smoking woman who had 2 peripheral pulmonary nodules of similar size at her right lower lobe and left upper lobe. The patient underwent a bilateral video-assisted thoracic surgery wedge resection, and pathologic diagnosis showed the 2 nodules were adenocarcinomas, but with different pathologic morphological features. Different ALK gene rearrangement expression types were found using ALK immunohistochemical staining, and further confirmed through use of the fluorescence in situ hybridization method. The 2 nodules were diagnosed finally as a double primary stage I lung cancer instead of an intrapulmonary metastasis of a primary lung cancer. This is the first case report of a possible role for ALK expression in the diagnosis of MPLC. We share this rare case and present a literature review. ***(Thorac Med 2018; 33: 242-248)***

Key words: multiple primary lung cancer, ALK (anaplastic lymphoma kinase)

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide and in Taiwan [1]. Despite continued improvements in diagnosis and therapy, the prognosis of lung cancer patients remains poor. Only 15% of patients present with localized disease that is amenable to resection, and many patients with lung cancer are diagnosed at advanced stages. Multiple primary lung cancer (MPLC) is a potentially curable malignancy, and an aggressive surgical approach should be safe and justified in most patients with MPLC [2]. However, it is difficult to make an accurate diagnosis solely based on morphology. MPLC is easily misdiagnosed as an intrapulmonary metastatic cancer, and therefore patients receive palliative therapy instead of an aggressive curative operation. Molecular analysis has recently become one of the most important diagnostic processes for lung cancer, especially adenocarcinoma, and molecular expression might be of potential help in making a diagnosis of MPLC [3]. Takuwa *et al*. reported a diagnosis of synchronous primary lung adenocarcinomas based on epidermal growth factor receptor (EGFR) gene status [4]. Aside from EGFR mutation, anaplastic lymphoma kinase (ALK) gene rearrangement could be found in around 4-5% of patients with lung cancer [5] and is also a critical target that is as important as EGFR mutation in lung cancer therapy [6]. Till now, no published article has explored whether ALK rearrangement has a role in the diagnosis of MPLC. Here, we present the case of a 47-year-old female with 2 pulmonary nodules that were finally diagnosed as double primary lung cancers based on the different morphological subtypes and different ALK expression. We share this rare case report and present a literature review.

Case Report

A 47-year-old never-smoking female without systemic disease visited our clinic for anterior chest wall pain lasting 2 weeks. No body weight loss, fever, cough or shortness of breath was noted. A physical examination revealed clear bilateral breathing sounds and no tenderness of the chest wall. Her vital signs, white blood cell count and C-reactive protein level were all within normal limits. A chest X-ray revealed 2 pulmonary nodules, both around 1 cm, in her left upper lung field and right upper lung field, respectively. Her serum carcinoembryonic antigen (CEA) value was 1.84 ng/ml. Further chest computer tomography (CT) (Figure 1) revealed 2 peripheral isolated pulmonary nodules, around 1 cm in size. One was in the superior segment of the right lower lobe and the other was in the left upper lobe of the lung. Neither visible mediastinal lymph node lesion nor any extra-pulmonary metastatic lesion was detected. Subsequent whole body bone scan exam and brain CT also revealed no evidence of distant metastases. In order to obtain pathologic evidence, the patient underwent a bilateral video-assisted thoracic surgery (VATS) wedge resection of the right lower lobe and left upper lobe nodules. The right lower lobe nodule was 1.0×0.5×0.5 cm in size and the left upper lobe nodule was 1.0×0.9×0.6 cm. Tumor necrosis was absent in both nodules. Lymphocytic infiltration was minimal, and without angiolymphatic or perineural invasion. The wedge resection margin had no tumor involvement. Morphology revealed both nodules were acinar-predominant adenocarcinomas but with different pathologic morphology. The right lower lobe tumor was

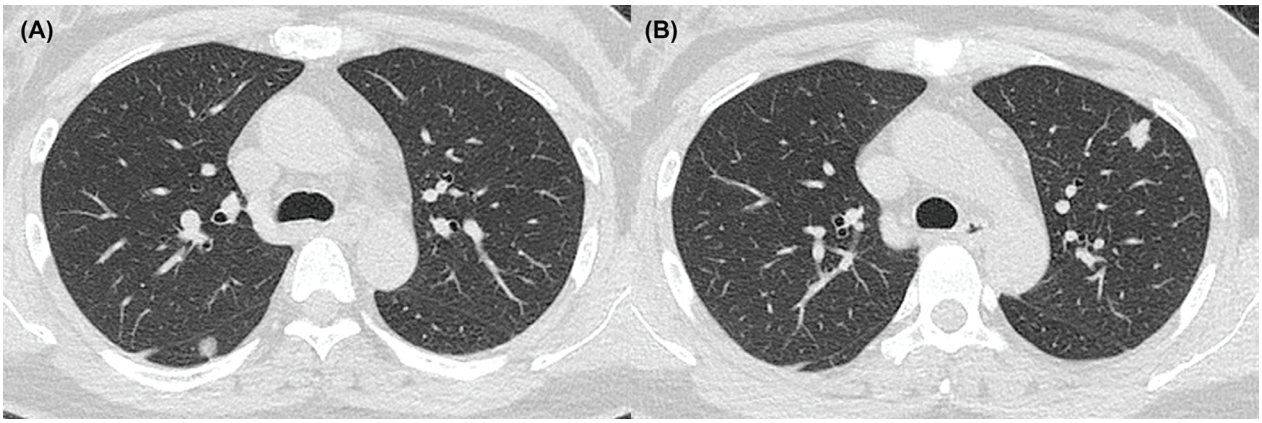

Fig. 1. Computed tomography (CT) revealed 2 peripheral isolated pulmonary nodules, each around 1 cm in diameter. (A) One was in the superior segment of the right lower lobe and (B) the other was in the left upper lobe of the lung.

composed of acinar (50%), micropapillary (5%) and lepidic (45%) growth patterns with the presence of signet ring cells and extracellular mucin (Figure 2A), and the left upper lobe tumor was composed of acinar (60%), micropapillary (20%) and papillary (20%) growth patterns without signet ring cells (Figure 2B). Both of the nodules had positive expression of cytokeratin 7 (CK-7) and thyroid transcription factor-1 (TTF-1) statin, which indicated they were of pulmonary origin. Epidermal growth factor receptor (EGFR) gene mutation analysis of the 2 nodules for exon 18-22 and the k-ras gene in codon 12 were both negative. To our surprise, immunohistochemical (IHC) staining (using 5A4 clone, Leica Biosystem) for ALK gene rearrangement analysis showed different results. The right lower lobe nodule had strong

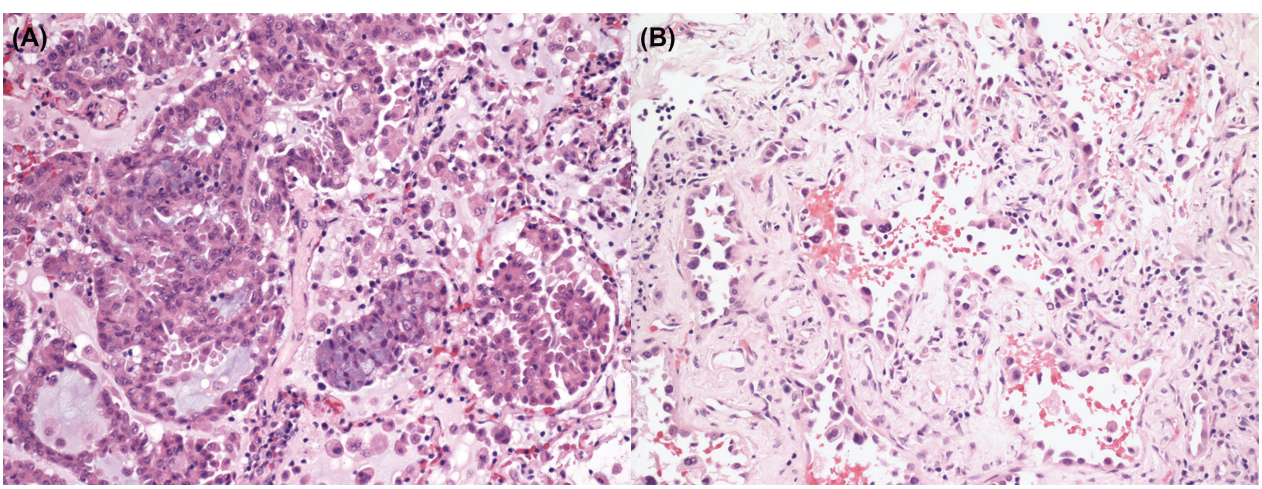

Fig. 2. Histopathological morphology of nodules in the right lower lobe and left upper lobe. Both were acinar-predominant adenocarcinomas but had different pathologic morphologies. (A) Right lower lobe tumor expressed acinar and micropapillary patterns with acinar predominance, with the presence of signet ring cells and extracellular mucin (H&E 200x). (B) Left upper lobe tumor expressed an acinar-predominant growth pattern without signet ring cells (H&E 200x).

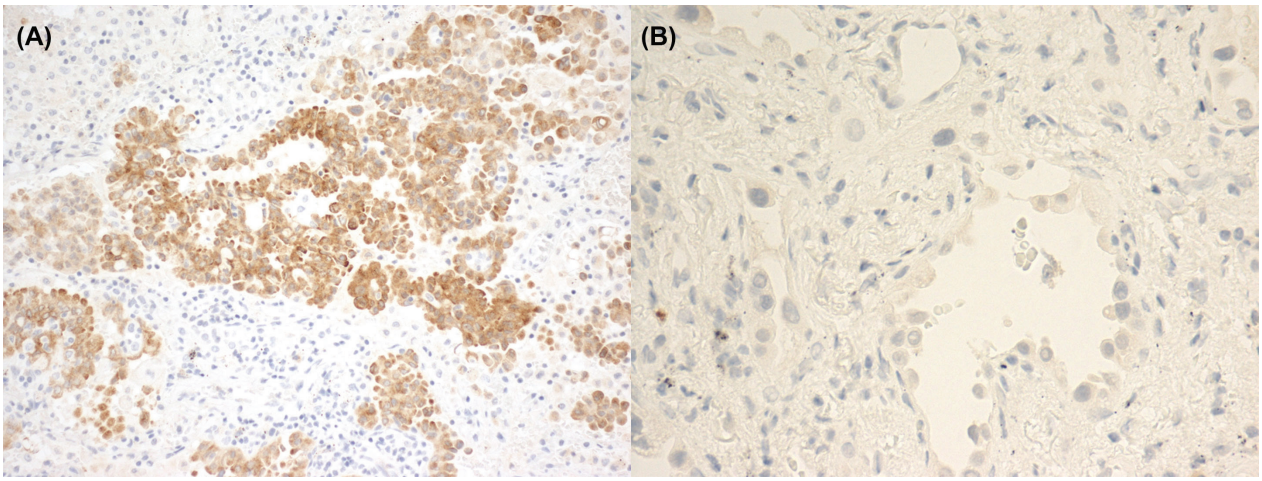

Fig. 3. ALK immunohistochemical stain showed (A) strong positive in the nodule from the right lower lobe (200X) and (B) negative in the nodule from the left upper lobe (400x).

positive expression for ALK rearrangement (Figure 3A), but the left upper lobe nodule had negative expression (Figure 3B). Final confirmation by fluorescence in situ hybridization (FISH) using the Vysis break-apart probe kit showed the same results. The results indicated that each of the 2 lung adenocarcinomas in this patient had a different pathogenesis, which was compatible with a diagnosis of double primary lung cancers. Therefore, the development of 2 separate stage I primary lung adenocarcinomas, rather than a stage IV (lung to lung metastasis) lung cancer, should be seriously considered in this situation. A case report such as this has never been documented, according to a Pubmed search.

Discussion

We successfully diagnosed a rare case of double primary lung cancers based on the pathological and molecular evidence. Distinct histological growth patterns with or without signet ring cells suggested the 2 resected pulmonary tumors may not be of the same origin, and further, ALK expression supported the existence of different origins for the 2 tumors. Different molecular expressions in resected tumors, such as in this case, could make the diagnosis of MPLC more solid. This is the first case report to propose that the result of ALK rearrangement has the potential to be a diagnostic tool for MPLC.

The term "multiple primary lung cancers" was proposed by Martini and Melamed [7] and modified by the American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines. The actual frequency of MPLC is unknown, but it has been reported to vary from 0.8% to 14.5%, depending on the different enrollment methods used, such as cancer registry, autopsy series, or surgical series [8].

MPLC includes synchronous and metachronous types. "Synchronous type" of MPLC means more than 1 pulmonary nodule at the same time. The criteria include that both lesions are malignant, they must arise independently in the lung, and the second malignant lesion must not represent a metastasis from the first lung lesion, i.e., it must have a different histology or origin from a separate focus of carcinoma in

situ, or the same histology but anatomically distinct, without involvement of the mediastinum and without systemic metastases. On the other hand, "metachronous MPLC" means the second cancer is detected sometime after the primary lesion. Since homogenous histological types of MPLC are common, it is difficult to differentiate a true solitary pulmonary nodule from metastatic or recurrent disease, especially in patients with synchronous lung cancers. The common histologic subtypes of lung cancer include adenocarcinoma, squamous cell carcinoma, and large cell and small cell lung cancer. Adenocarcinoma has been reported to be the most common histologic subtype, and has shown increasing trends in all non-small cell lung cancers (NSCLC) [9]. Due to the high prevalence, clinical scenarios such as the misdiagnosis of 2 or more adenocarcinomas that develop in a patient as metastatic lung cancer is common. Subtype morphology, such as lepidic, papillary, acinar pattern or mixed type, has been regarded as a distinct tool for diagnosing MPLC, but its usefulness is limited [10]. Therefore, new methods for diagnosing multiple primary lung adenocarcinoma are urgently needed.

Both IHC staining and molecular analysis have been promoted as useful tools in the diagnosis of MPLC. Shimizu *et al*. reported the use of p53 with loss of heterozygosity (LOH) [11], and Chen *et al*. used p53, p16, p27 and c-erbB2 [12] to obtain an increase in both sensitivity and specificity for differentiating the diagnosis of MPLC from metastatic cancers, though assays for molecular analysis are not popular in clinical practice. EGFR mutation and ALK rearrangement have unique expressions in lung cancer, and in the era of molecular genetic characteristics of NSCLC, the National Comprehensive Cancer Network (NCCN) suggests physicians routinely check for EGFR mutation and ALK rearrangement in primary lung adenocarcinoma [13], and that the 2 molecular markers may represent useful tools in the diagnosis of MPLC. Since EGFR mutation is an oncogenic mutation that occurs through activating tyrosine kinase activity, which plays an important role in tumor development and can predict the response of tyrosine kinase inhibitor (TKI) treatment [14], it has been reported that diagnosis of synchronous primary lung adenocarcinomas can be made mainly based on EGFR gene status [4]. The prevalence of ALK rearrangement is about 4-7% [5,15], and is more common in never or light smokers than in heavy smokers [5]. Although not well documented in Asian populations, it has been reported that Caucasian ALK fusion oncogene-positive adenocarcinoma patients are more likely to have signet ring cells than ALK-negative patients [16].

Till now, the US Food and Drug Administration (FDA) has approved only the Vysis break-apart probe kit (Abbott Molecular, Des Plaines, Ill) for positive ALK rearrangement diagnosis by FISH [17]. Though IHC also has high sensitivity and specificity [18], it has been regarded as a screening tool. In our case, IHC showed strong positive ALK staining, which was confirmed by FISH, in 1 of the 2 dissected pulmonary nodules, and negative staining in the other. In addition, morphology of the 2 nodules was distinctly different. One of the pulmonary nodules had an acinar and micropapillary pattern with the presence of signet ring cells, and the other had acinar predominance with a mixed papillary pattern without signet ring cells. Taking the above together with pathologic and molecular evidence, double primary lung adenocarcinoma was diagnosed, and further observation and regular follow-up were suggested.

In conclusion, we presented a rare case of 2 pulmonary nodules with different morphological features and different ALK expression types. The 2 separate nodules were diagnosed as double primary pulmonary cancers. Molecular examinations such as ALK expression analysis might be potential diagnostic tools for MPLC in some patients.

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雙重原發性肺腺癌呈現不同之組織型態表現及不同間變性淋巴瘤激酶表現在一位 47 歲的非吸菸女性—案例報告

潘奕宏 * 楊志仁 *,****,***** 李瑞英 ** 林智鴻 *** 黃明賢 *,*****

雖然肺癌的預後仍然相當差，而多發性原發肺癌是有機會能治癒的，但臨床上往往難僅由肺癌之形態組織學來做出準確診斷，尤其是肺內腫瘤擁有相同的組織型或相似的組織亞型時。分子病理診斷，如表皮生長因子受體突變 (EGFR mutation) 狀況曾被報告過用以協助多發性原發性肺癌之診斷。鑑於間變性淋巴瘤激酶重組 (ALK rearrangement) 型態在非小細胞肺癌中亦是重要的治療標的，或許它也是潛在能協助多發性肺癌診斷的工具。在此我們報告一位 47 歲非吸菸女性有兩顆大小相似之週邊肺結節，一在右下肺而另一在左上肺。這位女性接受雙側胸腔內視鏡輔助切除術。病理檢查呈現此兩個腫瘤皆為肺腺癌但有不同之病理形態表現。有趣的是，免疫化學染色法下的間變性淋巴瘤激酶型態表現完全不同，且此結果也透過螢光原位雜交法 (FISH) 來驗證。最終此兩個腫瘤被診斷為雙重原發性肺癌，而非轉移性肺癌。迄今為止，尚未有文獻報告利用間變性淋巴瘤激酶之表現做為多發性原發性肺癌的診斷工具。我們在此分享此一案例並進行文獻回顧。*(胸腔醫學* ***2018; 33: 242-248)***

關鍵詞：多發性肺癌，間變性淋巴瘤激酶

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Primary Pulmonary Lymphoepithelioma-like Carcinoma Presenting with a Cavitary Nodule

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Pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare malignant tumor of the lung that is histopathologically similar to undifferentiated nasopharyngeal carcinoma. Pulmonary LELC presenting as a cavitary lung nodule is seldom reported in the literature. We reported a case of primary pulmonary LELC with a cavitary lung nodule, a rare primary lung cancer with a rare radiological presentation. The nodule was removed with video assisted thoracoscopic surgery. There was no tumor recurrence at the 1-year clinical follow-up. ***(Thorac Med 2018; 33: 249-253)***

Key words: lymphoepithelioma-like carcinoma, primary lung cancer, cavitary nodule

Introduction

Pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare malignant tumor of the lung that is histopathologically similar to undifferentiated nasopharyngeal carcinoma. It is a subtype of other and unclassified carcinoma according to the WHO classification [1]. Most of the reported cases were in Southeast Asia. In Asian patients, LELC is considered to be Epstein-Barr virus (EBV) related, with a better prognosis than other types of non-small cell lung cancer (NSCLC). Pulmonary LELC might present as lobulated or spiculated nodules, or with a non-specific radiological appearance. It has been seldom reported as a cavitary nodule in the literature. Here, we report a case of primary pulmonary LELC presenting with a cavitary lung nodule.

Case Report

A 41-year-old non-smoking housewife had an abnormal chest x-ray during a regular health examination. She denied having systemic disease, but her mother had a history of lung cancer. The patient had had a mild cough in recent months. Otherwise, there was no fever, chest pain or body weight loss. Chest radiography showed a nodular density at the right middle

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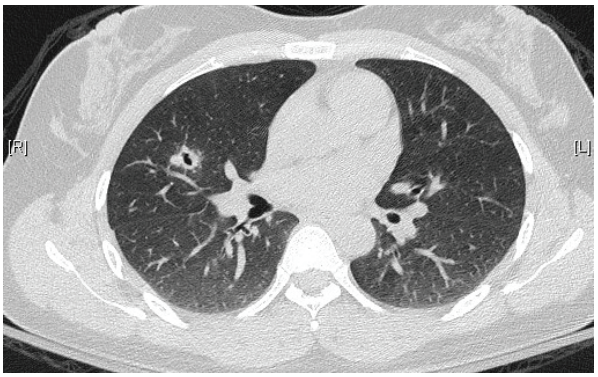
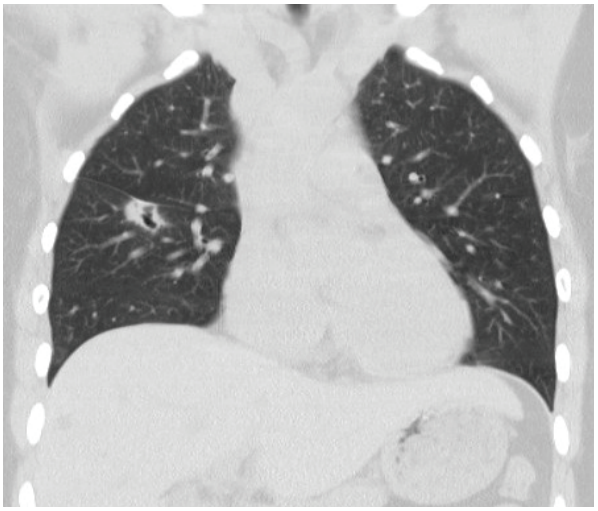


(A)



(B)

Fig. 1. CT revealed a 1.7-cm cavitary nodule at the right middle lung, with direct contact with a minor fissure.

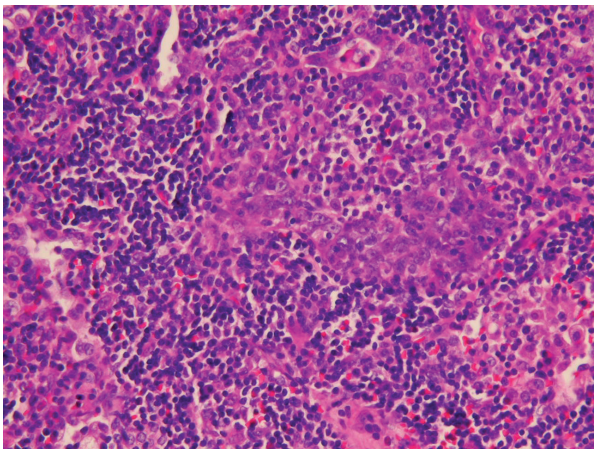


Fig. 2A. The tumor cells had large vesicular nuclei with prominent eosinophilic nucleoli.

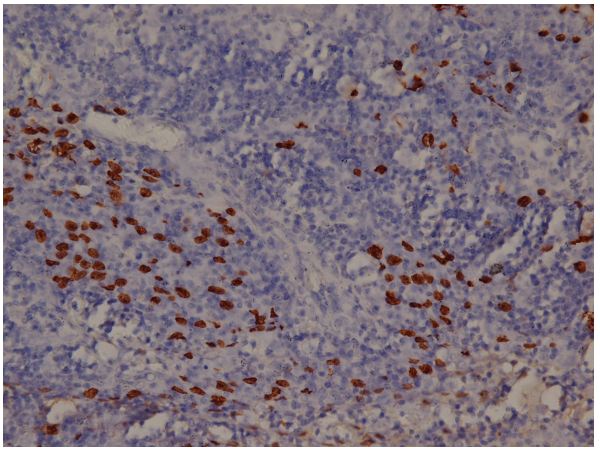


Fig. 2B. The presence of EBV in the epithelial tumor nuclei was detected by IHC stain of EBER-1.

lung. High-resolution computed tomography (CT) revealed a 1.7-cm spiculated nodule with an irregular border and an eccentric cavity at the right middle lung, with direct contact with minor fissure (Figure 1A,B). There was no other lung nodule or enlarged lymph node. Sputum acid-fast stains were negative and fungus culture grew no fungus. Carcinoembryonic antigen and squamous cell carcinoma (SCC) antigen were both within a normal range. Surgical lung biopsy by video-assisted thoracoscopic surgery was negative for malignancy, but atypical cell nests were found. The patient underwent right middle lobe segmentectomy due to suspicion of malignancy.

The lung tissue included a well-circumscribed tumor measuring 1.2×1.0×0.8 cm. Histological study revealed a nodular lesion composed of heavy infiltrates of lymphoid cells mixed with a few irregular shaped nests of pleomorphic cells (Figure 2A,B). Perivascular infiltrates without definite vascular permeation were noted. The tumor also showed foreign

body reaction, including multinucleated giant cells and cholesterol clefts. No pleural tissue was involved in the tumor. Immunohistochemical (IHC) study reported positive reactivity for BCL-2 and LMP-1, but negative reactivity for TTF-1, CK7, and CK20. The final histopathological study suggested LELC.

The EBV capsid antibody was positive (EB-VCA IgG >750.0 U/mL). Nasopharyngoscopy had excluded a nasopharyngeal lesion. Since the positron emission tomography scan for complete staging revealed multiple supradiaphragmatic lymph node lesions, the patient underwent right middle lobe lobectomy with radical lymph node dissection. There was no residual tumor, but a necrotic nodule surrounded by chronic inflammatory cells and fibrosis was seen. All the lymph nodes were free of tumor cells. At the 1-year follow up, there was no evidence of recurrence.

Discussion

Primary pulmonary LELC was first reported in 1987 [2]. It is classified by the WHO as a subtype of other and unclassified carcinoma of the lung. The histological morphology is similar to that of undifferentiated nasopharyngeal carcinoma [3]. Fewer than 300 cases of this rare malignant tumor have been reported during the past 25 years [4]. The incidence rate was 0.4~0.9% of primary lung cancers in previous reports [5-6]. Most cases were from Southeast Asia, and were closely related to EBV infection [7].

Primary pulmonary LELC more commonly presents with cough alone, with hemoptysis, or is incidentally found without symptoms [8]. Unlike other NSCLC, which has a strong relationship with smoking and is male predominant, primary pulmonary LELC has little relation to cigarette smoking and has no specific gender predilection [5]. Patients with primary pulmonary LELC usually have a better prognosis. The 2-year and 5-year survival rates are 79~81% and 51~53.5 %, respectively [6,9]. Metastasis is less frequently seen [10].

Few published articles have reported the characteristics of primary pulmonary LELC on CT images. Previous reports have suggested that the tumor has a non-specific radiologic appearance in the earlier stage, and tends to have a larger, centrally located tumor, with smooth margins, vascular encasement and peribronchovascular nodal spread in the later stage [3,8,11-12]. However, others studies have reported the lesions presented with lobulated and spiculated nodules in the peripheral areas and had direct contact with the adjacent pleural space, and sometimes had lymphadenopathy [5]. Pulmonary LELC presenting as a cavitary nodule is rarely seen in the literature.

In this report, our patient presented with cough, and the EBV antibody was positive, similar to cases previously reported [8]. The tumor was in an early stage with CT images showing a spiculated nodule with an eccentric cavity in a peripheral location and contact with the adjacent pleura. Among 41 patients reported by Ma and 22 reported by Mo, only 5 were recorded as having small cavities [5,12]. Another case report described a rare presentation with a thin-walled cavity [13]. In these reports, the characteristics of the cavitary lesions were not described in detail. Cavitary nodules in the lung may have a differential diagnosis that includes an infection like tuberculosis, lung abscess and a malignant tumor like SCC. LELC of the lung presenting with a cavity is less commonly reported, but should also be kept in mind. Dis-

tinguishing primary from metastatic LELC is difficult, so careful examination of the nasopharyngeal region should be carried out before the diagnosis of primary LELC of the lung is made.

Conclusion

To date, only a few reports have focused on the imaging presentation of pulmonary LELC. But, both large tumors with a central location and smooth margins, and peripheral tumors with direct pleural contact have been reported. In the case we reported, a cavitary pulmonary nodule was the initial presentation of a primary pulmonary LELC - this is, a rare presentation of a rare lung cancer. Although this is a rare malignant lung tumor, it should be considered in Asian patients, especially in younger non-smoking patients with solitary nodules or masses.

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以開洞結節表現的原發性肺部類淋巴上皮癌－病例報告

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洪明賜 *,**** 蔡熒煌 *,**

原發性肺部類淋巴上皮癌是一種形態學上類似未分化的鼻咽癌的罕見肺部腫瘤。好發在亞洲地區且被認為與 EB 病毒感染有關。相較於其他非小細胞肺癌預後較好。文中我們報告一位 41 歲女性在身體健康檢查中偶然發現右中肺開洞性結節，病灶經由胸腔內視鏡輔助手術切除，證實是原發性肺部類淋巴上皮癌。術後追蹤一年未發現腫瘤復發。*(胸腔醫學* ***2018; 33: 249-253)***

關鍵詞：肺部類淋巴上皮癌肺癌，原發性肺癌，開洞

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Near-Fatal Air Travel after Diving: A Case of Impending Tension Pneumothorax on an International Flight

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Pulmonary barotrauma and decompression sickness are serious complications of scuba diving, caused by an inappropriate ascent. For those diving abroad, a strict surface interval requirement for flying after diving has been recommended in the U.S. Navy Diving Manual. We herein report a rare case, that of an experienced scuba diver who had severe dyspnea on an international flight home after a diving vacation abroad. Repeated ambient pressure change during 2 flight transfers led a diving complication becoming an impending tension pneumothorax at the airport terminal. The patient recovered well after tube thoracotomy and blebectomy. ***(Thorac Med 2018; 33: 254-260)***

Key words: flying after diving, barotrauma, pneumothorax

Introduction

Pulmonary barotrauma (PBT) is the second leading cause of death among scuba divers, following drowning [1]. It is defined as physical damage to the lungs when the pulmonary air space fails to equilibrate its pressure with the environment following changes in ambient pressure. This situation typically occurs when a scuba diver, a free-diver or an airplane passenger ascends or descends [2]. According to Boyle's law, as a diver descends, the air in the lungs becomes compressed, and pulmonary edema or hemorrhage may occur when lung volume decreases below the residual volume [3-5]; as a diver ascends, the air in the lungs expands, followed by excessive trans-alveolar pressure, and overexpansion injury in the form of alveolar rupture, or burst lung, may occur. The latter is generally more common, causing more severe sequelae.

The clinical manifestations of PBT include pneumothorax, pulmonary interstitial emphysema, subcutaneous emphysema, pneumoperitoneum, pneumomediastinum or pneumopericardium, air embolism, tension lung cysts and a hyper-inflated left lower lobe [2]. Pneumothorax is relatively uncommon, developing in only approximately 10% of PBT episodes [6-7]. Although rare, recognition of PBT in divers is sometimes delayed, leading to a life-threatening situation. The determination of PBT risks is

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gradually formed by relevant associations, especially in individuals with a pre-existing lung condition. The implications with regard to further diving and air travel are often unappreciated.

Decompression sickness (DCS) is another common complication of scuba diving. It is a condition resulting from dissolved gases coming out of a solution as bubbles inside the body due to inappropriate depressurization. The liberated gas bubbles can affect organ functions and cause various symptoms such as joint pain, headache, rashes, or even paralysis and death [8]. Air travel after diving presents an increased risk of developing DCS [9-10]. With regard to the decompression stress of flying after diving, the U.S. Navy Diving Manual includes a table of surface intervals based on diving depth and time. The Divers Alert Network (DAN) and the Undersea and Hyperbaric Medical Society (UHMS) also developed consensus guidelines for surface intervals in 2004 [11].

Predisposed barotrauma tends to deteriorate in constant ambient pressure changes without immediate and proper medical intervention. There is currently no guidance for diving PBT when abroad. We herein present the case of an experienced scuba diver who developed PBT when on a diving vacation abroad in Maldives. The pulmonary situation worsened into impending tension pneumothorax after exposure to repeated ambient pressure changes in continuous dives and multiple flight transfers.

Case Report

A 58-year-old female without previous systemic disease presented at our emergency department with severe shortness of breath after flying back from a scuba diving vacation in Maldives. At first, she felt chest tightness when coming to the surface after diving 30 meters in depth on the 3rd day of diving. She continued diving to the same depth during the next 2 days, and the symptoms of shortness of breath, headache and nausea worsened on the 5th day. She did not call on a medical facility before her flight back to Taiwan the next day, which included consecutive transfers in Kuala Lumpur and Hong Kong. The patient mentioned that the symptoms of nausea, chest tightness and difficult breathing worsened every time the plane took off, requiring oxygen support in the cabin.

After arrival in Taiwan, the patient came directly to our emergency department, where she manifested severe dyspnea with respiratory distress and tachycardia. The chest film showed a large area of pneumothorax on the right side, with near total collapse of the right lung and a left shift of the mediastinum (Figure 1). Her

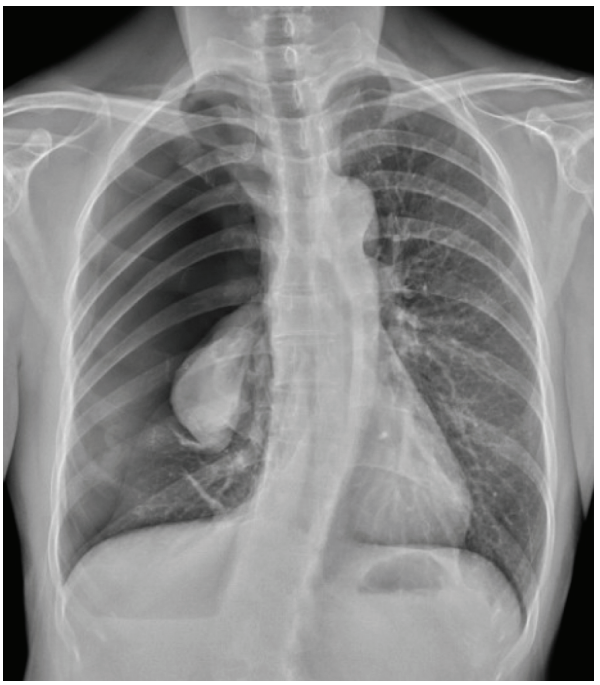

Fig. 1. Standing chest film revealed a large area of the right pneumothorax that caused right upper lobe collapse and a left shift of the mediastinum, and impending tension pneumothorax.

symptoms were relieved after an emergency chest tube insertion.

To further investigate this barotrauma caused by diving, we performed a video-assisted thoracic surgery (VATS). An area of emphysematous change about 2×1×1 cm^3 in size was found at the right upper lobe (Figure 2). The patient underwent surgery with wedge resection and mechanical pleurodesis. The pathology report of the resected lung showed blebs formation in the pulmonary tissue characterized by emphysematous change (Figure 3). After 10 days of hospitalization, the patient was discharged asymptomatically.

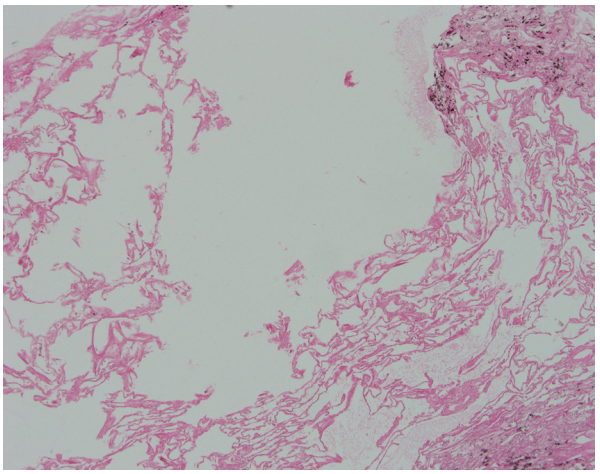

Fig. 3. Microscopic section of the resected lung shows a picture of blebs in the pulmonary tissue characterized by emphysematous change, hemorrhage and focal fibrosis.

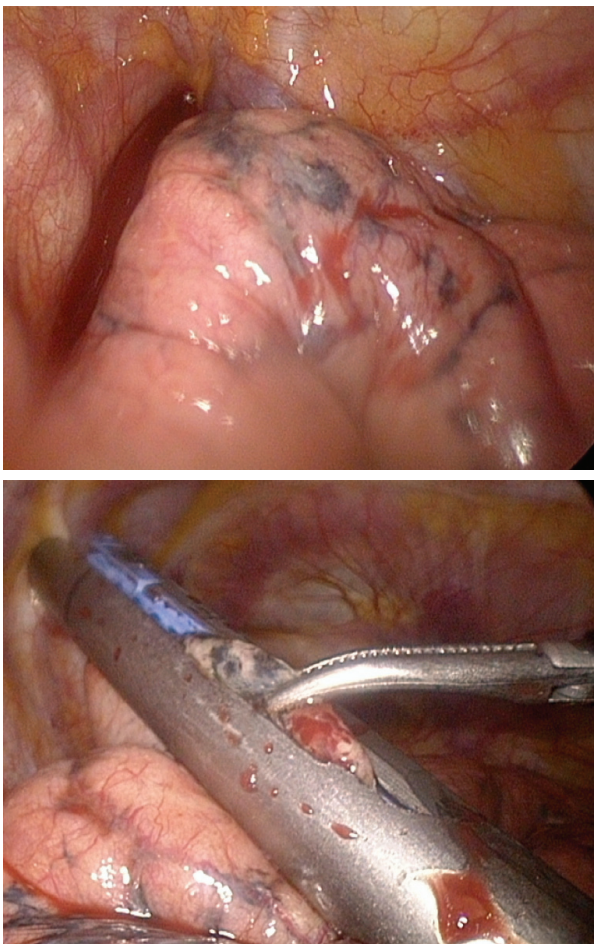

Fig. 2. Surgical findings from VATS: An area of emphysematous change about 2×1×1 cm^3 in size was found at the right upper lobe and was resected.

Discussion

Diving barotrauma can broadly manifest as a squeezing effect on the sinuses and ears [12-13], PBT [14] and arterial gas emboli [15]. With regard to the basic physics, Boyle's law states that volume and pressure are inversely related in a fixed mass of an ideal gas at constant temperature, and this leads to the fundamental pathogenesis of PBT. While diving, with increased pressure during descent, gas volume in closed air-containing body cavities is diminished; decreased pressure during the following ascent, either through expanding air volumes in the closed ventilating airways or a pressure difference transmitted hydrostatically through the tissue, directly causes alveolar ruptures. Elevated intrapulmonary pressure that results in a trans-pulmonary gradient of 95 to 110 cm H_2O can rupture alveoli [16]. Divers who hold their breath while ascending and those with obstructive airway diseases, who are inclined to form

over-distended alveoli, are at an increased risk of PBT [6]. The ruptured alveoli lead to an air leak into the surrounding tissues and space, causing multiple complications or even fatalities.

In this case, it was reasonable to speculate that the PBT leading to impending pneumothorax occurred during the dive on the 3rd day. However, the upcoming dives and the 2 flight transfers worsened the crisis. After the first episode of a burst lung during ascent, the air volume leaked into the pleural cavity, which was reserved as a closed space for entry only. During the next dive, inhaled gas (from the scuba) kept flowing into the pleural cavity by means of an increasing negative pressure gradient while descending, which impeded the volume reduction of the pleural cavity. According to Boyle's low, a volume of gas at 30 meters (4 ATA) will double at 10 meters (2 ATA) and double again at the surface (1 ATA). As a result, the residual pneumothorax area expanded 4-fold when returning to the surface, compared to the first episode. The pathogenic process was repeated during the next 2 dives on the 4th and 5th day, exacerbating the condition and the symptoms. Then, without proper medical help, she put herself into a situation leading to another identical crisis - taking an international flight after diving.

Flying after diving increases the decompression burden, since the atmospheric pressure in an aircraft cabin is lower than that at the surface of the sea. Although flight altitude varies from aircraft to aircraft, the US Federal Aviation Administration (FAA) has required that commercial aircraft cabins must be pressurized to simulate a cabin altitude of 8,000 feet (2,438 meters) at least, or approximately 0.76 ATA [17-18]. As the airplane ascends to the target altitude, the air in the pleural cavity may expand 1.4 times (1/0.76). This results in a 1.4-fold expansion of the pneumothorax area upon landing, compared to that before departure. This pathogenic process was repeated 3 times throughout the patient's flight, with 2 flight transfers in this case. Step by step, the initial diving PBT was turning into an impending tension pneumothorax by the end of the journey. The post-dive ascent to a higher altitude increases the decompression stress, no matter whether for PBT or DCS. A diver who is experiencing any symptoms consistent with PBT should visit a hospital before flying.

All divers are at risk of PBT, and this is not related to the dive depth or the dive time. There are 3 main causes of PBT for divers: voluntary breath-holding, rapid ascent and pre-existing lung condition [19]. Breath-holding and rapid ascent usually occur with some diving beginners who develop PBT, but it is the pre-existing lung condition that hinders the prevention of the diving complication. Any condition that causes air to be trapped in the lungs, such as asthma, emphysema, pneumatocele or lung cysts [19], some temporary conditions such as bronchitis or a cold, and even some permanent conditions such as pulmonary scars, fibrosis, or tuberculosis [6,20], can lead to PBT. This patient, an experienced diver, presented regional emphysematous change at the right upper lobe. The burst of the blebs during her dives indicated a rational origin of the PBT, and started the disease course.

Divers should be carefully screened to ensure they have no respiratory problems that predispose to PBT, like asthma or lung cysts. Divers who have experienced a burst in their lungs and survived are much more likely to have recurrences in the future [21-22]. In 2003,

the British Thoracic Society (BTS) Standards of Care Committee therefore established a national recommendation for assessing respiratory fitness to dive, which suggests paying particular attention to those with a history of lung disease, chest trauma and pneumothorax, and performing respiratory system examinations, such as a pulmonary function test [3]. Tetzlaff *et al* [19] noticed a reduced mid-expiratory flow of 25% of vital capacity in divers who had lung barotrauma, suggesting that an increased risk of PBT could be identified with the pulmonary function test. In the BTS recommendation, FEV_1 and PEF should normally be greater than 80% of predicted, and the FEV_1/FVC ratio should be greater than 70%. Routine chest radiography and computed tomography are not necessary in asymptomatic subjects, but are appropriate in some patients with specific respiratory illnesses [6].

In conclusion, flying after diving requires attention not only to the time interval, but also to any symptoms. Repeated ambient pressure changes may worsen the pulmonary complications of diving. Without appropriate medical intervention, a simple flight could turn diving PBT into fatal tension pneumothorax. Divers who have any pulmonary symptoms after diving should seek medical treatment locally or domestically before taking any transportation with altitude change.

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致命的潛水後飛行：國際航班上的壓力性氣胸個案

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肺部氣壓傷及減壓症皆為潛水的嚴重併發症，常發生於不正確的上升過程。針對國外的潛水，美國海軍潛水準則已嚴格地規定潛水後與飛行的海平面停留間隔。本罕見案例為一位具多年水肺潛水經驗的女性，在國外潛水假期後返國的航班上，發生嚴重的呼吸困難。兩次的航班轉機帶來反覆的環境壓力變化，導致病人在返國後發展成壓力性氣胸。病人經胸管引流術及肺泡摘除手術後痊癒。***(胸腔醫學 2018; 33: 254-260)***

關鍵詞：潛水後飛行，氣壓傷，氣胸

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