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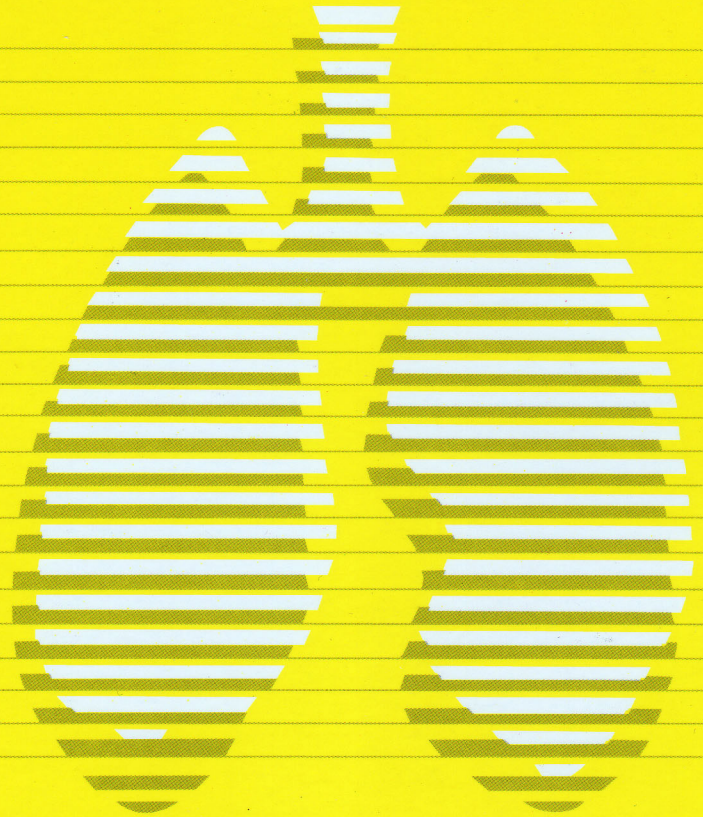

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Orginial Article

Case Reports

Survival Predictors in Patients with Acute Respiratory Distress Syndrome and Underlying Chronic Respiratory Diseases

Chi-Hsien Huang*, Ko-Wei Chang*, Li-Chung Chiu*, Chih-Hao Chang*, Chung-Shu Lee*, Han-Chung Hu*,**, Chung-Chi Huang*,**, Kuo-Chin Kao*,**

Introduction: Acute respiratory distress syndrome (ARDS) is a syndrome of severe hypoxemia with various risk factors. Chronic respiratory diseases are chronic diseases of the airways and lungs. In most of the large trials of ARDS, patients with chronic respiratory diseases were excluded. The aim of this study was to investigate the outcomes of patients with both ARDS and chronic respiratory diseases.

Material and Methods: We retrospectively collected patients documented with ARDS and chronic respiratory diseases at a tertiary care center from October 2012 to May 2015. Baseline clinical features, severity and causes of ARDS, parameters of mechanical ventilator use and the survival outcome were recorded.

Results: We enrolled 73 patients with ARDS and chronic respiratory diseases; 47.9% had COPD. The overall hospital mortality rate was 67.1% (49/73). In patients with mild, moderate and severe ARDS, the hospital mortality rates were 76.4% (13/17), 58.1% (18/31), and 72% (18/25), respectively (p=0.23). There was no significant difference in positive end-expiratory pressure, peak airway pressure and dynamic driving pressure between non-survivors and survivors. Tidal volume was significantly higher in non-survivors than in survivors (8.0 ± 1.7 ml/kgw vs. 7.2 ± 1.6 ml/kgw, p=0.03). In multivariate logistic regression, tidal volume was identified as the significant and independent predictive factor for survival (odds ratio 0.65, 95% confidence interval 0.44-0.95, p=0.03).

Conclusions: In this study on patients with ARDS and underlying chronic respiratory diseases, the hospital mortality rate was relatively high. Lower tidal volume was identified as the significant and independent predictive factor for hospital survival. ***(Thorac Med 2019; 34: 230-239)***

Key words: chronic respiratory disease, acute respiratory distress syndrome, outcome, low tidal volume

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Introduction

Acute respiratory distress syndrome (ARDS) is a syndrome of heterogeneity with various risk factors resulting in severe hypoxemia; pneumonia is the leading cause of ARDS [1]. According to the Berlin definition, and using the PaO_2/FiO_2 ratio, the severity of ARDS is classified into mild, moderate and severe, with hospital mortality rates of 34.9%, 40.3% and 46.1%, respectively [2]. In terms of therapy or management for ARDS, evidence shows that a lung protective strategy with lower tidal volume and higher positive end-expiratory pressure (PEEP), early neuromuscular blockade use and prone positioning could improve survival for ARDS patients [3-7].

Chronic respiratory diseases are diseases of the airways and other structures of the lungs. Major chronic respiratory diseases include asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, interstitial lung disease, occupational lung diseases and pulmonary hypertension [8-9]. These chronic respiratory diseases contribute to dyspnea, activity limitation, and impairment of gas exchange, and patients with these diseases are prone to acute exacerbation due to pneumonia [10-13]. It is not surprising that patients with chronic respiratory diseases may suffer from ARDS simultaneously. The largest epidemiological study of ARDS to date, the LUNG SAFE study, found that patients with underlying COPD comprised 21.7% of the ARDS population, but the outcome of this specific group was not well addressed [1]. Previous large randomized controlled trials of ARDS excluded patients with underlying chronic respiratory diseases [4,7]. Furthermore, it is not well known whether the lung protective strategy with low tidal volume for ARDS is effective for patients with underlying chronic respiratory diseases. Thus, the aim of this study was to investigate the outcomes of patients with both ARDS and chronic respiratory diseases.

Materials and methods

Study design and data collection

The study population was extracted from a prospective observational cohort at Chang Gung Memorial Hospital, Linkou Branch, from October 2012 to May 2015 [14]. Patients were enrolled in the study once they met the Berlin definition of ARDS [2]. Patients under 18 years of age were excluded. Information including demographics, baseline clinical features, laboratory data, severity of ARDS, and causes of ARDS was recorded upon ICU admission. Patient severity within 24 hours of ARDS diagnosis was documented as the Charlson Comorbidity Index (CCI) [15], Acute Physiology and Chronic Health Evaluation (APACHE) II score [16], and Sequential Organ Failure Assessment (SOFA) score [17]. Parameters of mechanical ventilation were recorded within the first 24 hours after recognizing ARDS, and included tidal volume, PaO_2/FiO_2 ratio, PEEP and peak airway pressure.

We retrospectively collected patients from the database with documented chronic respiratory diseases. Beside the baseline clinical information, severity and causes of ARDS, and mechanical ventilator settings, a chart review for the exact diagnosis of the chronic respiratory disease was performed. Survival outcome was recorded. The chronic respiratory diseases were defined as asthma, COPD, bronchiectasis, interstitial lung disease and pulmonary hypertension. The specific diagnoses of the patients with chronic respiratory diseases were made based

on in-patient and outpatient medical records, pulmonary function tests, and radiologic imaging (chest X-ray or computed tomography). The local Institutional Review Board for Human Research approved the study (CGMH IRB No. 102-1729B), and the need for informed consent was waived.

Management of ARDS

The mechanical ventilator settings of the patients with ARDS included a lung protective ventilation strategy using a low tidal volume of 4-8 ml/kg of predicted body weight (PBW), and a PEEP setting guided by a low PEEP-FiO_2 table for volume-controlled or pressure-controlled ventilation [4]. Pulse oximetry was used to monitor oxygenation by SpO_2, and the FiO_2 level was adjusted to maintain SpO_2 at more than 90%. The PiCCO plus monitor (version 5.2.2; Pulsion Medical System AG, Muenchen, Germany) was used to evaluate hemodynamics and lung water, if indicated by the clinical condition of the patient.

Statistical analysis

All statistical analyses were performed with SPSS software version 22 (SPSS for Windows, SPSS Inc., Chicago, IL, USA). Independent Student's *t* test was used to compare continuous variables, presented as mean ± SD, between survivors and non-survivors. Categorical data was compared via Chi square test. A p value <0.05 was regarded as statistically significant. To identify factors related to survival, univariate analysis was performed first, and the variables with a significance of $p<0.2$ were included for multivariate logistic regression with forward elimination of data.

Results

During the research period, 22,470 hospitalized adult patients undergoing invasive mechanical ventilation were screened; of this total, 1,034 (4.6%) met the criteria of ARDS. Seventy-three (7.1%) of the ARDS patients had documented chronic respiratory diseases, and their overall hospital mortality rate was 67.1% (49/73). Among patients with mild, moderate and severe ARDS, the hospital mortality rates were 76.4% (13/17), 58.1% (18/31), and 72% (18/25), respectively ($p=0.23$). A comparison of the demographic data and characteristics of the non-survivors (n=9) and survivors (n=24) is shown in Table 1. The main cause of ARDS was pneumonia (90.4%). The most common chronic respiratory disease was COPD (n=35, 47.9%), followed by asthma (n=15, 20.5%), interstitial lung disease (n=12, 16.4%) and bronchiectasis (n=5, 6.8%).

Patient disease severity upon admission to the intensive care unit (ICU) and the parameters of mechanical ventilation on the first day of intubation are listed in Table 2. The SOFA score of the non-survivors was higher than that of the survivors (9.4±3.3 vs. 7.7±2.2, $p=0.02$). Using the Berlin definition, there were 17 (23.3%) patients with mild ARDS, 31 (42.5%) with moderate ARDS and 25 (34.2%) with severe ARDS. Tidal volume of the non-survivors was significantly higher than that of the survivors (8.0±1.7 ml/kgw, PBW vs. 7.2±1.6 ml/kgw, PBW, $p=0.03$). There was no significant difference in PEEP, peak airway pressure and dynamic driving pressure between the non-survivors and survivors. There was no significant difference between the two groups in terms of those who had received renal replacement therapy, including intermittent hemodialysis (14.3% vs.

Table 1. Demographics and Characteristics of Hospital non-Survivors and Survivors Among ARDS Patients with Chronic Respiratory Diseases

Variables	Total (n=73)	Non-survivors (n=49)	Survivors (n=24)	*p* value
Age (years)	74.5 ± 12.1	74.6 ± 10.0	74.3 ± 15.8	0.95
Gender (male %)	58 (79.5%)	42 (85.7%)	16 (66.7%)	0.06
Body mass index (kgw/m^2)	22.9 ± 4.6	22.9 ± 4.1	22.7 ± 5.5	0.83
Smoking history (%)	33 (45.2%)	26 (53.1%)	7 (29.2%)	0.09
Charlson Comorbidity Index	2.7 ± 1.7	2.8 ± 1.6	2.6 ± 2.0	0.69
Cause of chronic respiratory disease (%)				0.15
COPD	35 (47.9%)	23 (46.9%)	12 (50.0%)	
Asthma	15 (20.5%)	11 (22.4%)	4 (16.7%)	
Bronchiectasis	5 (6.8%)	1 (2.0%)	4 (16.7%)	
Interstitial lung disease	12 (16.4%)	10 (20.4%)	2 (8.3%)	
Others	6 (8.2%)	4 (8.2%)	2 (8.3%)	
Causes of ARDS (%)				
Pneumonia	66 (90.4%)	43 (87.8%)	23 (95.8%)	
Sepsis	9 (12.3%)	7 (14.3%)	2 (8.3%)	
Aspiration	1 (1.4%)	1 (2.0%)	0 (0.0%)	
Postoperative complication	1 (1.4%)	1 (2.0%)	0 (0.0%)	
Trauma	0 (0.0%)	0 (0.0%)	0 (0.0%)	
TRALI	2 (2.7%)	2 (4.1%)	0 (0.0%)	
Diffuse alveolar hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Acute pancreatitis	1 (1.4%)	0 (0.0%)	1 (4.2%)	
Others	2 (2.7%)	2 (4.1%)	0 (0.0%)	

ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; TRALI: transfusion-related acute lung injury. All values are expressed as No. of patients (%) or mean ± SD. **p*-value <0.05

8.3%, *p*=0.47) and continuous renal replacement therapy (14.3% vs. 4.2%, *p*=0.19), and extracorporeal membrane oxygenation (4.1% vs. 4.2%, *p*=0.99).

Logistic regression analysis was carried out to determine the possible predictive factors for survival among patients with chronic respiratory diseases. After univariate logistic regression analysis, gender, smoking, SOFA score, and tidal volume were selected as variables for multivariate analysis. In the multivariate logistic regression test, tidal volume was identified as the significant and independent predictive factor for survival (odds ratio 0.65, 95% confidence interval 0.44-0.95, *p*=0.03) (Table 3).

Discussion

Among the 73 patients with both ARDS and chronic respiratory diseases, the hospital mortality rate was as high as 67.1%. In addition, after multivariate logistic regression analysis, lower tidal volume was identified as the significant and independent predictive factor for hospital survival.

Little has been reported regarding mortality

Table 2. Severity and Mechanical Ventilator Settings of Hospital Non-survivors and Survivors Among ARDS Patients with Chronic Respiratory Diseases

Variables	Total (n=73)	Non-survivors (n=49)	Survivors (n=24)	*p* value
APACHE II score	24.2 ± 6.5	24.8 ± 6.4	23.3 ± 6.7	0.34
SOFA score	8.8 ± 3.0	9.4 ± 3.3	7.7 ± 2.2	0.02*
Severity of ARDS (%)				0.35
Mild	17 (23.3%)	13 (26.5%)	4 (16.7%)	
Moderate	31 (42.5%)	18 (36.7%)	13 (54.2%)	
Severe	25 (34.2%)	18 (36.7%)	7 (29.2%)	
PaO_2/FiO_2 (mmHg)	140.3 ± 69.5	140.8 ± 71.3	139.2 ± 67.3	0.93
Tidal volume (ml/kgw, PBW)	7.8 ± 1.7	8.0 ± 1.7	7.2 ± 1.6	0.03*
PEEP (cm H_2O)	9.7 ± 2.0	9.8 ± 1.9	9.6 ± 2.1	0.67
Peak airway pressure (cm H_2O)	29.2 ± 4.7	28.8 ± 4.7	29.4 ± 5.1	0.38
Dynamic driving pressure (cm H_2O)	19.5 ± 4.6	19.0 ± 4.5	20.3 ± 4.8	0.28
ECMO (%)	3 (4.1%)	2 (4.1%)	1 (4.2%)	0.99

ARDS: acute respiratory distress syndrome; APACHE: Acute Physical and Chronic Health Evaluation; SOFA: Sequential Organ Function Assessment; PaO_2/FiO_2: alveolar oxygen pressure/fraction of inspiratory oxygen; PBW: predicted body weight; PEEP: positive end-expiratory pressure; ECMO: extra-corporeal membrane oxygenation. All values are expressed as No. of patients (%) or mean ± SD. *p-value <0.05

in patients with both ARDS and chronic respiratory diseases. In the ALIEN study, the hospital mortality rate in a multi-center cohort in Spain was 47.8%, and the outcome was associated with age, PaO_2/FiO_2, and plateau pressure at 24 hours after diagnosis of ARDS [18-19]. In the LUNG SAFE study, the hospital mortality rate was 39.6%, and older age, lower PaO2/FiO_2, and higher SOFA score were negative predictors for survival among ARDS patients [1,20]. However, in our study, patients with underlying chronic respiratory diseases coexisting with ARDS had a hospital mortality rate up to 67.1%, which is considerably higher than that in the ALIEN study (47.8%) and the LUNG SAFE study (39.6%). The possible explanation for the relatively high mortality rate in these subgroups of patients with ARDS might be the limited reserved lung function in underlying chronic respiratory diseases before ARDS develops.

It is well known that ventilator-induced lung injury can lead to multiple organ failure, the primary cause of death in patients suffering from ARDS [21]. To reduce lung injury subsequent to systemic inflammation, lower tidal volume ventilation emerged as the key management for ARDS. Meta-analysis and systematic reviews have shown that lower tidal volume was associated with improved survival outcome in patients with ARDS [22-24]. However, in a landmark trial of lower tidal volume in ARDS, patients with severe chronic respiratory diseases were excluded [4]. Thus, the issue of the optimal tidal volume for the group of patients with chronic respiratory diseases complicated with ARDS has not yet been addressed. Moreover, an increase of 1 ml/kg in initial tidal volume was associated with an increase in mortality of 23-26% in patients with ARDS [25-26]. In our

Table 3. Univariate and Multivariate Logistic Regression Analyses of Clinical Variables Associated with Hospital Survival Among ARDS Patients with Chronic Respiratory Diseases

Parameters	β coefficient	Standard error	Odds ratio (95% CI)	*p* value
Univariate				
Age (years)	-0.00	0.02	0.99 (0.96-1.04)	0.94
Gender (Male)	-1.10	0.60	0.33 (0.10-1.07)	0.07
Body mass index (kgw/m^2)	-0.01	0.06	0.99 (0.89-1.10)	0.83
Smoking history	-1.01	0.53	0.36 (0.13-1.03)	0.06
COPD	0.12	0.50	1.13 (0.43-3.00)	0.94
Charlson Comorbidity Index	-0.07	0.15	0.94 (0.70-1.25)	0.65
APACHE II score	-0.04	0.04	0.96 (0.89-1.04)	0.34
SOFA score	-0.22	0.10	0.80 (0.66-0.98)	0.03*
Severity of ARDS				
Mild (reference)	-	-	-	-
Moderate	0.85	0.68	2.35 (0.62-8.87)	0.21
Severe	0.23	0.73	1.26 (0.31-5.23)	0.74
ECMO	0.02	1.25	1.02 (0.09-11.86)	0.99
PaO_2/FiO_2 (mmHg)	0.00	0.00	1.00 (0.99-1.00)	0.92
Tidal volume (ml/kgw, PBW)	-0.34	0.16	0.71 (0.52-0.98)	0.04*
PEEP (cm H_2O)	-0.06	0.13	0.94 (0.73-1.22)	0.66
Peak airway pressure (cm H_2O)	0.05	0.06	1.05 (0.94-1.17)	0.38
Dynamic driving pressure (cm H_2O)	0.06	0.06	1.06 (0.95-1.19)	0.28
Multivariate				
Gender (male)	-0.90	0.77	0.41 (0.09-1.83)	0.24
Smoking history	-0.54	0.65	0.58 (0.16-2.05)	0.40
SOFA score	-0.21	0.11	0.81 (0.66-1.00)	0.06
Tidal volume (ml/kgw, PBW)	-0.42	0.19	0.66 (0.45-0.97)	0.03*

ARDS: acute respiratory distress syndrome; CI: confidence interval; APACHE: Acute Physical and Chronic Health Evaluation; SOFA: Sequential Organ Function Assessment; PaO_2/FiO_2: alveolar oxygen pressure/fraction of inspiratory oxygen; PBW: predicted body weight; PEEP: positive end-expiratory pressure. *p-value < 0.05

study focusing on patients with ARDS and underlying chronic respiratory diseases, the tidal volume used with hospital survivors was significantly lower than that used with non-survivors (7.2 ± 1.6 ml/kgw vs. 8.0 ± 1.7 ml/kgw, p= 0.03). Furthermore, tidal volume was identified as the significant and independent predictive factor for survival (odds ratio 0.65, 95% confidence interval 0.44-0.95, p=0.03). Thus, a lung protective strategy may be an important way to manage ARDS patients with chronic respiratory diseases.

The role of initial severity of ARDS in predicting mortality is controversial. In the LUNG SAFE study, severity of ARDS was significantly correlated with hospital mortality (34.9% in mild, 40.3% in moderate and 46.1% in severe ARDS patients, p<0.001) [1]. However, some

studies investigating the evolution of disease severity after ARDS onset found that the baseline definition does not necessarily provide reliable predictions of mortality [19,27-29]. Villar *et al*. reported significant differences between mortality and severity when reclassified by response to a standard ventilator setting at 24 hours after ARDS onset (p<0.0001) [27]. In the current study, the distribution of severity of ARDS and PaO_2/FiO_2 ratio on day 1 was not significantly different between non-survivors and survivors (140.8 ± 71.3 mmHg vs 139.2 ± 67.3 mm Hg, p=0.93). Moreover, a disproportional relationship between mortality rate and severity of ARDS was found in our study (mortality rates of 76.4%, 58.1%, 72% in mild, moderate and severe ARDS, p=0.23), despite its statistical insignificance. It is very likely that the initial classification of ARDS is insufficient to determine the severity and outcome of new onset lung injury, especially for patients with underlying chronic respiratory diseases. In these patients, the PaO_2/FiO_2 ratio may not actually reflect the severity of the underlying disease. For example, in obstructive airway diseases, severity of disease was classified using FEV1 instead of the PaO_2/FiO_2 ratio [11-13]. However, underlying chronic respiratory diseases may also have an impact on the PaO_2/FiO_2 ratio via development of hypoxemia. Taking all the above into consideration, the severity of ARDS may not represent the outcome in patients with underlying chronic respiratory disease.

There are some limitations in our study. First, this was a single-center study with a small sample size, which may not be representative of the actual population of patients with chronic respiratory diseases and ARDS. Second, our study was retrospective in design, not prospective. Although a study on outcomes of patients with chronic respiratory diseases suffering from ARDS seems impossible to perform prospectively, enrollment of more patients may provide more details in terms of clinical information, hemodynamic evaluation and outcome evaluation. Third, in this study, not all patients received a pulmonary function test prior to the ARDS diagnosis, which may have led to slight difference in categorization of chronic respiratory diseases. However, all of these patients had an imaging study and detailed chart review to assist in reaching the diagnosis of chronic respiratory disease. Further prospective and multi-centered research should be conducted to validate our results.

Conclusion

In this study on patients with ARDS and underlying chronic respiratory diseases, the hospital mortality rate was relatively high. Lower tidal volume was identified as the significant and independent predictive factor for hospital survival. A lung protective strategy may be an important way to manage the ARDS patients with chronic respiratory diseases.

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急性呼吸窘迫症候群併有慢性肺疾病患之存活預測因子

黃繼賢 * 張克威 * 邱立忠 * 張志豪 * 李忠恕 * 胡漢忠 *,**
黃崇旂 *,** 高國晉 *,**

背景：急性呼吸窘迫症候群的嚴重缺氧由許多因子造成。慢性肺疾乃呼吸道或肺部之慢性疾病。急性呼吸窘迫症候群的部分大型研究中慢性肺疾病患是被排除的。本篇研究中，我們針對罹患急性呼吸窘迫症候群的慢性肺疾病患，研究其存活預測因子。

方法：我們回溯性蒐集2012年10月至2015年5月所有入住一醫學中心有急性呼吸窘迫症候群的慢性肺疾病患。我們記錄了臨床資訊、急性呼吸窘迫症候群嚴重度及成因、呼吸器參數和存活預後等資料。

結果：本在73位有急性呼吸窘迫症候群及慢性肺疾的病患中，COPD 佔 47.9%。院內死亡率為67.1% (49/73)。在輕度、中度、重度急性呼吸窘迫症候群中，死亡率各為76.4% (13/17), 58.1% (18/31), 72% (18/25) (p=0.23)。吐氣末正壓、尖峰氣道壓力及動態驅動壓力在未存活與存活病患中並無差異，但未存活者有較高的潮氣容積(8.0 ± 1.7 ml/kgw vs. 7.2 ± 1.6 ml/kgw, p=0.03)。多因子羅吉氏迴歸分析中，只有潮氣容積為有意義且獨立的院內存活預測因子 (勝算比0.65, 95%信賴區間0.44-0.95, p=0.03)。

結論：本研究中，罹患急性呼吸窘迫症候群的慢性肺疾病患有很高的院內死亡率，而較低的潮氣容積是有意義且獨立的存活預測因子。*(胸腔醫學* ***2019; 34: 230-239)***

關鍵詞：慢性肺疾，急性呼吸窘迫症候群，預後，低潮氣容積

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Extracorporeal Membrane Oxygenation for Life-Threatening Status Asthmaticus Refractory to Conventional Mechanical Ventilation – A Case Report and Literature Review

You-Yi Chen, Zong-Han Yao

Despite continuous improvements in asthma treatment, severe asthma exacerbation requiring hospitalization or/and critical care remains a crucial healthcare issue. Status asthmaticus is a life-threatening condition caused by acute respiratory failure and is the most severe clinical presentation of asthma. It is generally characterized by cardiovascular dysfunction and hypercapnia with severe acidemia that requires invasive medication treatment and mechanical ventilation. Nonconventional interventions such as general anesthesia, heliox, bronchoscopic retrieval of mucous plugs and extracorporeal life support also have been advocated for patients with fulminant asthma. Immediate mortality rate of those patients who are mechanically ventilated for acute severe asthma is very low; however, mortality is often associated with out-of-hospital cardiac arrest before intubation. Patients who have been intubated for severe asthma are at an increased risk of death if conventional management fails to relieve dynamic hyperinflation and progressive hypercapnia. We report the case of a female suffering from life-threatening asthma. She presented with severe hypercapnia and life-threatening acidemia, and failed to respond to conventional therapy and mechanical ventilation. Under the circumstances, early and emergency administration of extracorporeal membrane oxygenation (ECMO) led to a dramatic improvement in lung mechanics and gas exchange. As an effective rescue therapy, ECMO plays a crucial role in the management of life-threatening asthma when conventional therapy fails. ***(Thorac Med 2019; 34: 240-245)***

Key words: extracorporeal membrane oxygenation (ECMO), asthma

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Introduction

Status asthmaticus is a severe life-threatening asthma exacerbation that requires aggressive management, including extended pharmacologic therapy and/or mechanical ventilatory support [1]. Indications for immediate intubation include cardiac arrest, respiratory arrest, depressed level of consciousness, extreme exhaustion, and severe hypercapnia accompanied by acidemia [2]. Despite the use of aggressive therapies, status asthmaticus still shows mortality of 8% in rare cases that have progressed with worsening dynamic hyperinflation, increased intrathoracic pressure or acidemia-related cardiovascular events [3-4].

Extracorporeal life support (ECLS) serves as salvage therapy and has shown survival benefits for adults with acute respiratory failure [5-7]. In addition, ECLS provides survival benefits in reversible cases of acute respiratory failure, compared to conventional ventilation [8]. Status asthmaticus, a pathophysiologically and clinically reversible process, represents the type of disease that may benefit from ECLS.

Case Report

A 70-year-old woman presented to the emergency room with a sudden onset of dyspnea and consciousness loss within 30 minutes prior to her arrival. She had been diagnosed with asthma for more than 10 years, based on classic respiratory symptoms such as episodic wheezing, coughing and chest tightness. Her symptoms were precipitated mostly by exposure to cold air and upper respiratory tract infections. The patient had been confirmed to have airflow limitation by bronchodilator reversibility test 5 years ago. She had poor drug compliance and therefore frequently experienced asthma attack. On arrival, she was diaphoretic, tachypneic, using her accessory muscles and irresponsive to external stimulation (Glasgow coma score (GCS): E1V1M3) with a respiratory rate of 35/min and blood pressure of 214/120 mmHg. Her initial arterial blood gas analysis (ABG) was pH: 7.013, PCO_2: 116 mmHg, PO_2: 64 mmHg, HCO_3-: 29.7 mEq/L. Physical examination revealed decreased breathing sounds and bilateral wheeze. Chest radiograph showed no obvious lung consolidation or atelectasis. Blood examination revealed leukocytosis (WBC: 17.9×10^3/μL) and eosinophilia (2.1×10^3/μL). Emergency intubation with mechanical ventilation was started with continuous nebulization therapy, including salbutamol, ipratropium bromide and epinephrine. Intravenous steroid, magnesium sulfate and antibiotics were also given. The patient was sedated with propofol, cisatracurium besylate, and fentanyl due to agitation and patient-ventilator dyssynchrony.

The initial ventilator setting was in pressure control mode with IP 25 cm H_2O and PEEP 8 cm H_2O. Her clinical condition continued to deteriorate during the next 30 minutes with a reduced level of consciousness (GCS: E1V1M1) and low tidal volume (<100 mL). On lung auscultation, there were more diminished breathing sounds, which were barely wheezing in nature. Follow-up chest radiograph showed no malposition of the endotracheal tube or signs of pneumothorax (Figure 1). Bradycardia developed and repeated ABG revealed more severe respiratory acidosis: pH: 6.957, $PaCO_2$: 155.7 mmHg, PaO_2: 113.1 mmHg, and HCO_3-: 25 mEq/L. Veno-venous extracorporeal membrane oxygenation (ECMO) was then begun in an urgent manner via bi-femoral venous cannulation with an initial femoral-atrial flow of 3 L/min.

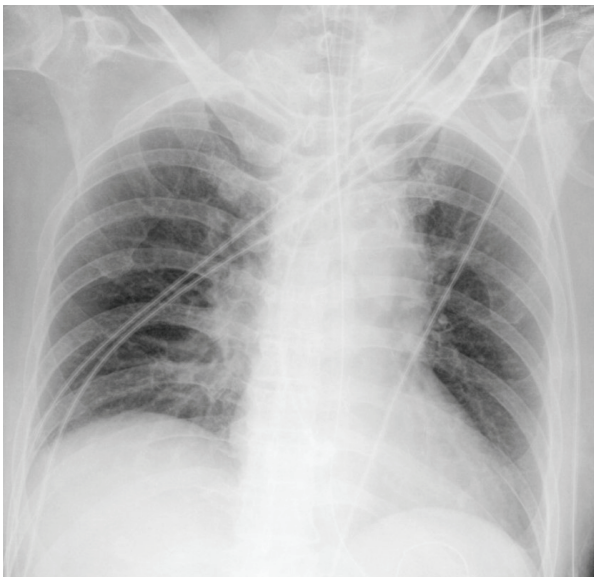

Fig. 1. Chest radiograph showing the correct position of the tracheal tube without a sign of pneumothorax

Following the establishment of ECMO, the blood gases rapidly normalized. Sixty minutes after the start of ECMO, the values became: pH: 7.236, $PaCO_2$: 49.3 mmHg, PaO_2: 397.5 mmHg, HCO_3^-: 21.1 mmol/L.

Despite the administration of high-dose steroid and inhaled bronchodilator use, airway resistance remained high on day 2 (Raw: 122 cm H_2O/L/sec) and day 3 (Raw: 102 cm H_2O/L/sec). In order to avoid hyperinflation and to assess the patient's readiness for a spontaneous breathing effort, we moderately tapered off the sedative agents and shifted ventilator support to synchronized intermittent mandatory ventilation mode transiently on day 3. Nevertheless, low tidal volume-related decompensated respiratory acidosis developed as a result of high airway resistance. The patient's eosinophilia fortunately resolved gradually, and airway resistance decreased to Raw: 12 cm H_2O/L/sec with adequate gas exchange under pressure support ventilation with IP 18 cm H_2O, PEEP 5 cm H_2O and FiO_2 0.4 on day 4. ECMO support was stopped on day 4, followed by weaning off the ventilator on day 5 without any sequelae. The ventilator setting parameters and ABG analyses during the treatment course are listed in Table 1. Total ICU stay was 7 days and the patient was discharged home on the 11th day of admission.

Discussion

Approximately 2~4% of hospitalized acute asthma exacerbation patients require mechanical ventilatory support, and have a reported 0.5~10.3% in-hospital mortality [9-10]. ECLS is rarely necessary for mechanically-ventilated status asthmaticus patients, and this condition accounts for only 1.9% of primary indications for ECLS in the International ECLS Organization Registry. Of the asthmatic patients treated with ECMO, 83.3% survived to hospital discharge, compared to the 50.8% hospital survival rate for patients with a non-asthmatic etiology for ECMO. Asthmatics were younger than non-asthmatics (31.3 vs. 38.3 years), underwent a shorter mechanical ventilation time before ECLS (65.2 vs. 109.5 hours), experienced a shorter duration on ECLS (111.9 vs. 222.0 hours), were more acidotic (7.17 vs. 7.27 pH level) and were less hypoxic (244 vs. 71 in PF ratio) [11].

The success of ECMO in asthma was attributed to the natural reversibility of the airflow obstruction and airway inflammation [12]. Despite the lack of randomized trials to guide optimal therapy, a conventional ventilation approach allows permissive hypercapnia and minimizes dynamic hyperinflation [13]. The initiation of ELCS for refractory status asthmaticus should be anticipated when severe dynamic hyperinflation or deteriorated respiratory acidosis

Table 1. Ventilator Parameters and Arterial Blood Gas Analysis.

	ER arrival	Immediately Before ECMO	1 hour After ECMO	D2 on ECMO	D3 on ECMO	Before weaning from ECMO	After weaning from ECMO
Ventilator parameters	NRM	PCV	PCV	PCV	SIMV	PSV	PSV
PEEP (cmH_2O)		8	8	8	5	5	5
IP (cmH_2O)		20	25	18	18	18	18
Raw (cmH_2O/L/sec)		160	152	122	102	12	10
FiO_2 (%)	100	100	60	40	40	40	40
I:E ratio		1:5	1:4.6	1:4.6	1:4.6	1:3	1:2
Tidal volume (ml)		45	53	130	237	451	450
Arterial blood gas							
PH	7.013	6.957	7.165	7.425	7.240	7.411	7.407
$PaCO_2$ (mmHg)	116.1	155.7	88.8	31.7	76.7	39.2	39.2
PaO_2 (mmHg)	81.1	313.1	65.4	177.9	134.2	170.4	143.6
HCO_3 (mmol/L)	29.7	35.1	32.3	21.0	33.2	25.2	24.9

NRM=Non-rebreather mask, PCV=Pressure-controlled ventilation, SIMV=Synchronized intermittent-mandatory ventilation, PSV=Pressure-support ventilation, PEEP=Positive end expiratory pressure, IP=Inspiratory pressure, FiO_2=Fraction of inspired oxygen, I:E ratio=Inspiratory/expiratory ratio, PaO_2=Partial pressure of oxygen, PCO_2=Partial pressure of carbon dioxide, ECMO=Extracorporeal membrane oxygenation

develops despite maximal medical treatment. ECMO reverses hyperinflation, eradicates hypercapnia and allows the lung to rest, thereby providing time for inflammation-causing bronchospasm to be relieved [14]. The severe derangement in the gas exchange of the patient was managed beyond the current clinical asthma guidelines. ECMO plays a crucial role in correcting hypoxemia and hypercapnia caused by a low ventilation-perfusion mismatch, shunting and hypoventilation by providing a bypass extracorporeal blood flow to achieve adequate oxygenation and CO_2 removal [15].

We have described a case with the successful use of ECMO in an elderly woman with status asthmaticus that could not be controlled, even with a maximal effort in mechanical ventilation and pharmacologic therapies. Life-threatening hypercapnia and acidemia were reversed rapidly by ECMO, and the patient was discharged with no complications after a short period of ECMO use (4 days) and ICU treatment (7 days). As seen in our case, early implementation of ECMO may greatly improve patient outcome, and the advantages outweigh the disadvantages in severe cases. In most case reports, ECLS was implemented only when the patient developed life-threatening acidosis or barotrauma [16-18]. With the increasing availability of ECLS, prospective clinical trials are urgently needed in order to develop evidence-based guidelines for this population of patients.

Conclusion

As a result of our experience, we strongly believe ECMO should be initiated early in severe asthma failing conventional therapy as a

life-saving therapeutic measure. Further investigation is required to determine the efficacy and timing for ECLS in severe asthma compared to conventional therapies.

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體外膜氧合 (ECMO) 使用於傳統呼吸器治療失敗之嚴重氣喘惡化：病例報告與文獻回顧

陳祐易　姚宗漢

氣喘目前已具有效的治療方式，但氣喘急性發作可能發生在接受治療中的病人且可能為嚴重甚至致命的疾病。本文提出的案例報告是一位沒有規律使用氣喘控制藥物之70歲女性，主訴為急性發作之呼吸困難與意識狀態變化30分鐘，經急性氣喘惡化之藥物處置與機械式呼吸器輔助治療下仍持續惡化至致命性心律不整，藉由體外膜氧合 (ECMO) 的治療成功避免嚴重併發症，且於一周的加護病房治療後成功脫離呼吸器與ECMO。目前在急性氣喘惡化使用體外心肺支持系統 (ECLS) 治療尚無明確的治療指引，但藉由此個案報告與文獻回顧，在嚴重氣喘惡化病人及早使用體外心肺支持系統確實能提供此類病人更好的治療預後。*(胸腔醫學* ***2019; 34: 240-245****)*

關鍵詞：體外膜氧合 (ECMO)，氣喘

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Pulmonary Leukemic Infiltration: A Case Report

Hsiang-Shi Shen*, Jia-Yi Feng**,***, Wei-Juin Su**,***

Pulmonary leukemic infiltration is usually asymptomatic, although it may present with critical clinical conditions. It is difficult to diagnose because of its non-specific radiographic patterns and laboratory findings. Therefore, invasive diagnostic procedures are usually required to reach the diagnosis. Leukostasis with leukemic alveoli migration is considered to be its characteristic pathologic finding. Here, we report a case of pulmonary leukemic infiltration requiring mechanical ventilation and extracorporeal membrane oxygenation support that was diagnosed using bronchoalveolar lavage and postmortem sono-guided lung biopsy. ***(Thorac Med 2019; 34: 246-254)***

Key words: pulmonary leukemic infiltration, leukostasis, necropsy

Introduction

Pulmonary leukemic infiltration (PLI) is a common noninfectious pulmonary complication of acute leukemia [1]. Although usually asymptomatic, fatal outcomes may occur [2]. PLI is characterized by migration of a large amount of leukemic cells with rapid proliferation in the pulmonary capillaries and alveoli [3]. It is difficult to diagnose due to non-specific radiographic patterns and laboratory examination results. Bronchoalveolar lavage (BAL) and lung biopsy are frequently required [4]. In this report, we describe a patient with PLI with acute respiratory failure.

Case Report

This 58-year-old man presented to our emergency department with shortness of breath and fever for 1 week. He had a medical history of myelodysplasia and was under regular packed RBC transfusion once every 2 weeks for 7 years. He also had a history of hypersensitivity pneumonitis, organizing pneumonia, and cryptococcus infection. He had been a biotech company manager and retired 2 years previous to this presentation. He had no travel or contact history before the present illness. He had smoked 3 packs of cigarettes per day for 40 years and had no alcohol drinking or betel nut

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chewing history. No family history of autoimmune disease or cancer was noted.

Two weeks prior to this presentation, he suffered from dry cough and general soreness. Fever developed afterward. He initially visited a regional hospital for evaluation. Chest plain film was obtained and revealed increased infiltrates at the bilateral lung fields. Under the suspicion of atypical pneumonia, intravenous piperacillin/tazobactam, oral trimethoprim/sulfamethoxazole, and oral levofloxacin were prescribed. However, his condition deteriorated and chest films showed progressive pulmonary infiltrates. Therefore, he was transferred to our hospital for further management.

Upon arrival at the emergency department, physical examination revealed temperature of 37.2°C, blood pressure of 116/55 mmHg, pulse rate of 104 beats/min, and respiratory rate of 40 breaths/min. Crackles, but no wheeze, were heard at the bilateral lungs. Epigastric tenderness and hepatosplenomegaly were noted on palpation. The rest of the physical examinations were unremarkable. His initial laboratory data showed a white blood cell count of 37,400/μL with band forms of 11%, hemoglobin of 7.9 g/dL, platelet count of 123,000/μL, C-reactive protein of 4.14 mg/dL, procalcitonin of 0.9 ng/ml, and a PaO_2/FiO_2 ratio of 85 (PaO_2 85 mmHg on 100% oxygen). The chest film revealed diffuse infiltrates in bilateral lung fields (Figure 1a). Due to hypoxic respiratory failure, the patient was intubated with mechanical ventilator support. Chest computed tomography (CT) was then arranged and showed diffuse ground glass opacities at the bilateral lung fields, a reticular pattern, a minimal amount of pleural effusion, and splenomegaly (Figure 2). Under the impression of severe community-acquired pneumonia and myelofibrosis with suspicious leukemic transformation, the patient was admitted to the intensive care unit (ICU) for further management.

After admission, intravenous meropenem, teicoplanin, levofloxacin, and micafungin were administered as empirical antibiotics. Intrave-

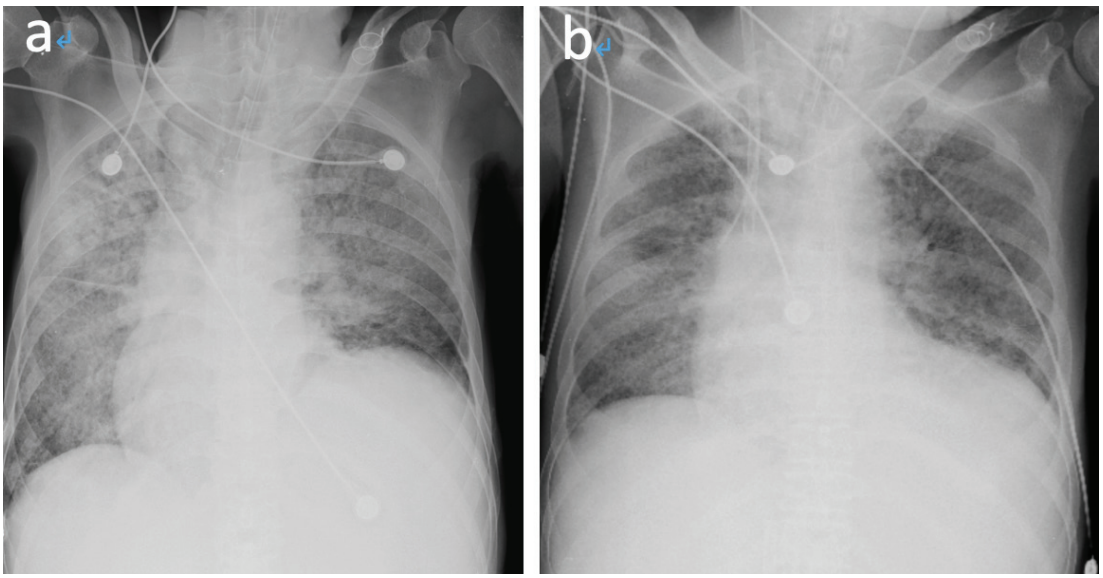

Fig. 1. a: Bilateral pulmonary infiltration, b: showing much improvement after treatment

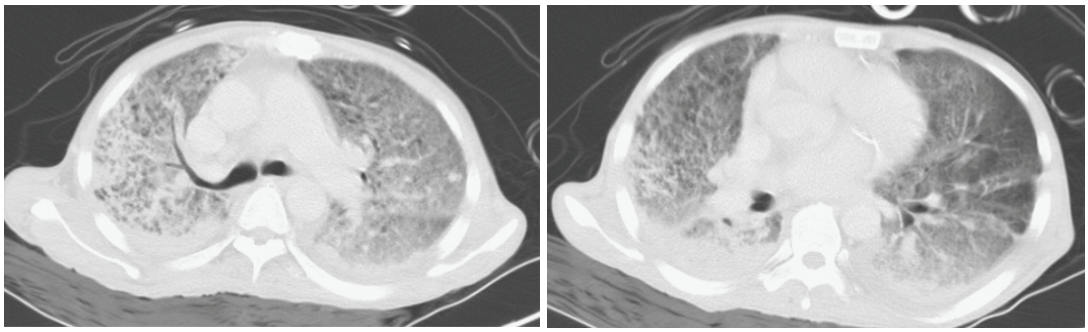

Fig. 2. Bilateral reticular interstitial pattern with subpleural involvement. Bronchovascular bundle thickness, bilateral diffuse ground-grass opacity, and pleural effusion were also noted.

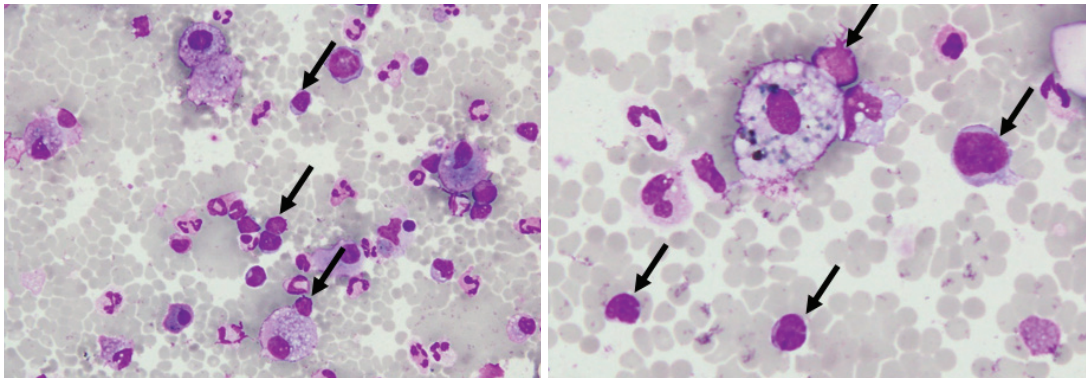

Fig. 3. Bronchoalveolar lavage fluid revealed blast cells (arrow) in a background of alveolar macrophages, neutrophils, and red blood cells.

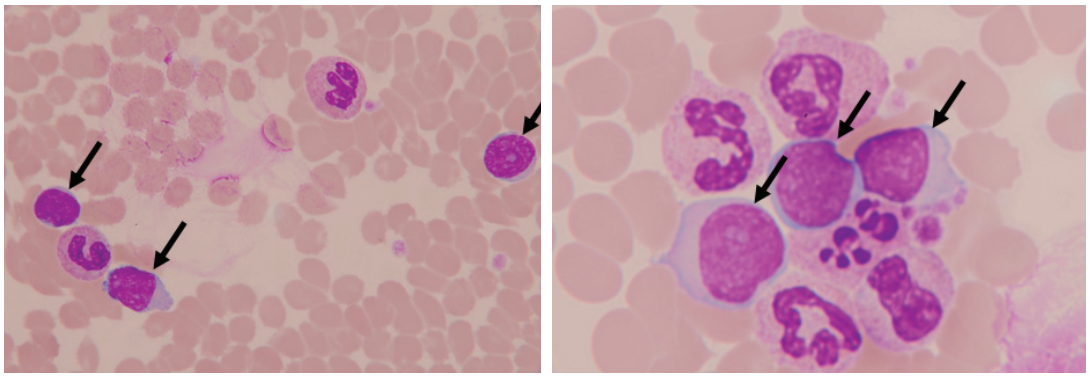

Fig. 4. Peripheral blood smear also showed blast cells (arrow).

nous methylprednisolone 31.25 mg Q12H was also given. We performed diagnostic BAL on the 2nd day of hospitalization. All the BAL fluid (BALF) and endotracheal aspiration cultures and stains showed negative results. Serologic testing for atypical pneumonia pathogens and virus also showed negative results. Cytology of the BALF showed blast cells (Figure 3). Immature cells were also found in the peripheral blood (Figure 4), and the blast count was 3,744/μL. Under the suspicion of myelodysplasia with leukemic transformation and PLI, a hematologist was consulted. Oral hydroxyurea was prescribed and leukapheresis was arranged

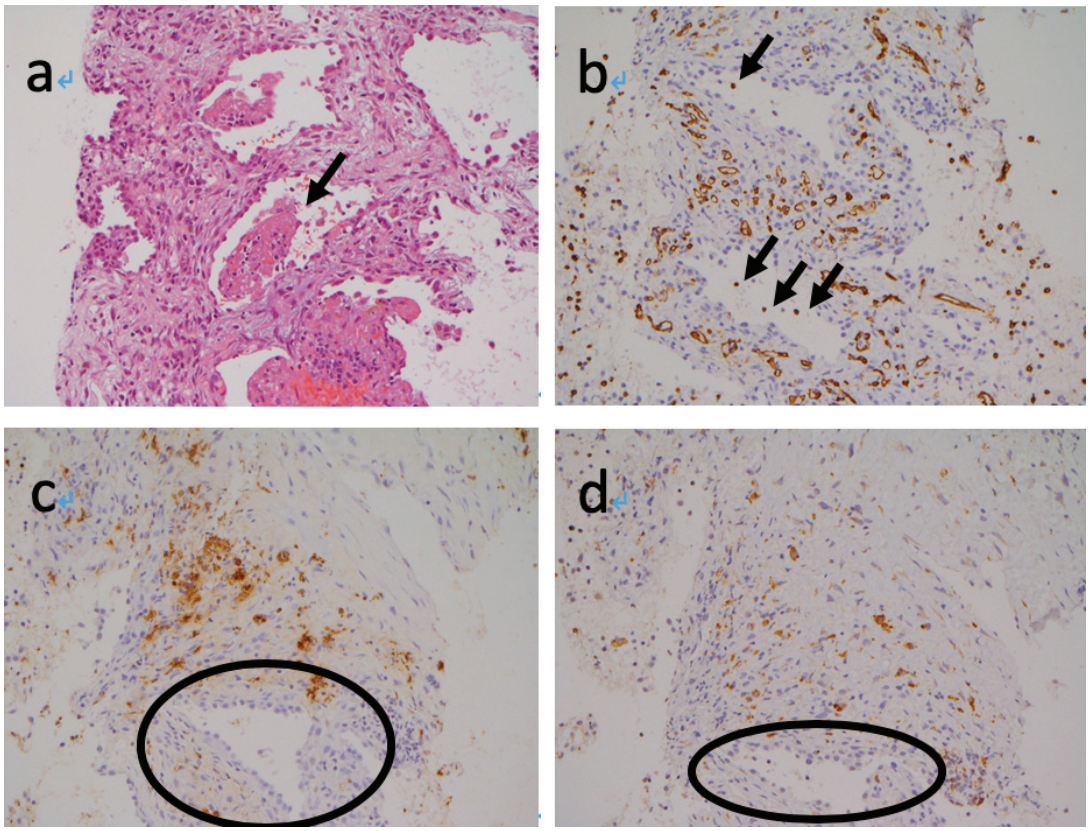

Fig. 5. Pathology of necropsy showed diffuse alveolar damage in the proliferative phase (a, arrow). Some atypical hematopoietic cells in the vascular channel and alveolar space were also found, and showed positive in CD34 IHC staining (b, arrow), but negative in MPO (c, circle) and CD117 staining (d, circle), compatible with circulating leukemic cells.

on the 3rd day of hospitalization. However, the hypoxemia deteriorated on the same day and veno-venous extracorporeal membrane oxygenation (VV-ECMO) was performed. Oral hydroxyurea was discontinued on the 8th day of hospitalization because of impaired renal function (creatine increased from 1.59 to 3.17 mg/dL) and improved leukostasis (white cell count decreased from 62,200/μL to 17,000/μL). High-dose intravenous furosemide was used for oliguria and fluid overload. Pulmonary infiltrates in the chest films gradually improved thereafter and oxygen demand in VV-ECMO also decreased (Figure 1b). VV-ECMO was terminated on the 17th day of hospitalization. However, the patient strongly requested endotracheal tube removal and refused reintubation. Therefore, the endotracheal tube was removed on the 17th day of hospitalization. Shortness of breath unfortunately occurred after extubation. The chest films showed newly developed pulmonary infiltrates at the bilateral lung fields (Figure 6). Atelectasis or secondary pulmonary infection were considered. A noninvasive positive pressure ventilator was applied and broad-spectrum antibiotics were administered. But desaturation and dyspnea continued to deteriorate. The patient and his family members confirmed a willingness for hospice care and refused further intensive care. The patient died on the 21st day of admission.

With the patient and his family's permission, necropsy was carried out immediately af-

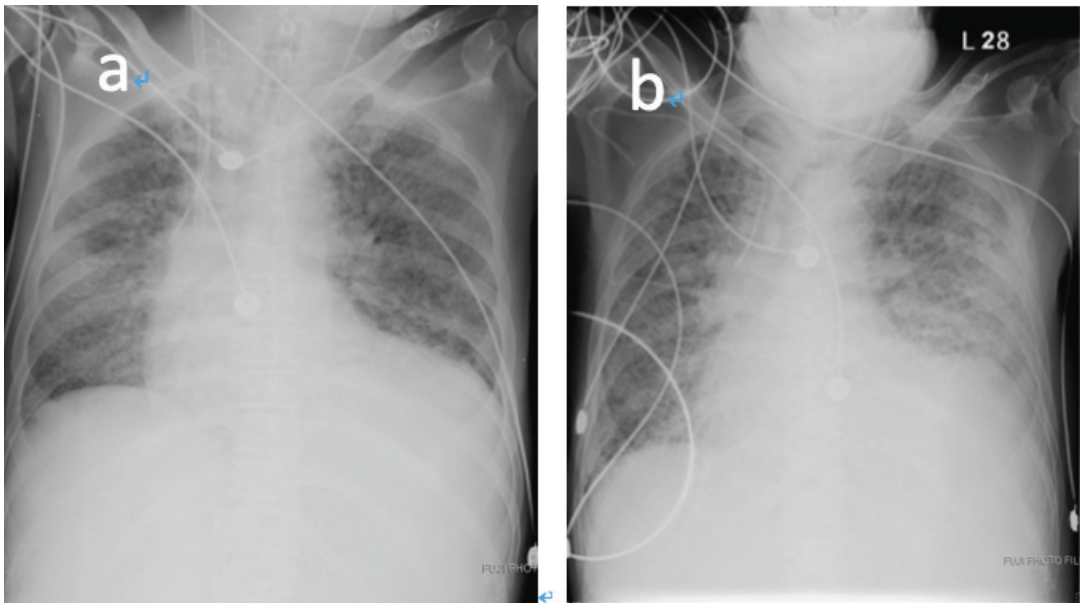

Fig. 6. Chest X-ray showed increased pulmonary infiltration after extubation (b), compared to the chest X-ray before extubation (a)

ter expiration. The sono-guided biopsy reported diffuse alveolar damage in the proliferative phase. Meanwhile, some atypical hematopoietic cells in the vascular channel and alveolar space, which may have been circulating leukemic cells, were also found (Figure 5). Bone marrow biopsy reported acute myeloid leukemia (AML). The patient was finally diagnosed with AML with PLI and acute respiratory failure.

Discussion

Pulmonary complications occur in approximately 80% of patients with acute leukemia, and are the leading cause of morbidity and mortality [5]. In a retrospective series of 1,541 patients with AML, 8% required mechanical ventilation within 2 weeks of remission induction chemotherapy, and were associated with a 70% mortality rate [6]. The etiology of pulmonary infiltration in patients with acute leukemia includes infiltration of leukemic cells, hemorrhage, infection, and others in the lungs [1]. In a study evaluating pulmonary infiltration, an infectious etiology could be established in 21 (40%) of 53 patients who underwent remission induction chemotherapy [7]. Another study of 38 patients with pulmonary infiltration found that 13 (34%) cases were of infectious origin, 16 (42%) were noninfectious, and 9 (24%) had an unknown cause [8]. Among these etiologies, PLI is frequently found during autopsy, as most patients are asymptomatic [1]. Tenholder and Hooper reported that 98% of autopsied patients with leukemia had pulmonary complications [9], with PLI being a major contributor [10]. Although most patients are asymptomatic, fever, dyspnea, hypoxemia, diffuse lung infiltrates, pleural effusions, and a rapidly fatal clinical course may occur in patients with PLI [2].

Two main pathogenetic factors are responsible for the development of hyperleukocytosis-related PLI: 1) rapid blast proliferation leading to a high leukemic tumor burden and 2) disruption in normal hematopoietic cell adhesion leading to a reduced affinity to the bone

marrow [11]. The high number of leukocytes, approximately >100,000/uL, may result in leukostasis via 2 main mechanisms. First, myeloid blasts are larger than immature lymphocytes or mature granulocytes, and leukemic blasts are considerably less deformable than mature leukocytes. This explains the higher incidence of leukostatic complications in AML compared to acute lymphocytic leukemia, chronic myeloid leukemia, or chronic lymphocytic leukemia [12]. Second, leukemic cells can promote their own adhesion to the endothelium and create a self-perpetuating loop in which the number of blast cells that migrate and attach to the endothelium is continuously increasing [3]. This explains the non-correlation between leukocyte count and severity/frequency of leukostasis [13-15].

There is no single gold standard for diagnosing pulmonary infiltration in leukemic patients because of its various etiologies [16]. Basic examinations for infection are crucial because infectious diseases are the major causes of pulmonary infiltration in leukemic patients. Other noninfectious etiologies, such as hemorrhage, pulmonary edema, and other uncommon causes, may have similar clinical and radiological presentations. Hence, noninfectious conditions are often diagnosed based on pathological and cytological studies [14].

In PLI, chest radiographic findings are usually nonspecific, and may include varying degrees of interstitial or alveolar opacities. However, the radiographic appearance may also be normal, even with respiratory failure [17].

High-resolution CT in patients with PLI shows interlobular thickening and bronchovascular bundle thickening. Pleural effusion, focal/diffuse consolidation, ground-grass opacity, and centrilobular nodules with occasionally poorly defined opacity confluence were also noted [18-19]. Bronchovascular bundle thickening and peripheral pulmonary arteries prominence have been shown to be correlated with histopathologic findings in the leukemic cellular infiltrate around the pulmonary arteries, bronchi, and bronchioles. Furthermore, leukemic cellular infiltration in the alveolar spaces and septa may also be related to nonlobular and nonsegmental ground-glass opacities [20].

Considering the nonspecific radiologic findings, invasive procedures are sometimes needed to make the diagnosis. Rossi *et al*. reported that the retrieval of leukemic cells in BAL fluid may establish the diagnosis, especially when the platelet count is too low to perform biopsy [4]. O'Leary M *et al*. reviewed the BAL fluid from 12 leukemia cases and reported that myeloid blast sheets were typically observed [21]. However, the absence of leukemic cells in BAL fluid cannot rule out PLI. PLI should still be considered, especially when blast cells in the peripheral blood are >40% [5].

Lung biopsy is frequently considered in patients with an uncertain diagnosis after BAL [16]. The applicable procedures include transbronchial needle biopsy, transthoracic needle biopsy, open lung biopsy, and video-assisted biopsy [22]. Although the risk of bleeding would be a concern during lung biopsy, a study found no procedure-related hemorrhage, pneumothorax, or death after BAL or transbronchial biopsy in 107 patients with platelet counts of <50,000/μL after the pre-procedure blood transfusion [23]. In our patient, infiltration of circulating leukemic cells in the alveoli was confirmed by postmortem sono-guided lung biopsy, which has been rarely reported, but made our diagnosis solid.

Regarding treatment, cytoreduction therapy is the main initial treatment for leukostasis-

related PLI. Hydroxyurea is commonly used before the proper induction regimen for leukemia [24]. Once the diagnosis is made, standard-dose or high-dose cytarabine plus anthracycline or mitoxantrone should be initiated [25-26]. In patients with suspected acute promyelocytic leukemia, all-trans-retinoic acid should be initiated immediately [27].

In hyperleukocytosis-induced pulmonary infiltration, leukapheresis can rapidly remove excessive leukocytes by mechanical separation. However, the majority of the leukemic burden is located in the bone marrow, and these cells are rapidly mobilized into the peripheral blood shortly after a successful leukapheresis [28]. Furthermore, leukapheresis showed no consistent clinical benefits in a systematic review [24]. Steroid use with conventional chemotherapy in patients with PLI may also be considered. One study investigated the benefits of corticosteroids and concluded that adding dexamethasone to the treatment of patients with AML-M5 with acute respiratory failure caused by leukemic infiltration can significantly decrease ICU mortality [29].

In summary, we reported a case of AML with PLI, initially suspected by BAL examination and confirmed by postmortem necropsy, which was rarely performed in previous reports. After excluding infectious diseases, treatment with leukopheresis, hydroxyurea, and methylprednisolone was initiated, and showed partial improvement. Without knowing the subtype of AML, dexamethasone may still have some advantage in controlling disease progression. However, induction chemotherapy remains the most important treatment for patients with AML, if stabilized after the initial treatment.

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白血病肺部浸潤：案例報告

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白血症肺部浸潤的病人大部分症狀不明顯，然而仍有可能會導致嚴重的症狀甚至死亡。因為缺乏特別的影像學及實驗室檢驗特徵，白血症肺部浸潤在診斷上常十分困難，因此也常需要藉由一些侵入性的檢查才能更加確立診斷。病理上常會看到白血球滯留以及白血球的肺泡移行。在此分享一個因為白血症肺部浸潤而導致呼吸衰竭，需要呼吸器以及葉克膜支持的病人，而我們藉由肺泡沖洗術及超音波導引切片確立診斷。*(胸腔醫學* ***2019; 34: 246-254)***

關鍵詞：白血症肺部浸潤，白血球滯留症，屍體剖檢

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Bronchoscopic Cryotherapy and Dilatation by Endotracheal Tube Cuff in a Patient with Central Airway Obstruction-Related Respiratory Failure

Allen Chung-Cheng Huang*, Chun-Liang Chou**,
Meng-Cheng Ko*, Chi-Hsien Huang*, Shu-Min Lin*,***

Granulation tissue formation is a common complication after implantation of metallic stents in patients with central airway obstruction. A combination of balloon dilatation and cryotherapy is a treatment option. Herein, we report the case of a 53-year-old female patient who underwent tracheal metallic stent implantation due to lung adenocarcinoma with treatment-related tracheo-esophageal fistula. One year after the procedure, acute respiratory failure developed due to extensive granulation formation with central airway obstruction at both ends of the stent. We performed bronchoscopic cryotherapy with cryogen applied to 4 granulation sites followed by the use of an endotracheal tube cuff as a balloon dilator. The airway obstruction was relieved by this procedure and the patient was extubated immediately thereafter. The presented case provides evidence that the combination of cryotherapy and endotracheal tube cuff as a balloon dilator is feasible and safe for the management of granulation tissue-induced central airway obstruction and respiratory failure. ***(Thorac Med 2019; 34: 255-260)***

Key words: cryotherapy, central airway obstruction, granulation tissue, adenocarcinoma; lung cancer, bronchoscopy

Introduction

Granulation tissue formation is a common complication after implantation of metallic stents in patients with central airway obstruction. Focal concentric strictures are typically managed best by endoscopic balloon dilation of the airway. However, limitations may be present in a patient with reparatory failure under endotracheal intubation due to the small diameter of the endotracheal tube. We present a case in which we managed to overcome such difficulties with a combination of endoscopic cryotherapy and use of an endotracheal tube cuff as a balloon dilator.

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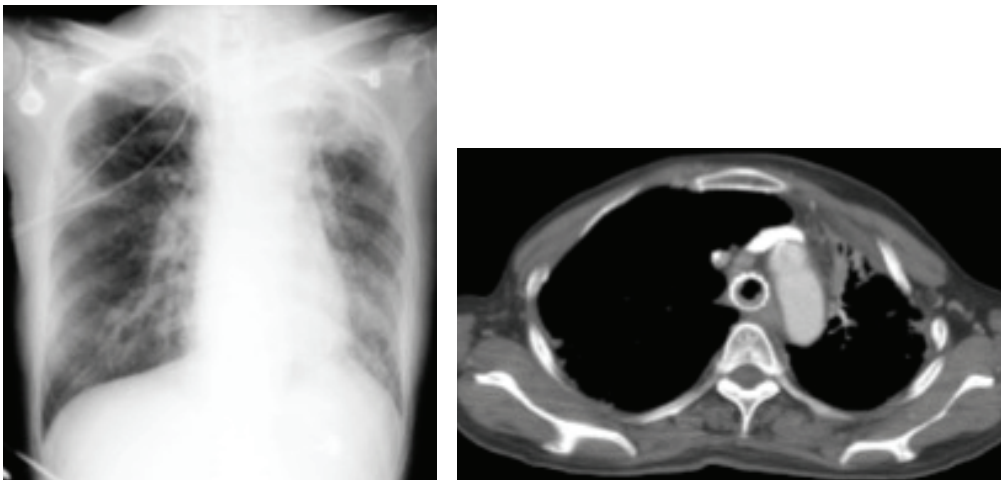

Fig. 1. The patient's chest plain film at admission, and CT scan 1 month prior to admission

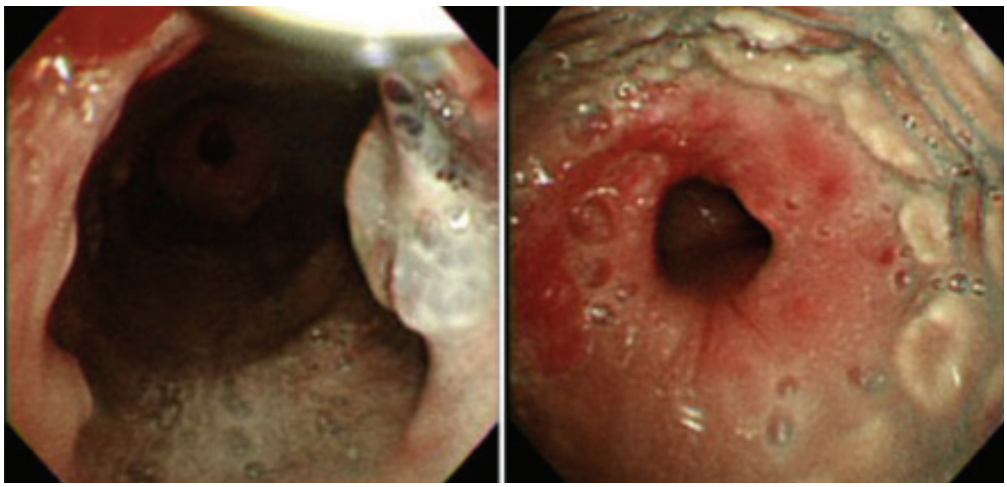

Fig. 2. Bronchoscopy showed 2 sites of narrowing: 1 cm above the proximal end of the stent, and 1 cm above the distal end with granulation tissue formation.

Case Presentation

A 53-year-old woman was diagnosed with adenocarcinoma of the left upper lung, cT-4N2M1b, stage IV, with direct invasion to the T-spine (T2-T3) and the esophagus. Because of a wild-type EGFR mutation, she underwent chemotherapy with cisplatin plus pemetrexed from February 2017 to September 2017, in addition to radiotherapy for the spinal invasion. A large tracheo-esophageal (T-E) fistula, 6x2 centimeters (cm) in size, developed after chemotherapy. A covered Ultraflex (Boston Scientific, Natick, Mass.) stent (2 cm in diameter, 8 cm in length) was subsequently implanted via flexible bronchoscopy for the T-E fistula. After implantation of the stent, the symptom of repeated aspiration improved. A year later, the patient was intubated for hypercapnic respiratory failure secondary to central airway obstruction and pneumonia (Figure 1). Bronchoscopy revealed 2 sites of narrowing-1 cm above stent the proximal end of the stent and 1 cm above the distal end with granulation tissue formation (Figure 2). The endotracheal tube was placed past the proximal site of narrowing under broncho-

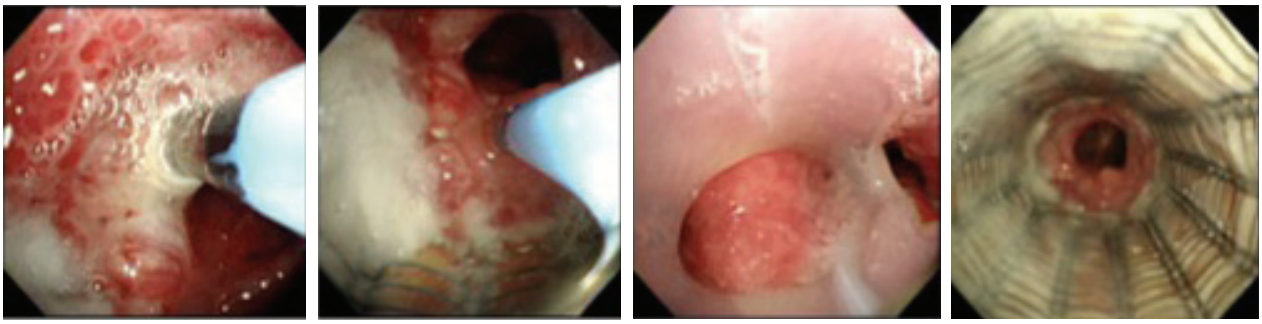

Fig. 3. A cryoprobe with a flexible bronchoscope was used on the granulation tissue at the 3, 6, 9, and 12 o'clock positions. The cuff on the ETT was used for dilatation 3 times. The ETT was removed subsequently.

scopic (BF-P240 or BF-40; Olympus, Tokyo, Japan) guidance. However, the endotracheal tube could not pass through the distal stenosis due to severe obstruction caused by concentric granulation tissue formation. After a week of antibiotic treatment, we performed cryotherapy with a flexible bronchoscope. The procedure was performed using a 1.9 mm flexible cryoprobe (Erbokryo CA, Erbe, Germany) with carbon dioxide as the cryogen. A temperature of approximately-70°C was achieved at the probe tip. A cryoprobe was used for 4 cycles (60 seconds per cycle) on 4 different sites of the granulation tissue, at 3, 6, 9, and 12 o'clock positions (Figure 3). After the cryotherapy procedure, the endotracheal tube could be advanced past the distal site of endobronchial obstruction. We used the cuff on the endotracheal tube as a balloon for dilatation 3 times. After the procedure, we immediately removed the endotracheal tube. The patient was successfully extubated and was later discharged from the ward uneventfully. The follow-up bronchoscopy a month later showed less granulation tissue (Figure 4).

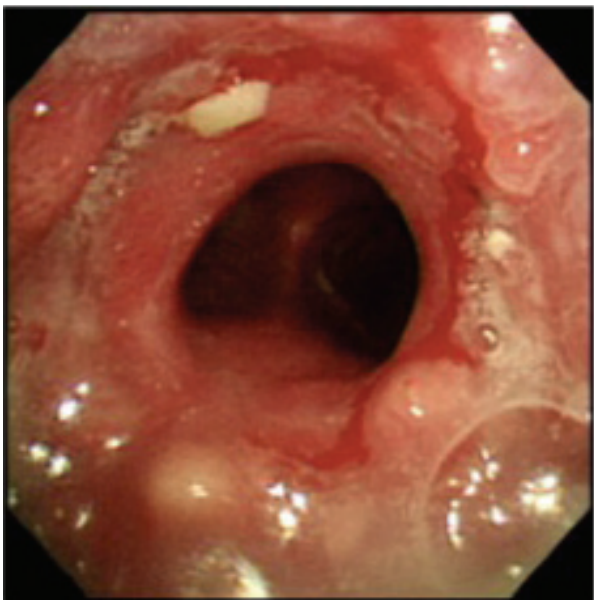

Fig. 4. Follow-up bronchoscopy 1 month later showed less granulation tissue.

Discussion

Granulation tissue formation is a common complication after implantation of metallic stents in patients with central airway obstruction [1]. Metallic stent related granulation tissue formation and stenosis are usually treated by dilation, at least as an initial step in their management. Balloon dilation can be performed with a therapeutic flexible bronchoscope and is currently the most common method of dilation [2]. Balloon dilators come in assorted sizes for accurate dilation diameters. The dilatation procedure results in immediate improvement of stenosis in almost all cases and offers an excellent short-term relief when used as a sole

treatment modality [2]. In most of the published large series evaluating balloon dilation in tracheobronchial stenosis, one-third to one-half of patients required other therapies including stent, laser, surgery, and cryotherapy [3]. In the present case, we employed an endotracheal tube cuff as a balloon dilator. Due to severe obstruction, endotracheal tube could not pass directly through the lesion site. Therefore, we performed cryotherapy at 4 sites of granulation followed by passing the endotracheal tube through the lesion site. The airway obstruction was relieved by the endotracheal cuff acting as a balloon for dilatation and the patient was extubated immediately after the procedure. The present case provides the evidence of combination of cryotherapy and endotracheal tube cuff as a balloon dilator is feasible and safe for the management of granulation tissue-induced central airway obstruction and respiratory failure.

Although the use of bronchoscopic cryotherapy for removing central airway lesions has been reported [2], its use in an intensive care unit (ICU) is rarely reported. Cryotherapy played an important role in liberating our patient from the ventilator for this patient. The patient suffered from granulation tissue formation caused by the metallic stent placed in her trachea. Granulation tissue formation is a complication of central airway stenting. Previous reports have estimated that granulation tissue formation occurs with approximately 25% of expanding metallic airway stents [4-5]. Because the granulation tissue in this patient grew in a concentric fashion, causing severe stenosis, previously reported cryo-recanalization technique [6] was not suitable for this patient. Instead, we used cryotherapy at 4 sites on the lesion and deployed the cuff on the endotracheal tube as a balloon for dilatation of the stenosis. This is a novel method of management of concentric granulation tissue utilizing a cryoprobe in a patient with central airway obstruction with respiratory failure. To the best of our knowledge, no previous studies have reported the incidence and management of patients with respiratory failure caused by granulation tissues. Considering the increasing prevalence of lung cancer and its treatment complications, bronchoscopic cryotherapy could be a useful tool in the management of associated airway obstruction.

The use of cryotherapy is increasingly favored in interventional bronchoscopy, in both diagnosis and therapeutics [7-8]. Through rapid freeze-thaw cycles, cryotherapy induces cell death and tissue necrosis, or tissue adherence. Because of this characteristic, cryotherapy can be used in a wide variety of clinical settings, including treatment of central airway obstruction, foreign body removal, endobronchial biopsy, and transbronchial lung biopsy. There are 2 essential components to cryotherapy – the cryoprobe and cryogen. The cryoprobe is a flexible catheter and requires the working channel of the flexible bronchoscope to direct it to the lesion. In our facility, we use a cryoprobe with carbon dioxide as the cryogen. The temperature of the tip of the cryoprobe is approximately -70°C. With regard to the diagnostic value, the specimen obtained via cryobiopsy is significantly larger than the specimen obtained by traditional forceps, whether endobronchial biopsy or transbronchial lung biopsy [7-8], allowing pathologists to make more accurate diagnosis. Various studies have investigated cryorecanalization – a technique of pulling the cryoprobe away from the lesion with the intent of removing and/or debulking the lesion – and found it is an effective way of treating malignant or benign airway obstruction [6]. Hetzel *et al*. [9] conducted a

prospective study regarding the use of flexible bronchoscopy for cryo-recanalization of 60 patients with high-grade stenosis of the respiratory tract due to exophytic tumors. The authors noted that as many as 83% of the obstructions were successfully or partially relieved. Tumor bleeding occurred in 10% of patients, but was stopped with argon plasma coagulator (APC) treatment [9].

Cryotherapy has generally good safety profiles. This technique, however, must be used with caution, especially in the ICU, due to the risk of bleeding and the need to allow the airway to thaw adherent tissue from the cryoprobe. The major complication reported in the cryo-recanalization studies was treatable bleeding. According to previous reports, the incidence of bleeding requiring APC ranged from 8% to 10% [10-11].

Conclusion

In the present report, we demonstrated that a combination of cryotherapy and balloon dilatation using an endotracheal cuff could be a treatment option for patients with respiratory failure induced by granulation-associated central airway obstruction. However, a prospective study is needed to investigate the feasibility and safety of this novel method in the management of central airway obstruction with respiratory failure caused by granulation tissues.

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支氣管鏡冷凍治療與氣管內管氣囊擴張於一位中央氣道阻塞引起呼吸衰竭之病患

黃宗楨 * 周俊良 ** 柯孟呈 * 黃繼賢 * 林恕民 *,***

患有中央氣道阻塞的患者在植入金屬支架後，肉芽組織形成是常見的併發症之一。球囊擴張與冷凍療法的組合是一個治療選擇。我們報告一名53歲的女性患者，由於肺腺癌治療後產生了氣管-食道瘻管，而植入了氣管金屬支架。一年後， 由於廣泛的肉芽組織形成，支架兩端出現中央氣道阻塞，造成了急性呼吸衰竭。我們進行支氣管鏡冷凍治療，將冷凍劑應用於病灶的四個部位，再使用氣管內管氣囊作為球囊擴張器，緩解氣道阻塞，並在術後立即拔管。本案例提供了在加護病房裡使用內視鏡冷凍治療加上氣管內管氣囊作為擴張器的範例，證實該治療對於控制肉芽組織引起的中央氣道阻塞以及呼吸衰竭是安全且可行的。*(胸腔醫學* ***2019; 34: 256-261)***

關鍵詞：冷凍治療，中央氣道阻塞，肉芽組織，腺癌，肺癌，支氣管鏡

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Atypical Carcinoid of the Thymus with Initial Presentation of Diffuse Bone Marrow Infiltration

Wan-Hsin Lin, Tzu-Hsiu Tsai, Jin-Yuan Shih

Thymic neuroendocrine tumors (NET) are rare primary thymic neoplasms with neuroendocrine differentiation. They are characterized by relatively aggressive behavior with a high propensity for local invasion and distant metastasis. However, thymic carcinoids metastasizing to the bone marrow have been very rarely reported in past decades. We present a case of atypical carcinoid of the thymus who had an initial presentation of non-specific low back pain, with magnetic resonance imaging (MRI) unexpectedly showed heterogenous signal intensities of the lumbar spine. An anterior mediastinal mass was later found by chest imaging; histopathology of the mediastinal mass and bone marrow both revealed atypical carcinoid tumors. The patient underwent mediastinal tumor excision, followed by cytotoxic chemotherapy. However, the follow-up bone marrow biopsy showed more extensive marrow replacement by NET cells. Systemic therapy was then shifted to everolimus with resultant disease control. This case emphasizes that a thymic carcinoid could spread to the bone marrow, and that MRI may play an important role in the investigation of marrow involvement in patients with non-specific musculoskeletal pain. Although the efficacy of systemic treatment for patients with metastatic diseases is unclear, there are systemic therapy options that may be effective in treating this rare thoracic malignancy. ***(Thorac Med 2019; 34: 261-269)***

Key words: thymic tumors, neuroendocrine tumors (NETs), atypical carcinoids, bone marrow metastasis, magnetic resonance imaging (MRI)

Introduction

Thymic neuroendocrine tumors (NETs) are primary thymic neoplasms with neuroendocrine differentiation, and generally present as a mass within the anterior mediastinum. The histologic diagnosis of NETs is based on the presence of neuroendocrine features such as peripheral palisading and rosettes, as well as the immunohistochemical expression of neuroendocrine markers such as synaptophysin and chromogranin [1]. Thymic NETs are histologically categorized as low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), or high-grade (large cell neuroendocrine carcinoma, small cell carcinoma) tumors. The criteria used to separate

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typical from atypical carcinoids are the same as those applied in the classification of pulmonary NETs [2]. Of the reported cases of thymic NETs, 40-50% were classified as atypical carcinoids [1].

Thymic NETs are rare neoplasms, with an estimated annual incidence of 1 per 5 million people [3-4]. They account for about 5% of all the neoplasms in the thymus and approximately 0.4% of all carcinoid tumors. In contrast to bronchopulmonary carcinoids, thymic NETs are characterized by relatively aggressive behavior, with a high propensity for local invasion, recurrence, and distant metastasis [1,5]. At the time of diagnosis, around half of the patients presented with mediastinal lymph node involvement, and 10-30% had distant metastases, with the most common metastatic sites being the lung and pleura, bone, liver, pancreas, and chest wall [3,6-7]. Only a few cases of thymic carcinoids with bone marrow metastasis have been reported in past decades, although bone marrow involvement of NETs of bronchopulmonary and other origins are occasionally seen [8-13]. Here, we report an extremely rare case of atypical carcinoid of the thymus with diffuse bone marrow infiltration at the initial diagnosis.

Case Presentation

A 53-year-old male visited our orthopedic clinic in June 2018 because of low back pain for 4 months. On physical examination, there were no specific neurological findings. Magnetic resonance imaging (MRI) of the lumbar spine showed abnormal signal intensity within the vertebral bodies and pelvic ring, in addition to mild degenerative disk disease of the spine. The spinal MRI findings were suggestive of either extensive bone metastasis or bone marrow infiltrative diseases (Figure 1). The patient was referred to the hematology clinic due to a suspicion of multiple myeloma or other bone marrow diseases. His peripheral blood cell counts were all within normal ranges, and he had neither renal insufficiency nor hypercalcemia. Serum protein electrophoresis detected no monoclonal gammopathy. However, whole body skeletal X-rays unexpectedly disclosed a large mediastinal mass.

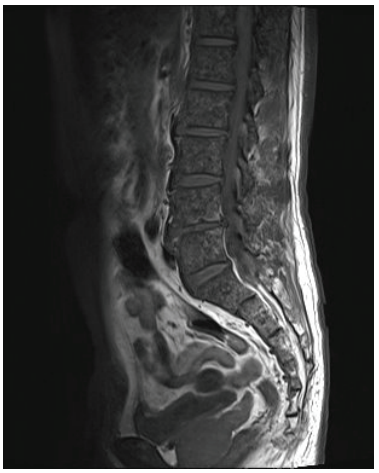


Fig. 1. T1-weighted MRI of the lumbar spine showed heterogeneous signal intensities within the vertebral bodies, suggesting infiltrative bone marrow lesions. Normal bone marrow contains a high proportion of fat, so it normally demonstrates homogeneously high signal intensity on T1-weighted images.

The patient had no respiratory symptoms. After referral to the pulmonologist, he underwent a computed tomography (CT) scan of the chest, abdomen and brain, which revealed a defined and heterogeneous soft-tissue mass within the anterior upper mediastinum, measuring 13.6×7.7 cm in size (Figure 2A). Two small subcutaneous soft-tissue nodules were also noted at the abdominal wall and the back, respectively (Figure 2B). Whole body bone scintigraphy with Technetium-99m methylene diphosphonate showed only mildly increased tracer activity at the scoliotic spine, bilateral

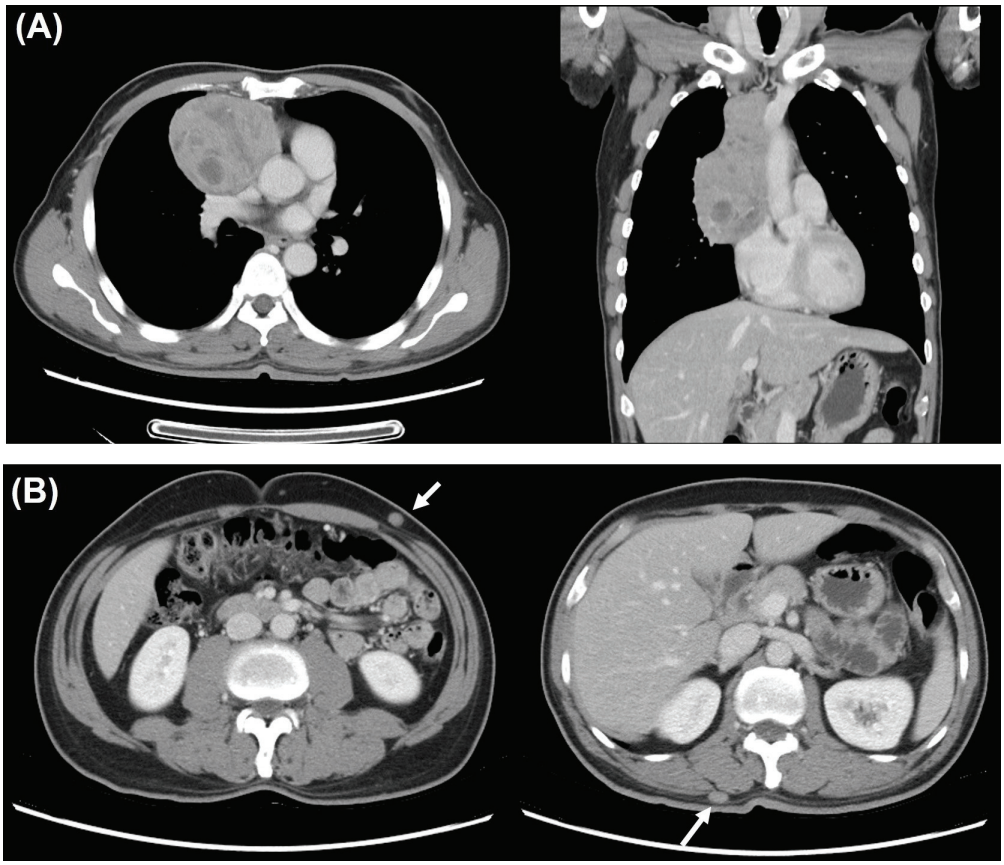


Fig. 2. (A) CT scan of the chest showed a defined and heterogeneous soft-tissue mass in the anterior upper mediastinum, which extended to the right lung. **(B)** Two small subcutaneous soft-tissue nodules at the abdominal wall and back, respectively, were also found on the CT scan (arrows).

sacroiliac joints, shoulders and knees, which was probably associated with degeneration or arthritis. However, bone scintigraphy showed no evidence of osteoblastic lesions suggestive of skeletal metastasis.

An ultrasound-guided transthoracic biopsy was performed for the mediastinal mass. Histopathology revealed small, round and relatively uniform tumor cells, with little cytoplasm, arranged in an organoid pattern with islands and trabeculae. Immunohistochemically, the tumor cells were strongly positive for cytokeratin (CK), synaptophysin, CD56 and thyroid transcription factor-1 (TTF-1). Tumor necrosis and mitotic activity were not identified. A biopsy of one of the subcutaneous nodules was also performed. The pathology report indicated atypical cells with positive immunohistochemical staining for CK and synaptophysin, consistent with a metastatic carcinoid. Because MRI of the lumbar spine showed findings suggestive of bone marrow disease, core needle biopsy of the bone marrow was performed, and revealed that the marrow spaces were focally replaced by tumor nests comprising neuroendocrine tumor cells (Figure 3).

The patient underwent sternotomy for excision of the huge mediastinal tumor in July 2018. Histopathology of the resected specimen showed tumor cells arranged in insular, nested, trabecular patterns with focal rosettes (Figure 4A). Although no tumor necrosis was seen, the

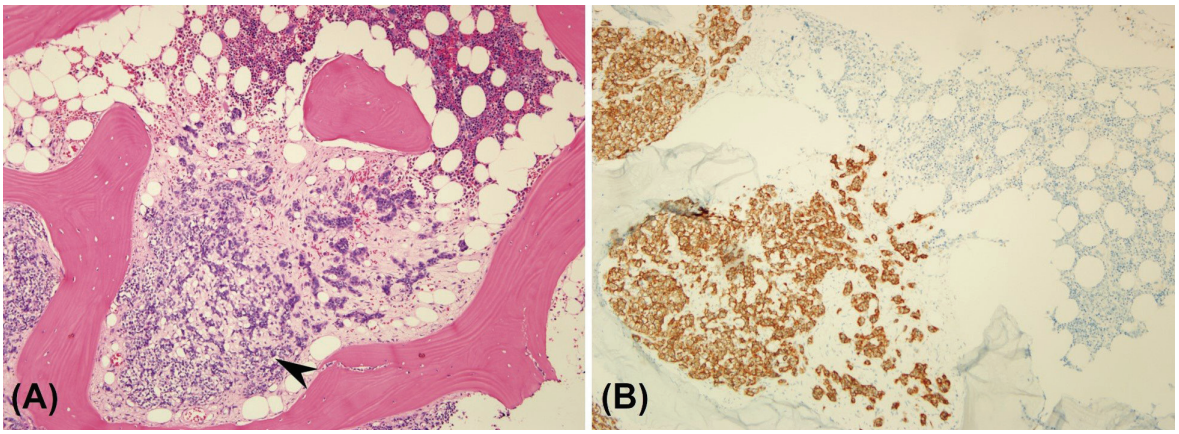
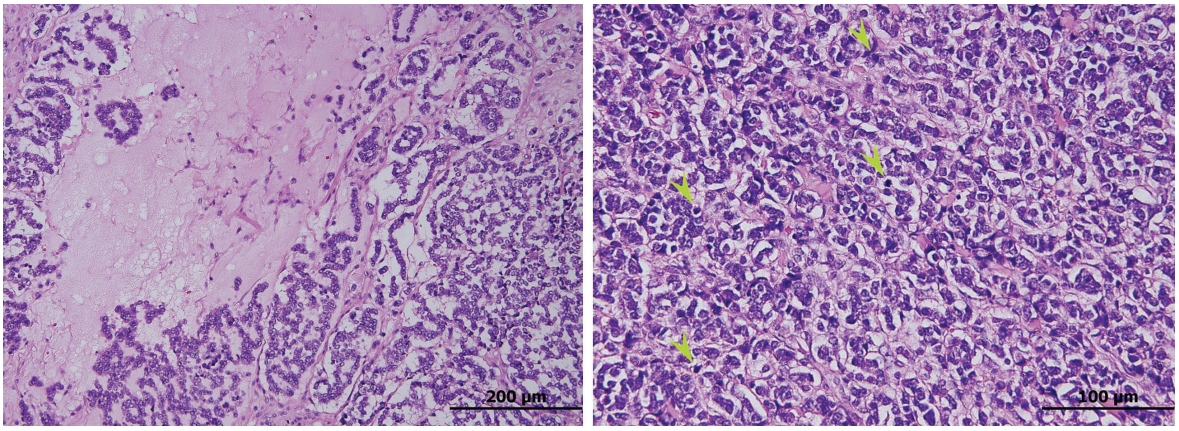


Fig. 3. (A) Histopathology of bone marrow biopsy showed that the marrow space was partially replaced by nests of tumor cells (arrowhead; hematoxylin-eosin stain, 100X). **(B)** Immunohistochemistry revealed these tumor cells were immunoreactive to synaptophysin staining, indicating NET cells.



(A) (B)

Fig. 4. (A) Histopathology of the resected thymic mass showed that the tumor cells were arranged in insular, nested and trabecular patterns with focal rosettes (hematoxylin-eosin stain, 200X), with **(B)** frequent mitotic figures (light green arrowhead; 400X).

mitotic figures were up to 3 mitoses per 2 mm^2 (Figure 4B). Immunohistochemistry showed the tumor cells were diffusely positive for CK, synaptophysin and CD56, and focally positive for chromogranin. The Ki67 proliferation index was focally up to 20-25%. Overall, the pathology featured an atypical carcinoid. The surgical margin was not involved, and some residual thymic tissue was found in the tumor.

The diagnosis of atypical carcinoid of the thymus with metastases to the bone marrow and soft tissue was finally made. Following surgery, the patient received cytotoxic chemotherapy with a regimen of etoposide plus cisplatin. After 3 cycles of chemotherapy, the CT scan in October 2018 showed slight enlargement of the metastatic subcutaneous nodules and a new pleural nodule at the right lung, while MRI of the spine still revealed diffuse abnormal signal intensity in the marrow. The patient still had low back pain, but his hemogram remained unremarkable. He underwent bone marrow biopsy again, which revealed that the marrow spaces were more extensively (50%) replaced by NET nests. Due to a concern of disease progression, we began administration of everolimus (10 mg

per day) in December 2018. The side effects of everolimus included loss of appetite, general malaise and stomatitis. The lower back pain was controlled with morphine analgesics. Follow-up CT scan in Jan 2019 showed that the subcutaneous and pleural lesions were relatively stationary in size.

Discussion

Bone marrow metastasis is a well-documented event in solid cancers, and the most common origins in adults are lung, breast and prostate cancers [14]. No specific manifestation is predictive of bone marrow involvement, but some clinical features, such as cytopenia and/or leucoerythroblastic change in the peripheral blood, elevated lactate dehydrogenase level and bone pain, may provide useful hints [14-15]. However, in contrast to those with hematologic malignancies, laboratory findings are not sensitive to the suggested diagnosis of bone marrow involvement in patients with solid cancers [14]. The patient we reported herein presented with low back pain. Because of the lack of a neurological deficit, the patient's back pain might be overlooked as a non-specific musculoskeletal symptom, which would preclude further surveys for the etiology.

The skeletal system is a frequent target of metastasis from solid cancers, and is the third most common site of metastasis [16]. Imaging studies, such as plain radiography, CT, MRI, radionuclide skeletal scintigraphy or PET-CT, may provide evidence of metastatic bone disease with varying performances. Plain radiographs have a low sensitivity to detect bone metastasis; CT and MRI are far more sensitive in detecting local bony destruction. The major advantage of skeletal scintigraphy is that it allows imaging of the whole skeleton with high sensitivity. The reported sensitivity and specificity of skeletal scintigraphy for the detection of bone metastasis is 78% and 48%, respectively [17]; however, 18F-FDG PET/CT may have higher sensitivity than skeletal scintigraphy. In a retrospective review of 257 patients with newly diagnosed lung cancer, the accuracy in detecting skeletal metastasis was 94% for 18F-FDG PET-CT and 85% for skeletal scintigraphy [18].

It is worth noting that in our case with pathologically confirmed bone marrow infiltration with NET tumor cells, skeletal scintigraphy, which has a high sensitivity for detecting bone metastasis, failed to reveal any bony lesions. This is probably because this technique is based on indirect detection of bone metastasis by registration of tracer uptake in areas of osteoblastic activities. By contrast, MRI is the only technique that allows direct visualization of the bone marrow with its high soft tissue contrast and spatial resolution. As normal bone marrow contains a high proportion of fat, it has high signal intensity on a T1-weighted MRI sequence. With metastasis to the bone marrow, tumor nests can be identified as discrete foci of low T1 signaling, corresponding to the replacement of normal fatty marrow by malignant cells. Thus, as demonstrated in our case, MRI might be the most sensitive imaging modality for the detection of bone marrow pathologies, and could depict bone marrow infiltration before osseous change occurs [19]. With clinical suspicion of bone marrow involvement, aspiration and biopsy of the bone marrow are the cornerstones to establishing a diagnosis, with immunocytochemical and molecular assays further increasing the rate of detecting tumor cells within the marrow [14].

The prognosis of patients with solid cancers and bone marrow metastases is generally dismal. Favorable prognostic factors include good performance status (Eastern Cooperative Oncology Group 0-1), higher platelet count, adequate systemic therapies and a prostate origin [15,20-21]. The impact of bone marrow metastasis on survival might depend on the specific types of primary cancer.

In a prospective study of patients with recurrent or metastatic breast cancer, the median survival from the first relapse of those with documented bone marrow metastasis was quite similar to that of those with negative bone marrow biopsy results [22]. However, patients with extensive small cell lung cancer and bone marrow involvement had significantly shorter overall survival than those without bone marrow metastasis [23-24]. The survival rate was even worse when thrombocytopenia was present at the time of diagnosis [14].

Data regarding the prognosis of patients with thymic NETs and bone marrow metastasis is sparse, due to the rarity of this disease entity. We know of a case of thymic carcinoid with bone marrow metastasis that was reported in 1999. The patient had multiple metastases to the lung, pleura, paraaortic lymph nodes and bone marrow at diagnosis, and then experienced a rapidly progressive course [25]. He did not receive surgical excision for his primary tumor, and despite chemotherapy treatment, survived for only 3 months after the diagnosis.

Gaur *et al* reported median survival times of 110, 59, and 35 months for patients with thymic NETS with localized, regional and distant metastatic diseases, respectively, based on the Surveillance, Epidemiology and End Results (SEER) registry [3]. Tumor size, stage and surgical resection were significant prognostic factors. Surgical resection is the mainstay of therapy for suitable cases [3,5,7,26-28]. One study found that 5-year survival in patients who underwent surgical therapy was 74%, compared to 34% for patients who did not receive surgery [28]. However, it is unclear whether surgical debulking of large tumors without curative intent confers a survival benefit [3,28]. Systemic therapies might be helpful in disease control for recurrent unresectable or metastatic diseases, with options including cytotoxic chemotherapy, everolimus and long-acting somatostatin analogs. Our patient received everolimus due to bone marrow biopsy results suggestive of disease progression with cytotoxic chemotherapy. The use of everolimus for treating advanced NETs was supported by the phase 3 RADIANT 4 study, which enrolled 302 patients with advanced, well-differentiated, non-functioning lung or gastrointestinal NETs. The median progression-free survival was 11.0 months (95% CI 9.2-13.3) in the everolimus group and 3.9 months (3.6-7.4) in the placebo group (hazard ratio [HR] 0.48 [95% CI 0.35-0.67], $p<0.00001$) [29]. Reported grade 3 or 4 adverse events were infrequent (9% in the everolimus group and 0 in the placebo group). In another phase 2 LUNA trial, 124 patients with advanced well-differentiated carcinoid tumors of the lung or thymus were randomly assigned to long-acting pasireotide, everolimus, or both in combination. The proportion of patients who were progression-free at the ninth month was 39.0%, 33.3% and 58.5%, respectively [30]. However, it was difficult to ascertain the efficacy of systemic treatment for thymic NETs because only 8 patients with thymic NETs were included in this study.

In conclusion, most thymic NETs are atypical carcinoids or higher grade tumors. They are

generally characterized by aggressive behavior, a tendency to recur locally and metastasize, and resistance to systemic therapies. Our case also emphasizes the important role of MRI in the investigation of bone marrow involvement in patients with non-specific musculoskeletal pain, given that metastasis to bone marrow may occur without obvious osseous changes. The impact of bone marrow metastasis on survival in patients with thymic NETs remains unknown. Although the efficacy of systemic treatment for patients with recurrent unresectable or metastatic diseases is unclear, there are systemic therapy options that might be effective in treating this rare thoracic malignancy.

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罕見胸腺非典型類癌合併瀰漫性骨髓轉移

林莞欣　蔡子修　施金元

胸腺神經內分泌腫瘤為非常罕見的前縱膈腔腫瘤，且在診斷時常已出現淋巴侵犯或遠端轉移。在此，我們報告一位53歲男性因下背痛四個月求診，在做脊椎核磁共振成像時意外發現瀰漫性骨髓病變，經進一步檢查後發現前縱膈腔的胸腺非典型類癌合併軟組織與骨髓轉移。病人接受手術切除前縱膈腔的主腫瘤，術後也銜接化學治療，但影像和骨髓病理切片都顯示骨髓轉移的程度在惡化。後來病人改接受everolimus治療，並用嗎啡類止痛藥控制疼痛。此案例提醒我們即使是下背痛如此常見的症狀，仍需要仔細評估病因，而核磁共振造影在偵測骨髓病變時具有優異的敏感性，是重要的評估工具。臨床上，目前仍欠缺針對已遠端轉移之胸腺神經內分泌腫瘤的有效治療，但可以參考其他部位之神經內分泌腫瘤的研究，提供患者治療的選擇。*(胸腔醫學* ***2019; 34: 261-269)***

關鍵詞：胸腺腫瘤，神經內分泌腫瘤，非典型類癌，骨髓轉移，核磁共振

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Pulmonary Metastasis from Glioblastoma Multiforme – A Rare Case Report

Chien-Hui He*,**, Yuh-Min Chen*, Jen-Fu Shih*, Yi-Chen Yeh***, Yi-Han Hsiao*

Glioblastoma multiforme (GBM) is the most common, aggressive brain tumor, and has a poor prognosis. Extracranial GBM metastases are rare because of the protection of the blood-brain barrier and the lack of a lymphatic drainage system in the central nervous system (CNS). We reported a 51-year-old female who was diagnosed as having GBM, and who underwent a craniotomy for tumor removal. CNS recurrence was noted 14 months later with the incidental finding of a soft-tissue mass in the right lower lobe of the lung. The cytopathological examination from the lung mass biopsy revealed large, pleomorphic, spindle- to bizarre-shaped cells with dense cytoplasm, immunoreactive for glial fibrillary acidic protein and non-reactive for cytokeratin, which could very well be compatible with a metastatic glioblastoma. Although less than 2% of GBM patients have been reported to have extra-CNS metastases, including to the lungs, pleura, lymph nodes, bones, and liver, this occurrence indicates there are other potential pathways such as vascular invasion that allow GBM to escape the CNS. With the progress there has been in optimal therapy and the probability of longer survival, physicians should be aware of this rare clinical entity, especially when approaching extra-CNS lesions in GBM patients. ***(Thorac Med 2019; 34: 270-277)***

Key words: glioblastoma multiforme (GBM), pulmonary metastasis

Introduction

Glioblastoma multiforme (GBM) is the most common primary malignant tumor, and has a grave prognosis when occurring in the neural tissue. The incidence in a published report was 3.19/100,000 patient-years, with a 5-year survival rate of less than 7% [1]. Standard treatment includes surgical resection followed by concurrent chemoradiotherapy (CCRT) [2-3]. GBM is believed to rarely metastasize outside of the central nervous system (CNS) because of inhibition by the blood-brain barrier (BBB) and an overall low median survival. However, with the progress there has been in optimal therapy and the probability of longer survival, extra-CNS metastasis of GBM has been reported in 0.2 to 2% of patients, with increased numbers in recent years [3]. The sites of metastasis included the lungs, pleura, lymph

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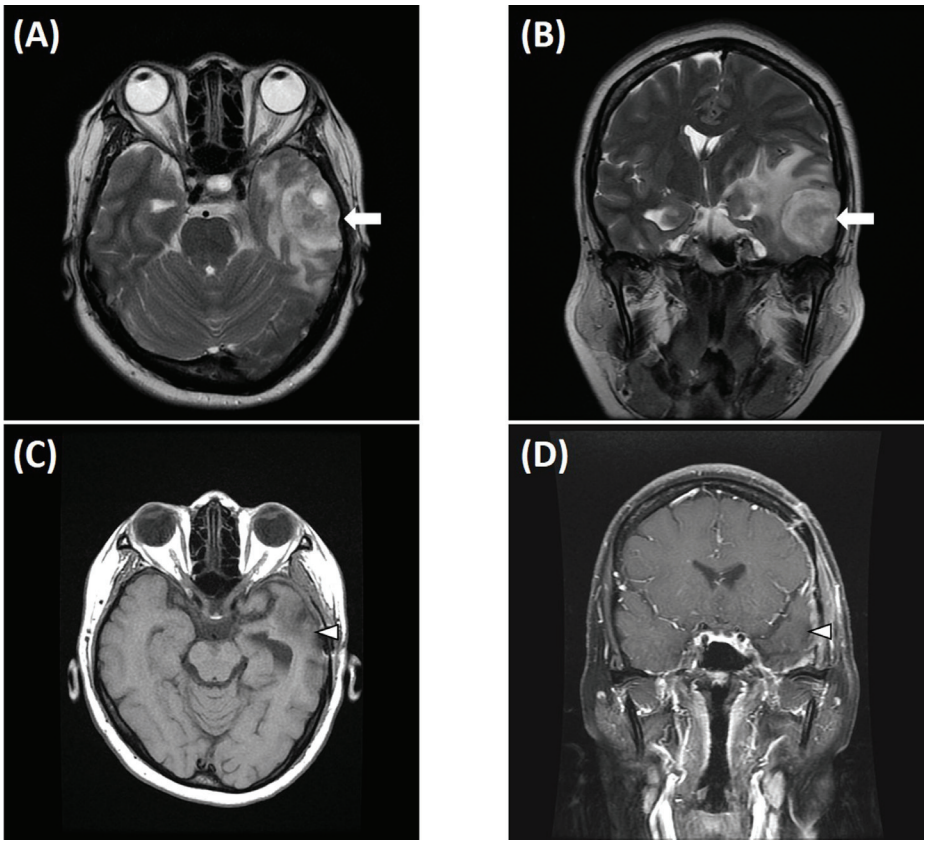

Fig. 1. Preoperative brain MRI (T2W image) showed a 4.1x3.2x4.5 cm tumor at the left temporal lobe, as indicated by arrows in the **(A)** transverse view and **(B)** coronal view, respectively. The patient underwent craniotomy with tumor removal, and the third-month postoperative brain MRI (T1W image) showed no residual tumor (arrowheads) in the **(C)** transverse view and **(D)** coronal view, respectively.

nodes, bones, and liver, indicating other potential pathways [4-5]. Pulmonary metastasis was found in around one-third of cases, making it the most common site of metastasis, despite fewer than 45 reported cases [6-7]. In Taiwan, a single case of endobronchial metastasis of GBM was reported by Chung *et al* in 1999 [8]. Herein, we report another case of recurrent intracranial GBM with an incidental finding of a pulmonary mass 14 months after surgical removal of the primary tumor and treatment with adjuvant CCRT. A second primary lung cancer was suspected at first, but the cytopathological examination from the lung mass biopsy proved it to be a metastatic glioblastoma.

Case Presentation

A 51-year-old woman was diagnosed as having GBM with the initial symptoms of progressive headache for 2 months, followed by slurred speech, nausea, vomiting, and hand tremor. She visited a local hospital, where brain MRI showed a 4.1×3.2×4.5 cm tumor growth at the left temporal lobe (Figure 1A, B, arrows). She then was referred to our hospital, where she underwent craniotomy for tumor removal.

The pathology examination of the removed tumor showed a proliferation of atypical spindle-shaped tumor cells with an eosinophilic cytoplasmic process and necrosis, which was

compatible with glioblastoma. The tumor was positive for glial fibrillary acidic protein (GFAP) stain and O(6)-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation. Therefore, adjuvant CCRT, including temozolomide with bevacizumab maintenance and radiotherapy, was begun.

At the third-month postoperative follow-up, brain MRI showed no residual tumor and a stable condition (Figure 1C, D, arrowheads). She was kept under regular imaging follow-up with bevacizumab maintenance. Tumor recurrence was noted (Figure 2A, arrow) 14 months later with the incidental finding of a lobulated soft-tissue mass at the right lower lobe (RLL) of the lung (Figure 2C, arrowhead). The size of the RLL mass was 4.5x3.5 cm, with mild central necrosis (Figure 2C), and a second primary lung cancer was initially suspected.

The patient underwent a computed tomography guided-biopsy for the RLL mass, and the imprint cytology revealed large, pleomorphic, spindle- to bizarre-shaped cells with dense cytoplasm (Figure 2E, 2F). The pathology examination showed a proliferation of atypical spindle-shaped tumor cells with an eosinophilic cytoplasmic process and necrosis. The tumor cells were strongly immunoreactive for GFAP stain and non-reactive for cytokeratin (CK), which could be compatible with a metastatic glioblastoma (Figure 3). Additional immunohistochemical stains for ROS1 and anaplastic lymphoma kinase (ALK) were performed, but all showed negative findings. Therefore, the patient received chemotherapy with dacarbazine plus 5-fluorouracil (5-FU) for recurrent GBM with extra-CNS metastasis, and palliative radiotherapy for a metastatic lung mass, but the response was very poor. The patient died of the advanced disease 5 months later. The overall survival (OS) from initial diagnosis was 1 year and 10 months.

Discussion

GBM is the most common, and also the most lethal primary brain tumor, with a high degree of anaplastic growth. The diagnosis is tissue-based, according to the World Health Organization classification, and includes immunohistochemistry (IHC) and a molecular test [9]. IHC of GBM shows a cellular neoplasm with nuclear pleomorphism, mitotic figures, endothelial vascular proliferation, and characteristic "geographic" necrosis rimmed by palisading nuclei. Molecular tests include IDH1/2 mutation, TP53 mutation, ATRX mutation, and TERT promoter mutations. Current standard therapy for GBM includes surgical resection, followed by radiation and co-administration of temozolomide, an oral derivative of the alkylating agent dacarbazine [10]. MGMT is an enzyme involved in DNA repair processes that counteracts mutagenesis from alkylating agents, and a high level of MGMT is likely to play an important role in therapeutic failure [11]. Patients with MGMT gene promoter methylation, leading to epigenetic silencing and loss of MGMT expression, were associated with longer OS when treated with temozolomide [12-13]. Nevertheless, GBM still carries a grave prognosis, with median survival of 13±2.4 months and a 5-year survival rate of 4.7-6.6% [1-3].

Extra-CNS metastasis of GBM is a rare entity, comprising just 0.2-2% of patients [3]. The reasons were suggested to be its grave prognosis, the functioning of the BBB, the lack of lymphatics in the CNS, and the differing microenvironment of the CNS from other systems [6]. However, with a better understanding of

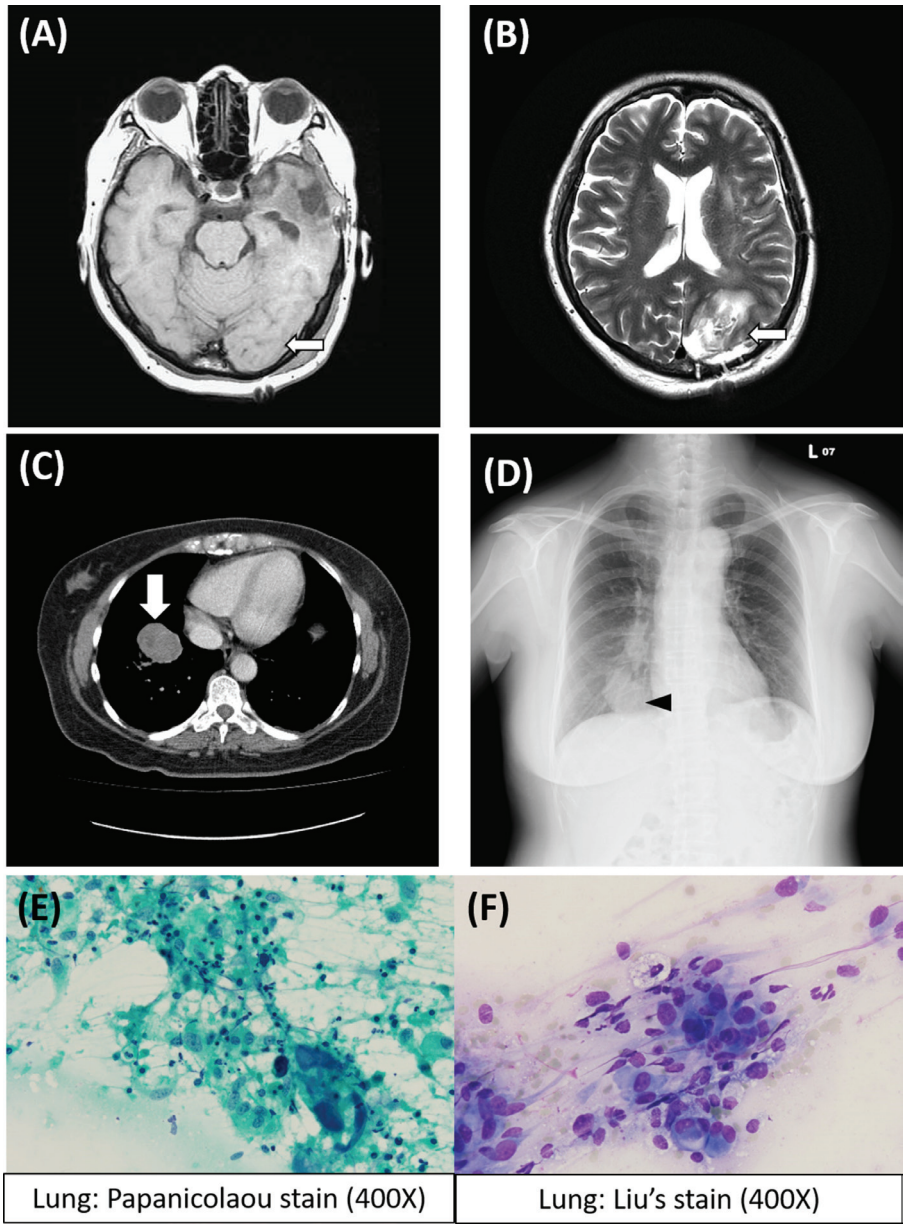

Fig. 2. (A)(B) Brain MRI (T1W/T2W image) found a recurrence of the tumor at the occipital lobe, and **(C)** chest computed tomography (CT) revealed a lobulated mass (arrows) with mild central necrosis, 4.5x3.5 cm in size, at the right lower lobe (RLL) of the lung. The patient underwent **(D)** CT-guided biopsy of the pulmonary mass (arrowhead) at the RLL of the lung during regular follow-up at 1 year after the operation. The cytological examination from the CT-guided biopsy of the RLL mass revealed large, pleomorphic, spindle- to bizarre-shaped cells with dense cytoplasm. **(E)** Papanicolaou stain 400X; **(F)** Liu's stain 400X.

its pathophysiology and discovery of potential treatment targets such as ROS1, ALK, c-Met and epidermal growth factor receptor (EGFR) [14-16], a remarkable increase in the number of cases of extra-CNS metastasis has been observed in recent years [3]. Multiple metastatic sites have been reported, including the lungs, pleura, lymph nodes, bones, and liver [4-5].

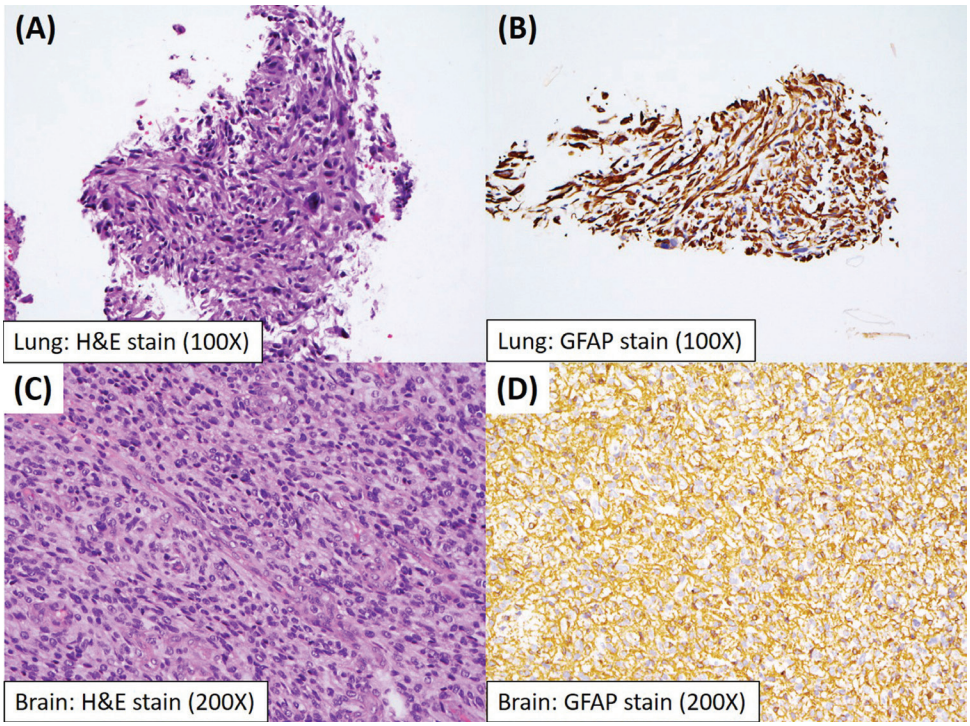

Fig. 3. The pathological examination from the CT-guided biopsy of the RLL mass showed **(A)** proliferation of atypical spindle-shaped tumor cells with an eosinophilic cytoplasmic process and necrosis. **(B)** The cells were strongly immunoreactive for glial fibrillary acidic protein (GFAP) stain, and as a result, were considered to be metastatic glioblastoma **(C)** strongly immunoreactive for GFAP stain **(D)**.

Pulmonary metastasis was the most common site, comprising one-third of cases [6-7]. Pietschmann *et al* [3] reviewed 105 patients with extra-CNS metastasis of GBM from 1928 to 2013 and found the median OS from diagnosis of metastasis was 6.0±0.8 months, and median OS from initial diagnosis was 13±2.4 months. However, neither gender, age, histological subtype, time interval between initial diagnosis and metastasis occurrence, nor pulmonary involvement was associated with differences in OS.

Several hypotheses have been developed to explain the extra-CNS metastasis of GBM. First, circulating tumor cells (CTCs) could be found in the peripheral blood [17-18]. Approximately 20% of GBM patients have detectable levels of CTCs in their blood at time points both before and after neurosurgery [17], which would support the potential for spread outside the CNS. However, none of the GBM patients with detectable CTCs developed extra-CNS metastasis [17], which may imply that the distant site at which CTCs have lodged is not favorable to the subsequent development of metastasis [19]. Second, the GBM cells may spread easily through the CNS, especially when tumor cells are located around the perivascular space, making them able to disrupt the astrocytic processes that help secure the BBB [20]. Third, the invasion of GBM cells may be facilitated by epithelial-mesenchymal transition, which enables epithelial cells to lose their cell-cell adhesion and gain migratory properties for metastasis [21]. Fourth, tumor cell implantation at the time of surgery is well described in the

literature, and involves a variety of forms of surgery; there have been occasional case reports of such metastases after neurosurgery [23-24]. However, due to the limited number of cases, these hypotheses await further verification.

Therapy for advanced GBM remains state-of-the-art. The combination of temozolomide and capecitabine, which is the prodrug of the pyrimidine analog 5-FU, was designed to overcome resistance, such as that of high MGMT expression [22]. During recent years, several molecular targets, including EGFR, vascular endothelial growth factor, c-Met amplification, ROS1, and ALK, have been identified and tested in GBM therapy, although with controversial results [10,14-16]. With the growing interest in immune checkpoint inhibitors therapy, preclinical studies using a murine model have demonstrated promising results. Several clinical studies using nivolumab and pembrolizumab alone or in combination with other agents (i.e., temozolomide) are still ongoing [10]. For extra-CNS metastatic diseases, local therapies including surgery and radiotherapy are reasonable options if the GBM remains focal outside of the CNS [6]. With the increased prevalence of extra-CNS metastasis of GBM, a multimodal approach, including surgery, chemotherapy and radiation therapy will be warranted for optimizing treatment.

We reported a 51-year-old female who underwent GBM removal and was found to have MGMT gene promoter methylation, indicating a better response to standard CCRT with temozolomide. The patient had stable disease until 14 months after the initial diagnosis, which could be considered a window to find the most common extra-CNS metastatic site in the lung. With the probability of longer survival and ongoing developments in therapeutic choices, physicians should be aware of this rare but increasingly common clinical entity.

Conclusion

GBM is the most lethal brain tumor, and extra-CNS metastasis remains rare. The possibility of extra-CNS metastasis should be kept in mind, especially in patients with positive MGMT gene promoter methylation, which indicates longer OS and a better chance to observe any metastatic disease. Further investigation is still warranted to optimize the treatment for this rare entity.

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罕見病例報告：膠質母細胞瘤合併肺轉移

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膠質母細胞瘤（GBM）是最常見和侵襲性且預後不良的腦腫瘤。由於中樞神經系統（CNS）中血腦屏障的保護和淋巴引流系統的分布，顱外膠質母細胞瘤轉移是罕見的。我們報導了一名51歲的女性被診斷為膠質母細胞瘤，接受了開顱手術切除腫瘤，14個月後發現腦部復發，偶然發現肺右下葉有軟組織腫塊。來自肺部組織檢查的細胞病理學檢查顯示:許多大且多形性梭形（spindle），怪異形狀（bizarre-shaped）的細胞，並具有緻密的細胞質，對GFAP具有免疫反應性，但對CK具沒有反應性，這符合轉移性膠質母細胞瘤的診斷。據報導，只有不到2%的膠質母細胞瘤患者有中樞神經外轉移，其中包括肺，胸膜，淋巴結，骨骼和肝臟。其中表示其他可能的轉移途徑如血管侵犯，使膠質母細胞瘤離開中樞神經系統。隨著治療的進展和病人有更長的生存概率，醫生應該意識到這種罕見的膠質母細胞瘤合併中樞神經外轉移的病例。*(胸腔醫學* ***2019; 34: 270-277)***

關鍵詞：膠質母細胞瘤，肺轉移

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