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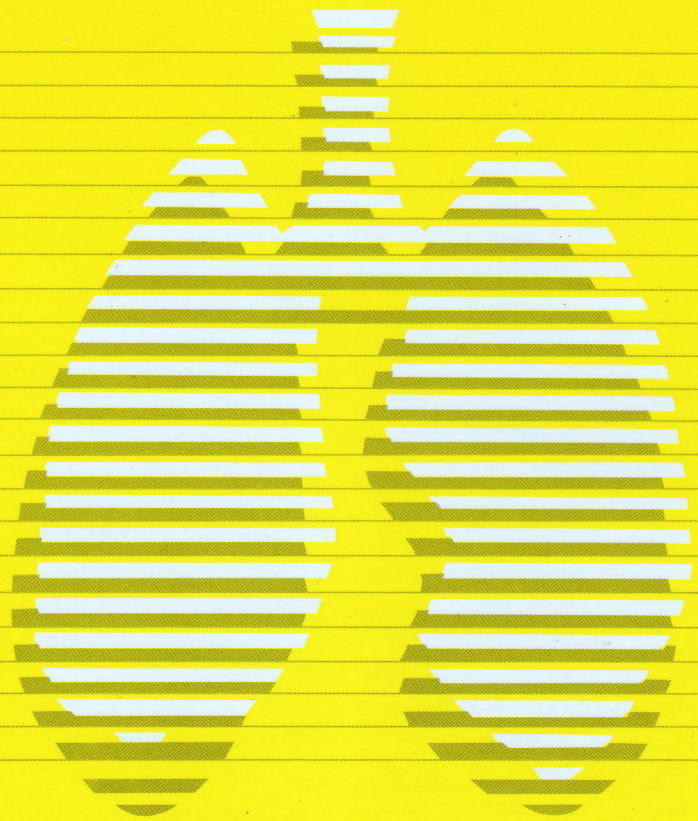

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10048 台北市常德街 1 號

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Orginial Articles

Case Reports

High-Resolution Computed Tomography Used to Assess Patients with Emphysema Following Pulmonary Rehabilitation

Shih-Min Chen, Yu Sophie Wang*, Jeng-Shing Wang**

Objectives: The purpose of our study was to evaluate the short-term effect of changes resulting from pulmonary rehabilitation on subjects with chest high-resolution computed tomography (HRCT)-diagnosed emphysema, both cross-sectionally and longitudinally, using repeated HRCT scans.

Methods: A detailed clinical history was taken and physical examination performed. We performed a serum study, lung function testing and HRCT scanning to assess emphysema. All patients participated in 12-week, outpatient-based pulmonary rehabilitation consisting of 3 sessions per week.

Results: After participating in the program, there was a significant improvement in the patients' body mass index (0.55 kg/m^2, p<0.001), and a significant, but smaller than normal decline in forced expiratory volume in 1 second (0.60%, p<0.001). There was also a significant decline in C-reactive protein (0.20 mg/L, p<0.001) and St. George's Respiratory Questionnaire (11, p<0.001). In the CT image, there were significant increases in mean lung density and attenuation value separating the lowest 15% of pixels (4.1 HU, p<0.001), but a significant decrease in the percentage of the relative area of the lungs with attenuation values < -950 Hounsfield unit (1.1%, p<0.001). There were significant declines in smoking (p<0.01), exacerbation, modified Medical Research Council scale, ADO index, DOES index, and emphysema severity (all p<0.05).

Conclusions: This study shows important changes in patients with emphysema assessed with HRCT following pulmonary rehabilitation. ***(Thorac Med 2015; 30: 327-336)***

Key words: emphysema, high-resolution computed tomography, mean lung density, percentile, relative area, pulmonary rehabilitation

Division of Internal Medicine, Antai Medical Care Cooperation, Antai Tian-Sheng Memorial Hospital, Pingtung, Taiwan; *Public Health Program, Faculty of Health Sciences, Simon Fraser University, Vancouver, Canada;
**Division of Respirology, Yuan's General Hospital, Kaohsiung, Taiwan
Address reprint requests to: Dr. Jeng-Shing Wang, Division of Respirology, Yuan's General Hospital, Kaohsiung, Taiwan, No.162 Cheng Kung 1st Road, Kaohsiung 80249, Taiwan

Introduction

The major advantage of high-resolution computed tomography (HRCT) in assessing pulmonary emphysema is that, in addition to providing data concerning overall lung destruction, it also identifies the specific locations in the lung where the alveolar surface has been destroyed [1-2]. Accurate diagnosis and quantification of pulmonary emphysema during life is important to understand the natural history of the disease, to assess the extent of the disease, and to evaluate and follow up therapeutic interventions. Our and other studies have addressed the capability of CT to accurately quantify the extent and severity of pulmonary emphysema [3-4]. However, the effect of pulmonary rehabilitation on lung density has not yet been fully investigated, and this may play a role in the evaluation of the severity and progression of lung diseases such as emphysema.

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation leading to reduced ventilatory capacity and is associated with shortness of breath. Pulmonary rehabilitation programs (PRPs) have been recommended as an integral part of management for COPD patients [5-6]. Exercise training is always regarded as an adjunct to therapy for most chronic diseases [7]. This study was designed to investigate the feasibility and safety of a scheduled home-based PRP with outpatient supervision that included exercise training and lecture series for patients with emphysema. The purpose of our study was to evaluate the short-term effect of changes in pulmonary rehabilitation on subjects with chest HRCT-diagnosed emphysema, both cross-sectionally and longitudinally, using repeated HRCT scans.

Methods

Subjects

We recruited patients who had stable symptoms of COPD at the outpatient department. All smokers had an FEV_1/FVC of less than 70%, and chest image revealed emphysematous change. The study was approved by the Hospital Ethics Review Board. Patients were prospectively recruited for the purpose of the study and gave their written informed consent prior to participation.

Clinical variables

A detailed clinical history was taken and physical examination performed. Lung function testing consisted of spirometry carried out according to the ATS guidelines [8]. The degree of dyspnea was checked with the use of the modified Medical Research Council (MMRC) dyspnea scale [9], and the scores on the MMRC were classified as 0, 1, 2, 3 and 4, with 0 the lowest and 4 the highest [10]. The ADO index includes age, dyspnea, and airflow obstruction, and does not require 6MWD, which may facilitate its use in primary care settings [11]. The DOSE index, another attempt to create a multicomponent assessment index of COPD severity, includes symptoms (MMRC dyspnea scale), airflow limitation (FEV_1), smoking status (current vs. former) and, of importance, previous exacerbation frequency per year [12]. The serum C-reactive protein (CRP) was measured using nephelometry in accordance with recommendations from the Centers for Disease Control and Prevention and the American Heart Association [13]. Health-related quality of life was assessed using the validated Chinese-language version of the St. George's Respiratory Questionnaire (SGRQ) [14]. The SGRQ is a self-

administered, disease-specific questionnaire. Scores range from 100 (worst possible health status) to 0 (best possible health status). All subjects were enrolled according to the GOLD criteria based on clinical assessment [15]. None of the patients was atopic and none showed significant bronchodilator reversibility (>12% of baseline FEV_1 and >200 ml).

Imaging variables

HRCT scanning was used for the evaluation of emphysema. Scans (Somatom Sensation 16 scanner, Siemens, Erlangen, Germany) were performed on full inspiration at 6 mm intervals with a collimation (slice thickness) of 1 mm. The scanner was subject to a weekly quality assessment with a phantom check, including uniformity, linearity, and noise. In addition, there was a 3-monthly engineering check of spatial and contrast resolution and an annual medical physics check. Scanning voltage was 120 kV and current was 120 mA. Hard copy images were photographed at a window level of -600 Hounsfield units (HU) and a window width of 1600 HU, as appropriate for viewing lung parenchyma. The scans were evaluated for the presence of emphysema both qualitatively by the radiologists independently of the remaining research, and quantitatively by computerized portable and expandable software (Osiris 4.19, University Hospital of Geneva, Geneva, Switzerland) for interactive display and manipulation of medical images from different imaging modalities. After processing the data through Microsoft® Office Excel 2007, 3 major lung density parameters were measured. Both lungs were divided into 6 areas comprising the upper, middle, and lower lung fields; an upper section was obtained 1 cm above the superior margin of the aortic arch, a middle section was taken at 1 cm below the carina, and a lower section was taken approximately 3 cm above the top of the diaphragm [16]. The severity of emphysema was scored as 0 points, no emphysematous lesions; 1 point, occupying less than 25% of the entire lung field; 2 points, occupying 25% to less than 50% of the entire lung field; 3 points, occupying 50% to less than 75% of the entire lung field; 4 points, occupying more than 75% of the entire lung field [17]. Mild emphysema was defined as a total score less than 8 points, moderate emphysema as a total score 8-16 points, and severe emphysema as a total score more than 16 points. Mean lung density (MLD) was the mean attenuation value of all pixels, excluding the mediastinum and trachea. The 15^{th} percentile (PERC15) was defined as the threshold value for which 15% of all pixels had a lower density. The relative area 950 (RA950) of low attenuation has been defined as the percentage of pixels within the lungs with a density lower than a predefined threshold (-950 HU). Histogram analysis, as well, was calculated from computerized data.

Pulmonary rehabilitation program

All patients participated in a 12-week, outpatient-based pulmonary rehabilitation program (PRP) consisting of 3 sessions per week. In each training session, formal education, including PRP, breathing retraining, proper use of medications and self-management skills, was provided individually. Lectures on a healthy lifestyle included information about normal lung anatomy and physiology, disease pathology, pulmonary medications, oxygen therapy, avoiding environmental irritants, and prevention and management of respiratory infections. Information about the disease, nutrition, proper use of inhalation therapy and general preven-

tive measures was given. Exercises following the education program included: a. respiratory muscle training, e.g., diaphragmatic breathing and pursed lip breathing; b. endurance training (aerobic training, e.g., walking and cycling); c. strength training and training in isolated muscle stretching.

Statistical analysis

Analysis of the data was done using Microsoft® Office Excel 2007 (Microsoft, Santa Rosa, CA, 2007) and a Statistical Package SPSS18 (SPSS, Chicago, IL, 2009) on a personal computer. The Kruskal-Wallis test for independent samples was applied and nonparametric data of several groups were compared; the Chi-Square test was performed to assess differences in categorical variables. A p value <0.05 was considered statistically significant. Continuous variables were expressed as mean±SD unless otherwise specified.

Results

Cross-sectional analysis of baseline scans

The final analysis was based on data from 47 patients. The average age was 64±9 years, and 70% (n=33) were male. Mean height was 163±8 cm, and weight was 59±8 kg. We assessed the HRCT of the emphysema patients subjectively and objectively using the mentioned variables. The patients had the following characteristics: moderately impaired health-related quality of life (SGRQ was 52±13), mod-

Table 1. Characteristics of the 47 Patients

Variables	Value
Age, years	64±9 (82-50)
FEV_1, %	56±12 (82-28)
BMI, kg/m^2	22.1±2.7 (27.6-15.4)
CRP, mg/L	3.6±0.7 (5.0-2.1)
SGRQ	52±13 (95-35)
MLD, HU	-875±23 (-840-980)
PERC15, HU	-951±17 (-918-994)
RA950, %	15±4 (26-7)
Smoking, pack-year	57±13 (100-40)
Exacerbation, 0/1/2	9(19)/34(72)/4(9)
MMRC scale, 0/1/2/3	1(2)/15(32)/24(51)/7(15)
ADO index, 1/2/3/4/5/6	2(4)/7(15)/12(26)/13(28)/9(19)/4(9)
DOSE index, 1/2/3/4/5	15(32)/20(43)/6(13)/2(4)/4(9)
COPD severity, mild/moderate/severe/very severe	0(0)/30(64)/15(32)/2(4)
Emphysema severity, mild/moderate/severe	12(26)/26(55)/9(19)

FEV_1 = forced expiratory volume in 1 second; BMI = body mass index; CRP = C-reactive protein; SGRQ = St. George's Respiratory Questionnaire; MLD = mean lung density; HU = Hounsfield unit; PERC15 = the 15^{th} percentile; RA950 = the relative area 950; MMRC = Modified Medical Research Council; ADO index including age, dyspnea, and airflow obstruction (from 0 to 10 points); DOSE index including dyspnea, airflow obstruction, smoking status, and previous exacerbation frequency per year (from 0 to 8 points); COPD = chronic obstructive pulmonary disease. Continuous variables are shown as mean±SD (range). Categorical variables are shown as number (percentage).

erate obstructive ventilatory impairment (FEV_1 was 56±15% predicted), mildly underweight (BMI was 21.3±2.3 kg/m^2), mild inflammation (CRP was 4.1±1.2 mg/L), heavy smoking (55±17 pack-years), moderately emphysematous (MLD was -877±23 HU, PERC15 was -953 ± 21 HU, RA950 was 16±5%), moderate COPD severity, few exacerbated, mild to moderate dyspnea, mild to moderate risk of a poor prognosis, and moderate emphysematous imaging (Table 1).

Longitudinal analysis of baseline and follow-up scans

After participation in the program, there was a significant improvement in BMI (0.55 kg/m^2, p<0.001) among the patients. There was a significant, but smaller than normal decline in FEV_1 (0.60%, p<0.001), and a significant decline in CRP (0.20 mg/L, p<0.001) and SGRQ (11, p<0.001). In the imaging, there were significant increases in MLD and PER15 (4.1 HU, p<0.001), and a significant decrease in RA950 (1.1%, p<0.001) (Table 2). There were also changes in the categorical variables of the patients following pulmonary rehabilitation, including significant declines in smoking (p<0.01), exacerbation, MMRC scale, ADO index, DOES index, and emphysema severity (all p<0.05) (Table 3).

Discussion

This was a clinical study to assess whether HRCT variables were as good as other known clinical variables in grading emphysema patients following pulmonary rehabilitation. The current results show that our emphysema patients were moderately emphysematous, and their MLD was -875±23 HU, PERC15 was -951±17 HU, and RA950 was 15±4% (Table 1). Besides, all imaging variables following pulmonary rehabilitation were potentially useful, similar to the other known clinical variables (Table 2 and Table 3). There were significant increases in MLD and PER15 (4.1 HU, p<0.001), but a significant decrease in RA950 (1.1%, p<0.001) and emphysema severity (p<0.05).

Our study did not show that pulmonary rehabilitation improved FEV_1, which is in accordance with previous reports, but showed beneficial interference with its progressive de-

Table 2. Change in Continuous Variables of the Patients Following Rehabilitation

Variables	change	*p*
FEV_1, %	-0.60±0.13	<0.001
BMI, kg/m^2	0.55±0.16	<0.001
CRP, mg/L	-0.20±0.06	<0.001
SGRQ	-11±4	<0.001
MLD, HU	4.1±1.4	<0.001
PERC15, HU	4.1±1.4	<0.001
RA950, %	-1.1±0.7	<0.001

FEV_1 = forced expiratory volume in 1 second; BMI = body mass index; CRP = C-reactive protein; SGRQ = St. George's Respiratory Questionnaire; MLD = mean lung density; HU = Hounsfield unit; PERC15 = the 15th percentile; RA950 = the relative area 950. Continuous variables are shown as mean±SD.

Table 3. Change in Categorical Variables of the Patients Following Rehabilitation

Variables	Before	After	*p*
Smoking			
no/yes	0/47	6/41	<0.01
Exacerbation			
0/1/2	9/34/4	17/28/2	<0.05
MMRC scale			
0/1/2/3	1/15/24/7	8/14/19/6	<0.05
ADO index			
0/1/2/3/4/5/6	0/2/7/12/13/9/4	5/5/9/11/9/6/2	<0.05
DOSE index			
0/1/2/3/4/5	0/15/20/6/2/4	7/15/18/4/1/2	<0.05
Emphysema severity			
nil/mild/moderate/severe	0/12/26/9	7/11/23/6	<0.05

MMRC = Modified Medical Research Council; ADO index including age, dyspnea, and airflow obstruction (from 0 to 10 points); DOSE index including dyspnea, airflow obstruction, smoking status, and previous exacerbation frequency per year (from 0 to 8 points); COPD = chronic obstructive pulmonary disease. Categorical variables are shown as number.

cline [18-19]. Small airways function and/or recruitment in patients participating in the PRP may increase. The reduction of FEV_1 decline due to pulmonary rehabilitation is another beneficial effect of the program for COPD patients. FEV_1 decline may serve as a predictor for risk of death from COPD, and therefore pulmonary rehabilitation should be considered as a disease modifier [20]. In the present study, 12 weeks of exercise training increased bodyweight in these patients. Nutritional supplementation combined with exercise training may increase bodyweight and fat-free mass in underweight patients with COPD [21-22]. Previous study suggested that exercise training per se may induce an anabolic response and weight gain in COPD patients [23]. CRP is often used as a clinical marker of metabolic and functional impairment in patients with advanced COPD [24]. Another study indicated that CRP was a significant predictor of BMI and fat mass index [24]. Our PRP led to significant improvement in the SGRQ score, as in a previous study [25]. PRPs are indicated for COPD patients with exercise intolerance, exertion dyspnea and impairment of daily activities [26]. Improved capillary function, oxidative capacity and skeletal muscle efficiency after exercise training result in improving exercise capacity [27]. Decreased lactic acidosis, ventilatory demand and dynamic hyperinflation have been seen after participation in PRPs [28-29]. Our study showed that pulmonary rehabilitation is associated with reduced lung function decline and COPD risk among smokers, as in a previous study [18]. In addition, the pulmonary rehabilitation regimen likely improves secretions evacuation, which can reduce airway infections/inflammation and decrease COPD exacerbations.

Although the supportive setting of rehabilitation should be helpful in enabling smoking cessation, to our knowledge, few published stu-

dies have investigated its effectiveness [30]. Participating in PRP for COPD provides a strong psychological motivation to stop smoking, and could have contributed to the outcomes observed. The outpatient rehabilitation setting, with the high frequency of appointments, the high health motivation, the reinforced self-esteem and the improved well-being, may also have contributed to the favorable outcome observed. The use of smoking cessation programs as a mandatory component of rehabilitation may be highly effective in increasing the smoking cessation rate and could be an additional strategy to reduce smoking.

Although HRCT should be very helpful in COPD monitoring, to our knowledge there are no published studies investigating its effectiveness in PRPs. Previous studies have shown that inflammation is present in active smokers [31-32], and another study has shown a decreased inflammatory response after smoking cessation [33]. Smoking induces emphysema and alveolar destruction with loss of lung density, so long-term smoking is associated with decreasing lung density [34]. The presence of areas of low lung density, referred to as RA950, is the main CT characteristic of emphysema, and is commonly used as a marker for emphysema [35-36]. PRPs increase small airway function and recruitment. In addition, the exercise regimen likely improves secretions evacuation, which can reduce airway infections/inflammation and decrease COPD exacerbations. Furthermore, regular exercise has been noted to protect against diseases associated with chronic inflammation [37]. Inflammation is an important factor in the pathogenesis of COPD.

Our study has some limitations. First, there was no control group to confirm that the results of this study were due to pulmonary rehabilitation alone, since the patients also received pharmacological treatment during study period. Second, it took time to perform automatic lung parenchyma segmentation manually on a slice-by-slice basis, and to calculate the variables related to the severity of the pulmonary emphysema component. Third, we had no control over the level of intensity of the exercise practiced at home. While some patients could have incorporated higher intensity, others may have employed lower intensity exercise regimens. However, studies have shown that both low-intensity and high-intensity exercise training improves quality of life and physical performance parameters in patients taking part in PRPs [38]. Fourth, we did not consider the influence of comorbidities. Finally, the study lacked histopathological corroboration to confirm structural changes in the lung, though we did show changes in function. For these reasons, our findings may not be applicable to all patients with COPD, and larger scale studies that adjust for these limits are needed to investigate the effects.

Further follow-up of our patients in the future could be of interest, and as yet, these data are not available. However, follow-up studies are planned, and these may provide further insight into the effect of pulmonary rehabilitation on lung density, as assessed by CT. This study shows important changes in HRCT in patients with emphysema following pulmonary rehabilitation.

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肺氣腫患者肺部復健後的高解析度電腦斷層掃描評估

陳世民　王貞云 *　王正信 **

目的：本研究的目的是評估胸部高解析度電腦斷層掃描（HRCT）- 診斷肺氣腫受試者肺部復健後的短期效應變化，無論是橫斷面和縱斷面，重複使用 HRCT 掃描。

方法：進行詳細臨床病史和體格檢查。我們進行血清研究，肺功能測試和 HRCT 掃描，以評估肺氣腫。所有患者參加為期 12 週，門診為基礎的肺部復健，包括每週三節。

結果：參與復健之後，身體質量指數顯著改善（0.55 千克 / 平方米，p<0.001）。第一秒用力呼氣容積顯著下降（0.60%，p<0.001），但小於正常的下降。還有 C 反應蛋白顯著下降（0.20 毫克 / L，p < 0.001）及聖喬治呼吸問卷顯著下降（11，p<0.001）。圖像方面，平均肺密度和衰減值分開至少 15% 的像素顯著增加（4.1 HU，p<0.001），但衰減值百分比 <-950 亨氏單位的肺部的相對面積顯著下降（1.1%，p<0.001）。吸煙（p<0.01），其他急性發作，modified Medical Research Council scale，ADO 指標，DOES 指標和肺氣腫的嚴重程度皆顯著下降（p<0.05）。

結論：本研究顯示肺氣腫患者肺部復健後的高解析度電腦斷層掃描評估的可能重要的變化。*(胸腔醫學* ***2015; 30: 327-336)***

關鍵詞：肺氣腫，高解析度電腦斷層掃描，平均肺密度，百分，相對面積，肺部復健

安泰醫療社團法人安泰醫院　內科，公共健康計劃，健康科學學院，加拿大溫哥華西門菲沙大學 *
阮綜合醫院　胸腔內科 **
索取抽印本請聯絡：王正信醫師，阮綜合醫院　胸腔內科，80249 高雄市成功一路 162 號

Factors Affecting Occurrence and Outcome of Unplanned Extubation among Patients in the Intensive Care Unit

Yi-Chih Huang*, Hsiang-Yu Huang***, Chou-Chin Lan*,**, Mei-Chen Yang*,**, Chun-Yao Huang*, Yao-Kuang Wu*,**

Background: Unplanned extubation (UE) is a frequent severe complication of mechanical ventilation in critically ill patients in the intensive care unit (ICU) and may be associated with increased morbidity and mortality. This study investigated the incidence, predictive factors, outcomes, and expenditures of patients with failed UE (re-intubation within 48 hours) in adult ICUs.

Methods: This case-control study included 193 cases and 579 controls (case-control ratio of 1:3) for the period covering January 1, 2007 to December 31, 2011.

Results: There were 193 episodes of UE, with a density of 0.25 per 100 ventilated days. The failed UE rate was 42.0% (81/193), and the hospital mortality rate was 29.5% (57/193). In multivariable analysis, higher APACHE II score (odds ratio [OR] 0.946), longer duration from intubation to UE (OR 0.940), lower consciousness level (OR 1.208), and full ventilator support (OR 3.868) were factors predictive of failed UE. The failed UE group had the worst outcomes, the most ventilator days, and the highest costs. They also had higher hospital mortality rates (54.3%) and lower hospital discharge rates (33.3%) than the controls.

Conclusion: Patients with failed UE had worse outcomes and higher costs in the ICU than the controls and those with successful UE. Aggressive weaning may be recommended for patients under partial ventilator support with low FiO2. Adequate restraint should be provided to prevent any failed UE in patients with a higher APACHE II score, more intubation days, and lower consciousness level, and those on full ventilator support. ***(Thorac Med 2015; 30: 337-346)***

Key words: intensive care, mechanical ventilation, reintubation, unplanned extubation

Introduction

Unplanned extubation (UE) is a common but dangerous adverse event in the intensive care unit (ICU) [1]. In the literature, morbidity rates of 5-28% have been reported in patients with UE [2]. Serious respiratory and cardiovascular complications have also been reported [3-

*Division of Pulmonary Medicine, Taipei Tzu-Chi Hospital, Buddhist Tzu-Chi Medical Foundation; **School of Medicine, Tzu-Chi University, Hualien, Taiwan; ***Division of Respiratory Therapy, Taipei Tzu-Chi Hospital, Buddhist Tzu-Chi Medical Foundation

Address reprint requests to: Dr. Yao-Kuang Wu, Division of Pulmonary Medicine, Taipei Tzu-Chi Hospital, Buddhist Tzu-Chi Medical Foundation, No. 289, Jianguo Road, Xindian City, New Taipei City, Taiwan, Republic of China

4]. Studies conducted during the last 10 years report UE rates ranging from 0.149 to 4.242 per 100 intubation days [5]. The re-intubation rate after UE varies from 1.8% to 88% [6-7]. In general, while UE results in prolonged mechanical ventilation (MV), longer ICU and hospital stays, and increased need for chronic care [7-8], it is not necessarily associated with increased mortality compared with matched controls [6,8], and the increase in hospital expenditure is exclusively related to patients who fail to tolerate UE.

Factors predicting re-intubation in the ICUs of established centers include higher acute physiological and chronic health evaluation (APACHE II) score [9], higher pre-extubation fraction of inspired oxygen (FiO_2) level [10-11], full ventilator support before UE [12], and pneumonia as the cause of respiratory failure [13]. This study aimed to survey the incidence, predictive factors, outcome, and expenditures of patients who failed UE (re-intubation within 48 hours) in adult ICUs.

Materials and Methods

Study Setting

Information on patients who had UE between January 1, 2007 and December 31, 2011 was reviewed and collected from their medical records. All patients over 18 years of age requiring an artificial airway (oro- or nasotracheal tube) and in the ICUs of Tzu Chi General Hospital (Xindian District, Taipei, Taiwan) were monitored for the occurrence of UE. The population represented a mix of patients with complex medical conditions and patients who underwent planned or emergency surgical, thoraco-surgical, or neurosurgical procedures. The ICU staff members, including in-charge intensivists, respiratory therapists, clinical nurse specialists, clinical dietitians, clinical pharmacists, and residents, provided 24-hour coverage in the units. The nursing staff worked in 3 shifts (morning shift: 8 am-4 pm, evening shift: 4 pm-12 am, and night shift: 12 am-8 am). Each shift had the same nurse-to-patient ratio of 1:2 and there were no differences in nursing experience by shift.

The study design was approved by the hospital's institutional review board. During the study period, 78,099 ventilation days via endotracheal tube were recorded. Endotracheal tubes were secured with waterproof tape around the tube, upper lip, and face. A patient prescribed and receiving benzodiazepines, opiates, or both were considered to be receiving sedatives. These agents were used for patients who were agitated or irritable based on the clinical assessment of the attending physicians. Nurses restrained patients following consultation with the physician based primarily on the subjective assessment of a patient's level of agitation or persistent failure to obey instructions. Methods of physical restraint included chest, arm and hand restraints.

Study Design and Treatment Procedure

A weaning protocol was systematically used in all participating ICU units. The weaning protocol criteria for starting the weaning process included reversal of the initial critical illness, adequate oxygenation with respect to fraction of inspired oxygen (FiO_2) <50% and positive end-expiratory pressure (PEEP) <8 cmH_2O, hemodynamic stability without the use of a vasopressor, and a tapering pressure support level followed by a spontaneous breathing trial (SBT). Hospital clinical practice called for a T-piece system or continuous positive airway

pressure of 5 cmH_2O. The criteria for evaluating the weaning process included adequate gas exchange with respect to pH >7.35; oxygen saturation >90%; hemodynamic stability with heart rate (HR) <130 beats/min, change in HR <20%, systolic blood pressure 90-200 mmHg, and change in BP <20%; stable ventilation pattern with respiratory rate (RR) <30 breaths/min and change in RR <50%; and subjective tolerance to distress and vaso-vagal signs.

UE was defined as the deliberate removal of an endotracheal tube by a patient or accidental removal during nursing care. Patients with UE were divided into failure or success based on whether or not re-intubation was required within 48 hours of extubation. In all cases, the decision to re-intubate was made by a physician in attendance based on clinical indicators of respiratory failure.

Incidence density sampling was used for the selection of controls; thus the controls were matched in terms of time [14]. For every UE event, 3 control patients were randomly selected from among all mechanically ventilated ICU patients present at the time of the UE. The controls were not matched to cases in terms of clinical characteristics like age and sex.

Measurements

Patient characteristics

The recorded data included demographics and clinical variables such as age, sex, cause of intubation, time between intubation and UE, UE time, self- or accidental extubation, and ICU location (medical or surgical); APACHE II scores, and serum albumin. The modified Glasgow Coma Scale (GCS; verbal score as 1) score and Richmond Agitation-Sedation Scale (RASS) score were also recorded at the time of UE. The ventilator settings (i.e., FiO_2, PEEP, tidal volume, and minute volume), whether there was a weaning trial or not (weaning trial defined as a pressure support mode ventilator with a level ≤14 cmH_2O or T-piece trial without a ventilator), and the use of sedation and/or physical restraints were determined.

The researcher recorded the data within 12 hours after the UE. The same data were recorded for the control patients. Re-intubation (within 48 hours) after UE was performed for patients who required it. Data monitoring for follow-up was the same for cases and controls.

Causes of Respiratory Failure

The reasons for respiratory failure were categorized follows [15]: 1) acute lung injury (i.e., pneumonia, acute respiratory distress syndrome, aspiration, and chest trauma); 2) chronic lung injury (COPD); 3) post-operative condition (e.g., coronary artery bypass grafting, abdominal surgery, and lobectomy); 4) cardiac disease (acute myocardial infarction and congestive heart failure); 5) neurologic disease (i.e., neuromuscular disease, cerebrovascular accident, cervical spine injury, and acquired critical neuromyopathy); 6) miscellaneous causes; and 7) cancer.

Outcome Measures

Outcome measures were length of hospital stay, total hospital costs, hospital mortality, and number of MV days. The number of patients successfully weaned and the length of time required between initiation of weaning attempt and becoming ventilator-independent were also recorded. There was no set time limit for MV or weaning attempts. ‘‘Ventilator-dependence’’ (including nocturnal MV) was defined as the discontinuation of weaning efforts after the inter-disciplinary team and the patient/family

agreed that these efforts should cease. Ventilator-dependent patients were transferred to the respiratory care ward or home.

Statistical Analyses

Mean values, standard deviations, and group sizes were used to summarize the results for continuous variables. The differences between the failed and successful UE groups and the control group were first examined by univariate analysis with Student's t test and χ^2 test. Statistical significance was set at $p<0.05$. Pre-determined variables or those significantly associated with failed extubation in univariate analysis ($p<0.05$) were tested for interaction with multiple logistic regression analysis. The comparison of outcome, days of MV and cost between the 3 groups (failed and successful UE groups and the control group) were examined by ANOVA (analysis of variance) and post-hoc analysis. The odds ratios (OR) and 95% confidence intervals (CI) were calculated. Statistical analysis was performed with SPSS13.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 193 episodes of UE were noted during the study period. The total ventilator duration was 78,099 days, with a UE density of 0.25 per 100 ventilated days. There were 81 episodes of failed UE (42.0% of all UEs) and 57 patients (29.5% of all UEs) died during hospitalization. Most of the UE patients were male (124/193, 64.2%) and had an average age of 71.1±15.3 years. A total of 139 episodes (72.0%) of UE occurred in the medical ICU, and 76 episodes (39.4%) were intubations due to pulmonary diseases. Most episodes (91.7% of all UEs) were self-extubations. There were no differences between the UE and control groups in terms of demographics, cause of intubation, UE location, and restraining methods (medical sedation or physical restraint) (Table 1).

In this study, successful UE occurred only in patients with lower FiO_2 and those on a weaning trial ($p<0.001$) (Table 2). Other factors like age, total intubation days, APACHE II scores, consciousness level, albumin level, cause of intubation, or ICU location were not related to the success or failure of UE (Table 2). The incidence of UE or the need for re-intubation during the 3 nursing shifts did not differ in this study (Table 2).

Multivariate analysis revealed 4 significant predictors of failed UE: higher APACHE II score (OR, 0.946; 95% CI, 0.914-0.979; $p=0.001$), longer duration from intubation to UE (OR, 0.940; 95% CI, 0.897-0.984; $p=0.009$), poor consciousness level (OR, 1.208; 95% CI, 1.067-1.368; $p=0.003$), and under full ventilator support (OR, 3.868; 95% CI, 1.683-8.887; $p=0.001$) (Table 3). The worst outcomes were noted in the failed UE group (Table 4).

Compared to the successful UE and control groups, the failed UE group had higher hospital mortality rates (54.3% vs. 11.6% vs. 30.2%, $p<0.001$) and lower hospital discharge rates (33.3% vs. 84.8% vs. 61.1%, $p<0.001$). The failed UE group also had the highest expenditures (NT\$415.3±289.6 × 10^3 vs. NT\$253.8±293.9 × 10^3 vs. NT\$309.6±270.4 × 10^3, $p<0.001$) and the most ventilator days (18.4±18.5 vs. 7.4±11.2 vs. 16.1±15.3, $p<0.001$).

Discussion

Many factors that lead to failed UE and the need for re-intubation within 48 hours are

Table 1. Demographic and Clinical Characteristics of Patients Who Underwent Unplanned Extubation and Mechanically Ventilated Controls

	Unplanned extubation (n=193)	Controls (n=579)	Total (n=772)	*p* value
Age	71.1±15.3	72.2±15.1	71.9±15.1	0.36
APACHE II	19.5±10.1	20.5±9.5	20.1±9.6	0.22
Female, n (%)	69 (35.8)	227 (39.2)	296 (38.3)	0.44
Disease, n (%)				0.20
Acute lung injury	53 (27.5)	147 (25.4)	200 (25.9)	
Chronic lung disease	23 (11.9)	49 (8.5)	72 (9.3)	
Cardiovascular disease	35 (18.1)	76 (13.1)	111(14.4)	
Post-surgery	13 (6.7)	48 (8.3)	61 (7.9)	
Neurological	23 (11.9)	78 (13.5)	101 (13.1)	
Miscellaneous	37 (19.2)	135 (23.3)	172 (22.3)	
Cancer	9 (4.7)	46 (7.9)	55 (7.1)	
Location				0.51
MICU, n (%)	139 (72.0)	433 (74.8)	572 (74.1)	
SICU, n (%)	54 (28.0)	146 (25.2)	200 (25.9)	
Modified GCS score	9.7±1.8	9.9±1.6	9.9±1.7	0.5
Restrain mode				
Physical+Sedation	36 (18.6%)	102 (17.6%)	138 (17.9%)	0.61
Sedation only	6 (3.1%)	30 (5.2%)	36 (4.6%)	
Physical only	126 (65.3%)	363 (62.7%)	489 (63.3%)	
None	25 (13.0%)	84 (14.5%)	109 (14.2%)	

[a] Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; SD, standard deviation; MICU, medical intensive care unit; SICU, surgical intensive care unit; GCS, Glasgow coma scale

discussed in the literature, and include older age, longer intubation time, higher APACHE II scores, intubation due to pulmonary causes, accidental extubation, stay in a medical ICU, higher FiO_2 and PEEP, and full ventilator support (not on a weaning trial) [5].

UE, which usually indicates poor care quality, is a tragedy in the ICU and is associated with higher mortality and morbidity [16]. The incidence of UE is expressed as the number of UE per 100 ventilated patients or as the number of UE per 100 days of MV [5]. In studies during the last 10 years, the incidence of UE was reported to be 0.1-4.2 per 100 ventilated days [5], which is similar to the 0.25 found in this study. Variations can be partially explained by the heterogeneity of the studied ICU populations [8]. Also, the 42% rate of failed UE (need for subsequent re-intubation within 48 hours) in our study is consistent with the reported 37-46% [6-7,10].

There are many risk factors to which UE may be attributed. Older age is noted as a potential risk factor by Chen *et al*. [17]. In this study, the average age of UE patients was 71.1±15.3 years. However, age, which did not differ between the UE group and the controls, also did not differ between the groups regard-

Table 2. Demographic and Clinical Variables of the Differences between Unplanned Extubation (UE) Groups*

	UE with re-intubation (n=81)	UE without re-intubation (n=112)	Total	*p* value
Age	72.9±12.7	69.7±16.8	71.1±15.3	0.07
Days from intubation to UE	7.1±9.3	5.7±8.0	6.3±8.6	0.09
APACHE II	22.5±10.5	17.3±9.3	19.5±10.1	0.52
Modified GCS score	9.5±1.9	9.9±1.6	9.7±1.8	0.06
RASS	-1.2±1.5	-0.8±1.3	-1.0±1.4	0.77
FiO_2	45.8±21.0	35.8±11.0	40.0±16.6	<0.001
Pressure support level	16.5±5.7	17.4±4.9	17.0±5.5	0.27
PEEP	7.4±1.4	6.7±1.3	7.0±1.3	0.45
Albumin	2.5±0.8	2.6±0.7	2.6±0.7	0.89
Intubation cause n (%)				0.15
Acute lung injury	26 (32.1%)	27 (24.1%)	53 (27.5%)	
Chronic lung disease	12 (14.8%)	11 (9.8%)	23 (11.9%)	
Cardiovascular disease	9 (11.1%)	26 (23.2%)	35 (18.1%)	
Post-surgery	5 (6.2%)	8 (7.1%)	13 (6.7%)	
Neurological	7 (8.6%)	16 (14.3%)	23 (11.9%)	
Miscellaneous	16 (19.8%)	21 (18.8%)	37 (19.2%)	
Cancer	6 (7.4%)	3 (2.7%)	9 (4.7%)	
Mode				<0.001
Full support	58 (71.6%)	44 (39.3%)	102 (52.8%)	
Partial support	23 (28.4%)	68 (60.7%)	91 (47.2%)	
Sex female (%)	21 (25.9%)	48 (42.9%)	69 (35.8%)	0.02
Location				0.18
MICU	63 (77.8%)	76 (67.9%)	139 (72.0%)	
SICU	18 (22.2%)	36 (32.1%)	54 (28.0%)	
UE time†				0.37
Day time	23 (28.4%)	32 (28.6%)	55 (28.5%)	
Evening time	31 (38.3%)	33 (29.5%)	64 (33.2%)	
Night time	27 (33.3%)	47 (42.0%)	74 (38.3%)	
Restraint mode				0.50
Physical + Sedation	17 (21.0%)	19 (17.0%)	36 (18.7%)	
Sedation only	3 (3.7%)	3 (2.7%)	6 (3.1%)	
Physical only	48 (59.3%)	78 (69.6%)	126 (65.3%)	
None	13 (16.0%)	12 (10.7%)	25 (13.0%)	
Extubation manner				0.35
Self-extubation	72 (88.9%)	105 (93.7%)	177 (91.7%)	
Accidental	9 (11.1%)	7 (6.3%)	16 (8.3%)	

* Data presented as mean±standard deviation (range) or n (%)

† daytime 8 am-4 pm, evening 4 pm-12 am, night time 12 am-8 am

[a] Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; GCS, Glasgow coma scale; MICU, medical intensive care unit; SICU, surgical intensive care unit; RASS, Richmond Agitation-Sedation Scale; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure

Table 3. Multivariate Analysis of Predictors of Successful Unplanned Extubation (UE)

Variables	Odds ratio	95% CI	*p* value
APACHE II score	0.946	0.914-0.979	0.001
Duration from intubation to UE	0.940	0.897-0.984	0.009
Modified GCS score	1.208	1.067-1.368	0.003
Partial support mode	3.868	1.683-8.887	0.001

[a] Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; OR, odds ratio; 95% CI, 95% confidence interval; UE, unplanned extubation; GCS, Glasgow coma scale

Table 4. Outcome of the Unplanned Extubation (UE) Groups and Controls

Outcome	UE with re-intubation (Group 1) (n=81)	UE without re-intubation (Group 2) (n=112)	Control (Group 3) (n=579)	*p* value
Hospital days	36.4±21.6	27.36±24.9	33.8±30.8	0.06
Days of MV[b]	18.4±18.5	7.4±11.2	16.1±15.3	<0.001
Cost[c]	415303.3±289567.7	253807.4±293857.7	309640.8±270392.3	<0.001
Outcome				<0.001
Expire[d]	44 (54.3)	13 (11.6)	175 (30.2)	<0.001
Discharge[e]	27 (33.3)	95 (84.8)	354 (61.1)	<0.001
Ventilator dependent	7 (8.6)	2 (1.8)	35 (6.1)	0.09
Transfer to other hospital	3 (3.7)	2 (1.8)	15 (2.6)	0.72

[a] Abbreviations: UE, unplanned extubation; MV, mechanical ventilation

[b] The *p* value in each group: Group 1 vs. Group 2: $p<0.001$; Group 1 vs. Group 3: $p=0.27$; Group 2 vs. Group 3: $p<0.001$

[c] The *p* value in each group: Group 1 vs. Group 2: $p<0.001$; Group 1 vs. Group 3: $p=0.06$; Group 2 vs. Group 3: $p<0.001$

[d] The *p* value in each group: Group 1 vs. Group 2: $p<0.001$; Group 1 vs. Group 3: $p<0.001$; Group 2 vs. Group 3: $p<0.001$

[e] The *p* value in each group: Group 1 vs. Group 2: $p<0.001$; Group 1 vs. Group 3: $p<0.001$; Group 2 vs. Group 3: $p<0.001$

less of re-intubation or not. Thus, it does not seem to be an important factor in this study. Nursing care quality, like day and night shifts or nurse-to-patient ratio, is another issue. UE occurs more frequently during the night shift [8] and with less experienced nurses [18]. In this study, the 3 shifts had a similar UE rate (28.5-38.3%, $p=0.37$). This can be explained by the different shifts in the ICUs having the same nurse-to-patient ratio (1:2).

Higher APACHE II score (17; OR 9.01, 95% CI 1.02-80.5) [19] and intubation due to pulmonary causes (OR 2.3-2.4, 95% CI 1.0-5.3) [8,20] have been identified as risk factors for UE in past multivariate analyses. In this study, there was no relationship between the UE and control groups in terms of APACHE II score, causes of intubation, or intubation locations. In our study, females were more likely to have successful UE (25.9% in the with intubation group vs. 42.9% in the without re-intubation group, $p=0.02$). This situation was not found in previous studies and needs further analysis.

Agitation or irritability was a major risk factor for UE in many past studies [2,16,21]. Physical and/or chemical (sedation) restraint is broadly used to prevent UE in irritable patients in the ICU. The percentage of restrained

patients at the time of UE ranged from 25% to 87% [18,21-22]. In this study, 87% of patients underwent physical and/or chemical restraint before UE. Most were restrained by physical methods alone (65.3% of all UEs) and the rate of UE did not decrease despite the application of both methods, suggesting none or inadequate sedation in these patients.

One limitation of this study is that there were no data on related sedative agents in these patients. Midazolam is a popular sedative agent often used in the ICU and was associated with an increased risk of UE. [16]. A possible explanation is that midazolam is known for its paradoxical reaction and is associated with delirium in ICU patients. Further randomized-controlled studies should be carried out to determine the dose-response relationship.

Almost half of patients (42%) needed re-intubation within 48 hours after UE. Failed UE patients had the longest MV and hospital stay, highest medical expenditures, most mortality and lowest discharge percentage compared to the successful UE and control groups in this study. Because of the potential complications of cardiac arrest or arrhythmia, or organ damage resulting from acute or chronic desaturation or aspiration pneumonia after UE, and because of invasive nature of re-intubation itself, patients who need re-intubation after UE may be correlated with an adverse outcome [17].

Epstein *et al*. found a lower mortality rate in patients re-intubated within 12 hours of UE than in those re-intubated later [11]. Multivariate analysis was conducted to identify patients at high risk of re-intubation after UE. Four significant predictors that correlated with re-intubation after UE were found: higher APACHE II score (OR, 0.946), longer intubated duration before UE (OR, 0.940), lower consciousness level (OR, 1.208), and full ventilator support (OR, 3.868). Adequate physical and/or chemical restraints are recommended to prevent UE, and early re-intubation is important if UE occurs, so as to avoid further worsening of outcomes [11].

Similar to previous studies [7-8], the present study found that patients who do not need re-intubation after UE have a shorter hospital stay, shorter duration of MV, lower medical costs, and less mortality. Most of these patients remove the endotracheal tube by themselves rather than accidentally (93.7% vs. 6.3%). Further analysis in this group reveals that more than half (60.7%) are under partial MV (on a weaning trial), with a significantly lower level of FiO_2 than in the failed UE group (35.8±11.0 vs. 45.8±21.0, $p<0.001$). Patients in the surgical ICU have a higher percentage of successful UE than patients in the medical ICU (66.7% vs. 54.7%). These findings suggest that patients with successful UE have better clinical conditions and are more alert and stronger than those with failed UE, and can extubate by themselves. We also found that patients with successful UE have better outcomes in terms of shorter MV duration, lower costs, lower mortality and higher hospital discharge rates than the control patients. This observation lends support to the notion that successful UE patients could be extubated earlier. Therefore, we suggest that a more rapid weaning protocol and earlier extubation are necessary in this group to prevent UE.

In conclusion, patients with failed UE have the worst outcomes and highest costs in the ICU. Adequate and reasonable restraint by physical and/or chemical methods should be provided to prevent failed UE in patients with a higher APACHE II score, shorter intubation days, lower consciousness level, and on full ventilator

support. An aggressive and effective weaning protocol should be designed and applied to all ICU patients to ensure safe and earlier extubation, especially for those who are under a partial ventilator support weaning program with lower FiO_2.

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影響加護病房病人非計畫性拔管發生的原因及結果

黃奕智 * 黃湘喻 *** 藍胄進 *,** 楊美貞 *,** 黃俊耀 * 吳燿光 *,**

背景：在加護病房中，使用呼吸器的病人發生非計畫性拔管是一個常見的併發症而且常常造成死亡率增加。本研究探討加護病房病人非計畫性拔管的機率，以及造成非計畫性拔管失敗（拔管後 48 小時內再插管）的危險因子，可能的結果及對醫療支出的影響。

方法：本研究利用病例對照研究法，自 2007 年 1 月至 2011 年 12 月共納入 193 位病人及 579 位對照組。

結果：非計畫性拔管共發生 193 次，比率約為每使用 100 天呼吸器發生 0.25 次。非計畫性拔管失敗比率為 42%（81/193），死亡率為 29.5%（57/193）。經多變量分析後發現，高疾病嚴重度（APACHE II score），插管時間較長，意識狀況不佳以及充分呼吸器支持（full ventilator support）的病人在非計畫性拔管後容易失敗。同時，非計畫性拔管失敗的病人預後最差，死亡率最高，使用呼吸器的時間最久而且醫療支出最高。

結論：和對照組及非計畫性拔管成功的族群相比，非計畫性拔管失敗的病人預後最差且醫療花費最高。針對不須充分呼吸器支持且使用較低氧氣分壓的病人，應更積極設法脫離避免非計畫性拔管。針對暫時無法脫離，高疾病嚴重度且意識狀況不佳的病人則應適當約束以免非計畫性拔管失敗造成死亡率上升及更多醫療支出花費。*(胸腔醫學* ***2015; 30: 337-346)***

關鍵詞：重症加護照顧，機械通氣，再插管，非計畫性拔管

台北慈濟醫院 胸腔內科 *，花蓮慈濟大學醫學院 **，台北慈濟醫院 呼吸治療科 ***
索取抽印本請聯絡：吳燿光醫師，台北慈濟醫院 胸腔內科，新北市新店區建國路 289 號

Left Massive Hemothorax Caused by Celiac Artery Aneurysm Rupture – A Case Report

Pin-Ru Chen, Chien-Kuang Chen, Yu-Sen Lin

Celiac artery aneurysm (CAA) is a rare form of visceral artery aneurysm. Most patients are diagnosed as having CAA when they are symptomatic or incidentally detected. We present the case of a 31-year-old female who had epigastric discomfort followed by left massive hemothorax after nausea, and vomiting with hematemesis. She was first diagnosed with esophageal rupture. After further examination, CAA with rupture was suspected. Severe epigastric pain developed on day 9 after hospitalization. Aortic stenting with a superior mesenteric artery (SMA) chimney and embolization of the pseudoaneurysm were performed. Antibiotics were prescribed, and she was then discharged uneventfully. We reviewed the literature regarding the symptoms, diagnosis and treatment of CAA. The incidence of CAA is low, and the symptoms of epigastric pain followed by left massive hemothorax after vomiting could be confused with esophageal rupture initially. We should keep this uncommon disease in mind and deal with patients carefully. ***(Thorac Med 2015; 30: 347-351)***

Key words: celiac artery aneurysm, hemothorax

Introduction

Celiac artery aneurysms (CAA) are one of the rarest forms of visceral artery aneurysms [1]. More cases have been diagnosed in recent years with the increased use of ultrasonography, computed tomography (CT) and arteriography. We report a patient with a CAA leak who presented with left hemothorax after vomiting. Successful repair was achieved by endovascular stenting.

Case Report

A 31-year-old female had a sudden onset of epigastric discomfort. Esophagogastroduodenoscopy at local clinics revealed reflux esophagitis, ulcer, and hemorrhagic gastritis. Nausea and vomiting with hematemesis developed 2 days later. She was referred to a local hospital where esophageal rupture was suspected due to left bloody pleural effusion after thoracocentesis. CT of the chest was arranged and wall thickening at the lower third of the thoracic esophagus was noted. She was then transferred to our emergency department, where chest CT with oral contrast intake disclosed bilateral pleural effusion, thickening of the lower third of the esophageal wall, pericardial effusion, and

Department of Thoracic Surgery, China Medical University Hospital, Taichung, Taiwan
Address reprint requests to: Dr. Yu-Sen Lin, Division of Chest Surgery, Department of Surgery, China Medical University Hospital, 2, Yuh-Der Road, Taichung, Taiwan

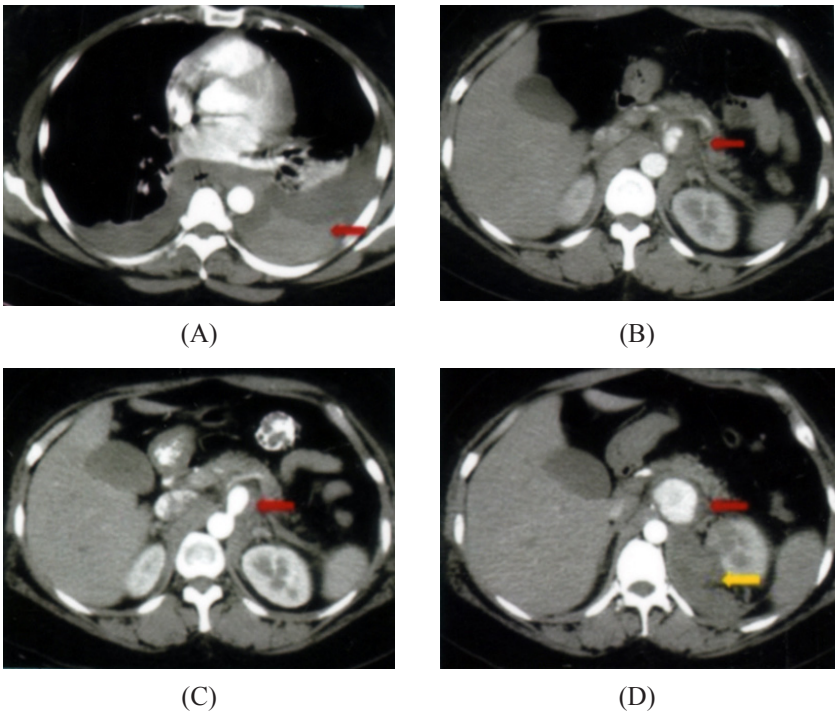

Fig. 1. HRCT of the left massive hemothorax. A, B: Chest CT, contrast, at the time of initial left hemothorax. Left hemothorax and suspicious CAA (arrow site); C, D: Chest CT, contrast, 9 days after hospitalization. Enlarging CAA (red arrow) and retroperitoneal hematoma (yellow arrow).

focal upper retroperitoneal oval high density from the aorta. Aortic CT followed, leading to suspicion of CAA, pseudoaneurysm, mycotic aneurysm, or others (Figure 1A, B).

She underwent left thoracocentesis, and left pleural effusion assay revealed amylase 29 and lipase 23. Esophagogastroduodenoscopy was performed again, and no obvious esophageal tear or rupture was seen. She was then admitted to the SICU for close observation because there was no obvious contrast leak from the aneurysm or pseudoaneurysm on the CT image. On hospital day 2, superior mesenteric artery (SMA) angiography was arranged, and an aneurysm in the proximal celiac trunk was noted. On hospital day 9, the patient complained of severe abdominal pain. The cardiovascular specialist was consulted again, and CT of the abdomen revealed an enlarged CAA / pseudoaneurysm, about 3.5 cm in maximal axial diameter, with possible rupture and acute hematoma extending to the left perirenal space, compressing and displacing the left kidney (Figure 1C, D; Figure 2A, B). On hospital day 12, aortic stenting with an SMA chimney (8 mm Viabhan) and embolization of the pseudoaneurysm were performed (Figure 2C, D). Antibiotics were prescribed due to a suspicion of mycotic aneurysm. On hospital day 21, she was discharged uneventfully.

Discussion

Aneurysms of the celiac artery are rare vascular lesions that represent only 3.6% to 4%

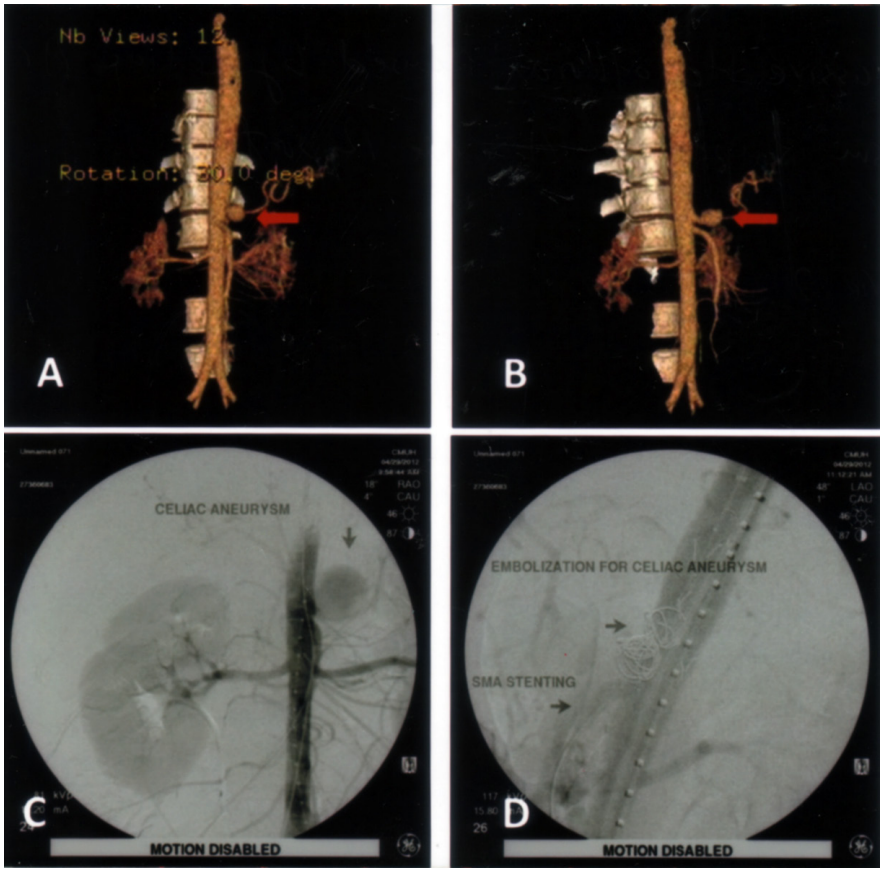

Fig. 2. A, B: 3D reconstruction of HRCT showing CAA (arrow site). C, D: Aortic stent with SMA chimney and coil embolization of the aneurysm.

of splanchnic artery aneurysms [1]. The estimated incidence of CAA ranges from 0.005% to 0.01% [1]. Advances in diagnostic imaging have led to an increased rate of detecting CAA. Most CAA are asymptomatic and more than 60% of symptomatic CAA present abdominal discomfort localized to the epigastrium. Many CAA are detected incidentally on ultrasonography, CT scan or magnetic resonance imaging (MRI), performed for other reasons. However, the diagnosis usually requires a selective arteriogram or CT angiogram. Management options include observation for small aneurysms, surgical repair, endovascular treatment with catheter-based embolization, and in selected patients, stent-graft therapy [8]. The risk of CAA rupture can range from 5% for aneurysms that are from 15 to 22 mm in diameter to 50% to 70% for aneurysms with a diameter of more than 32 mm [9].

The aneurysm may rupture into the peritoneal cavity, retroperitoneum, or thorax [10]. In our case, epigastric abdominal pain followed by severe vomiting and left pleural effusion were present, leading to a suspicion of esophageal rupture. After a detailed history-taking and advanced imaging study, CAA rupture was suspected. CAA may rupture into the retroperitoneum, and the hematoma could then dissect along the retroperitoneal fascia into the left

pleural cavity and cause hemothorax. The epigastric abdominal pain and vomiting could also be caused by CAA rupture with retroperitoneal hematoma.

Recognition of the abnormality on our subsequent chest and aortic CT and repeated esophagogastroduodenoscopy led to close observation for elective surgery or endovascular treatment due to the suspicious seal-off of the rupture site. The CAA enlarged to 35 mm during hospitalization, which led to emergency endovascular stent grafting with coil embolization, and finally, the smooth discharge of the patient.

CAA is very rare. It may present as abdominal pain, or be asymptomatic. CAA can rupture into the peritoneal cavity, retroperitoneum or thorax. Severe vomiting with hematemesis is a rare presentation, and combined with left pleural effusion, could mimic esophageal rupture. Careful survey of the detailed history, advanced imaging, and even repeated esophagogastroduodenoscopy should be considered. Endoluminal exclusion might be considered in selected patients.

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腹腔動脈瘤破裂導致左側大量血胸－病例報告

陳品儒　陳建光　林昱森

腹腔動脈瘤在臟器血管瘤中相當少見。大多數被診斷的病人都有症狀或是意外被發現。在此我們介紹一位患者初期表現出上腹痛及嘔吐，之後出現左側血胸。在急診初期被懷疑為食道破裂引起血胸，但經過進一步影像學檢查及上消化道內視鏡檢查後，懷疑為腹腔動脈瘤破裂併左側血胸。患者因血液動力學相對穩定，因此計畫先觀察後再安排至血管外科治療。但在住院期間，即因再次腹痛追蹤電腦斷層檢查，腹腔動脈瘤明顯增大，並有後腹腔血腫。因此安排血管支架手術治療，術後患者順利出院，共住院二十一天。在此我們回顧文獻關於腹腔動脈瘤的報告相當少，而以上腹痛後併嘔吐左側血胸的表現容易與食道破裂混淆。因此在診斷此類患者時要相當謹慎，並小心的處理病人。*(胸腔醫學 **2015; 30: 347-351**)*

關鍵詞：腹腔動脈瘤，血胸

中國醫藥大學附設醫院　胸腔外科
索取抽印本請聯絡：林昱森醫師，中國醫藥大學附設醫院　胸腔外科，台中市育德路 2 號

Disseminated Tuberculosis Presenting as Progressive Abdominal Pain in a Patient with Down's Syndrome: A Case Report and Literature Review

Tzu-Yu Kuo*, Chih-Hung Lin**, Jong-Rung Tsai*,***, Inn-Wen Chong*,***

A 38-year-old female with Down's syndrome presented with intermittent anorexia and body weight loss of 10 kilograms during the past year. Intermittent epigastralgia also developed in the most recent 3 months. She was sent to the emergency department, where obvious fever, progressive diffuse abdominal pain, and hypotension were noted. Computed tomography scan of the abdomen and chest after admission led to the diagnosis of diffuse lymphadenopathy, considered to be disseminated tuberculosis infection or lymphoma. Disseminated tuberculosis was confirmed by thoracoscopic lymph node biopsy and sputum culture, which revealed *Mycobacterium tuberculosis* complex. Patients with Down's syndrome have a higher risk of developing lymphoma and leukemia. Down's syndrome patients may have impaired cellular immunity, leaving them susceptible to pulmonary tuberculosis infection and extra-pulmonary involvement. Clinicians should be aware of the presentation of disseminated tuberculosis infection in patients with underlying Down's syndrome. ***(Thorac Med 2015; 30: 352-359)***

Key words: disseminated tuberculosis, Down's syndrome

Introduction

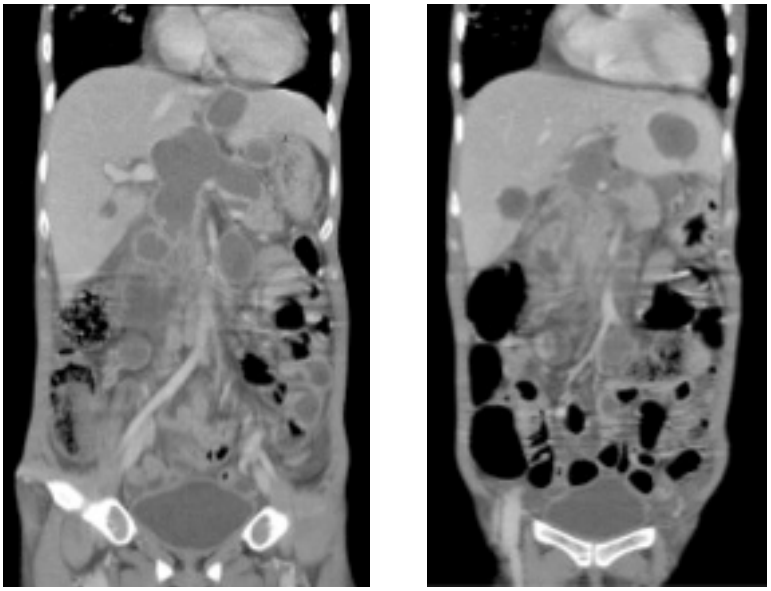
In past decades, the prevalence of tuberculosis (TB) has increased in both industrialized and developing countries. This is partially attributed to the increasing incidence of the use of immunomodulator agents and immunosuppressive agents. Disseminated TB, recognized as having an important role in morbidity and mortality, accounts for a small group of TB-infected people, especially in areas of high human immunodeficiency virus (HIV) prevalence. Clinical and image presentations of disseminated TB vary, which often delays the diagnosis. Here, we report the case of a patient with Down's syndrome whose initial presentation was progressive abdominal pain and febrile episode, and who finally was diagnosed as having disseminated TB.

*Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital; **Department of Pathology, Kaohsiung Medical University Hospital; ***Department of Respiratory Therapy, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
Address reprint requests to: Dr. Jong-Rung Tsai, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, No. 100, Tzyou 1st Road, Kaohsiung 807, Taiwan

Case Report

A 38-year-old female with Down's syndrome had a 3-month history of intermittent epigastralgia. The associated symptoms included anorexia and significant body weight loss of more than 10 kg in the past year. She had visited local clinics several times in the past 3 months, but her anorexia did not improve. She was sent to our emergency department due to fever and progressive abdominal pain for 2 days, accompanied with nausea, vomiting and diarrhea. She denied cough, dyspnea, urinary frequency, urinary burning sensation, tarry stool, hematochezia, tenesmus or small caliber stool.

The patient was thin and malnourished (body height: 150 cm, body weight: 38.3 kg, body mass index: 17.02). In the emergency department, she had fever up to 38.3°C and hypotension despite fluid resuscitation. The abdominal pain was characterized as dullness but not colic, located at the epigastric area with extension to the pan-abdomen with concurrent abdominal muscle guarding and abdominal rebounding pain. Some palpable painless lymph nodes were identified at the left neck. The bilateral breathing sound was mildly coarse. Plain abdominal X-ray revealed normal bowel gas distribution. She then underwent abdominal CT for acute abdominal survey. CT (Figure 1) disclosed mild ascites at the cul-de-sac, multifocal hypodense cystic lesions in the liver, hepato-duodenal ligament, gastro-duodenal ligament, and mesentery, and peri-caval, aorto-caval, para-aortic and bilateral renal hilar spaces, leading to a suspicion of lymphadenopathy related to malignancy or an infectious process. Chest plain film (Figure 2A) showed both lower lung reticulo-nodular lesions and widening of the upper mediastinum. Hemogram showed leukocytosis (17000/uL), neutrophilia (neutrophils 95%) and



(A) (B)

Fig. 1. Abdominal CT revealed multiple hypodense cystic lesions in the bilateral liver, and peri-caval, aorto-caval, mesentery and para-aortic spaces.

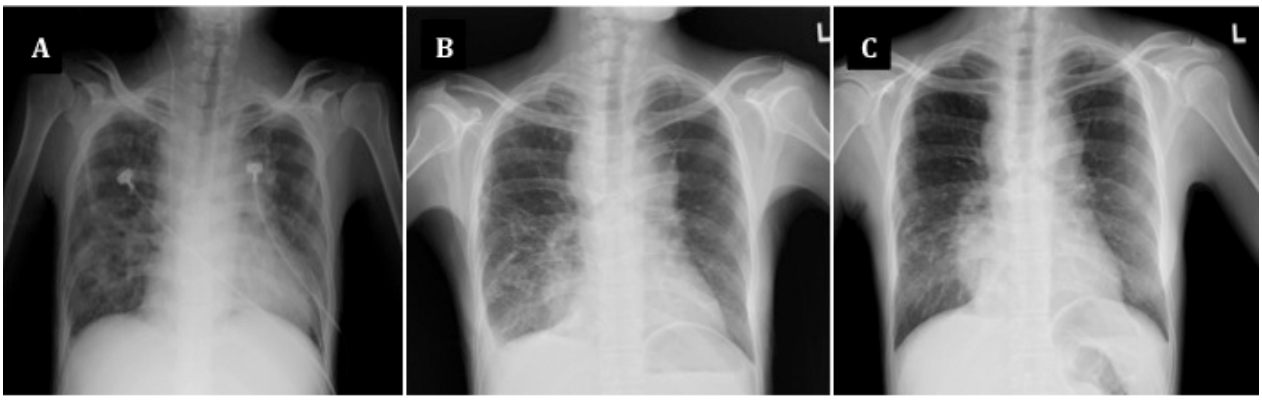


Fig. 2. (A) Initial chest X-ray showed mediastinum widening, and reticulo-nodular lesions scattered in both lung fields (B) One month post-anti-TB regimen: although the right middle lobe had a consolidation lesion with exudative parapneumonic effusion, there was shrinkage of the mediastinal lymph nodes and a decrease in infiltrates in both lung fields (C) Four months post-anti-TB regimen. Remarkable improvement in infiltrates in both lungs and diminished right pleural effusion; the right lower lobe mass was stable and had stopped worsening.

normocytic anemia (Hb 9.2 g/dL, MCV 88.2%). Other biochemistry results showed normal renal and liver function, except elevated C-reactive protein (118.59 mg/L). Under the impression of septic shock focused on intra-abdominal infection, she was sent to the medical intensive care unit.

We prescribed ertapenem 1g QD for the patient's intra-abdominal infection. Three consecutive sputum sets of acid-fast stain were all negative. The cultures and cytology of ascites were all negative. Tumor markers, including carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), 12-O-tetradecanoylphorbol-13-acetate (TPA), carcinoma antigen 125 (CA-125), alpha-fetoprotein (AFP) and lymphoma-related titers (lactic dehydrogenase, beta-2-microglobulin) for malignancy survey, were all within normal range. Iron deficiency anemia was diagnosed by low ferritin (19.7 ng/mL) and low serum iron/T.I.B.C. (22 ug/dL over 208.5 ug/dL). HIV ELISA, autoimmune markers and hepatitis markers were also all negative. We arranged chest CT because of widening of the upper mediastinum and the reticulo-nodular pattern of both lower lungs, and found bilateral reticulo-nodular lesions, right-side pleural effusion and multiple hypodense cystic lesions in the bilateral supra-clavicular, peri-vascular, para-bronchial, peri-carinal, and aorto-pulmonary window, and subcarinal spaces.

After her hemodynamic status had stabilized, the family agreed to the patient undergoing video-assisted thoracic surgery (VATS) for the para-mediastinum lymph nodes. Bronchoscope and liver biopsy were contraindicated because she could not cooperate well. Pathology reported prominent geographic necrosis with few infiltrating inflammatory cells, and granulomatous reaction with some multinucleated giant cells. Acid-fast stain revealed some bacilli (Figure 3). No malignant cells were identified under microscopy or in immunohistochemical studies. Neither mycobacterium nor bacteria was observed in the pleural effusion that was obtained during operation. We prescribed her anti-TB therapy with full-dose rifampicin, isoniazid, ethambutol and pyrazinamide.

Two sets of sputum culture later yielded

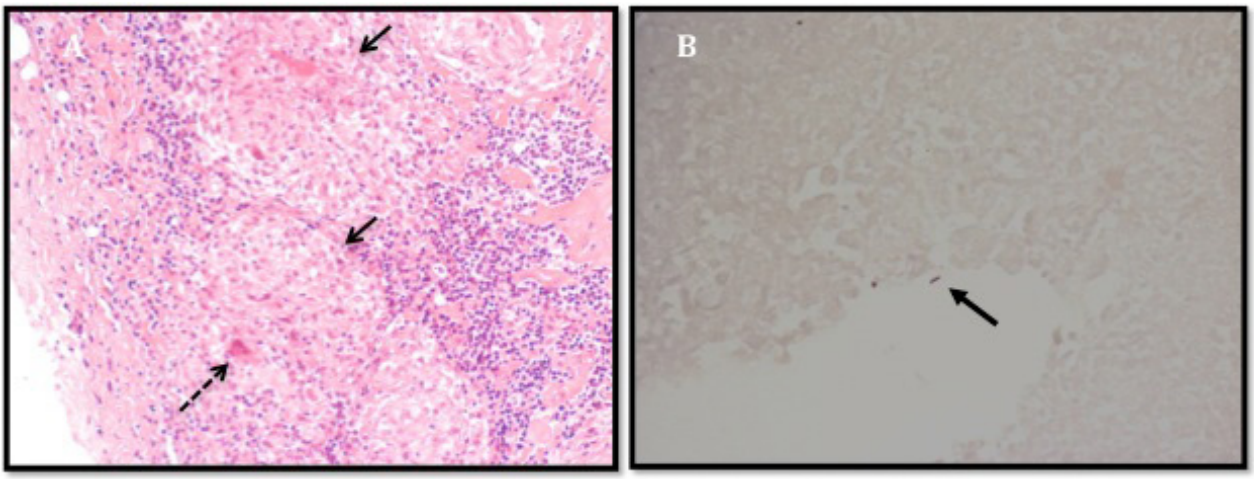


Fig. 3. Mediastinum lymph node biopsy. (A) Granulomatous reactions (arrow) with some multinucleated giant cells (dashed arrow) can be seen under hematoxylin and eosin stain (100x). (B) Some bacilli (arrow) can be identified under acid-fast stain.

Mycobacterium tuberculosis complex, and the sensitivity tests were all sensitive. After anti-TB therapy had been initiated for 2 weeks, she regained her appetite, and had no fever after that. The chest X-ray (Figure 2B) 1 month post-treatment showed increased right-side pleural effusion and a right lower lung mass-like lesion. The chest CT (Figure 4) 3 months later revealed lymphadenopathies involving the mediastinum, mesentery, intra-peritoneum, and retro-peritoneum, and liver masses mildly decreased in size, but the right lower lung still presented a mass with central necrosis. She did not undergo needle aspiration from the right lower lung mass because she was unable to cooperate well. The following lab data showed no leukocytosis, no anemia, and no abnormal biochemistry, and no mycobacterium yield in the blood culture. The anti-TB regimen was shifted to rifampicin, isoniazid and ethambutol on Day 61; she is still undergoing treatment as of this writing. At 4 months after treatment, the chest X-ray (Figure 2C) showed remarkable improvement of the lung infiltrates, right pleural effusion and mediastinal lymphadenopathy; the right lower lobe mass was stable and was no longer worsening.

Discussion

When immunocompromised populations are infected with TB, dissemination may occur. Disseminated TB refers to 2 or more noncontiguous sites involved with mycobacterium infection. The reported prevalence of disseminated TB among northern Taiwan TB patients was 5.4% from January 1995 to December 2004 [2], which was lower than in a previous report (10%) [1]. This may attribute to the relatively high incidence of TB infection and lower prevalence of HIV/AIDS in Taiwan [2]. About 1-2% of all TB-infected patients have disseminated TB, and only around 8% of all extrapulmonary TB cases are found in immunocompetent individuals [3].

Leading factors predisposing individuals to disseminated TB include HIV infection, malnutrition, chronic renal failure under dialysis, drugs (immunosuppressive drugs, immunomodulator drugs, steroid), alcoholism, diabetes

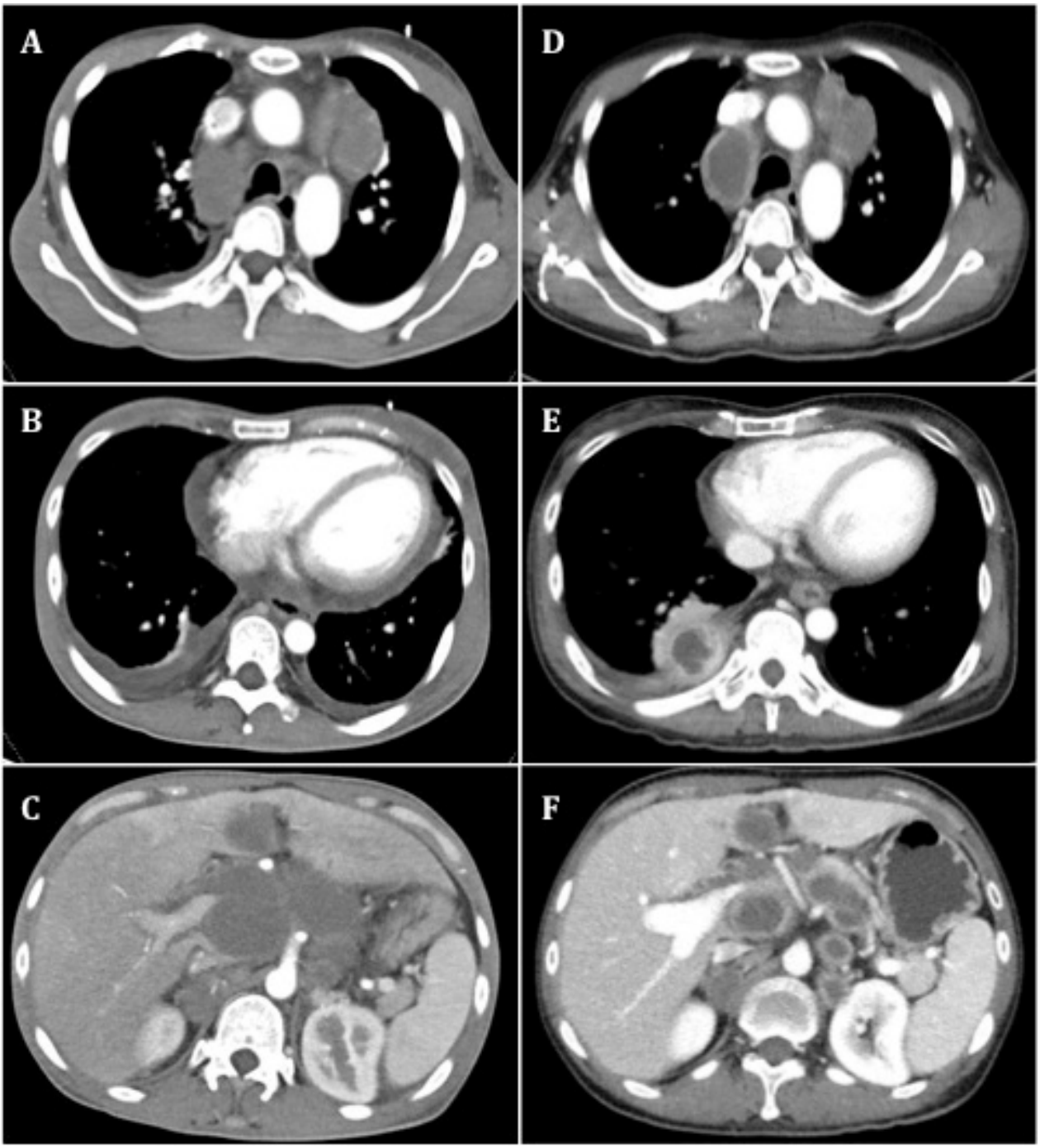


Fig. 4. (A, B, C) CT revealed multiple hypodense cystic lesions in the bilateral peri-vascular, para-bronchial, and aorto-pulmonary window, subcarinal, liver, and peri-caval, aorto-caval, and para-aortic spaces. (D, E, F) After taking the anti-TB medication for 3 months. Although the right lower lung presented a mass with central necrosis, lymphadenopathies involving the mediastinum, mesentery, intra-peritoneum, retro-peritoneum and liver masses mildly decreased in size; right-side pleural effusion was also resolved.

mellitus and underlying malignancy. Infants and elderly are also high-risk groups [3]. In HIV seronegative patients, the most common underlying conditions were immunosuppressive therapy and heart disease [4].

Symptoms of disseminated TB are protean and often delay the diagnosis. Fever, long duration of febrile days, cough and body weight loss are common characteristics at the time of diagnosis [5-6]. Although clinical presentations vary, patients who present miliary lung lesions, elevated serum ferritin (>1000 ug/L), infiltrative liver disease (ALP/GGT defined as twice the reference value) and elevated serum calcium (>2.6 mmol/L, after adjusting to albumin level) may have disseminated TB [2]. Hilar enlargement is more likely to be observed in HIV-seropositive patients than miliary pulmonary lesion [7].

It is important to obtain cultures and biopsies from infected sites; the leading sites of disseminated TB involvement are the lungs, lymphatic systems, musculoskeletal system and urogenital system. An Indian report [8] discussed the advantage of bronchial washing in smear-negative patients. Fluid such as pleural effusion, ascites, cerebrospinal fluid, pericardial effusion or synovial joint fluid are less diagnostic than tissue culture. Body fluid analysis usually shows polymorphonuclear leukocyte-predominant, and then lymphocyte-predominant within 2 weeks.

Wang *et al* [2] reported the poor prognostic factors of disseminated TB as hypoalbuminemia (albumin <3.5 g/dL), hyperbilirubinemia (total bilirubin >1.0 mg/dL), renal insufficiency (creatinine >1.5 mg/dL) and delayed anti-TB treatment. Patients who received fluoroquinolone prior to the standard anti-TB prescription had a poorer prognosis [9]. Crump *et al* [10] found that in patients with bacteremic TB, the mortality within 1 month was 5 times greater than in patients without bacteremic TB. Even in immunocompromised patients, Mycobacterium culture might not be obtained until the late disseminated stage. In Taiwan, mandatory chest plain film is necessary for patients who suffer from prolonged anorexia, body weight loss or febrile episode, even without respiratory symptoms. If it is available, fiberoptic bronchoscopic alveolar lavage should be considered for patients with a suspicion of TB infection, even with sputum acid-fast stain presenting as negative.

Patients with Down's syndrome may be susceptible to lower respiratory tract infections. One of the reasons is immune system dysfunction, which is due to derangement in the number and activity of T cells ($CD4^+$ and suppressor T cells) and natural killer cells [11-12]. Humoral immunity defect may also be present [13]. In our case, the patient's impaired cellular immunity, malnutrition and delayed diagnosis contributed to the disseminated TB. In addition, insufficient ability to express discomfort and the lack of a long-term febrile episode may also delay the diagnosis. It should be mentioned that currently there is no strong evidence to indicate that all patients with Down's syndrome are immunocompromised, and also no evidence has shown a difference in incidence of TB infection or treatment effect between Down's syndrome patients and the general population. If a Down's syndrome patient had recurrent lower respiratory tract infection or disseminated TB, we may check his/her immunity function for further confirmation.

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一位唐氏症患者以漸進性腹痛來表現散在性結核：病例報告與文獻回顧

郭子右 * 林智鴻 ** 蔡忠榮 *,*** 鍾飲文 *,***

一位 38 歲女性患者過去三個月因反覆上腹痛而時常就診；過去一年患者已有食慾不振的症狀以及體重減輕 10 公斤。除了唐氏症病史外，患者並沒有其他顯著病史。患者因腹痛漸趨嚴重及反覆發燒而至急診求診，同時在急診發現有休克情形。腹部及胸部電腦斷層檢查懷疑結核菌感染或是惡性淋巴腫瘤；後續痰液培養報告以及縱膈腔淋巴結取樣的病理報告皆顯示為結核菌感染。唐氏症的患者已被證實有較高機率罹患白血病和淋巴癌，但是否易受到感染則尚未有明確定論。我們回顧過去有關唐氏症免疫異常及散在性結核病的相關文獻，並希望借此提醒臨床醫師要更注意唐氏症患者，及其有可能有較高機會由肺結核發展為散在性結核病。*(胸腔醫學 **2015; 30: 352-359**)*

關鍵詞：散在性結核，唐氏症

高雄醫學大學 附設中和紀念醫院 內科部 胸腔內科 *，附設中和紀念醫院 病理部 **，醫學院 呼吸治療學系 ***
索取抽印本請聯絡：蔡忠榮醫師，高雄醫學大學 附設中和紀念醫院 內科部 胸腔內科，高雄市 807 自由一路 100 號

Aspergillus Tracheobronchitis – A Case Report

Yu-Ping Chang*, Huang-Chih Chang*, Chin-Chou Wang*,**, Meng-Chih Lin*,***, An-Shen Lin*

Tracheobronchial aspergillosis accounts for a small percentage of *Aspergillus*-related respiratory disease and has been classified into invasive, allergic and saprophytic forms. Although this disease is generally observed in severely immunocompromised patients, it may occur in less immunocompromised or even immunocompetent patients. Herein, we report a 74-year-old woman with exertional dyspnea for 6 months. Initial chest radiograph showed right upper lobe collapse. Chest computed tomography revealed a right upper endobronchial lesion with right upper lobe collapse. Bronchoscopy showed thick mucus plugs obstructing the right upper lobe bronchial orifice, with mucosa infiltration; biopsy revealed fungal hyphae with acute angle branching and tissue necrosis, which was compatible with aspergillosis. After oral voriconazole therapy for 4 months, the chest radiograph showed no improvement. Possible causes of treatment failure are discussed. ***(Thorac Med 2015; 30: 360-366)***

Key words: *Aspergillus*, tracheobronchitis

Introduction

Aspergillus causes a wide variety of clinical syndromes, including tracheobronchial aspergillosis, allergic bronchopulmonary aspergillosis, mycetomas, chronic necrotizing pulmonary aspergillosis and invasive aspergillosis [1]. In recent years, the incidence of pulmonary aspergillosis has increased due to an increased number of susceptible individuals, clinical alertness and improved detection techniques [2]. The development of clinical syndromes is affected by the relationship between organism virulence and host defense [3]. Obstructing bronchial aspergillosis is a saprophytic form of tracheobronchial aspergillosis, and is defined as thick mucus plugs formed by *Aspergillus* hyphae that obstruct tracheobronchial airways without evidence of invasion or allergic reaction [4]. Here, we report a case of obstructing bronchial aspergillosis presenting as endobronchial lesion with lobar collapse.

*Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan; **Graduate Institute of Occupational Safety and Health, Kaohsiung Medical University, Kaohsiung, Taiwan; ***Department of Respiratory Care, Chang Gung Institute of Technology, Chiayi, Taiwan
Address reprint requests to: Dr. An-Shen Lin, Division of Pulmonary & Critical Care Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, 123 Dabi Road, Niaosung, Kaohsiung, Taiwan

Case Report

A 74-year-old woman, a never-smoker, came to our hospital due to cough with scanty sputum and exertional dyspnea for 6 months, and body weight loss of 5 kg within 2 months. Her past history included hypertension, type 2 diabetes mellitus under oral anti-diabetic agent control (HbA_1C: 7.8%) for years, and sigmoid colon adenocarcinoma post-operation years ago. There was no fever or hemoptysis. She initially went to another hospital where chest radiograph revealed right upper lobe collapse. She then underwent bronchoscopy and chest computed tomography (CT). Chest CT showed right upper endobronchial lesion with right upper lobe collapse (Figure 1). Bronchoscopic biopsy from the right upper lobe showed extensive necrosis and fungal hyphae and spores, compatible with candida infection. She came to our hospital for a second opinion. Physical examination was unremarkable. There was no wheezing or enlarged neck lymph nodes. Chest radiograph showed an ill-defined mass-like lesion at the proximal part of the right upper lobe with partial collapse (Figure 2). White cell counts and differential count, and C-reactive protein levels were normal. The blood creatinine level was 0.85 mg/dL and fasting blood glucose level was 159 mg/dL. Fiberoptic bronchoscopy revealed white necrotic plugs obstructing the right upper lobe orifice, with mucosa infiltration (Figure 3). Biopsy was performed, and pathology showed fungal hyphae with acute angle branching and tissue necrosis, which was compatible with aspergillosis (Figure 4). There was no evidence of mucosa invasion. Both Gomori Methenamine

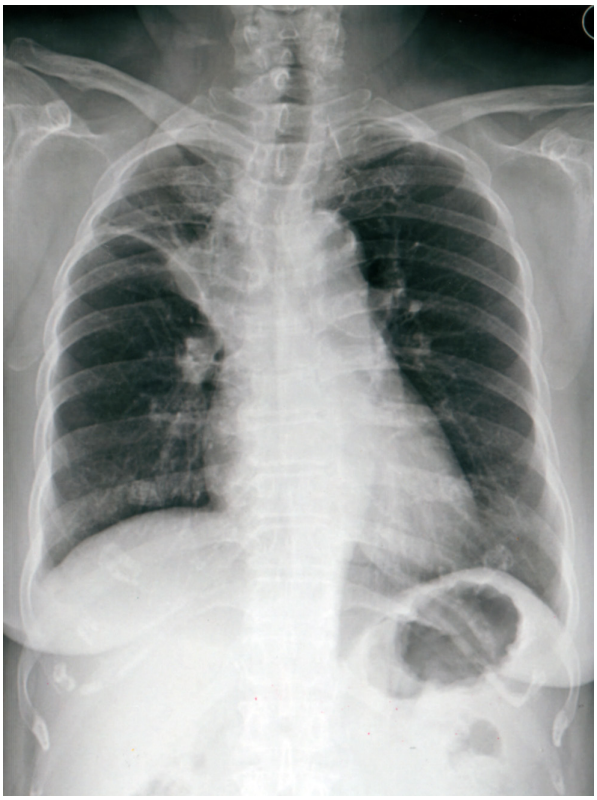

Fig. 2. Chest radiograph shows an ill-defined mass in the proximal part of the right upper lobe, causing mediastinal bulging and volume loss of the right upper lobe.

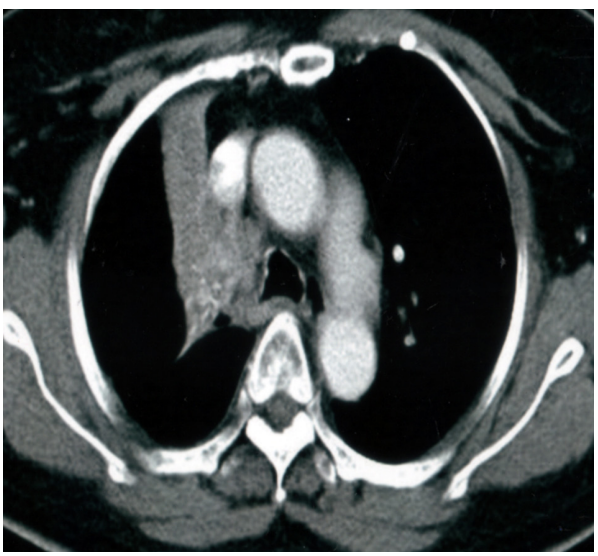

Fig. 1. Chest computed tomography shows an ill-defined mass in the proximal part of the right upper lobe, extending to the mediastinum, and causing right upper lobe partial collapse.

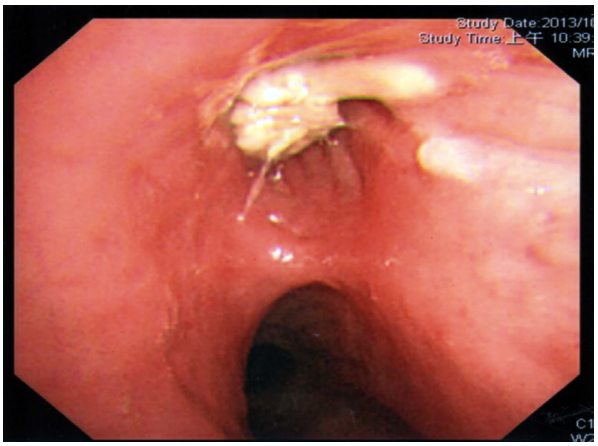

Fig. 3. Fiberoptic bronchoscopy reveals white mucus plugs obstructing the right upper lobe orifice with mucosa inflammation.

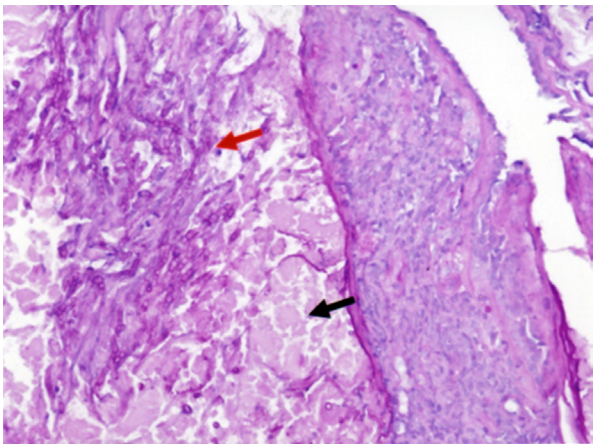

Fig. 4. Periodic acid-Schiff stain of bronchial biopsy tissue shows fungal hyphae with acute angle branching (red arrow) and tissue necrosis (black arrow), compatible with aspergillosis.

Silver stain and Periodic acid-Schiff stain were positive. Based on the bronchoscopic findings and bronchial biopsy report, obstructing bronchial aspergillosis was diagnosed. Oral voriconazole 200 mg Q12H was prescribed for 4 months. Follow-up chest radiograph (Figure 5) showed no improvement. We suggested a repeat bronchoscopy examination, but the patient refused and was lost to follow-up. We also arranged a colonoscopy which showed no tumor recurrence.

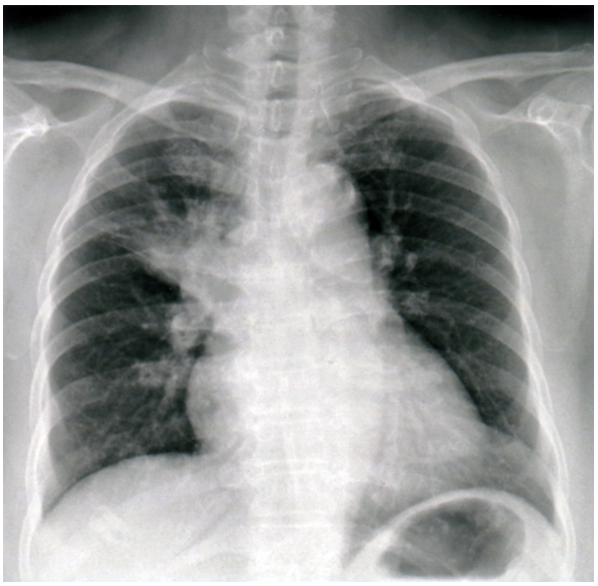

Fig. 5. Chest radiograph after oral voriconazole treatment for 4 months shows enlargement of the right upper lobe mass and opacities in the lower part of the right hilum.

Discussion

Aspergillus is a genus of molds with a ubiquitous presence in soils, organic debris and water. *Aspergillus* spores are present almost everywhere in the air [5]. Respiratory diseases caused by *Aspergillus* can affect the upper airways, trachea, bronchi and pulmonary parenchyma [3].

Patients with neutropenia, hematologic malignancies, solid organ transplantation, hematopoietic stem cell transplantation, or chronic corticosteroid therapy are at risk of developing *Aspergillus* tracheobronchitis [6]. However, *Aspergillus* tracheobronchitis also could occur in immunocompetent or less immunocompromised people [6-8].

Tracheobronchial aspergillosis varies from

colonization to destructive tracheobronchitis, and has been classified into saprophytic, allergic, and invasive forms, based on host defense and host-fungus relationships [1,3,9]. The invasive form includes *Aspergillus* tracheobronchitis, ulcerative *Aspergillus* tracheobronchitis, and pseudomembranous *Aspergillus* tracheobronchitis. *Aspergillus* tracheobronchitis is characterized by extensive tracheobronchial inflammation caused by *Aspergillus* in patients with leukemia or acquired immunodeficiency syndrome (AIDS). Ulcerative *Aspergillus* bronchitis typically presents with ulcers in the tracheobronchial wall in patients with lung transplantation or AIDS. Pseudomembranous *Aspergillus* tracheobronchitis is characterized by a necrotic pseudo-membrane overlying the mucosal surface in severely immunocompromised hosts with leukemia [3,9-10]. The 3 invasive forms may represent progressive change in the disease. The saprophytic form includes mucoid impaction and obstructing bronchial aspergillosis. The allergic form includes allergic bronchopulmonary aspergillosis (ABPA) and bronchocentric granulomatosis [3,9]. Our patient showed features of obstructing bronchial aspergillosis based on the bronchoscopic finding and bronchial biopsy report.

Obstructing tracheobronchial aspergillosis is defined as thick mucus plugs formed by *Aspergillus* hyphae that obstruct tracheobronchial airways without evidence of invasion or allergic reaction [4]. The symptoms are usually subacute, and include cough, dyspnea, chest pain, hemoptysis and the coughing out of fungal casts [9]. Like invasive *Aspergillus* tracheobronchitis, this disease usually occurs in immunocompromised patients with hematological malignancies or AIDS [3,10]. This disease is also thought to be an early stage of invasive pulmonary aspergillosis and may progress to invasive disease [11-12]. In a review of endobronchial fungal disease, obstructing tracheobronchial aspergillosis was found in 6 of 121 patients (5%) with endobronchial aspergillosis [13]. Obstructing tracheobronchial aspergillosis was considered to be refractory to antifungal therapy due to poor tissue penetration, and to have a poor outcome like pseudomembranous *Aspergillus* tracheobronchitis, since most patients were immunocompromised with hematologic malignancies, and diagnosis and treatment were both difficult [10]. However, in a case series of isolated invasive *Aspergillus* tracheobronchitis, 6 patients were classified as having an occlusion type and only 1 patient died of primary malignancy [14]. The relatively good outcome may be due to most patients being immunocompetent, with lung cancer or tracheobronchial tuberculosis as underlying diseases. In the review mentioned above, overall mortality of patients with endobronchial aspergillosis was 48% [13].

Treatment of tracheobronchial aspergillosis is similar to that for invasive aspergillosis. Voriconazole is suggested as primary therapy by the Infectious Diseases Society of America (IDSA), while alternative therapies include liposomal amphotericin B, amphotericin B lipid complex, caspofungin, micafungin, posaconazole and itraconazole [15]. Antifungal therapy combined with bronchoscopic intervention, including electrocauterization, cryotherapy, mechanical debridement and intraluminal antifungal instillation, has been reported [14]. Other adjunctive local therapy such as laser ablation and endoscopic resection of necrotic tissue has also been reported [6].

Although our patient had a history of diabetes and colon adenocarcinoma, her diabetes was under oral anti-diabetic agent control with

an HbA_1C level of 7.8%, and the colon cancer had been treated. Her immune status was not severely compromised. Oral voriconazole 200 mg Q12H was prescribed for 4 months, but the follow-up chest radiograph showed no improvement. Possible reasons for treatment failure included poor tissue penetration of voriconazole, resistance of *Aspergillus* to voriconazole [2-3,15], and poor compliance of the patient. We suggested a repeat bronchoscopy examination, but the patient refused and was lost to follow-up. Whether surgery or local bronchoscopic intervention would have been beneficial for her is an unanswered question. Although some surgical indications have been proposed by the IDSA, such as lesions near great vessels or the pericardium, chest wall invasion, pericardial infection, skin and soft tissue infection, etc. [15], precise surgical indications of *Aspergillus* tracheobronchitis are not well established.

Conclusion

We present a case of obstructing tracheobronchial aspergillosis with the initial presentation of chronic cough and endobronchial lesion causing right upper lobe collapse. *Aspergillus* tracheobronchitis should be considered even in patients not severely immunocompromised, since early symptoms are non-specific and chest radiograph may be normal. Bronchoscopy plays a key role in disease assessment and sample collection. Antifungal therapy may not be effective. Indications for and benefits of surgery need further investigation.

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麴菌氣管支氣管炎個案報告

張育平 * 張晃智 * 王金洲 *,** 林孟志 *,*** 林安伸 *

麴菌氣管支氣管炎佔麴菌所造成的呼吸道疾病的一小部分，且被分類成侵襲性、過敏性、腐生性三種型式。雖然麴菌氣管支氣管炎通常發生於嚴重免疫功能不全的病人身上，但也可能發生在免疫功能低下程度較輕微或甚至免疫功能正常的病人。我們報告一個 74 歲女性糖尿病患者，一開始表現為持續 6 個月的咳嗽及活動性喘，胸部 X 光片顯示右上肺葉腫塊及塌陷，胸部電腦斷層發現右上肺葉支氣管內病灶合併右上肺葉塌陷。支氣管鏡發現右上肺葉開口有白色壞死組織塊阻塞且合併黏膜浸潤，切片的病理組織顯示為麴菌。經過 4 個月的口服 voriconazole 治療，胸部 X 光並無進步。治療失敗的可能原因亦有討論。*(胸腔醫學* ***2015; 30: 360-366)***

關鍵詞：麴菌，氣管支氣管炎

* 長庚大學醫學院 高雄長庚紀念醫院 內科部 胸腔內科
** 高雄醫學大學 職業安全衛生研究所，*** 長庚科技大學 呼吸照護系
索取抽印本請聯絡：林安伸醫師，高雄長庚紀念醫院 內科部 胸腔內科，高雄市鳥松區大埤路 123 號

Huge Intra-cardiac Mass in a Patient with an Infectious Left Atrial Thrombus: Case Report and Literature Review

Hung-Ling Huang*, Ming-Ju Tsai*, Shan-Yin Tsai**, Inn-Wen Chong*,***, Chau-Chyun Sheu*,****

The differential diagnosis of an intra-cardiac mass is always challenging. Imaging tools including transthoracic echocardiography, trans-esophageal echocardiography, computed tomography and magnetic resonance imaging can provide a useful assessment and overall visualization of the mass. However, the etiology will not be confirmed without a biopsy. Although thrombus is the most common etiology of an intra-cardiac mass, infectious thrombus has been rarely reported. Its risk factors, presentations, prognosis, and optimal treatments are largely unknown. We report the case of a patient with advanced thyroid follicular cancer and atrial fibrillation, who was admitted for bradycardia and heart failure caused by digoxin intoxication. The patient had no obvious septic presentations on admission. Echocardiography accidentally found a huge mass in the left atrium. Surgical excision confirmed the diagnosis of an infectious thrombus. Despite aggressive treatment, the patient finally died. We report this case of a 76-year-old woman with a huge infectious thrombus in the left atrium and hope that it will raise the level of suspicion of an infectious thrombus in patients with a huge, rapidly-enlarging intra-cardiac mass. The initial manifestations of an infectious intra-cardiac thrombus may be subtle until disease progression. Imaging studies are useful for initial assessment, but only surgical pathology can confirm the diagnosis. Early surgical excision with prolonged antibiotic treatment may increase the chance of survival. ***(Thorac Med 2015; 30: 367-374)***

Key words: infectious thrombus, left atrium, intra-cardiac mass

Introduction

The differential diagnoses of left intra-cardiac mass are varied, and include tumor, thrombus, vegetation, or cyst [1]. Thrombus is the most common etiology, especially in those with valvular disease or atrial fibrillation. An intra-cardiac thrombus can be found typically in the left ventricle and atrial appendage, but can also extend to the body of the left atrium [2].

*Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; **Department of Pathology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; ***Departments of Respiratory Therapy, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; ****Department of Internal Medicine, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
Address reprint requests to: Dr. Chau-Chyun Sheu, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, No. 100 Tzyou 1st Road, Kaohsiung 807, Taiwan

Intra-cardiac infectious thrombus is very rare, as most cases are usually reported in the ventricular chamber and are frequently associated with the complication of myocardial infarction [3]. To the best of our knowledge, only 5 cases of left atrial infectious thrombus have been reported in the literature [3-7].

Imaging studies including transthoracic echocardiography (TTE) and trans-esophageal echocardiography (TEE) are useful for initial assessment of an intra-cardiac mass [8]. Advanced imaging tools, including computed tomography (CT) and magnetic resonance imaging (MRI), can provide additional information and insight [9]. However, the final diagnosis can be made only with histological examination. Prompt surgical resection of the infectious thrombus is necessary, and should be followed by prolonged antibiotic treatment [4-5].

Case Presentation

A 76-year-old woman had the underlying diseases of thyroid follicular carcinoma with bone, liver and lung metastases, congestive heart failure and atrial fibrillation. She had regularly taken levothyroxine, bisoprolol, valsartan, digoxin, furosemide and aspirin for 6 years. She presented to the emergency department because of dyspnea, palpitation, and chest tightness for 1 week. She noted a decreased urine amount and pitting edema in the bilateral lower limbs. She also complained of intermittent mild fever and muscle soreness for 1 month, for which she took some over-the-counter analgesics and antipyretics.

Physical examination revealed an acutely ill-looking appearance, Glasgow coma scale of 14, blood pressure of 88/46 mmHg, irregular slow pulse rate of 46/min, respiratory rate of 22/min, and an oxygen saturation of 91% in ambiant air. On auscultation, she had bilateral basal crackles when breathing. Her heart sound included slow, irregular heartbeats with a harsh murmur (grade III/IV) at the apex, which radiated to the left sternal edge. The 12-lead electrocardiogram showed atrial fibrillation with a slow ventricular rate. Laboratory tests revealed mild neutrophilic leukocytosis (WBC: 11600/uL, neutrophil: 80%), a slightly elevated C-reactive protein level (20.9 mg/L), renal function impairment (blood urea nitrogen: 62.5 mg/dL; creatinine: 4.91 mg/dL), and a high D-dimer level (29.21 mg/L), high B-type natriuretic peptide level (193 pg/mL), and high digoxin level (5.08 ng/mL). Urinalysis showed pyuria. Chest radiography revealed mild pulmonary congestion, cardiomegaly, and multiple metastatic nodules.

She was given oxygen therapy, fluid resuscitation, and dopamine infusion. A transvenous pacemaker was implanted. Levofloxacin (500 mg/day) was empirically administered for urinary tract infection. She was then admitted to the medical intensive care unit. TTE on admission accidently found a huge (5.4 × 3.2 cm), well-encapsulated, central-hypoechoic, and pedunculated mass at the posterior wall of the dilated left atrium, floating with heartbeats (Figure 1), with adequate systolic function (ejection fraction of 58%), severe mitral regurgitation, and mild aortic regurgitation. Worthy of mention is that the Doppler echocardiogram revealed a transient increased velocity across the mitral valve as the floating thrombus moved toward the mitral valve (MV peak velocity=2.7 m/s, peak gradient=37 mmHg), which could be reversed to normal range when the mass moved away. No intra-cardiac mass was recorded in the echocardiogram 6 months prior to admis-

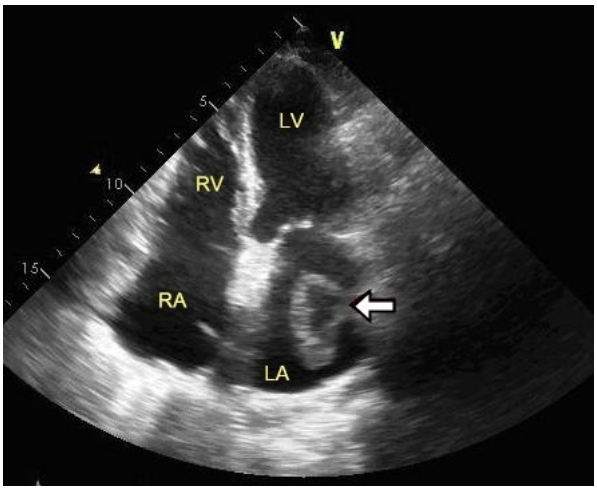

Fig. 1. Apical 4-chamber view of the transthoracic echocardiography revealed a well-encapsulated, central-hypoechoic, pedunculated mass (arrow), measuring 5.4 cm × 3.2 cm in size, floating at the posterior wall of the left atrium. LV: left ventricle; LA: left atrium; RV: right ventricle; RA: right atrium.

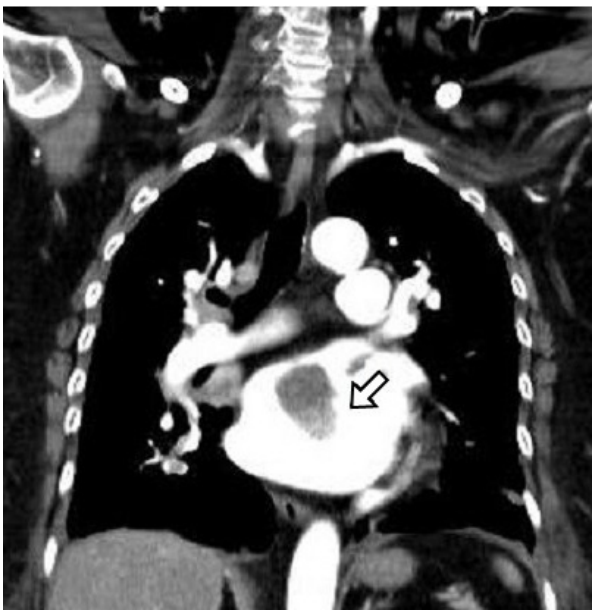

Fig. 2. Axial view of the contrast-enhanced chest computed tomography revealed a huge, pine cone-like, pedunculated, floating, smoothly encapsulated mass with central heterogeneous attenuation in the left atrium (arrow).

sion. Contrast-enhanced chest CT revealed a pedunculated mass in the left atrium, with heterogeneous and hypodense content inside (Figure 2). Coronary angiography examination and CT revealed no vessel supplying the mass. Her bradycardia persisted, even after the serum digoxin level returned to normal. Because of intermittent obstruction on echocardiography and the risk of systemic embolism, the mass was removed surgically through a trans-atrial approach.

The mass was a soft, encapsulated, well-circumscribed lesion with a small stalk. Mass excision revealed a large amount of gross pus inside. The pathohistological examination revealed pockets of neutrophils with microabscess, which turned out to be a calcified septic thrombus (Figure 3). Special stains for microorganisms, including Gomori's Methenamine Silver, Gram's, Giemsa, Warthin-Starry, and acid-fast stains were all negative. Even with aggressive treatment, the patient had severe cardiogenic shock (cardiac index of 1.4 L/min/m^2 and pulmonary artery occlusive pressure of 24 mmHg) postoperatively and died 4 days after the operation.

Discussion

We presented the case of a critically ill patient with a huge, pedunculated, floating, well-encapsulated cystic mass in the left atrium, which was histologically proven to be an infectious thrombus. The spectrum of differential diagnoses for an intra-cardiac mass is broad, and includes tumor, thrombus, vegetation, or cyst [1]. A huge intra-cardiac mass is very rare and may result in systemic thromboembolism and sudden death [9]. Thrombus is the most common etiology of a huge intra-cardiac mass, and

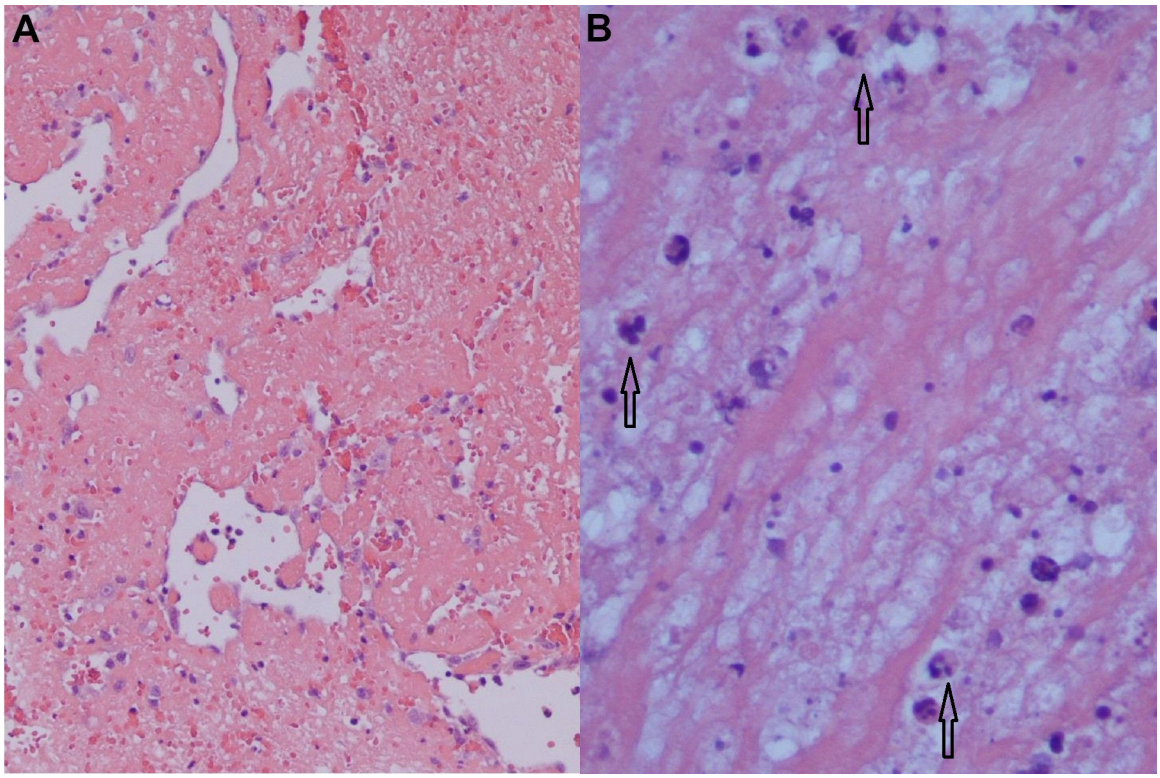

Fig. 3. Hematoxylin and Eosin stain histopathology showed pockets of neutrophils with micro-abscesses (arrows). No microorganisms were identified. 40× (A), 100× (B).

is highly associated with valvular disease and atrial fibrillation. It typically is located in the left ventricle or atrial appendage, but can also extrude to the body of the left atrium [2]. Myxoma should always be taken into the differential diagnosis because it is the most common primary cardiac tumor in adults. It often originates from the fossa ovalis [9,12], and may result in severe complications due to its fragility and high mobility in nature. Our patient had a metastatic thyroid follicular cancer, thus a metastatic lesion should be excluded. Cardiac metastases account for about 2% of patients with malignancies of other systems, and may involve invasion to the myocardial tissue or pericardium [8]. Based on the cystic morphology, the differential diagnoses also include a hydatid cyst, intra-cardiac varices, a bronchogenic cyst, and rarely a myxoma [13]. Since the intra-cardiac mass in our patient was not seen in the previous echocardiogram, a huge thrombus was the most likely etiology. However, we did not expect an infectious thrombus before operation because there were no obvious septic presentations and few sets of blood culture were all negative. Infectious thrombus is very rare: only 5 cases of infectious thrombus in the left atrium have ever been reported (Table 1) [3-7].

According to the reported cases, the initial presentations of infectious left atrial thrombi varied. Fever appears to be the most common initial manifestation. Other symptoms include dyspnea, palpitation, and even hemodynamic change.

Table 1. Summary of 6 Cases of Infectious Thrombi in the Left Atrium

Case	Underlying heart disease	Initial Presentation	Pathogens	Blood culture	Thrombus Culture	Treatment	Outcome
Fernández-Ruiz, *et al*. [3]	Nil	Fever (7 months), asthenia, hyporexia, weight loss	*Coxiella burnetii*	Nil*	Nil**	OP Doxycycline	Survived
Okayama H, *et al*. [4]	MS	Fever (7 days), hypotension	*E. coli*	*E. coli*	*E. coli*	OP Ceftriaxone, gentamycin, metronidazole	Mortality CNS infection, brain stem herniation
Dedeilias P, *et al*. [5]	MS	Fever, mental alteration	*E. coli*	*E. coli*	*E. coli*	OP	Mortality
Divchev D, *et al*. [6]	patent foramen ovale	Palpitation	Nil	Nil	Nil	OP	Survived
Yunus M, *et al*. [7]	MS, MR, AR	Fever, shortness of breath, palpitation, and facial puffiness	Nil	Nil	Nil	OP	Survived
Current case	MR, AR		Nil	Nil	Nil	OP Levofloxacin	Mortality

* Tissue PCR (+), polymerase chain reaction (PCR) assay using primers of the H fragment (879 bp) of the QpH1 plasmid

** positive in serologic tests and complement fixation

OP: operation; MR: mitral regurgitation; MS: mitral stenosis; AR: aortic regurgitation

TTE, a non-invasive imaging tool, is usually the first choice for evaluation of an intracardiac mass. However, TEE is superior when attempting to define the characteristics of a mass in the left atrial appendage [8]. CT and MRI can provide further information, but they may involve higher costs and are somewhat time-consuming as a routine procedure [12,14]. Furthermore, none of the imaging studies can easily clarify the differential diagnosis, because of the similar characteristics, the morphology, and ill-defined attachment sites. For example, potential errors can be made in the differential diagnosis of thrombus with myxoma, as they mimic each other in many case reports [1-2,13,15-17]. Histological confirmation is therefore required for a definitive diagnosis.

In most of the reported cases, infectious thrombus was found in the ventricular chambers, and was frequently associated with the complication of myocardial infarction [7]. The isolated microorganisms included *Staphylococcus aureus* and Gram-negative bacilli, mainly Enterobacteriaceae, such as *Escherichia coli*, *Klebsiella pneumonia*, and *Salmonella spp*. [3-5] (Table 1). Other unusual pathogens, which cannot be identified easily, should also be taken into consideration, especially atypical bacteria,

such as *Coxiella*, *Bartonella*, *Legionella* or *Chlamydia* species, which account for the majority of cases of blood culture negative infective endocarditis (BCNE) [5,10,18-19]. *Coxiella burnetii* was identified in 1 case using molecular tools, including direct immunofluorescence assay and polymerase chain reaction (PCR), and electron microscopic examination [3]. Moreover, fungi such as *Aspergillus* species or *Histoplasma capsulatum*, can be the causal pathogen, particularly in immunocompromised patients [10,20]. No microorganisms were isolated in our case. The possible explanations include partial treatment with antibiotics and possible non-bacterial microorganisms.

At present, there are no treatment guidelines for an infectious intra-cardiac thrombus, due to its rarity. Thrombus is always a poorly-visualized organized mass, which leads to a poor response to systemic antibiotics [7]. Prompt surgical resection of the infectious thrombus is necessary, and should be followed up by prolonged antibiotic treatment. The infection of an intra-cardiac thrombus leads to a high mortality rate, caused by difficulty in making a confirmed diagnosis. Some authors suggest initial use of anticoagulation therapy for thrombus to differentiate from other etiologies [1-2,15-16]. However, this may delay proper treatment.

Conclusion

The initial manifestations of an infectious intra-cardiac thrombus may be subtle until disease progression. Clinicians should maintain a high level of suspicion of an infectious thrombus with any "huge" intra-cardiac mass. The outcome of this disease is usually dismal. Early surgical excision is the key to confirm the diagnosis and, together with prolonged antibiotic treatment, may increase the chance of survival. However, more case studies are needed for a better understanding of the epidemiology and appropriate management of an infectious intra-cardiac thrombus.

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巨大之心臟內腫塊－一個左心房感染性血栓之罕見病例報告與文獻回顧

黃虹綾 * 蔡明儒 * 蔡善茵 ** 鍾飲文 *,*** 許超群 *,****

心臟內腫塊之鑑別診斷常常是頗具挑戰的。影像學檢查，包括經體表心臟超音波、經食道心臟超音波、電腦斷層及核磁共振掃描可顯像整個腫塊，並提供初步評估，然而真正的成因仍需靠切片確診。雖然血栓是心臟內腫塊最常見的成因，感染性血栓是很少見的，而其危險因子、臨床表徵、預後及合適的治療等亦大多不明。我們報告此 76 歲女性患者在左心房內有巨大之感染性血栓之案例，希望提高臨床醫師對於心臟內感染性血栓之警覺。心臟內感染性血栓的臨床表徵常常要隨疾病進展才會逐漸顯現，影像學檢查是初期評估的重要工具，但只有外科病理檢查能確定診斷，而盡早手術切除併長時間抗生素治療應可增加病人的存活率。*(胸腔醫學* ***2015; 30: 367-374)***

關鍵詞：感染性血栓，左心房，心臟內腫塊

高雄醫學大學 附設中和紀念醫院 內科部 胸腔內科 *，高雄醫學大學 附設中和紀念醫院 病理部 **
高雄醫學大學醫學院 呼吸治療學系 ***，高雄醫學大學醫學院 醫學系 ****
索取抽印本請聯絡：許超群醫師，高雄醫學大學 附設中和紀念醫院 內科部 胸腔內科，高雄市 807 自由一路 100 號

Difficulty in Diagnosis and Tumor Staging in Coexisting Lung Cancer and Pulmonary Tuberculosis: A Case Report

Wei-Chun Lee, Chin-Kuo Lin, Kam-Fai Lee*, Meng-Jer Hsieh, Ying-Huang Tsai

A solitary pulmonary mass is a common presentation of lung cancer. However, other inflammatory or infectious diseases, such as pulmonary tuberculosis (TB), also present similar imaging characteristics and may coexist with lung cancer. This makes the diagnosis and identifying the correct tumor stage difficult for physicians. Herein we present the case of a patient with coexisting lung squamous cell carcinoma and active pulmonary TB infection, which presented a solitary pulmonary mass. Tissue biopsy was performed twice via different approaches. However, imaging studies could not confirm the diagnosis and tumor stage, which were finally established after surgical intervention. ***(Thorac Med 2015; 30: 375-381)***

Key words: pulmonary tuberculosis, lung cancer, biopsy

Introduction

Lung cancer is the most common cancer worldwide, with an estimated 1,600,000 new cases and 1,380,000 deaths in 2008 [1]. Although several diagnostic tools, such as computed tomography (CT) and positron emission tomography-CT (PET-CT), have made rapid advances in recent years, determining the clinical stage is still a great challenge for physicians, and this ultimately impacts the treatment strategy and disease outcome. Besides, pulmonary tuberculosis (TB) shares similar imaging characteristics and clinical presentations to lung cancer. This clinical condition presents a dilemma in the diagnosis, staging, and treatment of cancer, particularly in TB-endemic regions [2-3]. Herein we report the case of a patient with coexisting lung squamous cell carcinoma and pulmonary TB seen as a solitary pulmonary mass, which made it difficult for the physicians to establish the diagnosis and decide on treatment.

Case Report

A 73-year-old male smoker presented with dry cough for 3 months. He denied the occurrence of fever, chills, night sweating, hemoptysis, and loss of body weight during this period.

Division of Pulmonary and Critical Care Medicine, Chang Gung Memorial Hospital, Chiayi, Taiwan; *Division of Pathology and Laboratory Medicine, Chang Gung Memorial Hospital, Chiayi, Taiwan
Address reprint requests to: Dr. Chin-Kuo Lin, Division of Pulmonary and Critical Care Medicine, Chang Gung Memorial Hospital, Chiayi, Taiwan, No. 6, Sec. W, Jiapu Rd., Puzi City, Chiayi County 613, Taiwan (R.O.C.)

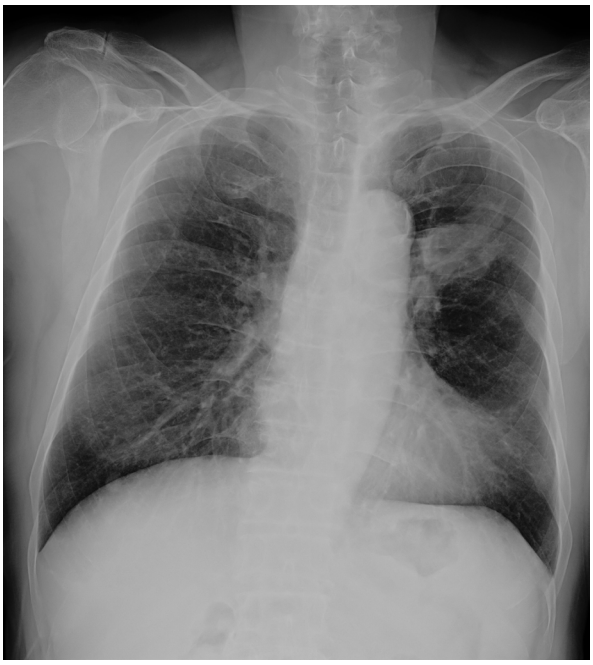
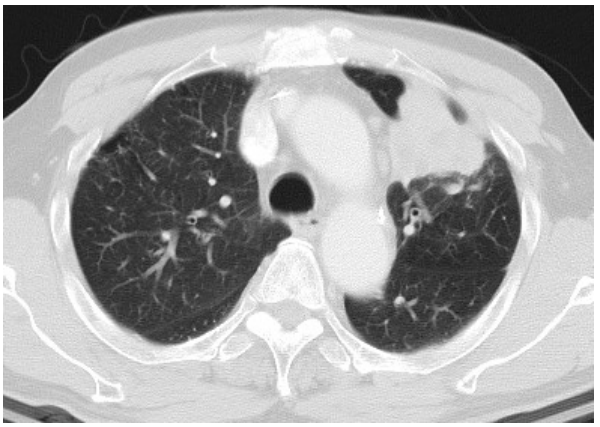


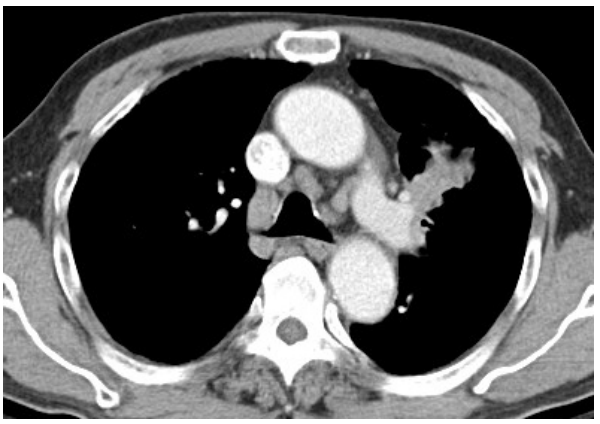
Fig. 1A. Chest X-ray reveals a 4 × 4.5 cm mass lesion in the LUL field

The initial chest X-ray revealed a solitary mass in the left upper lobe (LUL) of the lung (Figure 1A).

Under the impression of lung cancer, he underwent CT scan, which showed a 4.2 × 4.7 cm mass in the LUL with left lung hilar and mediastinal invasion (Figure 1B,1C). CT-guided biopsy was performed for tissue confirmation, but the pathology showed necrotizing granulomatous inflammation (Figure 2A). Lung cancer was still highly suspected as a result of the imaging study, so, after discussion, he underwent transbronchial biopsy at the apical subsegment of the LUL of the lung, and the pathology showed squamous cell carcinoma (Figure 2B). Meanwhile, bronchial washing fluid that was obtained from the same area showed the presence of *Mycobacterium tuberculosis* (MTB) upon culture. This resulted in the uncertainty of the etiology of mediastinal lymphadenopathy.



(1B)



(1C)

Fig. 1B, 1C. CT reveals an irregular soft tissue mass about 4.2 × 4.7 cm in the LUL field with left lung hilum and mediastinum invasion and enlargement of ipsilateral mediastinal lymph nodes

To identify the definite N stage of lung cancer, F-18 FDG PET-CT was performed, and revealed a 6.1 × 4.8 × 4.4 cm^3 mass lesion in the LUL of the lung (SUVmax as 12.46 early and 14.16 delay), left upper hilar areas (SUVmax as 3.13, 3.19 early and 2.94, 2.65 delay), and left subcarinal and right upper hilar areas (SUVmax as 3.11, 3.13 early and 4.56, 2.87 delay) (Figure 1D). Based on the PET finding, lung cancer with T2bN0M0 stage IIA was confirmed. The patient then underwent thoracoscopic LUL lobectomy and radical lymph node dissections

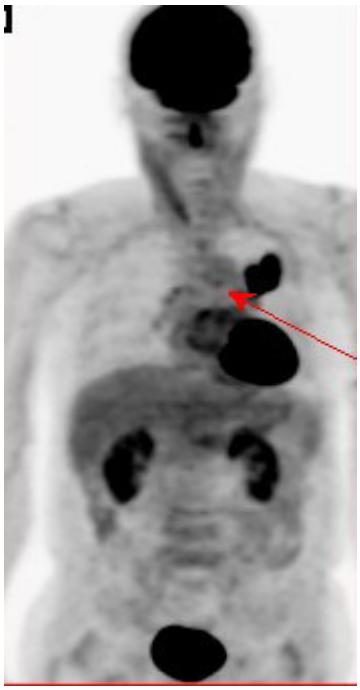


Fig. 1D. Avid lesion at the LUL is probably the primary malignant lung tumor. In addition, avid subcarinal lymph node lesions (SUVmax as 3.11 early and 2.87 delay, score 1) were probably benign lymphadenopathy.

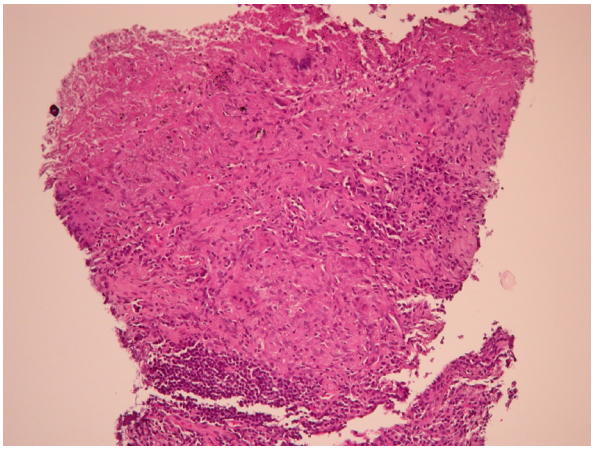


Fig. 2A. CT guided biopsy (100X)
The section reveals granulomatous inflammatory change with multinucleated giant cells

(levels 3, 5, 6, 9). The pathology of the resected tumor revealed a mass measuring 2.1 × 1.8 cm, surrounded by necrotizing granulomatous tissue (Figure 2C). The pathology of all the lymph nodes revealed necrotizing granulomatous inflammation. No metastatic lymphadenopathy was identified. We sent the TB tissue for polymerase chain reaction analysis, which revealed MTB-positive complex DNA. Thus, the final diagnosis for this patient was LUL squamous cell carcinoma, pT1bN0M0, stage 1A, combined with MTB complex infection.

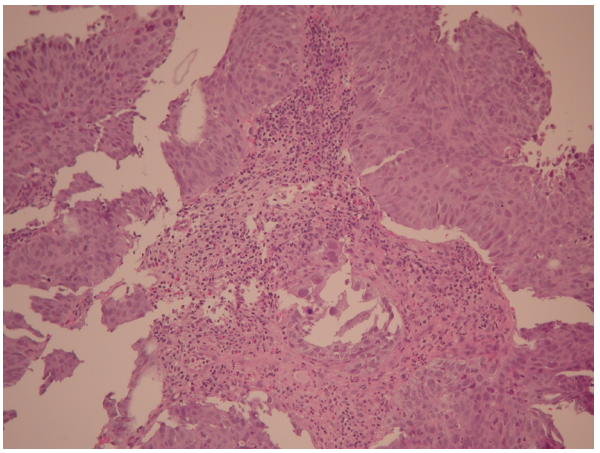


Fig. 2B. Transbronchial biopsy by bronchoscope (200X)
The section reveals poorly differentiated carcinoma

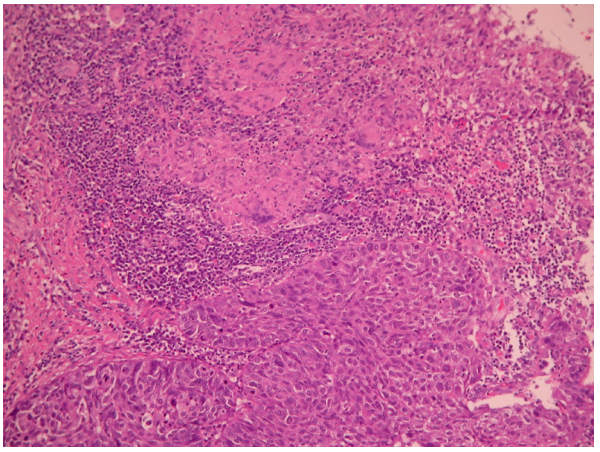


Fig. 2C. Surgical pathology result (100X)
The section reveals granulomatous inflammation (upper) combined with poorly differentiated squamous carcinoma (bottom).

Discussion

We report the case of a patient with a mass lesion in the LUL of the lung. The initial diagnosis of necrotizing granulomatous inflammation was made using CT-guided biopsy. The secondary evaluation showed squamous cell carcinoma, cT4N2Mx, at least stage IIIB according to the re-biopsy and CT scan. However, F-18 FDG PET-CT reported the lesion as cT2bN0M0, stage IIA. The final pathology result showed it as squamous cell carcinoma, pT1bN0M0, stage 1A, coexisting with MTB complex infection. The treatment plan changed from neo-adjuvant CCRT for lung cancer stage IIIB to curable operation for stage IA and anti-TB agents for active pulmonary TB.

In Taiwan, lung cancer has accounted for the highest incidence and highest mortality rates of all cancers in recent years. Therefore, a definite diagnosis of the initial stage and the molecular characterization of lung cancer are very important for determining further treatment. In general, to establish the diagnosis of lung cancer in a patient, we need to arrange a pathology review, check the performance status, and arrange chest and upper abdominal CT (including adrenal) during the initial evaluation. Following that, staging and pretreatment evaluation will include pulmonary function test, bronchoscope, mediastinoscope, and PET-CT scan; sometimes, magnetic resonance imaging of the brain needs to be performed [4].

For the initial staging of lung cancer, CT scan provides useful information on tumor size, invasion of the lymph node, and distal metastasis. However, CT scans have known limitations in defining lymph node involvement in lung cancer [5]. Besides, as the coexistence of lung carcinoma and pulmonary TB infection is not uncommon in TB-endemic areas, such as Taiwan, there is a diagnostic dilemma in defining the stage of the lung cancer and making decisions on further therapy. Biopsy is a standard diagnostic method to distinguish a malignant or benign lesion from a mass lesion. However, CT-guided core needle biopsy of lung lesions would be required to provide high diagnostic efficacy [6-7]. Factors such as physician's technique, acquisition of 2 or fewer specimens, a lesion in the lower lobe, malignant lesion, and lesions too large or too small significantly increase the rate of false-negative diagnoses [7-8]. In the present case study, the first difficulty was determining if the patient had a 4.2 × 4.7 cm mass lesion. However, the tumor that was finally resected was just 2.1 × 1.8 cm, surrounded by necrotizing granulomatous tissue. Because of the coexisting condition, a false-negative result was obtained from the first CT-guided biopsy. Therefore, re-biopsy is very important when malignancy is highly suspected clinically, but the pathologic result is not compatible. In this case, we performed endobronchial ultrasonography-assisted transbronchial lung biopsy and finally obtained the malignant tissue.

Another diagnostic tool, the PET-CT, can also provide us with more information. Several studies have reported that the PET scan was more sensitive than the CT scan in identifying mediastinal node disease [9-11]. In another study, the sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET were reported to be 73%, 98%, 70%, and 98%, while those of CT were 55%, 96%, 55%, and 96%, respectively [12]. The PET standardized uptake value (SUV) max can also predict the negativity of mediastinal lymph node status [13]. However, PET-CT may show lower sensitivity in the lymph node staging of non-

small cell lung carcinoma in TB-endemic regions [14]. Prior research also reported that TB has been a common mimic of malignancy in PET-CT scans. Interpretation with a concurrent tubercular and neoplastic etiology is difficult [15-16]. The secondary issue that is difficult to approach in clinical practice is found in active TB infection with lymph node adenopathy; PET-CT may yield a false-positive or false-negative result. To avoid this error, real-time endobronchial ultrasound with fine-needle aspiration (EBUS-TBNA) and mediastinoscope can offer a more accurate diagnostic rate in the assessment of mediastinal and hilar lymph nodes and the diagnosis of lung and mediastinal tumors. This technique has become a standard diagnostic method in recent years [4,17-18]. In our case, the largest mediastinal lymph node was 1.0 × 1.9 cm. EBUS-TBNA and mediastinoscope, if performed, could yield a definitive result; however, it was not performed for the patient in the present case study.

In conclusion, coexistence of active TB infection and lung cancer may not be an uncommon condition, especially in TB-endemic regions, which could result in misdiagnosis and inappropriate treatment. A careful work-up, caution in interpreting the imaging study, and biopsy are the solutions in such a situation.

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肺癌病灶同時合併肺結核感染致困難診斷與腫瘤分期－病例報告

李威諄　林進國　李錦輝*　謝孟哲　蔡熒煌

肺部腫塊或結節於臨床上首要排除惡性腫瘤。然而，慢性感染或發炎，如結核病，可同時存在於肺部甚至同一結節病灶，並影響淋巴結反應，從而導致分期診斷的困難，而影響後續治療方向。在本文中我們報告一位 73 歲男性，因結核菌感染與肺癌同時存在於單一肺部結節並影響淋巴結反應性增生，從而影響組織切片與影像診斷的結果，導致腫瘤分期困難，最終以手術切除才獲得正確之診斷與治療。*(胸腔醫學 **2015; 30: 375-381**)*

關鍵詞：肺癌，肺結核，切片

嘉義長庚醫院　內科部　胸腔暨重症科系，嘉義長庚醫院　病理科*
索取抽印本請聯絡：林進國醫師，嘉義長庚醫院　內科部　胸腔暨重症科系，嘉義縣朴子市嘉朴路西段 6 號

Invasive Tracheobronchial Aspergillosis in Its Most Severe Form Presenting as Hypoxemic Respiratory Failure-Report of 2 Cases and Review of the Literature

Chun-Yu Lin, Jui-Ying Fu, Kuo-chin Kao, Ning-Hung Chen, Chung-Chi Huang

Invasive pulmonary aspergillosis (IPA) usually develops in overtly immunosuppressed patients. Invasive tracheobronchial aspergillosis (ITA) is a rare subtype of IPA. The mortality rate of patients with ITA ranges from 20% to 100%, depending on the invasiveness and extensiveness of the *Aspergillus*. Accumulating evidence supports combined antifungal therapy, but the benefit to survival remains unknown. We reported 2 patients with ITA presenting as hypoxemic respiratory failure. Initial manifestation was delayed resolution of pneumonia. Both patients were diagnosed via bronchoscopy with pathologic confirmation. Serial bronchoscopic debridement, combined antifungal therapy and extracorporeal membrane oxygenation (ECMO) support were arranged. In spite of our efforts, the 2 patients died of multidrug-resistant *Acinetobacter baumannii* bacteremia after prolonged intensive care unit stay.

Acute hypoxemic respiratory failure, with both airway and parenchymal involvement, may be the most important prognostic factor for ITA. Awareness, early bronchoscope-guided diagnosis, combination antifungal treatment and aggressive surgical intervention are the keys to successful treatment of patients with ITA. ***(Thorac Med 2015; 30: 382-389)***

Key words: invasive tracheobronchial aspergillosis

Introduction

After inhaling small spores of *Aspergillus* spp, patients will have different disease presentations based on their individualized immune response [1-2]. Invasive pulmonary aspergillosis (IPA) is a life-threatening disease, generally occurring in immunocompromised hosts. In recent decades, a relatively high prevalence of IPA has been noticed in critical care units. Chronic obstructive pulmonary disease (COPD) is the most common IPA-associated underlying disease, followed by solid organ transplant [3]. Invasive tracheobronchial aspergillosis (ITA) is an extremely rare subtype of IPA. It has an insidious manifestation and is difficult to recognize. The mortality rate ranges widely, from 20% to 100% [4-6].

Herein, we present the cases of 2 patients with ITA that resulted in severe pneumonia and

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan
Address reprint requests to: Dr. Chung-Chi Huang, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital, 5 Fu-Hsing Street, Kweishan, Taoyuan 333, Taiwan

profound hypoxemia.

Case Report

Case 1

A 68-year-old female presented with dry cough for 2 weeks. She had recently been diagnosed as having type 2 diabetes mellitus and idiopathic thrombocytopenia under treatment with prednisolone 60 mg/day for 6 weeks. Initial chest radiograph showed right middle lung consolidation. After antibiotics treatment for 7 days, the chest radiograph showed progressive right middle lung infiltration. Bronchoscope-guided biopsy confirmed *Aspergillus* infection. Bronchial washing grew *Aspergillus fumigatus*. Despite treatment with voriconazole for 5 days, she experienced hypoxemic respiratory failure on the 20th day after admission. Meanwhile, she also developed right-side bacterial empyema and pneumothorax. Chest radiograph revealed left lung consolidation (Figure 1A). Extracorpo-

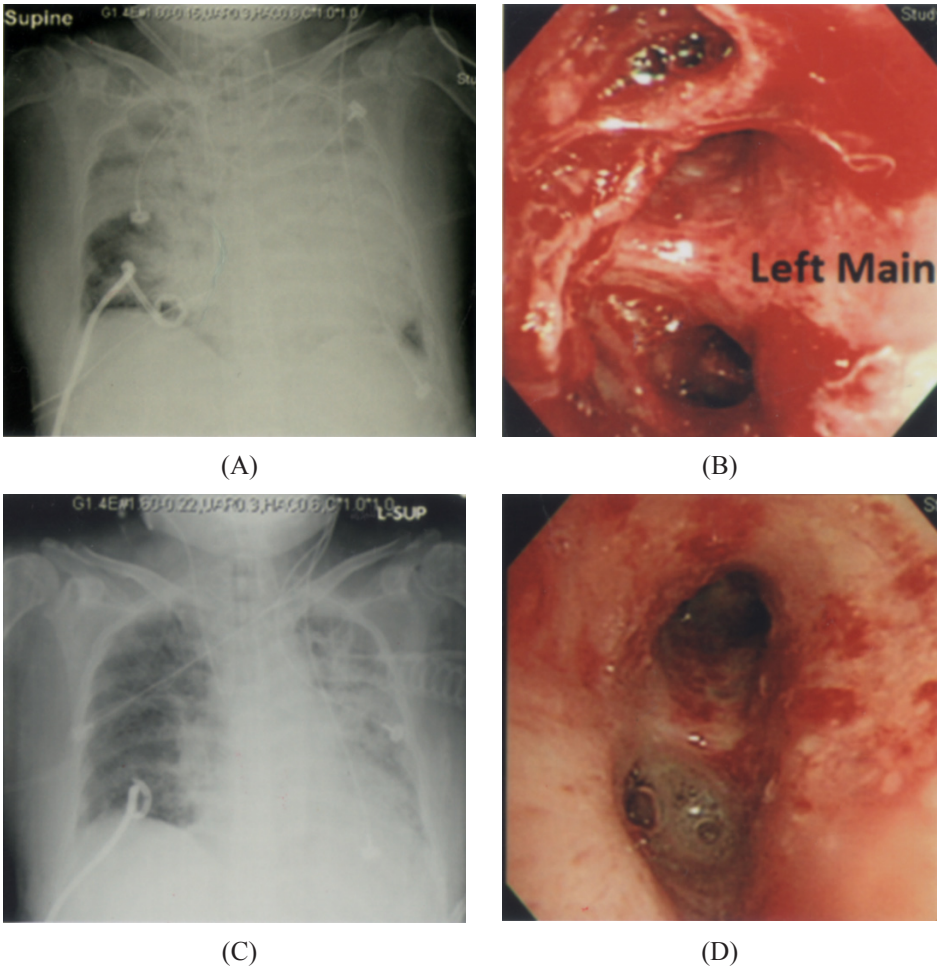

Fig. 1. Chest radiography on the 1st day of ventilator and ECMO support (A); Bronchoscopy showed debris in the left main bronchus (B); Chest radiography on the 10th day of combination antifungal therapy and broncoscopic debridement (C); Bronchoscopy revealed improvement in mucosal ulceration and debris formation in the left main bronchus (D).

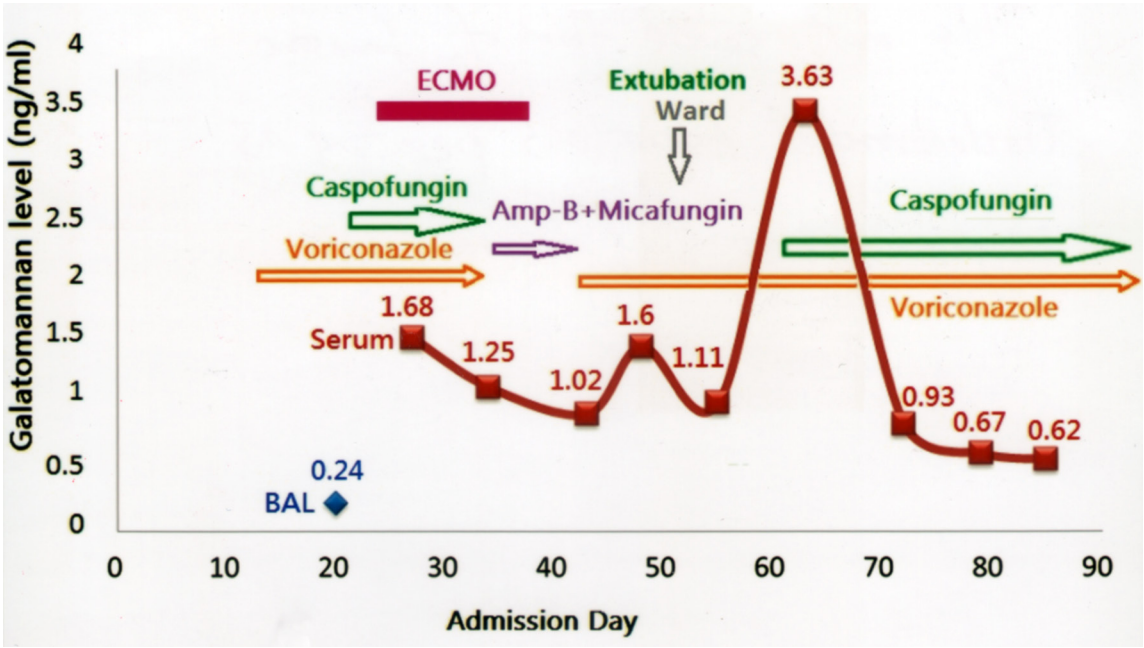

Fig. 2. Time course of the serum/BAL galatomannan level and anti-fungal agents in Case 1.

real membrane oxygenation (ECMO) was used for profound hypoxemia 2 hours after intubation and mechanical ventilator support on the 21st day.

Bronchoscopy revealed a great deal of debris in the left main bronchus, accompanied with mucosal ulceration (Figure 1B). The pathologic report showed *Aspergillus* hyphae. Bronchoscopic intervention was arranged 3 times for debridement. We initially administered caspofungin with voriconazole for poorly controlled invasive aspergillosis. The 2-week combined antifungal therapy was changed to liposomal amphotericin B and micafungin, owing to cholestasis. The serial serum galatomannan level declined gradually (Figure 2). The follow-up bronchoscopy found significant improvement in the bronchial mucosal ulceration without debris formation (Figure 1D). Chest radiography showed full expansion of the left lung (Figure 1C). She was successfully weaned from ECMO on the 34th day and the ventilator was discontinued on the 51th day.

After transfer to the ward, we changed the combined anti-fungal therapy to voriconazole mono-therapy. The serum galatomannan level then elevated, and the patient suffered from hypercapneic respiratory failure secondary to recurrent sepsis. We shifted back to combination anti-fungal therapy, which was followed by improvement in the infiltration on chest radiography and a decline in the serum galatomannan level. The patient died on the 100th day due to multidrug-resistant *Acinetobacter baumannii* (MDR-AB) bacteremia.

Case 2

A 61-year-old male presented with productive cough for 1 week. He had hypertension under observation. There was no history of

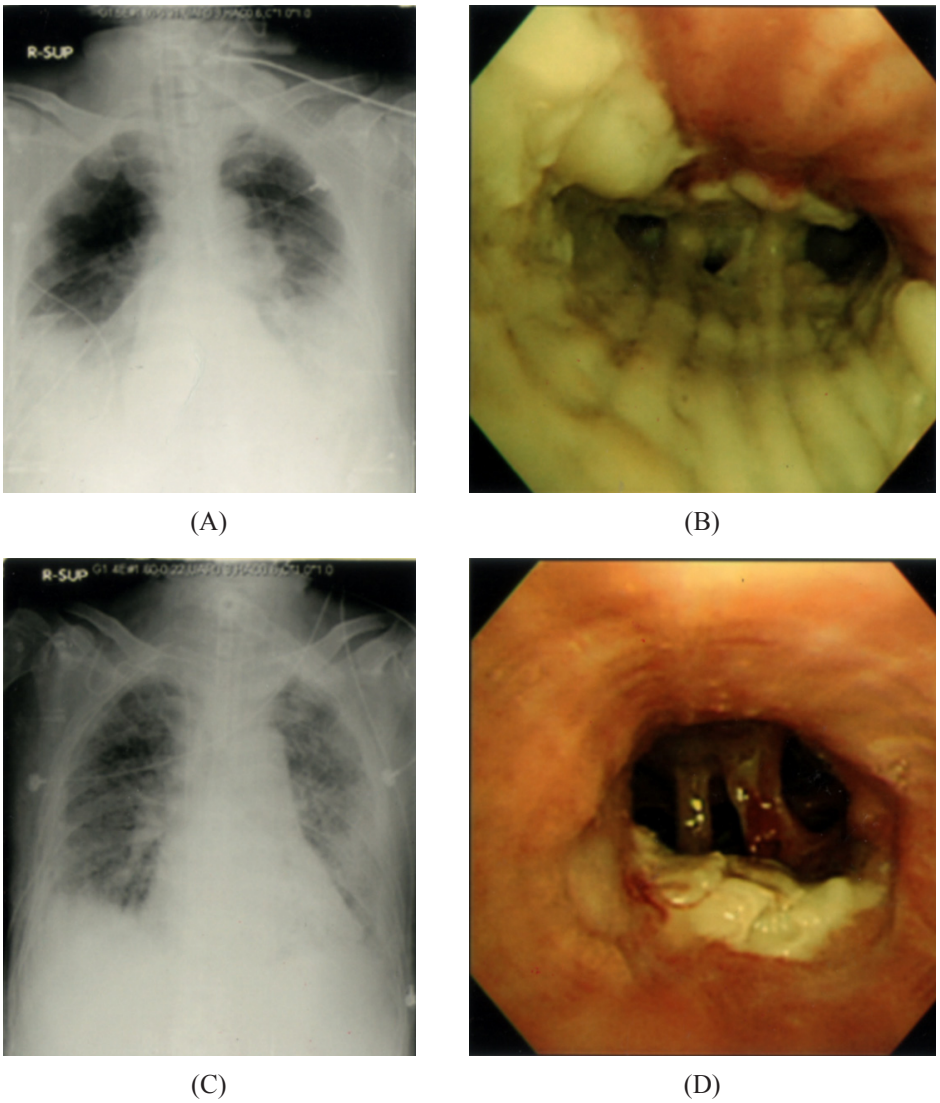

Fig. 3. Chest radiography showed bilateral infiltration on the 8th day (A); Bronchoscopy reported pseudomembranous tissue covering the left lower bronchus (B); Chest radiography showed significant improvement on the 69th day (C); Bronchoscopy revealed less pseudomembranous tissue covering the left lower bronchus (D).

systemic disease, such as malignancy, diabetes mellitus, and organ transplantation, nor systemic steroid use. He was treated initially as having community-acquired pneumonia in a local hospital. Chest radiography showed bilateral lower lung progressive infiltration 3 weeks later (Figure 3A). He was referred to our hospital for hypoxemic respiratory failure.

Laboratory data revealed leukocytosis. The CD4/CD8 cell count was within normal range. The ELISA test for HIV was negative. Bronchoscopy on the 8th day of admission showed much debris in the right main bronchus and pseudomembranous tissue extensively covering the left lower bronchus (Figure 3B). Pathology reported the white pseudomembranous tissue

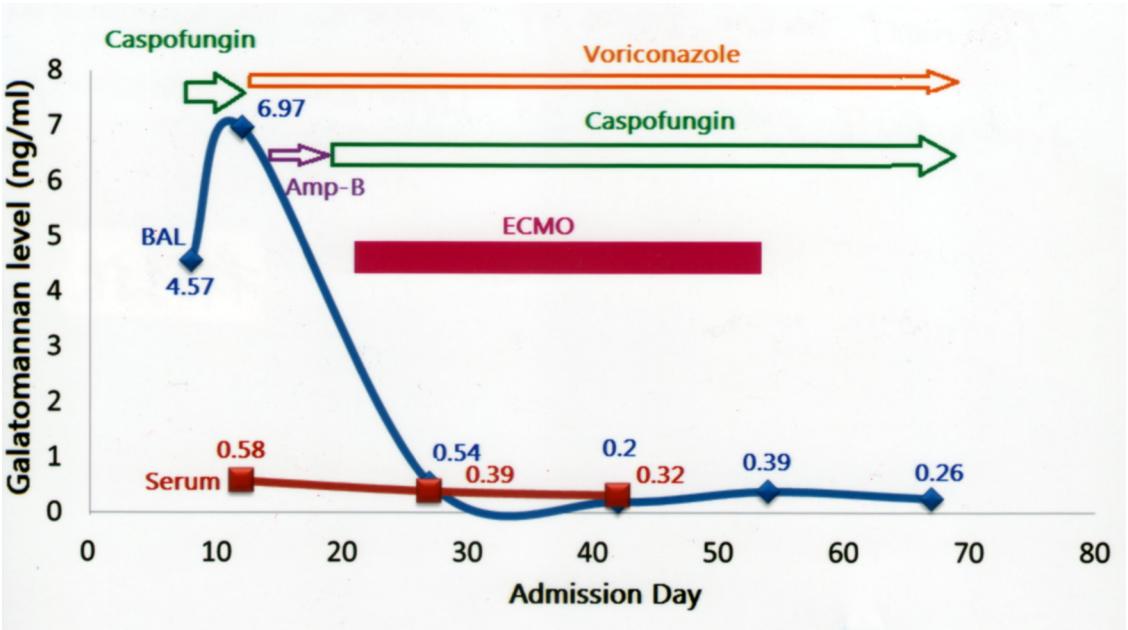

Fig. 4. Time course of the serum/BAL galatomannan level and anti-fungal agents in Case 2.

was *Aspergillus* infection. Bronchial washing grew both *Aspergillus fumigatus* and *Aspergillus flavus*. We initially used caspofungin on the 9th day and shifted to voriconazole on the 12th day. Amphotericin B was added on the 15th day due to an elevated galatomannan level in the bronchoalveolar lavage fluid and worsening pulmonary infiltration on chest radiography (Figure 3C). We changed to caspofungin and voriconazole combined therapy on the 19th day because of deteriorated renal function. With the patient under high-level ventilator support, ECMO was used on the 22nd day for profound hypoxemia. During the treatment course, we arranged serial bronchoscopic debridement and followed the galatomannan level in the bronchoalveolar lavage fluid (Figure 4). The area covered by pseudomembranous tissue decreased (Figure 3D) and the galatomannan level of the bronchoalveolar lavage fluid declined gradually. Chest radiography revealed significant improvement in the bilateral lower lung consolidation. ECMO was discontinued on the 52th day.

The patient became ventilator-dependent due to extensively severe pulmonary fibrosis post-infection, and died of MDR-AB bacteremia on the 84th day. Combined antifungal therapy with voriconazole and caspofungin was maintained until the patient died. However, the final bronchoscopy on the 69th day still found some pseudomembranous tissue in the left lower bronchus with a negative fungal culture and normal galatomannan level in the serum/bronchoalveolar lavage fluid.

Discussion

Invasive aspergillosis is associated with high mortality in overtly immunocompromised patients. ITA is an uncommon subtype, with a wide range of mortality rates and atypical

presentations. The 2 patients we reported had a delayed resolution of pneumonia as the initial manifestation. Both of them developed profound hypoxemia and had to be supported by ECMO. They died of MDR-AB bacteremia after a prolonged hospital stay and broad-spectrum antibiotics treatment.

Based on the revised definitions of invasive fungal disease of the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) [7], IPA is easily under-diagnosed due to the rigorous criteria for the host. More immunocompetent patients were found to have ITA [3,5-6]. Besides systemic immune defense, locally impaired defense secondary to structural change in the airway or lung parenchyma played an important role [5-6]. But the second patient was not in an immunocompromised state, and had no structural lung disease history.

Bronchoscopy is the only diagnostic tool for ITA. Several classifications based on bronchoscopic features have been mentioned, including ulcerative, pseudomembranous, and obstructive types [5]. Other proposed classifications are: superficial infiltration type, full-layer involvement type, occlusion type and mixed type [8]. The full-layer involvement type is the most severe form, and had 100% mortality in that study. The first case we reported presented with ulcerative mucosal change, while the second case presented with pseudomembranous formation, meeting the criteria for the full-layer involvement type.

Aspergillus spp infections with parenchymal invasion, rather than being limited to the tracheobronchial tree, have a poor outcome. Neutropenia and acute respiratory failure at presentation are independent prognostic factors [9]. In addition to the most severe presentation in their bronchoscopic features, our patients developed respiratory failure rapidly, experienced profound hypoxemia and had to be supported by ECMO. Although not in a neutropenic state, they suffered from the most severe condition and died after a prolonged hospital stay complicated with secondary nosocomial infection.

Early diagnosis and effective treatment are necessary. In addition to the pathologic report, the galatomannan level in serum and bronchoalveolar lavage fluid proved to be of diagnostic value [10]. The serial galatomannan level is useful in following the response to treatment. A 35% reduction in the serum galatomannan level after 1 week of treatment predicted the probability of a satisfactory clinical response [11]. None of our patients reached a 35% reduction in the serum galatomannan level. This may explain, in part, the poor outcome of these patients.

According to the Infectious Diseases Society of America (IDSA) guideline [12], voriconazole is the first-line therapy for invasive aspergillosis. The highly varying serum concentration level is a concern in terms of efficacy. With suboptimal treatment outcomes, clinicians have resorted to the use of combination therapy that targets both the cell membrane and cell wall. The combined regimens are mainly echinocandin with either azole or polyene. This therapy might be helpful in fungal infection control, but has limited benefit to survival [13-16]. There is no consensus on the duration of antifungal therapy for IPA; it has ranged from 10-75 days. The first patient was treated with combination therapy for 2 months, with interruption. The second patient was treated with the most effective regimen continuously for 66 days, and had an unsatisfying result. Bronchoscopic intervention for debridement and intra-luminal antifun-

gal instillation has been reported before [8]. Nebulized amphotericin B also had a significant response after treatment [17]. We did not use the above treatments due to a lack of convincing evidence, but these methods may be alternative choices in a treatment failure situation.

In conclusion, ITA is uncommon, but potentially devastating in immunocompetent patients. Acute respiratory failure, with both airway and parenchymal involvement, may be the most important prognostic factor for ITA. Early bronchoscopic diagnosis, serial galatomannan level follow-up, a combined antifungal regimen, and a nebulized antifungal agent may have benefit in reducing treatment duration, lessening ICU stay, and improving survival.

Acknowledgment

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極嚴重之侵入性呼吸道麴菌感染表現爲缺氧性呼吸衰竭－兩則病例報告與文獻回顧

林錞語　傅瑞英　高國晉　陳濘宏　黃崇旂

侵入性肺部麴菌感染較常見於免疫不全患者，侵入性呼吸道麴菌感染為其中一類罕見的分型。死亡率差異性很大，主要與麴菌之侵入性與影響範圍有關。結合兩種黴菌藥物的治療方式逐漸獲得重視，但對於存活率沒有明確的幫助。我們提出之病例報告為兩名患者罹患侵入性呼吸道麴菌感染表現為缺氧性呼吸衰竭，經支氣管鏡檢查確診為侵入性呼吸道麴菌感染。經過連續的支氣管鏡清除壞死組織，結合兩種黴菌藥物及葉克膜治療，兩名患者仍死於菌血症，可能與過久的加護病房治療有關。急性呼吸衰竭與同時氣道及肺實質皆受到麴菌感染是重要的預後因子。盡早藉由支氣管鏡評估、診斷與清瘡，結合兩種黴菌藥物治療及吸入性抗黴菌藥物，或許是能改善侵入性呼吸道麴菌感染的唯一方法。*(胸腔醫學* ***2015; 30: 382-389)***

關鍵詞：侵入性呼吸道麴菌感染

長庚紀念醫院林口醫學中心　內科部　呼吸胸腔科
索取抽印本請聯絡：黃崇旂醫師，林口長庚醫院　胸腔內科，桃園縣龜山鄉復興街 5 號

A Young Adult with Primary Signet Ring Cell Carcinoma of the Lung: A Case Report and Literature Review

Fan-Min Lin, Ren-Zhi Chen*, Shang-Tao Chien**, Shao-Ting Zhou, Ren-Xian Lin, Shu-Fan Huang

Primary signet ring cell carcinoma rarely occurs in the lung and is more commonly known to affect the stomach. In general, the prognosis of patients with signet ring cell carcinoma at any site is poor. We report the case of a 34-year-old man with chronic productive cough, chest pain, and low-grade fever; he was admitted to our institution with an initial diagnosis of pneumonia. After a few days of empirical antibiotic treatment, chest radiography showed no improvement, and acid-fast staining of the sputum was negative. Bronchoscopy revealed a tumor located in the left main bronchus, and histological examination demonstrated an adenocarcinoma with signet ring cell differentiation. The location of the tumor in the central bronchus was unusual, as a majority of lung adenocarcinomas localize in the peripheral region. Pathological examination of both the associated neck lymph node and pleural tissue revealed the same tumor histology. Tumor gene expression analyses were negative for EGFR mutation, ALK rearrangement, and K-ras mutation. We reviewed previously published reports on this rare tumor type in an attempt to identify potential treatment strategies. ***(Thorac Med 2015; 30: 390-396)***

Key words: lung adenocarcinoma, signet ring cell, anaplastic lymphoma kinase

Introduction

Signet ring cell carcinoma (SRCC) may arise in different organs, including the breast, gallbladder, pancreas, urinary bladder, and colon, but it most commonly occurs in the gastrointestinal tract, with 90% of SRCCs occurring in the stomach [1]. First described by Kish *et al*. in 1989, the reported incidence of primary SRCC of the lung has varied from 0.14% to 1.9% of all lung cancers [2]. The largest series of patients with primary SRCC of the lung was reported by Tsuta *et al*. They found that 39 of 2640 surgically resected primary lung carcinomas had SRC components. The mean age of patients in their study was 54.6 years, the male-to-female ratio was 1.16:1.00, and 26 patients (66.7%) were smokers. The size of the tumor

Division of Pulmonary Medicine, Department of Internal Medicine, Kaohsiung Armed Forces General Hospital; *Division of Thoracic Surgery, Department of Surgery, Kaohsiung Armed Forces General Hospital; **Department of Clinical Pathology, Kaohsiung Armed Forces General Hospital
Address reprint requests to: Dr. Shu-Fan Huang, Division of Pulmonary Medicine, Department of Internal Medicine, Kaohsiung Armed Forces General Hospital, No. 2, Zhongzheng 1st Rd., Lingya Dist., Kaohsiung City 802, Taiwan

SRC components was found to positively correlate with tumor aggressiveness and poor outcomes, with a 5-year survival rate of 28% [3].

We report the case of a 34-year-old man with chronic productive cough that persisted for more than 3 months, chest pain, and low-grade fever; he was admitted to our institution with an initial diagnosis of pneumonia. We became aware that these symptoms had been present over a longer duration and had delayed the resolution of observed pulmonary consolidation. Differential diagnosis for this presentation included tuberculosis, malignancy, and lymphoma, in addition to many inflammatory diseases. Tuberculosis is the most common cause of delayed resolution of consolidation in all age groups and is a curable disease. Malignancy is the other common cause of delayed resolution of consolidation in elderly patients. Unusual or resistant pathogens and non-infectious etiologies should also be considered when evaluating cases of delayed resolution of consolidation.

The patient was without a specific contact, travel, or family history that could be related to the disease. However, the final diagnosis underlying the delayed lung consolidation was central invasion of an adenocarcinoma of the lung with a high degree of SRC components and lymph node metastases. We reviewed a number of previous reports of SRCC in lung adenocarcinoma in an attempt to identify potential treatment therapies other than continued chemotherapy.

Case Report

A 34-year-old man presented to an emergency department with a 3-month history of productive cough and chest pain. He reported low-grade fever, no loss of body weight, no hemoptysis, and no rashes. The patient denied any current medical disease, and had been smoking 1-2 packs of cigarettes per day for more than 10 years. He drank alcohol occasionally and reported no drug abuse. His family history was unremarkable. The patient had been working as a hardware manufacturer for several years. He had no recent travel history and no known exposure to tuberculosis.

His vitals at the time of admission to the emergency department were as follows: temperature, 37.2°C; heart rate, 103 beats per minute; blood pressure, 149/73 mmHg; respiratory rate, 20 breaths per minute; and oxygen saturation of 96% (while breathing ambient air). Rhonchi were heard bilaterally, particularly at the left upper and left lower lung fields. A palpable cluster of enlarged lymph nodes was noted at the left neck along the sternomastoid muscle. Physical examination was otherwise normal. The white cell count was 11,700/μL with 80.4% neutrophils and 10.8% lymphocytes. Laboratory examinations revealed a serum sodium level of 138 mmol/L, potassium level of 4.1 mmol/L, and creatinine level of 0.9 mg/dL. Liver function tests were within normal limits: blood hemoglobin level, 15.4 g/dL; hematocrit, 48.6%; and platelets, 366,000/μL. Plain chest radiography revealed increased interstitial marking and ground-glass opacities in both lungs with some opacity at the left upper lung field and blunting of the costophrenic angle. The patient was admitted, and treatment with antibiotic therapy was initiated with daily intravenous administration of ceftriaxone (2.0 g). On day 6 of hospitalization, plain chest radiography revealed no noticeable improvement (Figure 1). No growth was observed in blood cultures. Other infectious workup, including bacterial and fungal cultures and specific assays for acid-fast staining bacteria, Cryptococcus antigens, serum

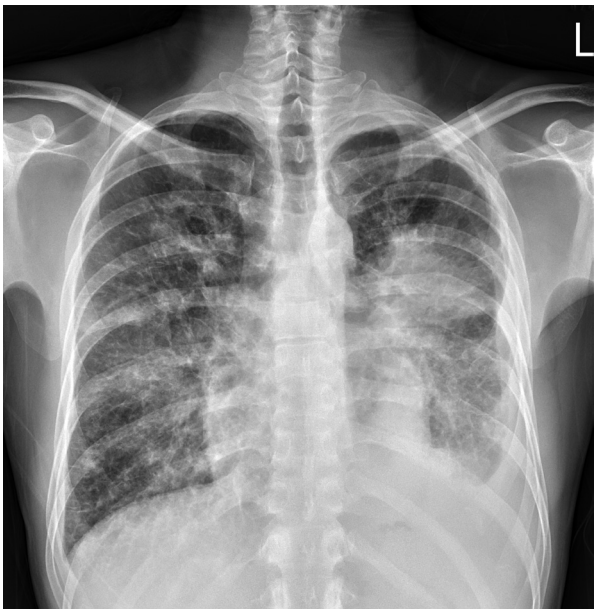


Fig. 1. Plain chest radiography showing no improvement in the left lung field after 6 days of antibiotic treatment.

nerve, esophagus, vertebral body, and carina. Furthermore, distinct tumor nodules were noted in the ipsilateral lung; bilateral pericardial and pleural effusions were also observed (Figure 2). Neck lymph node biopsy showed the presence of SRC infiltrates in the lymphoid tissue. Tumor cells contained abundant cytoplasmic mucin, which was observed to displace nuclei to the cell peripheries and express TTF-1 (Figure 3A). Bronchoscopy revealed nodular lesions in the left main bronchus and left upper lobe bronchial mucosa; tissue pathology examination confirmed adenocarcinoma with SRC differentiation (Figure 3B). Video-assisted thoracic surgery with pericardiotomy and pleural biopsy were performed, and adenocarcinoma with SRC

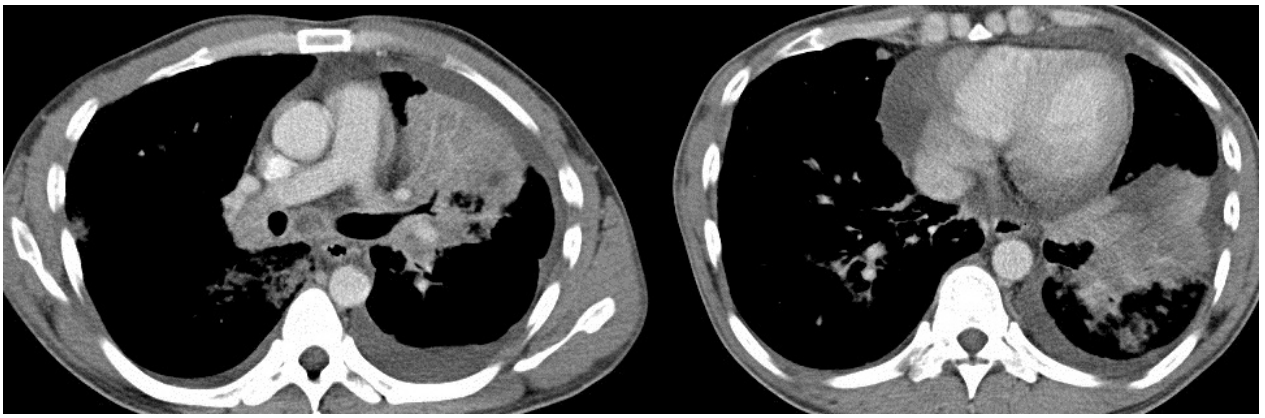
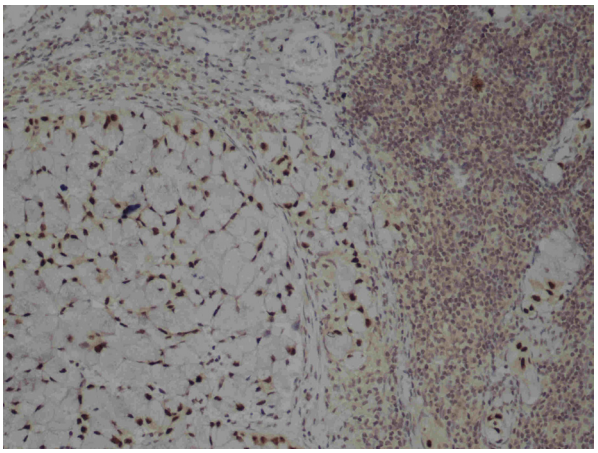


Fig. 2. Chest CT revealing tumors affecting the upper and lower lobes of the left lung with invasion into the mediastinum and great vessels. Pleural and pericardial effusions were also noted.

mycoplasma antibodies, urine Pneumococcus antigens, and human immunodeficiency virus were negative. Contrast-enhanced computed tomography (CT) of the chest was performed, revealing tumors in the upper and lower lobes of the left lung and invasion into the mediastinum, heart, great vessels, trachea, recurrent laryngeal

differentiation was noted peri-operatively (Figure 3C). Tumor gene expression analyses were negative for EGFR mutation, ALK rearrangement, and K-ras mutation. Whole-abdomen CT revealed multiple metastases in the spine and pelvic bones. Panendoscopy revealed no lesion affecting the upper gastrointestinal tract. There-



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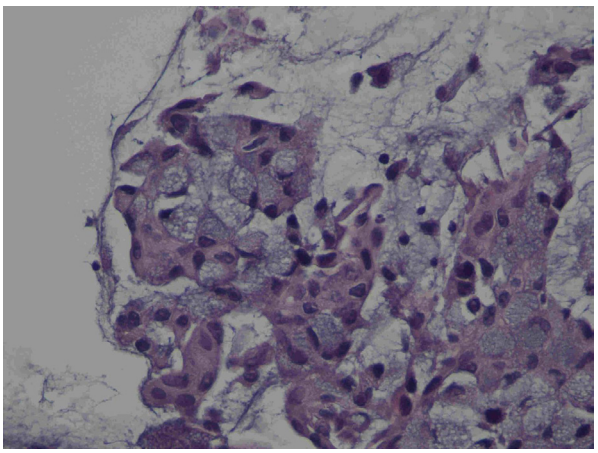

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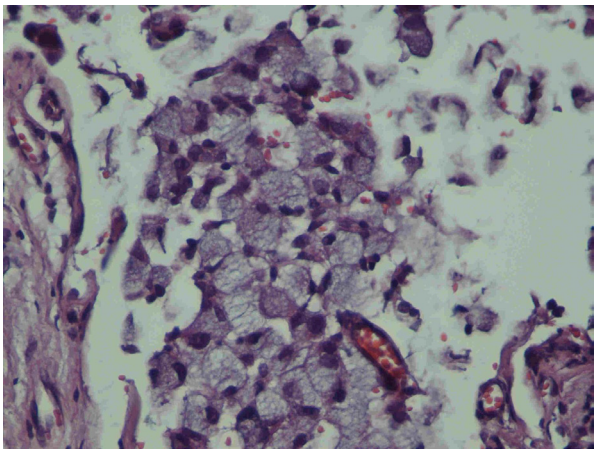

(C)

Fig. 3. (A) Neck lymph node: TTF-1(+) nests of signet ring cells were observed infiltrating into lymphoid tissue. Tumor cells were found to contain abundant cytoplasmic mucin that was seen to displace nuclei to cellular peripheries. (B) Left main bronchus: presence of a moderately-differentiated adenocarcinoma composed of neoplastic mucous glands with mucin production. (C) Pleural biopsy: poorly-differentiated adenocarcinoma with signet ring cell differentiation.

fore, a diagnosis of stage IV poorly differentiated SRC-type primary adenocarcinoma of the lung was made. The patient subsequently received 1 course of combined first-line platinum-doublet chemotherapy, and was transferred to a medical center for further management.

Discussion

This case involved an unusual histological growth pattern of primary lung adenocarcinoma that could be mistaken for metastasis from an occult primary tumor, particularly of the stomach. In the present case, TTF-1-positive SRCC was identified by lymph node biopsy, and the same pathologic pattern was observed in the pleural biopsy examination. SRCC metastases from the stomach, breast, and other organs were excluded. Thus, a diagnosis of primary SRC adenocarcinoma of the lung was made.

Primary mucinous adenocarcinoma of the lung with SRC, similar to SRCC at other sites, represents a clinically silent yet aggressive disease capable of widespread metastasis. It is generally fatal, as observed in the present case. In making the diagnosis of extragastric SRCC, it is critical that SRCC metastases from the stomach, breast, and other organs are conclu-

sively ruled out [3]. Tsuta *et al*. [4] compared the clinicopathological characteristics of L-SRCC (SRC component <50%) and H-SRCC (SRC component >50%) tumors with those of tumors without SRCC components. The age of occurrence of H-SRCC tumors was significantly lower than that of non-SRCC tumors. Lymphatic invasion, vascular invasion, and lymph node metastasis were significantly more frequent with H-SRCC tumors, and the pathologic stage was more advanced than with non-SRCC tumors. The analysis failed to reveal any differences in gender or tumor size between groups. The reported 5-year survival rates for non-SRCC, L-SRCC, and H-SRCC were 52.7%, 50%, and 28.4%, respectively [4]. A significant difference in the 5-year survival rates of non-SRCC and H-SRCC patients was observed ($P = 0.003$). In the present case, all lung tissue and lymph node specimens were found to have SRC components of more than 50%; this finding was similar to that of the reported H-SRCC group, in which patients were generally younger and lymph node metastasis was more prevalent.

Several studies have investigated the predictive utility of assessing pathological and morphological features in detecting ALK-rearranged tumors. The morphological features of ALK rearrangement have been summarized in several studies; the presence of tumor cells with signet ring morphology was found to be the most significant independent predictor of ALK rearrangement in both primary lung adenocarcinoma and metastatic disease [5-7]. Although ALK gene rearrangements are observed in just 3-7% of all lung cancers, they are more frequent in adenocarcinomas and in patients who have never or rarely smoked, and appear to be mutually exclusive of activating EGFR or K-ras mutation.

In patients with advanced-stage ALK-positive NSCLC, crizotinib therapy is associated with improved survival compared to crizotinib-naive controls. It should be noted that ALK gene rearrangements are observed in 70% of pulmonary adenocarcinomas, but only in just over 10% of tumors with SRC components [8]. However, ALK rearrangement has been shown to not be a favorable prognostic factor in advanced NSCLC [9]. Cui S *et al*. analyzed the efficacy and tolerability of crizotinib in the treatment of 72 Chinese patients with ALK-positive, advanced NSCLC [10]. Crizotinib was found to be tolerated well and demonstrated promising efficacy in the treatment of ALK-positive, advanced NSCLC. However, no specific analysis of crizotinib efficacy based on SRCC subtype was performed in this study.

Administration of 6 rounds of cisplatin and docetaxel treatment was described in the case report of a patient having primary SRCC and brain metastases. Following chemotherapy, PET-CT scanning done to evaluate the therapeutic response demonstrated complete regression of the primary tumor and affected mediastinal lymph nodes [11]. There is a lack of reports of cases of SRCC, and no standardized chemotherapy protocols have been described for SRCC subgroups. Genetic testing for ALK rearrangement in adenocarcinoma of the lung with SRC components may be appropriate as ALK gene rearrangement is reportedly more frequent in this type of adenocarcinoma. Targeted therapy with ALK thyroxine kinase inhibitors may be a therapeutic alternative for the treatment of SRC subgroups of adenocarcinoma.

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一位年輕成年人原發性指環細胞型肺腺癌：病例報告及文獻回顧

林凡閔　陳仁智 *　錢尚道 **　周紹庭　林任先　黃樹訪

原發性指環型細胞癌罕見發生於肺部，此類病理型態好發於胃。在一般情況下，在任何部位原發性指環型細胞癌，患者的預都很差。我們報告一個 34 歲的年輕人，以慢性咳嗽，胸痛，輕微發燒為表現。開始以疑似肺炎入院。經過幾天的抗生素治療，胸部 X 光片沒有改善且抗酸性痰塗片三套均為陰性。支氣管鏡檢查發現左主支氣管腫瘤，切片組織學表現腺癌合併指環型細胞分化。腫瘤位置侵犯靠近中央的支氣管，和大部分肺腺癌好發在周邊有所不同。頸部淋巴結，肋膜組織切片也呈現相同病理表現。腫瘤基因檢測 EGFR mutation, ALK rearrangement 以及 K-ras mutation 皆為陰性。我們回顧一些文獻介紹關於這種罕見腫瘤類型特點，並試圖找出有潛力的治療策略。*(胸腔醫學 **2015; 30: 390-396**)*

關鍵詞：肺腺癌，指環細胞，間變性淋巴瘤激酶

國軍高雄總醫院　內科部　胸腔內科，國軍高雄總醫院　外科部　胸腔外科 *
國軍高雄總醫院　臨床病理部 **
索取抽印本請聯絡：黃樹訪醫師，國軍高雄總醫院　內科部　胸腔內科，高雄市苓雅區中正一路 2 號