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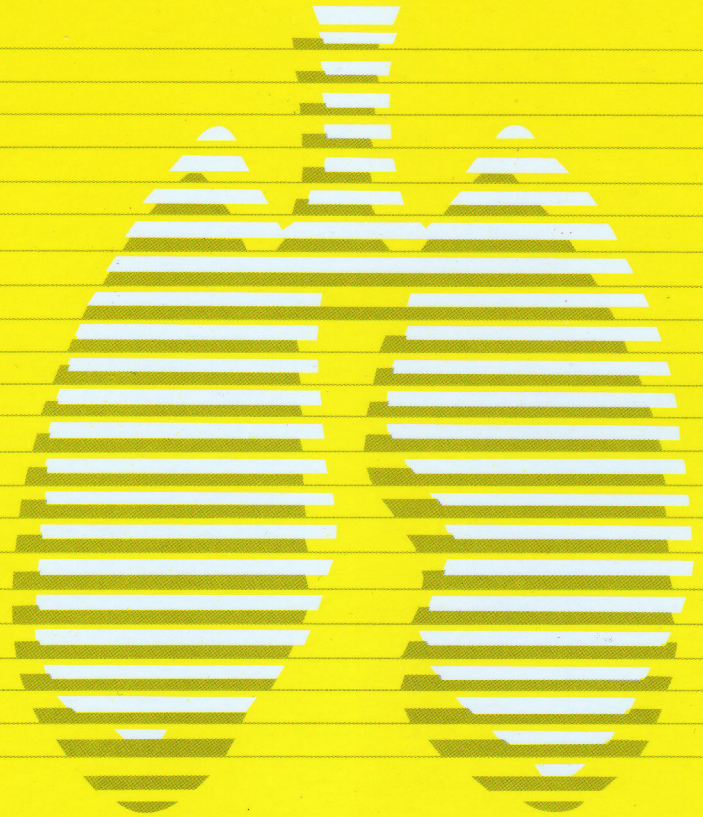

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Orginial Article

Case Reports

Driving Pressure Greater than 14 cmH_2O is Associated with Increased Mortality When Tidal Volume is Less than 8 ml/kg in Sepsis Patients with Acute Respiratory Failure

Yen-Tseng Lin*, Ming-Cheng Chan*,**,***, Jeng-Sen Tseng*,****, Sou-Jen Shih******, Chi-Yuan Yi*****, Hsiu-Hui Yu*****, Chieh-Liang Wu******,*******, Yen-Hsiang Huang*

Background: Driving pressure is associated with outcome in acute respiratory distress syndrome patients; it can be determined by both ventilator setting and lung compliance. In order to clarify this, we conducted a retrospective analysis to determine the relationship between tidal volume setting, driving pressure and patient outcome.

Materials and Methods: This was a retrospective analysis of prospectively acquired data from an intensive care unit of a tertiary referral hospital in central Taiwan. Patients with respiratory failure needing invasive mechanical ventilation due to sepsis, from April 2008 to November 2009, were included for analysis.

Results: A total of 220 patients were included for analysis. The median age of these patients was 76 years, and they had a mean Acute Physiology and Chronic Health Evaluation II score of 25.0±6.5. The hospital mortality rate was 39.1%. Driving pressure at 8 hours after intensive care unit admission (driving pressure-8) greater than 14 cmH_2O was associated with an increased risk of hospital mortality. Also, in a multivariate logistical regression analysis, driving pressure-8 was an independent risk factor for mortality. Patients with driving pressure-8 greater than 14 cmH_2O while ventilated, with a tidal volume less than 8 ml/kg of predicted body weight, had the highest risk of hospital mortality.

Conclusion: Driving pressure is a valuable predictor of hospital mortality in septic patients with acute respiratory failure needing mechanical ventilation. Those patients with a higher driving pressure while ventilated with a lower tidal volume were at an increased risk of hospital mortality. ***(Thorac Med 2019; 34: 92-102)***

Key words: acute respiratory failure, driving pressure, tidal volume, sepsis

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Introduction

Sepsis is a leading cause of intensive care unit (ICU) admission and its importance is increasing [1-4]. Septic patients admitted to the ICU are often accompanied with a variety of organ dysfunctions, and respiratory failure is the most common among these [5]. During the critical period, these patients often need invasive mechanical ventilation to improve oxygenation and rest the respiratory muscles. However, positive pressure ventilation may lead to ventilator-induced lung injury (VILI), not only in previously damaged lungs, but also in normal lungs [6]. Thus, guidelines suggest ventilating septic patients with protective strategies by targeting a tidal volume 6 ml/kg of predicted body weight, limiting plateau pressure to less than 30 cmH_2O and maintaining appropriate positive end-expiratory pressure (PEEP) for patients with acute respiratory distress syndrome (ARDS) [7-8]. Plateau pressure is not only a target of the ventilator setting for these patients, it can also serve as a prognostic marker [9]. However, critical care physicians often face the dilemma of either setting a higher PEEP or keeping plateau pressure lower, because previous clinical trials reported conflicting results [10-12]. Amato *et al* calculated driving pressure as the ratio of tidal volume over compliance of the respiratory system. They found a lower driving pressure was associated with increased survival and suggested using driving pressure as a ventilator variable for risk stratification [13]. But driving pressure can be influenced by ventilator setting and respiratory system compliance. In order to clarify this, we conducted a retrospective analysis of our previous data to determine the relationship between tidal volume setting, driving pressure and patient outcome.

Methods

Subjects

This is a retrospective analysis of prospectively acquired data of a cohort of patients with sepsis and acute respiratory failure admitted to the 24-bed ICU of Taichung Veterans General Hospital between April 2008 and November 2009. Patients with severe sepsis or septic shock needing invasive mechanical ventilation were included for analysis. Sepsis was defined as having 2 or more components of systemic inflammatory response syndrome (SIRS). Severe sepsis was sepsis with at least 1 major organ dysfunction. Septic shock was defined as measured mean arterial blood pressure (MAP) less than 65 mmHg or a need of inotropic agents to maintain MAP above that level. All of the patients had acute respiratory failure requiring invasive mechanical ventilation. They received bundled treatment based on the Surviving Sepsis Campaign Guidelines [7-8]. Patients were excluded for any of the following reasons: their treatments had deviated from the treatment protocol for any reason, there was a major cause of acute respiratory failure other than sepsis, non-invasive mechanical ventilation was used, or data records were incomplete. The hospital ethical committee/institutional review board approved the study protocol and the requirement for informed consent was waived (protocol no./ IRB TCVGH no. CE12307).

Sepsis bundle treatment protocol and data records

We set a protocol to implement bundle treatment based on the guidelines for managing and monitoring of septic patients within the first 24 hours of ICU admission. In this protocol, the initial resuscitation bundle included lactate

measurement, antibiotics and infection source control, pathogen identification and cultures, hemodynamic stabilization, stress dose steroid use, appropriate glycemic control, and limiting inspiratory plateau pressure for ventilated patients. Fluid resuscitation, blood product transfusion, and inotropic agents were used for hemodynamic stabilization. The goals of fluid resuscitation included monitoring and achieving the following: MAP greater than 65 mmHg, central venous pressure (CVP) of 11-16 cm-H_2O, oxygen saturation of central venous blood ($ScvO_2$) above 70%, and urine output of more than 0.5 ml/kg/hour.

Mechanical ventilation

Mechanical ventilation parameters including tidal volume (Vt), peak inspiratory pressure, plateau pressure, and positive end-expiratory pressure (PEEP) were measured and recorded at admission and regularly at certain subsequent time points (0th, 8^{th}, 12^{th}, and 24^{th} hour) within the first 24 hours of ICU admission. Plateau pressure was measured with a pause of breath for 0.5 second at end-inspiration. For measurement of respiratory mechanics, patients were sedated and neuromuscular blockade was used if needed. Driving pressure was calculated as plateau pressure – PEEP. Respiratory compliance was calculated as VT/ (plateau pressure – PEEP). The Vt (ml/kg) was normalized to ideal body weight [male (Height (in cm) - 80) x 0.7; female (Height - 70) x 0.6].

In addition, diagnoses, demographics, comorbidities and hemodynamic data were recorded. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated on the day of admission. Chart review and chest radiograph readings were conducted by 2 intensive care physicians.

Statistical analysis

The patients were divided into survivor and non-survivor groups upon discharge from the hospital. Univariate analyses using Student's *t*-test and the chi-square test were conducted to compare the demographic, hemodynamic, and laboratory variables, and the mechanical ventilation parameters between the 2 groups. Multivariate analyses using a logistic regression model were done to evaluate the power of driving pressure at 8 hours after the start of sepsis bundle treatment to predict hospital mortality. The analyses were adjusted by relevant factors that influenced driving pressure measurement (i.e., VT and PEEP) and variables of hospital mortality with $p<0.2$ by univariate analysis. A Kaplan Meier estimate of probability of hospital survival was performed. Chi-square tests were used to compare groups of different driving pressure and tidal volume combinations. Analysis was performed using SPSS (version 15.0.0) for Windows XP. Statistical significance was set at a 2-tailed $p<0.05$.

Results

Subject characteristics and univariate analysis of hospital mortality

In all, 220 patients were included for analysis. The hospital mortality rate was 39.1%. The median age was 76 years (range 22 to 94 years). Pneumonia was the main cause of sepsis (188/220, 85.5%). The mean APACHE II score was 25.0±6.5 and the mean PaO_2/FiO_2 ratio was 174.5±107.6 at admission to the ICU. In univariate analysis for hospital mortality, the survivors had a higher rate of diabetes (29.9% vs 16.3%, $p=0.03$) and lower APACHE II scores (24.2±6.1 vs 26.2±6.8, $p=0.02$). The PaO_2/FiO_2 ratio did not differ between survivors and non-survivors

(188.0±122.5 vs 174.2±87.6, p=0.37). Factors regarding sepsis management, including lactate, mean arterial blood pressure, central venous pressure and mixed venous saturation ($ScvO_2$), did not differ between survivors and non-survivors. Also, mechanical ventilation parameters, including tidal volume, PEEP, plateau pressure, driving pressure and compliance, were not significantly different between survivors and non-survivors at admission (Table 1).

Driving pressure and outcome of patients

The calculated driving pressure did not differ among patients at ICU admission. But the non-survivors had significantly higher driving pressure than the survivors in the subsequent time points of the first 24 hours of admission (Table 2). We further divided the patients into 3 groups based on the driving pressure at 8 hours after ICU admission (driving pressure-8). Patients with lower driving pressure-8 were associated with an increased chance of hospital

Table 1. Characteristics of 220 Septic Subjects with Acute Respiratory Failure Requiring Mechanical Ventilation Categorized by Hospital Mortality.

	All (n=220)	Alive (n=134)	Dead (n=86)	p value
Median age, y (range)	76 (22-94)	70.6±14.8	73.2±11.6	0.15
Males, No. (%)	188 (85.5)	115 (85.8)	73 (84.9)	0.85
Co-morbidity				
Diabetes mellitus	54 (24.5)	40 (29.9)	14 (16.3)	0.03
COPD	34 (15.5)	22 (16.4)	12 (14.0)	0.70
Old stroke	31 (14.1)	22 (16.4)	9 (10.5)	0.24
Cardiovascular disease	45 (20.5)	30 (22.3)	15 (17.4)	0.40
Chronic kidney disease	19 (8.6)	11 (8.2)	8 (9.3)	0.81
Chronic liver disease	14 (6.4)	9 (6.7)	5 (5.8)	>0.99
Origin of sepsis				
Pulmonary	188 (85.5%)	112 (83.6)	76 (88.4)	0.43
Non-pulmonary	32 (14.5%)	22 (16.4)	10 (11.6)	
APACHE II score	25.0±6.5	24.2±6.1	26.2±6.8	0.02
PaO_2/FiO_2 ratio (mmHg)	174.5±107.6	188.0±122.5	174.2±87.6	0.37
Sepsis management				
Lactate (mg/dl)	32.5±28.6	33.6±31.6	30.7±22.9	0.48
Mean blood pressure (mmHg)	71.7±15.4	72.7±15.8	70.0±14.6	0.22
Central venous pressure (mmHg)	16.8±6.7	17.0±6.6	16.3±6.9	0.43
$ScvO_2$ (%)	72.4±10.0	72.5±10.3	72.2±9.6	0.82
Mechanical ventilation				
Tidal volume (ml/kg)	9.0±1.6	9.2±1.3	8.7±1.9	0.13
PEEP (cmH_2O)	7.1±3.1	6.8±2.9	7.6±3.4	0.51
Plateau pressure (P_{plat}, cmH_2O)	23.0±5.5	22.2±5.3	24.1±5.6	0.11
Driving pressure (cmH_2O)	15.9±4.9	15.5±4.5	16.5±5.3	0.12
Compliance (ml/cmH_2O)	39.7±14.7	40.7±14.6	38.1±14.9	0.20

Table 2. Driving Pressure within First 24 Hours of ICU Admission Categorized by Hospital Mortality.

Hours after admission	Alive	Dead	*p* value
0	15.5±4.5	16.5±5.3	0.12
8	15.2±4.6	17.0±4.8	<0.01
16	15.3±4.6	16.6±4.7	0.04
24	15.2±4.5	16.4±4.1	0.05

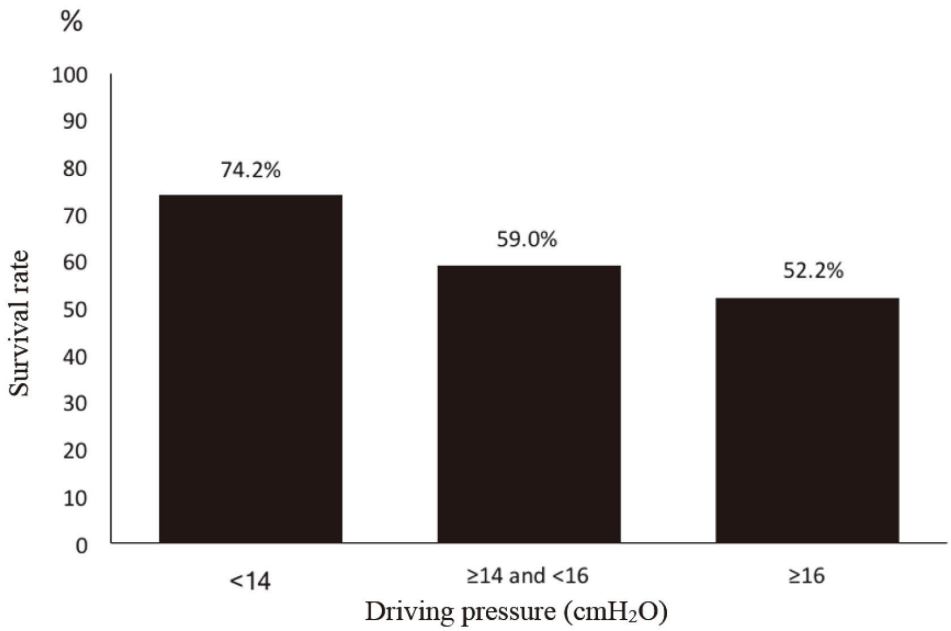

Fig. 1. Relationship between driving pressure at 8 hours of ICU admission (driving pressure-8) and hospital mortality of 220 septic patients with acute respiratory failure. Lower driving pressure was associated with increased chance of survival (p=0.026).

survival (driving pressure-8 <14 cmH_2O 74.2%, ≥14 and <16 cmH_2O 59%, ≥16 cmH_2O 52.2%, p=0.026, Figure 1).

Patients with driving pressure-8 less than 14 cmH_2O had a higher chance of hospital survival (Figure 2, Kaplan-Meier curve with log rank test, p=0.044). In a multivariate analysis of factors that may possibly influence hospital mortality in the univariate analysis (Table 3), including age, diabetes, APACHE II score, driving pressure-8, compliance, tidal volume and plateau pressure, driving pressure-8 remained an independent risk factor for hospital mortality (95% C.I. 1.008-1.142, p=0.026 and H.R. 1.073).

Figure 3 shows the relationship of between different tidal volumes and driving pressure-8 combinations and hospital mortality. Patients with driving pressure-8 greater than or equal to 14 cmH_2O and tidal volume less than or equal to 8 ml/kg of predicted body weight (PBW) had the lowest chance of hospital survival (50.0%). Patients with driving pressure-8 less than 14 cmH_2O and tidal volume greater than 8 ml/kg of

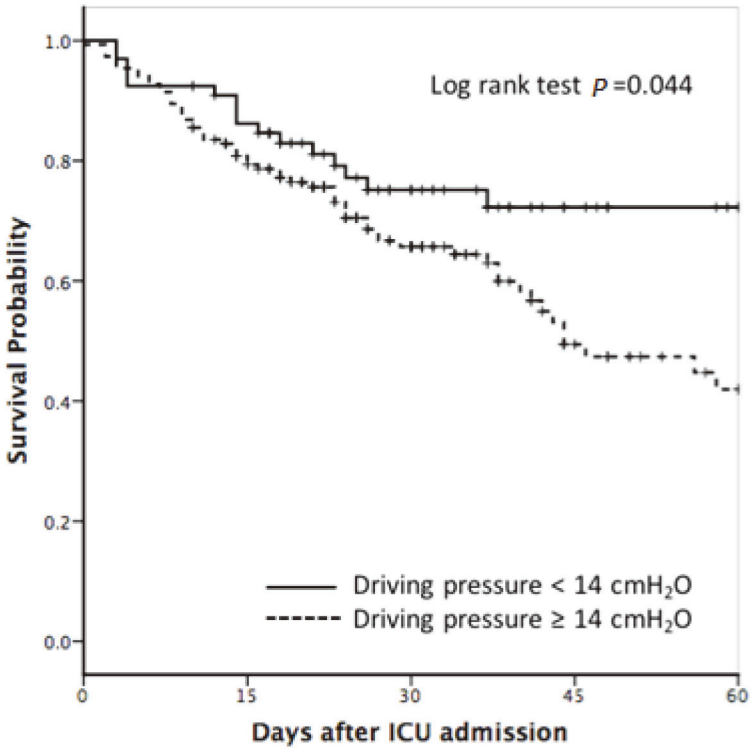

Fig. 2. Kaplan-Meier survival curve for hospital mortality categorized by a driving pressure of 14 cmH_2O at 8 hours after ICU admission. Patients with driving pressure-8 greater than or equal to 14 cmH_2O were associated with an increased risk of death (log rank test p=0.044).

PBW were associated with the greatest chance of hospital survival (82.4%). There was a significant difference between driving pressure-8 and tidal volume combinations (p=0.021).

Discussion

In this retrospective analysis of severe sepsis patients with acute respiratory failure, driving pressure-8 greater than or equal to 14 cmH_2O was an independent risk factor for hospital mortality. The mortality rate was even higher in these patients if they were ventilated with a tidal volume less than or equal to 8 ml/kg of PBW. These findings indicate that we should consider ventilator setting when using driving pressure for risk stratification.

Although there has been a lot of progress in the understanding and management of ARDS, the protective ventilation strategy of limiting pressure and volume to avoid VILI remains the cornerstone for ventilating patients with ARDS [14]. However, the best strategy to integrate pressure and volume limitation remains unclear. In a post-hoc analysis of previous clinical trials, Amato *et al* found that driving pressure, rather than tidal volume, is the key determinant of outcomes of ARDS patients receiving mechanical ventilation [13]. However, driving pressure is mathematically linked to tidal volume and compliance. Although airway driving pressure is significantly related to lung stress from me-

Table 3. Multivariate Model for Hospital Mortality among Sepsis Patients with Acute Respiratory Failure.

	H.R.	95% C.I.	*p* value
Age (year)*	1.013	0.994-1.033	0.189
APACHE II score*	1.015	0.975-1.056	0.461
DM (yes)+	0.613	0.323-1.163	0.134
Driving pressure-8 (cmH_2O)*	1.073	1.008-1.142	0.026
Plateau pressure (cmH_2O)*	1.005	0.930-1.086	0.895
Compliance (ml/cmH_2O)*	0.971	0.971-1.031	0.971
Tidal volume (ml/kg PBW)*	0.851	0.685-1.059	0.148

* continuous variables

+ categorical variables, 0: no; 1: yes.

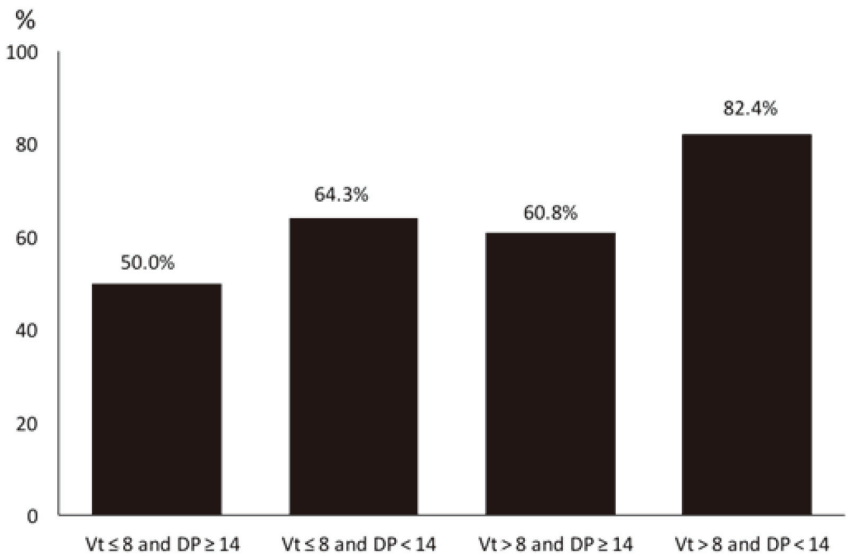

Fig. 3. Relationship among tidal volume, driving pressure and survival rate. (p=0.021)

chanical ventilation [15], it may also represent a worse lung condition with poor compliance. In another secondary analysis of 2 trials evaluating adjunctive therapies in ARDS, driving pressure was still found to present a risk of mortality even under low tidal volume ventilation [16]. Our results show that patients with a higher driving pressure have a worse outcome no matter whether lung protection ventilation is applied or not. In view of these findings, we suggest critical care physicians take both tidal volume and driving pressure into consideration when using mechanical ventilation for ARDS patients [17].

Limiting plateau pressure to below 30 cmH_2O is generally accepted as part of a protective ventilator strategy. In previous retrospective analyses, limiting tidal volume or further reduc-

ing plateau pressure were associated with lower mortality, even when plateau pressure was already below 30 cmH_2O [18]. Driving pressure has been shown to be an indicator for mortality in several retrospective analyses [13,16,19], but the safety margin of driving pressure is unknown. Our data show that septic patients with a higher driving pressure while ventilated with a lower tidal volume are associated with the worst outcome. This implies that critical care physicians should be alert when using a protective ventilator strategy with a driving pressure greater than 14 cmH_2O. These results may encourage critical care physicians to consider ultra-protective ventilation [20-22] with an even lower tidal volume when the driving pressure is still high. As there is no evidence to guide ventilation under such conditions, a well-designed prospective trial to evaluate this strategy is urgently needed.

Hypoxemia is the most important clinical presentation of ARDS and the PaO_2/FiO_2 ratio has long been used as a marker to stratify severity [23-24]. However, the PaO_2/FiO_2 ratio can be influenced by a variety of factors, including PEEP and tidal volume, and thus a systematic method for evaluating ARDS severity is needed [25]. The Berlin definition of ARDS adopted this concept and 5 cmH_2O PEEP or CPAP is required for stratification of severity. But there is not much difference in mortality between different severity groups. In order to better predict ARDS outcome, Villar *et al* suggested using PEEP 10 cmH_2O and PaO_2/FiO_2 150 as cutoff values to group patients for risk stratification. They also found that prediction power is even better at 24 hours after onset than that at ARDS onset. In our study, driving pressure did not differ between survivors and non-survivors at ICU admission. But after 8 hours of ICU admission, driving pressure began to show a difference between survivors and non-survivors, as well as at the subsequent time points. Since determining the prognosis is an important responsibility of critical care physicians, respiratory parameters, including driving pressure and PaO_2/FiO_2, can be better used as a marker for outcome prediction when the ventilator setting is stabilized.

The major limitation of the present study is that we used a retrospective design without blinding, and pre-specified end points which may be biased by a variety of known and unknown confounders. We could not establish the cause and effect relationship between driving pressure and outcome in this study. However, we believe this relationship is important and needs to be examined in a prospective fashion. Another important issue is that the mechanical ventilation setting did not adhere to the current available evidence. The average tidal volume in this study was higher than 8 ml/kg PBW. ARDS has often been under-recognized and undertreated in previous epidemiological studies [19,26-27]. This highlights the importance of education and the potential for improvement in managing ARDS in real-life practice.

Conclusion

Driving pressure greater than 14 cmH_2O after 8 hours of ICU admission is associated with increased mortality of septic patients with acute respiratory failure needing mechanical ventilation. Among these patients, those with a higher driving pressure while ventilated with a lower tidal volume were at increased risk of hospital mortality.

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探討低潮氣容積通氣下之敗血症病人合併急性呼吸衰竭其 Driving Pressure（驅動壓力）與死亡率之相關性

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吳杰亮 ******,******* 黃彥翔 *

前言：驅動壓力（driving pressure）取決於呼吸器設定與肺部順應性，且影響急性呼吸窘迫症候群病人的預後。因此，我們設計了一個回溯性研究來探討潮氣容積設定、driving pressure 與病人預後三者之關係。

方法：此回溯性研究分析，納入台中榮民總醫院呼吸加護病房於 2008 年 4 月 1 日至 2009 年 11 月 30 日，因敗血症造成急性呼吸衰竭並接受侵入性機械通氣之病人，我們研究探討呼吸器設定參數與病人預後之關聯。

結果：本研究共收案 220 位因敗血症接受侵入性機械通氣之病人。病人年齡中位數為 76 歲，平均 APACHE II 分數為 25.0 6.5 分。住院中死亡率為 39.1%。病人轉入加護病房後第八小時之驅動壓力大於 14cmH_2O 為獨立風險因子。在低潮氣容積設定下 (小於 8 ml/kg 預測體重，predict body weight, PBW)，第八小時之驅動壓力大於 14cmH_2O 之病人群住院中死亡最高。

結論：Driving pressure 對於敗血症造成呼吸衰竭且接受侵入性機械通氣之急重症病人而言，是預測住院中死亡率的重要風險因子。低潮氣容積通氣設定下有高驅動壓力的病人其住院中死亡率有顯著上升。*(胸腔醫學 **2019; 34: 92-102**)*

關鍵詞：急性呼吸衰竭，驅動壓力，潮氣容積，敗血症

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Coinfection of *Pneumocystis jiroveci* and *Mycobacterium tuberculosis* in a Patient without Human Immunodeficiency Virus Infection: A Case Report

Yun-Kai Yeh, Fang-Chi Lin*

Coinfection with *Pneumocystis jiroveci* (Pj) and *Mycobacterium tuberculosis* (MTB) is not rare, and is more common among patients with cellular immunodeficiency, such as human immunodeficiency virus (HIV) infection. Risk factors associated with co-incidence of Pneumocystis jiroveci pneumonia and active tuberculosis in patients without HIV infection include corticosteroid use, chemotherapy, alcohol-related hepatic cirrhosis, severe malnutrition, pancytopenia, and depletion of CD4+ T-cells. We report a 96-year-old, HIV-uninfected man who presented with community-acquired pneumonia and acute hypoxemic respiratory failure. He was diagnosed with Pj and MTB coinfection by the presence of Pj and MTB in respiratory specimens via bronchoalveolar lavage. We discussed the clinical characteristics of Pj and MTB coinfection, and factors associated with onset of Pneumocystis jiroveci pneumonia from colonization of Pj in the respiratory tract, if a patient is coinfected with MTB. ***(Thorac Med 2019; 34: 103-109)***

Key words: Pneumocystis jirovecii pneumonia, *Mycobacterium tuberculosis*, human immunodeficiency virus, corticosteroid, bronchoalveolar lavage

Introduction

Pneumocystis jirovecii pneumonia (PjP) is the most common opportunistic infection in human immunodeficiency virus (HIV)-infected patients [1]. The incidence of active tuberculosis (TB) is increasing among HIV-infected patients in Africa and Asia, where TB is highly endemic [2]. Active TB is the most common illness among HIV-infected people and is the major cause of HIV-related deaths [3]. In a 22-month follow-up study in South Africa, the incidence of *Mycobacterium tuberculosis* (MTB) coinfection was around 9.9% in Pj patients coinfected with HIV [4]. In another study conducted in Myanmar in 2003, 3 out of 60 HIV-infected patients (5%) who complained of dry cough for at least 2 weeks were proven

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to have PjP and active TB [5]. In the era of antiretroviral therapy, the major risk group for developing PjP is immunocompromised hosts, such as patients with malignancy or rheumatological diseases, and those who were transplant recipients [6-8]. According to a case series published in 2008, the risk factors for Pj and MTB coinfection in 12 HIV-uninfected patients included corticosteroid us, chemotherapy, visceral leishmaniasis, alcohol-related hepatic cirrhosis, severe malnutrition, pancytopenia, and depletion of CD4+ T-cells [8-9]. Here, we describe an HIV-uninfected patient admitted to an intensive care unit (ICU) with the diagnosis of Pj and MTB coinfection. The risk factors for developing PjP and TB are also discussed.

Case Report

A 96-year-old man presented to the emergency department with the complaints of progressive shortness of breath and productive cough for a week. The patient had gouty arthritis, hypertension, and hepatocellular carcinoma status post-subsegmentectomy. Daily medications included colchicine and lercanidipine. He was a non-smoker without underling respiratory diseases such as asthma, bronchiectasis, or chronic obstructive pulmonary disease (COPD). Recent travel or exposures to individuals with infectious diseases were denied. There was no apparent history of alcohol consumption, illicit drugs, herbs, or immunosuppressants. However, short-term (less than 7 days) corticosteroid might have been prescribed for the acute gouty arthritis. He was lethargic and his blood pressure was undetectable on arrival at the emergency department. The other vital signs were as follows: heart rate: 95 beats per minute, respiratory rate: 30 breaths per minute and body temperature: 38.7°C. Physical examination revealed malnutrition, cyanosis, and respiratory distress. Chest radiograph (CXR) showed consolidation in the right upper lobe (RUL), ground-glass opacity (GGO) in the left upper lobe (LUL), and infiltration at the bilateral lower lung fields (Figure 1). Blood test revealed a total leukocyte count of 10,500 cells/mm3 with a left shift (segments 89.9% and lymphocytes 4.2%), hemoglobin of 8.2 g/dl, serum creatinine of 3.47 mg/dl, serum potassium of 3.0 mmol/L, C-reactive protein of 27.05 mg/dl, and serum albumin of 2.5 g/dl. He was intubated and admitted to the ICU. Piperacillin/tazobactam and teicoplanin were started due to a suspicion of community-acquired pneumonia. However, arterial oxygen saturation did not improve within 48 hours and progression of consolidation in the RUL and LUL was observed on CXR. (Figure 2) Chest computed tomography (CT) revealed GGO with

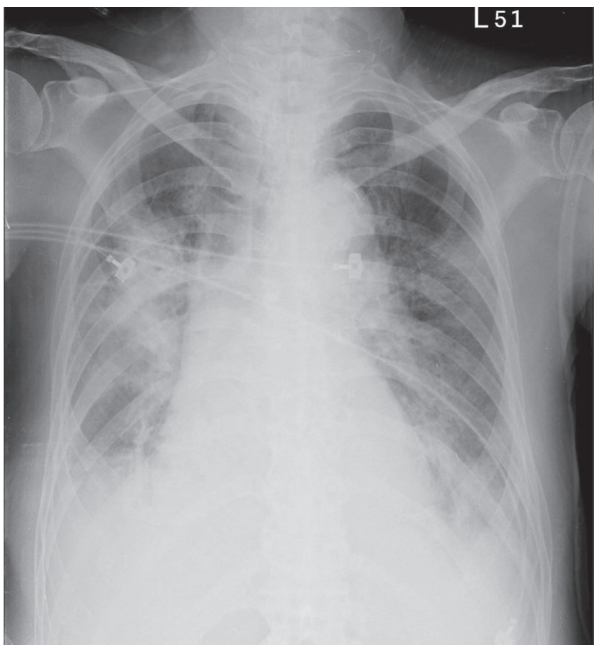

Fig. 1. Chest radiograph showing consolidation in the right upper lobe, ground-glass opacity in the left upper lobe, and infiltrations at the bilateral lower lung fields.

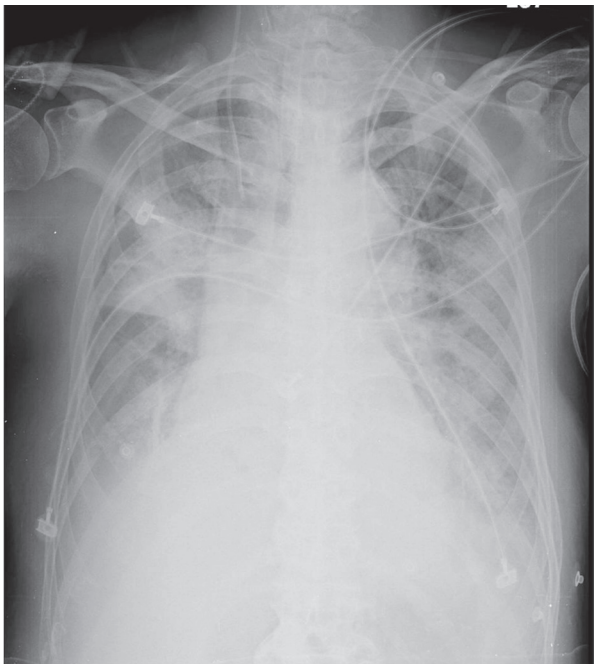

Fig. 2. Chest radiograph follow-up 48 h after starting broad-spectrum antibiotics with piperacillin/tazobactam and teicoplanin.

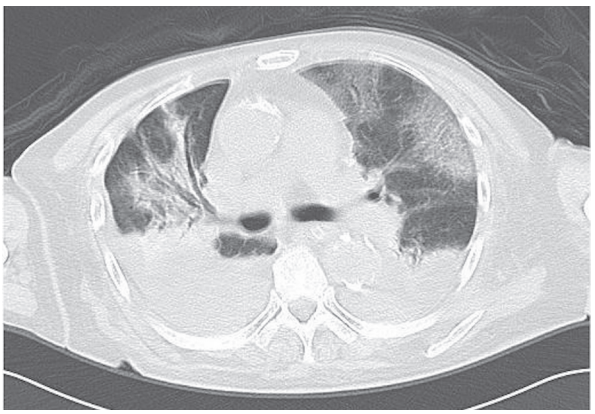

Fig. 3. Chest computed tomography revealed a ground-glass opacity with interlobular septal thickening in non-dependent parts, atelectasis in dependent parts, and bilateral pleural effusions. (The patient was irritable during the examination in which the motion artifact was noted.)

interlobular septal thickening in non-dependent parts and bilateral pleural effusions (Figure 3). The pleural effusion was exudate, with a high neutrophil-lymphocyte ratio (2.3). No bacteria was observed in the Gram staining of the sputum on hospital day 2. Bacterial cultures of the blood, sputum, and pleural effusion obtained upon admission were negative on hospital day 4. Fiberoptic bronchoscopy with diagnostic bronchoalveolar lavage (BAL) was performed on hospital day 4, and Pj was found in the BAL fluid (Figure 4). MTB was identified from the endotracheal aspirate using Ziehl-Neelsen stain and nucleiotide assay (GenXpert). Serological surveys were performed and the results were negative for HIV antigen or HIV antibody, hepatitis B surface antigen (HBsAg), cytomegalovirus by polymerase chain reaction (PCR), IgM antibody against herpes simplex virus and varicella zoster virus, IgG antibody against anti-hepatitis C virus, and autoantibodies including antinuclear antibodies, rheumatoid factor, anti-double stranded DNA and antineutrophilic cytoplasmic antibody. Lateral flow immunoassay for cryptococcal antigen (serotype A/B/C/D) from BAL fluid revealed a negative result. Conventional anti-TB chemotherapy with isoniazid, rifampin, pyrazinamide, and ethambutol was empirically prescribed. Trimethoprim-sulfamethoxazole was not administered because the

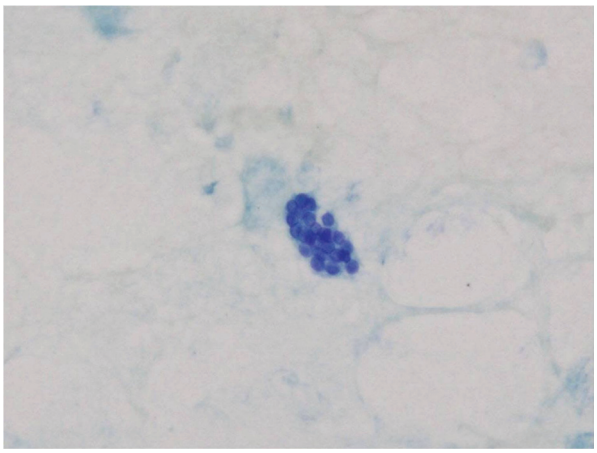

Fig. 4. *Pneumocystis jirovecii* cysts were observed by staining a bronchoalveolar lavage fluid specimen (400×) with toluidine blue O.

family members were doubtful regarding the safety of the drug. Gram-negative bacilli were found in endotracheal aspirates on hospital day 6. On hospital day 7, piperacillin/tazobactam was replaced by meropenem for use against *Enterobacter aerogenes*, based on the result of the endotracheal aspirates culture. Unfortunately, no clinical or radiologic amelioration was observed after anti-TB chemotherapy and broad-spectrum antibiotics. The patient died of another episode of septic shock 3 weeks after meropenem and anti-TB chemotherapy. Three days after the patient expired, *M. tuberculosis* complex was identified through cultures.

Discussion

P. jirovecii infection is a potentially life-threatening opportunistic infection in immunocompromised hosts; however, there are differences in clinical characteristics and prognosis between patients with and without HIV infection [10-11]. PjP may be more fulminant among immunocompromised HIV-uninfected patients than among HIV-infected patients [9]. Mortality rates were lower in HIV-infected individuals (10-20%) than in HIV-uninfected individuals (30-60%) [12]. In a case series [4], 24 of 39 HIV-infected patients received both conventional anti-TB chemotherapy and anti-Pj therapies, and 22 improved. Only 10 patients receiving isolated conventional anti-TB chemotherapy showed improvement, and only 1 of 4 patients receiving anti-Pj therapy without anti-TB chemotherapy improved. The remaining patients did not show improvement without anti-TB chemotherapy or anti-Pj therapy. HIV-infected patients without anti-TB chemotherapy had worse outcomes than those without anti-Pj therapy. TB may be the more severe side of TB and Pj coinfection.[4]. As for Pj and MTB coinfection in HIV-uninfected patients, 8 out of 12 HIV-uninfected patients with Pj and MTB coinfection had improved status, according to a case series published in 2008 [8]. The mortality rate with Pj and MTB coinfection was 33% (4/12). High mortality with coinfection of Pj and MTB has been noted, but not always lethal.

Risk factors for PjP and TB coincidence are corticosteroid treatment, chemotherapy, visceral leishmaniasis, alcohol-related hepatic cirrhosis, severe malnutrition, pancytopenia, and depletion of CD4+ T-cells [8]. The patient in this case report might have taken short-term corticosteroids for acute gouty arthritis. However, the exact dosage and duration of corticosteroid use were unclear. Malnutrition might have been another risk factor in this patient, as evidenced by the low body mass index (16 kg/m^2) and hypoalbuminemia (serum albumin level of 2.5 g/dl). Elderly people are especially at high risk for reactivation of latent TB and are susceptible to new TB infection. Furthermore, malnutrition might disrupt protective barriers and impair microbial clearance mechanisms, which, in turn, accelerate age-related deterioration of cellular immune responses to TB [13]. The number of CD4+ T cells was not available for this patient; however, he did have a reduced absolute lymphocyte count upon admission ($441/mm^3$). In several studies [7,9,14], active TB infection may have led to lymphocytopenia. The lymphocytopenia in this patient might have resulted from TB infection, since the patient did not take immunosuppressants and was without a disease potentially associated with lymphocytopenia, such as leukemia, HIV infection or autoimmune disorders. Acute inflammation resulting from *Enterobacter* pneumonia may also have been responsible for the lymphocytopenia, and the

patient's extremely old age can be considered as another factor leading to the immunocompromised status associated with PjP and active TB coincidence.

However, PjP is not often reported in immunocompetent patients. PjP in immunocompetent patients may present with fever, dry cough, and acute hypoxemic respiratory failure [15-16]. PjP and miliary TB co-incidence was reported in a young woman who had no remarkable medical history, but developed acute respiratory failure. Acquired or primary immunodeficiency was excluded after extensive investigations, suggesting that she was immunocompetent [17]. The natural reservoir of Pj is unclear, but its transmission via the airborne route has been proven [10]. Differing percentages of colonization of Pj can be observed in both immunocompetent and immunocompromised individuals: 0-65% in the general population, 20-69% in HIV-infected patients, and 16-55% in patients with COPD. Colonized individuals may be at risk of developing PjP [18]. Development of TB in an immunocompetent individual might be a risk factor for transition of Pj from colonization to overt pneumonia [16].

The culture method for Pj is currently unavailable. Microscopic demonstration of organisms in adequate pulmonary specimens remains the gold standard. Various PCR targets and methods are available. However, the fair sensitivity of PCR in diagnosing PjP in patients with a low fungal burden may also lead to overdetection of Pj DNA in patients with colonization [19]. A positive PCR without microscopic detection is difficult to interpret [20]. For HIV-uninfected patients who have a low fungal burden, BAL fluid or lung biopsies obtained via invasive procedures may be required to confirm a diagnosis [9]. Clinicians should be aware that Pj might be present in a patient without a definite history of immunodeficiency.

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同時感染肺囊蟲肺炎和肺結核於非人類免疫缺乏病毒感染症病患－病例報告

葉雲凱　林芳綺 *

同時感染肺囊蟲肺炎和結核菌的案例並不算少見，尤其是細胞免疫缺陷的病人身上更是常見。危險因子有使用類固醇，化學治療，酒精性肝硬化，嚴重營養不良，全血球低下症，CD4+ T細胞淋巴球缺乏症等因素。此外，肺囊蟲移生現象無論在免疫健全和免疫缺乏的人身上皆可以觀察到。被肺囊蟲移生的個體可能有發展成肺囊蟲感染的風險。我們在這裡展現一個案例，一個 96 歲的非人類免疫缺乏病毒感染病患，因肺炎以及呼吸衰竭，住進加護病房。並經由氣管鏡肺泡沖洗術和痰液培養，證實了同時感染肺結核和肺囊蟲肺炎。*(胸腔醫學 **2019; 34: 103-109**)*

關鍵詞：肺囊蟲肺炎，結核菌，人類免疫缺乏病毒，類固醇，氣管鏡肺泡沖洗術

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Electrical Impedance Tomography for Optimal Positive End-Expiratory Pressure Application in Unilateral Acute Lung Injury with Profound Hypoxemia: A Case Report

Chan-Chun Chang, Chien-Hung Gow, Yeong-Long Hsu

Massive aspiration pneumonia with unilateral acute lung injury and profound hypoxemia is a common condition seen in the intensive care unit (ICU). Application of optimal positive end-expiratory pressure (PEEP) based on acute respiratory distress syndrome network guidelines may over-distend the uninvolved, more compliant lung. Some of these patients may require double lumen endotracheal intubation and independent lung ventilation to rescue the worsening ventilation/perfusion mismatch and decreasing oxygenation during suboptimal PEEP titrations. Electrical impedance tomography (EIT) is a non-invasive and portable lung imaging technique for dynamic evaluation of lung volume distribution. The reliability of EIT has been validated by comparing it with different conventional methods. Application of EIT in the ICU has been proposed for patients with mild, moderate, and severe lung disease, for assessing ventilation distribution, or even for guiding respiratory therapies. Here, we presented a patient with massive aspiration pneumonia with unilateral acute lung injury. Under real-time EIT, the PEEP was adjusted to optimal levels, and the patient was eventually successfully extubated without sequelae. ***(Thorac Med 2019; 34: 110-118)***

Key words: electrical impedance tomography, optimal positive end expiratory pressure, unilateral acute lung injury

Introduction

Massive aspiration pneumonia with unilateral acute lung injury and profound hypoxemia is a common condition in the intensive care unit (ICU). Application of positive end-expiratory pressure (PEEP) based on the ARDS (acute respiratory distress syndrome) network guidelines for bilateral acute lung injury may result in over-distention of the uninvolved, more compliant lung, or diversion of the pulmonary flow to the injured lung, leading to a worsening ventilation/perfusion mismatch and decreasing oxygenation [1-2].

There is currently no consensus regarding the appropriate levels of PEEP and tidal volume

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in patients with unilateral lung injury [4]. Positioning the patient with the "good lung down" may cause aspirated material to spill into the contralateral healthy lung, spreading the pneumonia, and also make it difficult to remove the aspirated material or hypertonic solution.

Independent lung ventilation (ILV) involves differential ventilation via a double-lumen endotracheal tube to isolate a diseased lung and prevent contamination of the non-diseased lung, and selective application of different PEEP and tidal volumes based on different levels of lung compliance. ILV is a seldom-used and technically demanding procedure for managing unilateral lung disease or injury in patients with whom conventional modes of mechanical ventilation (MV) have failed [5-6]. However, if ILV is not possible due to the absence of a double-lumen endotracheal tube or the unavailability of a synchronized MV, or if the patient's family refuses double-lumen endotracheal tube intubation, optimal adjustment of PEEP levels is difficult.

Electrical impedance tomography (EIT) is a non-invasive and portable lung imaging technique for dynamic evaluation of lung volume distribution in real-time [3]. The reliability of EIT has been validated by comparison with different conventional methods. It has been proposed that EIT should be applied in the ICU with patients with mild, moderate, and severe lung diseases, to assess ventilation distribution or to guide respiratory therapies [13-14].

Here, we report a patient with massive aspiration pneumonia with unilateral acute lung injury. The patient manifested profound shock and hypoxemia after endotracheal intubation and MV application. We used real-time EIT at the bedside to adjust the PEEP optimally, and the patient was finally successfully weaned from MV.

Case Report

A 70-year-old male visited our gastrointestinal outpatient department due to epigastralgia and nausea with postprandial vomiting of 2 weeks' duration. He had a medical history of coronary artery disease and had previously undergone percutaneous occlusion balloon angioplasty and stenting; he had reflux esophagitis, chronic gastritis, and a duodenal ulcer. Upper gastrointestinal pan-endoscopic and colon fiberscopic examinations were arranged. He was given *Niflec*® powder for colonic preparation and drank 2000 mL of water 6 hours before the examination. However, vigorous vomiting with choking and aspiration occurred during the pan-endoscopic examination. The study was recorded as incomplete and he remained in the recovery room for observation. He developed fever up to 40°C, chills, progressive dyspnea, and cyanosis of the lips and all 4 limbs 1 hour later.

He was transferred to our emergency department and anteroposterior plain abdominal radiography revealed a distended gastric bulb, compatible with gastric outlet obstruction (Figure 1A). Chest radiography showed left lung multilobar consolidation by air bronchogram, which was compatible with left lung aspiration pneumonia. Laboratory data revealed leukocytosis (white blood cell count 21,880/μL) and hypoxemia (arterial blood gas, pH 7.31; $PaCO_2$, 47.2 mmHg; PaO_2, 46.5 mmHg; bicarbonate, 23.6 mmol/L).

Due to progressive tachypnea, a paradoxical respiratory pattern, and impaired consciousness, the patient was promptly intubated, mechanically ventilated, and admitted to our ICU.

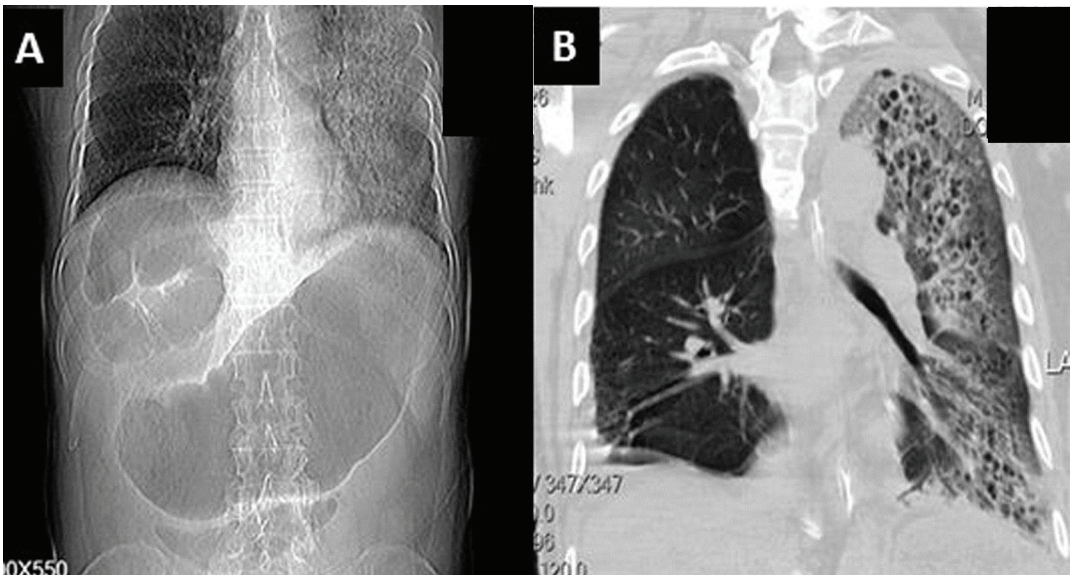

Fig. 1. (A) Anteroposterior plain abdomen radiography shows a distended gastric bulb, compatible with gastric outlet obstruction. (B) Computed tomography scan of the lung shows multiple cystic lesions within dependent parts of the consolidated left lung.

He received empirical antibiotics (piperacillin-tazobactam and levofloxacin). Bronchoscopic examination, with 200 mL of normal saline for bronchoalveolar lavage of the left lung, was performed, but no *Niflec*® was retrieved. A sedative agent (midazolam), muscle relaxant (atracurium), and narcotic (fentanyl infusion) were required to manage irritability and allow intermittent troubleshooting of MV function. On volume-controlled MV with constant-flow inflation, a low tidal volume (400 mL, 6 mL/kg predicted body weight), high PEEP (16 cmH_2O), and high oxygenation (fraction of inspired oxygen: 0.8, PaO_2/FiO_2: 62) were maintained. The end-inspiratory pressure was 38 cmH_2O.

However, progressive whiteout of the left hemithorax on chest X-ray developed 1 day later. Inhaled nitric oxide was attempted, but there was no improvement in hypoxemia (PaO_2/FiO_2 <80). The "good lung down" in the right decubitus position or prone position was not attempted, because of the high risk of spreading the aspirated material to the healthy right lung, and the patient was considered a "non-responder" to position changing due to his poor response to nitric oxide inhalation. Chest computed tomography (CT) revealed multiple cystic lesions within the affected part of the consolidated left lung (Figure 1B). To prevent over-distention with barotrauma under high PEEP, anatomical lung separation with independent lung ventilation by means of double-lumen endotracheal intubation was suggested, but the family refused. Therefore, we adjusted the MV to pressure-controlled ventilation. EIT was then arranged.

The study was approved by the Far Eastern Memorial Hospital Ethics Committee (FEMH-IRB-103133-E). Written informed consent was obtained from the patient's family prior to the study. EIT examination of the chest was performed at the level of the fifth intercostal space (EIT Evaluation KIT 2, Dräger Medi-

cal, Lübeck, Germany). Electrical alternating currents (50 kHz, 5 mA peak-to-peak) were applied in a sequential rotating process and the resulting surface potential differences were measured between neighboring electrode pairs. EIT data were recorded and reconstructed at 20 Hz. The inspiratory pressure setting of the MV (Dräger Evita 4, PCV mode) was 35 cmH_2O, inspiratory time was 1.0 s, fraction of inspired oxygen was 0.80, and respiratory rate was 12/min. The PEEP level was titrated incrementally from 0 to 16 cmH_2O for lung recruitment, and then decrementally from 16 to 0 cmH_2O every 2 mins (Figure 2A), with close monitoring of the inspiratory tidal volume, minute ventilation, SpO_2, PaO_2, and arterial blood pressure. Volume distribution in the 4 quadrants of the lung (region of interest [ROI] zone 1 was the right lung ventral region, zone 2 was the left lung ventral region, zone 3 was the right lung dorsal region, and zone 4 was the left lung dorsal region) (Figure 2B), area of over-distension (light blue to white color at end-inspiration) (Figure 2C), and area of derecruitment (orange color in the ROI, representing a decrease of more than 10% of the end-expiratory lung volume impedance between cursors 2 and 1 [ΔEELI, as shown in Figure 2A]) (Figure 2D) were assessed. The definition of optimal PEEP should meet all of the following criteria. First, it should be the lowest PEEP that recruited the atelectatic left lung (zone 2 plus 4) for more than 10% of the ΔEELI. Second, it should be the highest PEEP that derecruited the over-distended normal lung (zones 1 plus 3) for more than 10% of the ΔEELI. Third, it should be the highest PEEP that maintained mean arterial pressure above 70 mmHg.

The results of optimal PEEP titration were as follows: First, as PEEP increased from 12 to 16 cmH_2O, it was difficult to interpret whether over-distension could be prevented based on the color changes in the ROIs (Figure 2B vs.2C). However, changes in ΔEELI between inhomogeneous lung zones revealed decreased aeration in the right ventral, left ventral, and part of the right dorsal lung zones, but increased aeration in the left dorsal and part of the right

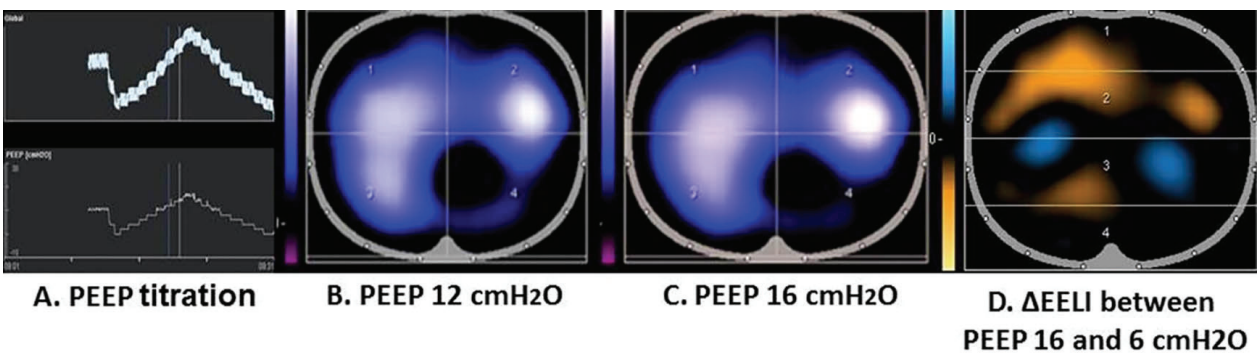

Fig. 2. (A) Positive end-expiratory pressure (PEEP) level was titrated incrementally from 0 to 16 cmH_2O for lung recruitment, and then decrementally from 16 to 0 cmH_2O, every 2 minutes. (B) Volume distribution in 4 quadrants of the lung at PEEP 12 cmH_2O. Region of interest (ROI) zone 1 was the right lung ventral region, zone 2 was the left lung ventral region, zone 3 was the right lung dorsal region and zone 4 was the left lung dorsal region. (C) Area of over-distension at PEEP 16 cmH_2O (light blue to white color at end-inspiration). (D) Area of derecruitment (orange color in the ROI, decrease by more than 10% of ΔEELI, i.e., the end-expiratory lung volume impedance between cursor 2 (PEEP 16 cmH_2O) and cursor 1 (PEEP 6 cmH_2O).

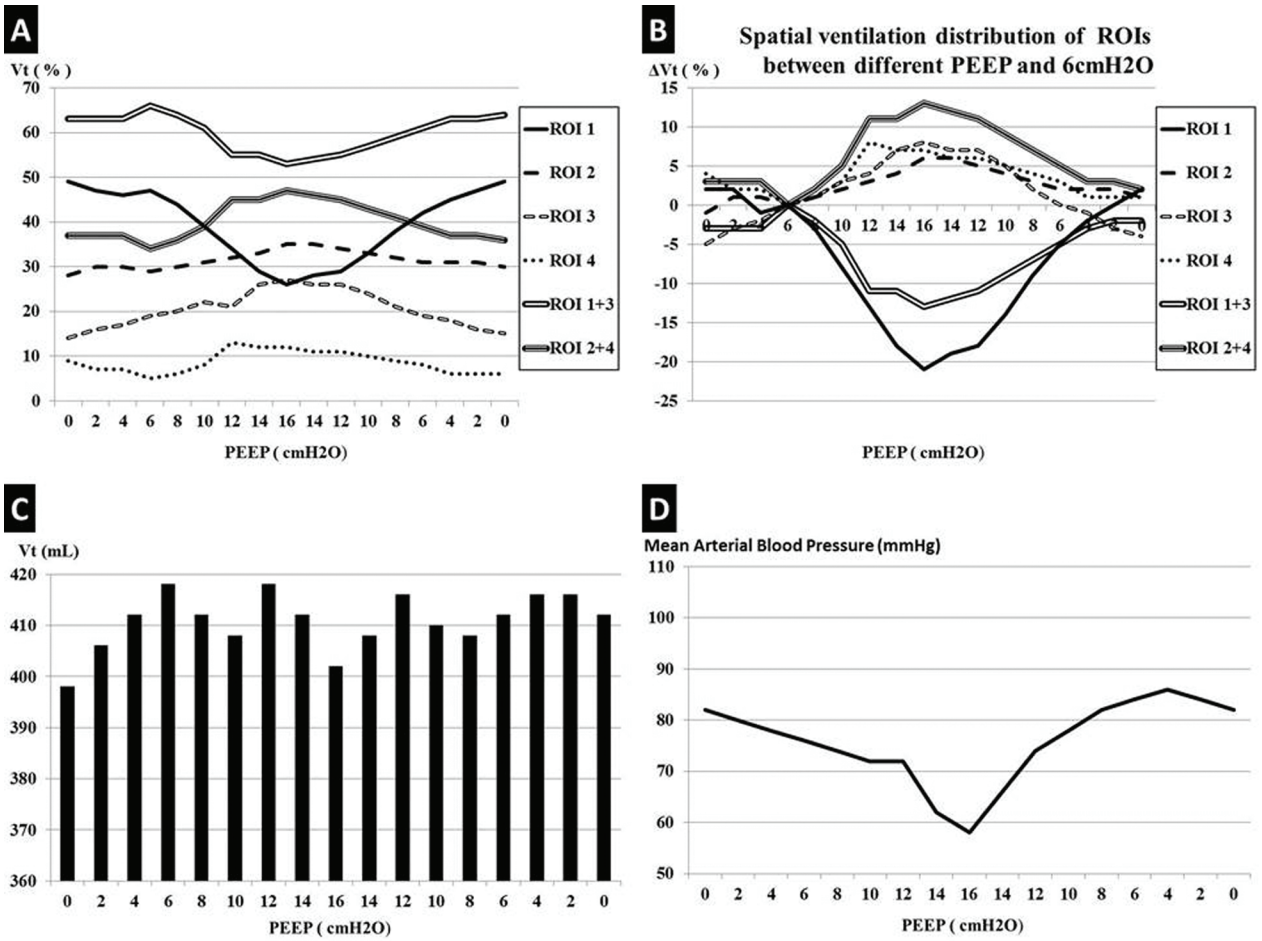

Fig. 3. (A) Under pressure control ventilation, the tidal volume distribution at end-inspiration among lung zones revealed an abrupt decrease in ROI 1 and a gradual increase in ROIs 2, 3, and 4 when PEEP increased from 6 to 16 cmH_2O. The reverse phenomenon was noted during lung derecruitment. (B) A comparison of ROIs for zones 1+3 and for zones 2+4 zones revealed that the increase in ΔVt% in the atelectatic left lung reached a plateau after PEEP exceeded 12 cmH_2O. Once the regions in the ROI of zones 2+4 were recruited, this effect lasted until the PEEP level decreased to 4 cmH_2O during the derecruitment procedure. (C) Static lung compliance, represented by the inspired tidal volume during pressure-controlled ventilation. (D). Mean arterial pressure (mmHg) during PEEP titration.

dorsal zones. This finding confirmed that we had increased aeration of the left dorsal part of the lung, which had been targeted for recruitment (Figure 3A). Second, under pressure-control ventilation, the tidal volume distribution among the lung zones at end-inspiration revealed an abrupt decrease in the ROI zone 1, and a gradual increase in the ROI zones 2, 3, and 4 when the PEEP was increased from 6 to 16 cmH_2O. The reverse phenomenon was noted during lung derecruitment. When we compared the ROI zones 1+3 and zones 2+4, the results suggested that the increase in ΔVt% in the atelectatic left lung reached a plateau once the PEEP level exceeded 12 cmH_2O. Once the ROI zones 2+4 were recruited, this effect lasted until the PEEP level had decreased to 4 cmH_2O during the derecruitment procedure (Figure 3B and 3C). Thus, based on the changes in the ΔEELI, we confirmed that the lowest PEEP that could

keep the left lung recruited (maintain ΔEELI >10%) was 12 cmH_2O, while the highest PEEP that could prevent derecruitment of the left lung (maintain ΔVt% >10%) was also 12 cmH_2O (Figure 3B). Third, the inspired tidal volume delivered by MV in the pressure-control mode varied between different PEEPs; however, static lung compliance was better with a PEEP level of 12 cmH_2O than with 14 and 16 cmH_2O (Figure 3C). Fourth, during PEEP titration, unstable hemodynamics, with a mean arterial blood pressure below 70 mmHg (Figure 3D), was noted when the PEEP level exceeded 12 cmH_2O. Taken together, we concluded that the optimal PEEP for best left lung recruitment in this patient was 12 cmH_2O.

When we implemented this MV setting, the oxygenation of the patient improved gradually. We tapered FiO_2 to below 0.5 over 2 days, but left-lung post-inflammatory fibrosis developed thereafter. Gastro-jejuno-bypass surgery and jejunostomy were performed to avoid further vomiting and aspiration. Due to ventilator-associated pneumonia, catheter-related blood stream infection, and malnutrition during the prolonged total parenteral nutrition support period, it was difficult to wean the patient from MV. He was transferred to our respiratory care center on the 23rd MV day. With EIT as previously described for evaluation of diaphragmatic movement [3], we used external continuous positive airway pressure of 7.5 cmH_2O for a spontaneous breathing trial weaning protocol. The patient tolerated the gradual weaning afforded by this protocol and was successfully extubated 17 days later. The patient was then discharged from our hospital and was able to breathe room air, with no additional oxygen required.

Discussion

Massive aspiration pneumonia complicated by ARDS and profound hypoxemia are commonly seen in the ICU. Unilateral pulmonary injury caused by traumatic lung contusion, massive unilateral lung aspiration, unilateral bronchiolitis obliterans and bronchopleural fistula after single lung transplantation are not rare occurrences in medical center ICUs. Asymmetry of bilateral lung physiological parameters, including differences in compliance, airway resistance, amount of airway secretions, ventilation/perfusion mismatch, and pulmonary artery resistance, all influence the lower and upper inflection points during PEEP application.

Application of PEEP according to the ARDS network guidelines for bilateral consolidation patients [4] may over-distend the uninvolved, more compliant lung, cause a collapse of the affected lung [5-6] or barotrauma [7-8], divert pulmonary blood flow to the injured lung, and impair physiological pulmonary vasoconstriction during hypoxia [7-10], thus worsening the ventilation/perfusion mismatch and decreasing oxygenation. There is currently no consensus regarding the appropriate levels of PEEP and tidal volume in patients with unilateral lung injury. Positioning the patient with the "good lung down" can improve gas exchange without inducing deleterious hemodynamic effects, and allows a reduction in the inspirated oxygen concentration [11], but may lead to spreading of the pneumonia and may hamper removal of aspirated material [12]. This patient was administered *Niflec*® powder as colonic preparation for further procedures; each sachet of *Niflec*® powder is composed of sodium chloride 21.3 g, potassium chloride 10.8 g, sodium bicarbonate 24.5 g, and sodium sulfate anhydrous 82.9 g. Plac-

ing this patient in the right decubitus position would have caused spill-over of the hypertonic solution, spreading the chemical pneumonitis to the unaffected lung.

EIT is based on alternate current injection and voltage measurement by surface electrodes on the chest wall, and allows dynamic evaluation of lung volume distribution [13-14]. Previous studies had documented that PEEP titration for ARDS patients and "best" or "optimal" PEEP for recruiting the atelectatic lung could be achieved using EIT techniques [15-17].

Chest CT revealed cystic lesions, which provided information about barotrauma during high PEEP (15 cmH_2O in the CT room) (Figure 1B). EIT under pressure-control-mode ventilation revealed a decrease in volume distribution in the normal, compliant lung (zone 1), while the consolidated lung (zones 2 and 4) was recruited during application of PEEP from 0 to 16 cmH_2O (Figure 3A and 3B). Lung compliance decreased after application of PEEP above 6 cmH_2O, but increased again at a PEEP of 12 cmH_2O, which revealed that the lower inflection point for the atelectatic left lung should be above 12 cmH_2O (Figure 3C). Furthermore, hemodynamic instability occurred with application of PEEP above 14 cmH_2O. Taken together, these observations indicated that the optimal PEEP level at that time for this patient, intubated with a single-lumen endotracheal tube, was 12 cmH_2O.

An optimal PEEP titration method and the heterogeneity between the bilateral, but not the dependent and non-dependent lung fields, has not been reported previously [18-19]. Previous studies have focused on pulmonary physiology during PEEP increments, but not on the concurrent hemodynamic changes in the patient, as discussed in this report. This case report therefore highlights the usefulness of applying EIT for PEEP adjustment in patients with unilateral lung consolidation.

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利用電阻抗斷層攝影找出單側急性肺損傷併嚴重低血氧患者最佳吐氣末正壓：一案例報告

張建群　高劍虹　許永隆

單側急性肺損傷併嚴重低血氧在加護病房並非不常見。若是根據急性呼吸窘迫症候群聯網所建議之最佳吐氣末正壓值使用在這些病人的呼吸器設定上，可能會造成正常順應性的單側肺過度充氣。一部分這類病人在上述不適當之吐氣末正壓設定下，可能造成加重通氣 / 灌流與血氧和之惡化，甚至需使用到雙側肺獨立通氣之機械通氣設定。肺部電阻抗斷層攝影，一種新式無輻射、非侵入性、可重覆操作且可提供即時肺部氣體容積分布的影像檢查，其可靠性在國內外的研究皆已證實與許多傳統檢查不相上下。在加護病房，肺部電阻抗斷層攝影的臨床運用已逐漸普及到評估與調整多種呼吸治療的儀器設定上。在此，我們敘述了如何使用電阻抗斷層攝影，在不插雙腔氣管內管與使用雙側肺獨立通氣的情況下，即時找到最佳吐氣末正壓值，幫助病人成功脫離呼吸器。*(胸腔醫學 **2019; 34: 110-118**)*

關鍵詞：電阻抗斷層攝影，最佳吐氣末正壓，單側急性肺損傷

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Mycoplasma Pneumonia Complicated with Cold Agglutinin Hemolysis, Ischemic Stroke, and Acute Kidney Injury in a Middle-Aged Woman with Type II Diabetes: A Case Report and Literature Review

Chia-Jung Chan, Ching-Lung Liu

Mycoplasma pneumoniae is an essential common human pathogen in the etiology of atypical pneumonia in children and adults. In some rare instances, however, it might result in secondary cold agglutinin disease (i.e., cold agglutinin-associated autoimmune hemolytic anemia) or ischemic stroke. We report a case of the 47-year-old woman with type II diabetes mellitus who was diagnosed as having Mycoplasma pneumonia as the result of positive mycoplasma IgM antibody and cold agglutinin tests. Complications including severe hemolytic anemia, jaundice, ischemic stroke due to RBC cold agglutination, and acute kidney injury occurred later. Under treatment with levofloxacin, plasmapheresis and hemodialysis, she recovered gradually and could carry out daily activities independently. This case shows that mycoplasma pneumonia can lead to complications with extrapulmonary diseases involving a wide variety of organs. Multiple extrapulmonary manifestations often indicate an ominous prognosis. In clinical practice, even though mycoplasma infection is common, the extrapulmonary manifestations should be evaluated and managed seriously. ***(Thorac Med 2019; 34: 119-125)***

Key words: mycoplasma pneumonia, cold agglutinin, hemolytic anemia, ischemic stroke, acute kidney injury

Introduction

Mycoplasma pneumoniae is a common respiratory pathogen causing atypical pneumonia with a wide spectrum of disease pathologies ranging from mild upper or lower respiratory tract infection to severe pneumonia complicated with multiple organ failure. The general conception of mycoplasma infection is that it often comes and goes asymptomatically. For symptomatic individuals, the onset is usually gradual and heralded by headache, malaise and low-grade fever. The incidence of upper respiratory illness due to *M. pneumoniae* is up to about 20 times that of pneumonia caused by the organism. Pneumonia develops in 3-13% of infected

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individuals. Mycoplasma infection may also cause extrapulmonary symptoms. Around 20-25% of *M. pneumoniae* infection has simultaneous extrapulmonary manifestations, including skin (Stevens-Johnson syndrome, erythema multiforme), gastrointestinal (abdominal pain, diarrhea), neurological (encephalitis, meningoencephalitis), and cardiac (arrhythmia, myocarditis) conditions [1-2]. Cold agglutinin hemolysis associated with an IgM reaction against erythrocyte I antigen commonly occurs in 50-75% of patients after 1-2 weeks of infection, however, it is usually not clinically significant.

Here, we report a rare case of mycoplasma pneumonia complicated with severe cold agglutinin-associated autoimmune hemolytic anemia (AIHA), ischemic stroke, and acute kidney injury.

Case Presentation

A 47-year-old woman with a past medical history of type 2 diabetes mellitus presented to our hospital with worsening cough, dyspnea, and intermittent fever. Ten days prior to presentation during the winter, she complained of 4 days of intermittent fever, rhinorrhea, cough and sputum. She was diagnosed as having community-acquired pneumonia because of left lower lung infiltrates in her chest X-ray (Figure 1A) taken in Hospital A. She was treated empirically with a 7-day course of cephalosporin and 2 days of clarithromycin (the clarithromycin treatment course was not completed because mycoplasma serology tests yielded negative results initially in Hospital A). She noted that her symptoms improved while under the initial antibiotics treatment. But, 3 days later, she came to our emergency department because of intractable cough, worsening dyspnea, and new onset of fever.

On admission, the woman had a body temperature of 39.4° Celsius, heart rate: 121 beats per minute, respiratory rate: 20 breaths per minute, and blood pressure: 96/66 mmHg. The physical examination revealed minimal coarse crackles in the left basal lung field. A chest CT scan also showed air bronchogram, acinar infil-

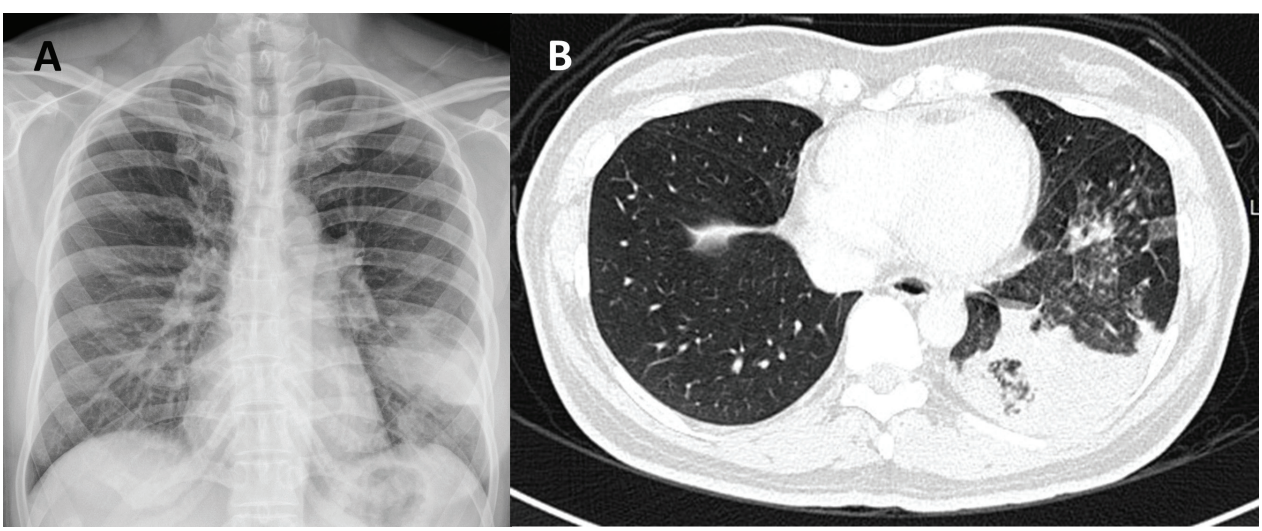

Fig. l. (A) 10 days prior to admission in Hospital A, chest X-ray showed infiltrates in the left lower lung field. (B) On admission, atelectasis and consolidation were seen in the left lower lobe on chest CT scan.

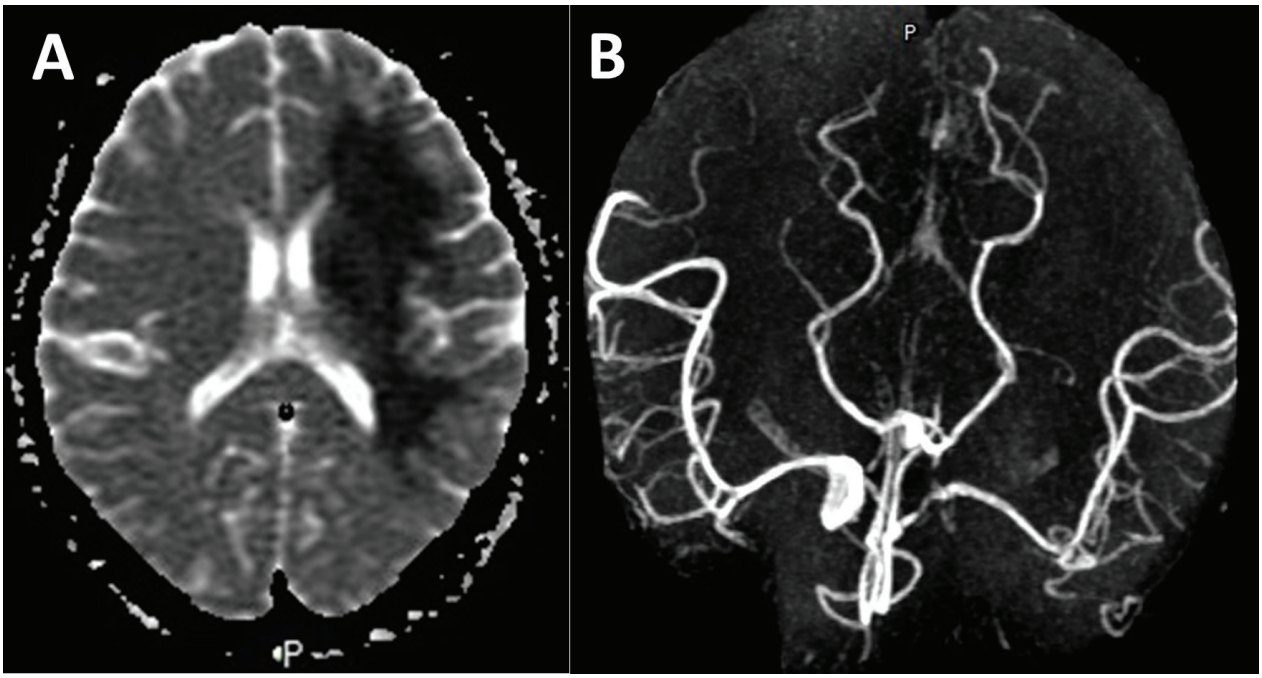

Fig. 2. (A) Brain MRI reveals a low ADC (apparent diffusion coefficient) signal at the left MCA territory, indicating a left MCA ischemic infarct. (B) Brain MRI TOF MRA shows no occlusion at the left MCA.

trations and consolidation in the left lower lobe (Figure 1B).

The chest radiography findings, paired samples of serum *M. pneumoniae* antibodies (IgM, >27 AU/mL, normal <10 AU/mL; IgG, 2.4 AU/mL, normal <10.0 AU/mL) and positive cold agglutination test results (512X, normal <10X) were suggestive of *M. pneumoniae* infection. The patient was then treated with intravenous levofloxacin.

On the second day of hospitalization, a cold wave arrived, with very low temperatures in Tamsui, Taiwan. The patient developed malaise and weakness. Jaundice with icteric sclera and a pale appearance were noted. At 08:00 PM, she suffered from a sudden onset of right-side limbs weakness and slurred speech. A complete blood count (CBC) test revealed normocytic anemia with a dramatically lowered serum hemoglobin of 4.0 g/dL (baseline hemoglobin: 10.9 g/dL). RBC cold agglutination with hemolysis was also found in further peripheral blood smear. Her total bilirubin was significantly raised to 5.25 mg/dL (normal level of direct bilirubin: 0.75 mg/dL). The Coombs tests (indirect and direct) were positive. Her serum creatinine deteriorated to 8.21 mg/dL (baseline creatinine: 0.8 mg/dL). A brain MRI scan revealed an increased signal in the distribution of the left middle cerebral artery (MCA) (Figure 2, A&B). On day 3, the patient developed a markedly depressed level of consciousness (Glasgow Coma Scale: E3V1M5), and she was urgently admitted to the medical intensive care unit (ICU). Her vitals were body temperature: 38^{o} Celsius, heart rate: 94 beats per minute, respiratory rate: 18 breaths per minute, and blood pressure: 115/70 mmHg. In the ICU, focal livedo reticularis at the right knee was noted on physical examination. The diagnosis of cold

agglutinin disease complicated by mycoplasma infection was made by clinical manifestations, serologic studies, and peripheral blood smear. The focal livedo reticularis disappeared soon after the patient began being kept warm (heat lamp and blood transfusion through a blood warming device used to keep body temperature above 37°C). She was subsequently treated with plasmapheresis to lower the serum antibody of mycoplasma IgM, and hemodialysis, along with systemic antibiotics and hypoglycemic agents. One month later, she showed gradual recovery. The patient was discharged from the hospital and was able to return to partial activities of daily living under rehabilitation.

Discussion

In this case, the presence of cold agglutinin and a high titer of antibodies against *M. pneumoniae* were highly suggestive of *M. pneumoniae* infection. Autoimmune hemolytic anemia associated with cold autoantibodies is a well-known and generally mild complication of *M. pneumoniae* infection [3-4]. This case, complicated with various extrapulmonary manifestations, including cold-agglutination disease, hemolytic anemia, ischemic stroke, and acute kidney injury, is rare.

Cold agglutinin disease (i.e., cold agglutinin-associated autoimmune hemolytic anemia [AIHA]) is characterized by the presence of clinical symptoms associated with exposure to cold, hemolytic anemia, and antibodies (most commonly IgM, rarely IgA or IgG) directed against polysaccharide antigens on the red blood cell surface that are responsible for the agglutination of red cells at low temperatures. Cold agglutinins cause red blood cells to clump together (agglutinate) upon exposure to cold ambient temperatures; this may become apparent in clinical presentations of livedo reticularis and acrocyanosis, a dark, purple to gray discoloration of the skin. These changes disappear upon warming of the part, and there is little or no reactive hyperemia, as occurs in the Raynaud phenomenon. Cold agglutinin disease is rare, and it most often affects females. The symptoms include acrocyanosis, fatigue, weakness, dyspnea on exertion, and hemoglobinuria. In our case, the woman had severe acute hemolytic anemia with hyperbilirubinemia, which could be monitored by analyzing the serum cold agglutinin titers (Figure 3). After plasmapheresis, the titer of cold agglutinin declined and the hemolytic anemia with hyperbilirubinemia improved significantly. As for the neurological symptoms/signs, encephalitis and meningoencephalitis frequently occur in the pediatric group, but ischemic stroke, as in our case, is less common. Stroke is not just a cholesterol storage disorder in the vasculature, but is a sustained, dynamic and chronic inflammatory process which can be caused by bacterial or viral pathogens [5]. The mechanisms of stroke due to *M. pneumoniae* infections are still unclear, but may be associated with autoimmune vasculitis with subsequent ischemia and thrombosis with a hyper-coagulation status. A population-based epidemiological study found that mycoplasma infection is independently associated with the risk of subsequent ischemic stroke development, which may be related to direct invasion or immune reaction [6]. Although *M. pneumoniae* pneumonia is generally self-limited, appropriate antimicrobial therapy significantly shortens the duration of clinical illness; however, it does not appear to shorten the duration of detection of *M. pneumoniae* by culture or PCR. Early recognition and diagnosis of *M. pneumoniae* infection

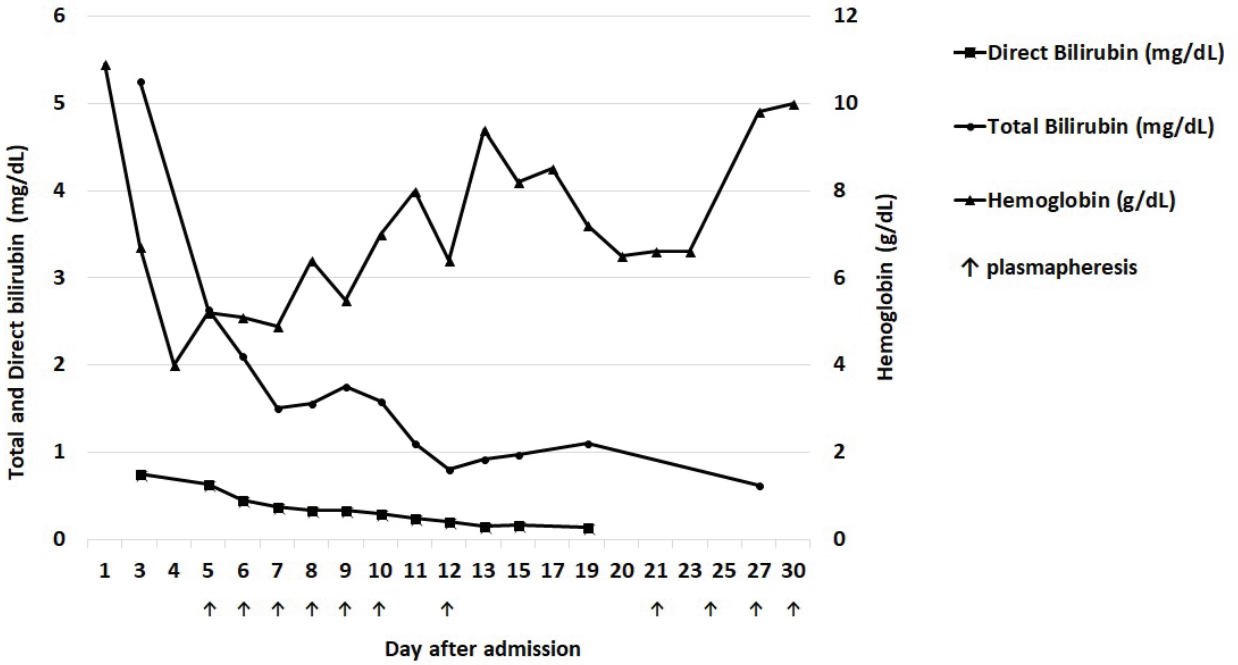

Fig. 3. Disease course showing hemoglobin and total bilirubin correlation with plasmapheresis therapy. The simultaneous increase of hemoglobin and clinical improvement of hemolytic anemia was correlated with the plasmapheresis therapy.

and use of adequate antibiotics are essential for infection control. In our case, the *M. pneumoniae* antibody IgM titers remained high, even after the pneumonia improved. Plasmapheresis contributed to both the decline in serum cold hemagglutinin titers (from 512x+ to 128x+) and the improvement of hemolytic anemia with hyperbilirubinemia. Therefore, there is a risk of *M. pneumoniae* infection-related stroke due to a consistent immune reaction, even with early antimicrobial treatment. In an attempt to reach an early diagnosis of *M. pneumoniae* pneumonia, the respiratory culture sensitivity is less than 60% (specificity 100%) because the organism may take weeks to grow and is often difficult to isolate from clinical specimens. However, a negative respiratory culture result cannot exclude the diagnosis of *M. pneumoniae* infection. Although serologic studies have 55-100% sensitivity and specificity for diagnosis, the antibodies of a systemic immune reaction may take 2 weeks to develop. *M. pneumoniae* PCR (sensitivity 65-90%, specificity 90-100%) may be a better tool for early diagnosis.

Renal manifestations are rare in mycoplasma infection and only a few cases have been reported in children with glomerulonephritis [7] and acute renal tubular necrosis [8] confirmed by renal biopsy. Acute kidney injury is commonly seen in patients with sepsis and septic shock in the ICU. However, in our case, the patient did not have severe septic shock during her ICU stay. The acute kidney injury associated with hemoglobinuria probably resulted from intravascular hemolysis, leading to acute renal tubular necrosis. Renal biopsy was not done, however, due to her unstable condition with severe hemolytic anemia and ischemic stroke.

Table 1. Extra-Pulmonary Manifestations of *Mycoplasma pneumoniae*.

Extra-pulmonary site	Clinical manifestations
Neurological	meningitis, meningoencephalitis, ischemic stroke, cerebellar ataxia, transverse myelitis, Guillain-Barre syndrome, polyradiculoneuritis, psychosis, myositis/myalgia
Cardiovascular	arrhythmia, conduction defects, cardiogenic failure, Raynaud's phenomenon, peripheral symmetric gangrene, Henoch-Schönlein purpura
Hematological	hemolytic anemia, paroxysmal col hemoglobinuria, hemolysis with renal failure
Gastrointestinal	hepatitis, pancreatitis
Musculoskeletal	polyarthralgia, monoarticular arthritis or rheumatic-like form
Dermatological	erythema multiforme, Stevens-Johnson syndrome, erythema marginatum, erythema nodosum, urticaria, measles-like exanthema
Urogenital	progressive glomerulonephritis, nephrotic syndrome, massive transient proteinuria, acute interstitial nephritis, cystitis, urethritis, isolated hematuria, acute/chronic renal failure, hemolytic-uremic syndrome

In general, mycoplasma infection usually takes a benign self-limiting course. Extrapulmonary diseases during *M. pneumoniae* infection can involve a wide variety of organs (Table 1). Multiple extrapulmonary manifestations often indicate an ominous prognosis [9-10]. In a clinical setting, the extra-pulmonary manifestations of mycoplasma infection should always be kept in mind, even though the infection itself is common.

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第二型糖尿病中年女性之黴漿菌肺炎併發冷凝集素溶血性貧血，缺血性中風，及急性腎衰竭：病例報告和文獻回顧

詹家榮　劉景隆

黴漿菌，從兒童至成人，是導致非典型肺部感染的重要致病原之一。稀少的病例顯示黴漿菌會導致冷凝集疾病（如：冷凝集相關之自體免疫溶血性貧血）或是缺血性中風。本文報告一位 47 歲中年婦女，本身為糖尿病患者，臨床上出現發燒，咳嗽，流鼻水，以及胸部 X 光片上有一肺炎浸潤。經過 10 天的治療後，咳嗽持續惡化並合併再次發燒。因黴漿菌血清學抗體檢驗及冷凝集測試均呈現陽性，因此確立黴漿菌肺炎診斷。臨床上，更發生嚴重之溶血性貧血，黃膽，併發右側肢體無力，中風及急性腎衰竭。該病患在完整的抗生素治療，血漿置換，及血液透析治療下，病情獲得明顯改善，逐漸復原並能恢復其日常之行動功能。該病例說明黴漿菌肺炎可能涉及肺外多重器官的複雜疾病。多重肺外器官表現通常代表不良預後。在臨床診療上，即使黴漿菌感染很常見，也應該審慎評估及處理黴漿菌感染的肺外表現。*(胸腔醫學* ***2019; 34: 119-125)***

關鍵詞：黴漿菌肺炎，冷凝集，自體免疫溶血性貧血，缺血性中風，急性腎衰竭

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Legionnaires' Disease and Rhabdomyolysis: A Case Report and Literature Review

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Legionnaires' disease, an important cause of severe community-acquired pneumonia, is usually suspected when patients present with extrapulmonary features along with the diagnosis of pneumonia. We describe a patient diagnosed with Legionnaires' disease due to the presence of a constellation of rare, characteristic extrapulmonary features, including rhabdomyolysis, relative bradycardia, elevated liver function and troponin I levels, hyponatremia, and mild hypokalemia. Given that Legionnaires' disease has been reported as the most common condition that causes rhabdomyolysis in patients diagnosed with bacterial pneumonia, preemptive levofloxacin was administered intravenously before the rapid urinary antigen test had confirmed the diagnosis. The patient made a full recovery. Based on the presentation of this case, we concluded that rhabdomyolysis that is otherwise unexplained in patients diagnosed with pneumonia should increase a suspicion of Legionnaires' disease. ***(Thorac Med 2019; 34: 126-132)***

Key words: Legionnaires' disease, rhabdomyolysis, extrapulmonary features

Introduction

Since its identification after the major outbreak of Legionnaires' disease in 1976, Legionella bacteria have been found to account for approximately 1% to 14% of all adult cases of community-acquired pneumonia (CAP) that require hospitalization [1]. Without prompt diagnosis and antibiotic treatment, mortality from the disease can be as high as 80% [2]. Herein, we report a case presenting with several characteristic extrapulmonary features, particularly rhabdomyolysis, that indicated the diagnosis of Legionnaires' disease and highlight the importance of the early initiation of effective antibiotics even before the diagnosis is confirmed by laboratory tests.

Case Report

A 69-year-old man, a lifelong nonsmoker, presented with a 4-day duration of fever and flu-like symptoms, including rhinorrhea, mild coughing, and scanty phlegm production. He also had fallen several times because of dizziness and, as a result, sustained small, patchy ecchymoses on his head and right elbow. He denied chest tightness or pain, nausea, vomit-

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Table 1. Laboratory Testing Results on Admission

	Values	Reference Values
Leukocyte count ↑	10,180/μL	3,540-9,060/μL
Granulocytes ↑	87.4 %	41.2-74.7 %
C-reactive protein (CRP) ↑↑	>80.0 mg/L	<5 mg/L
Procalcitonin ↑↑	1.57 ng/mL	<0.046 ng/mL
[Na+] ↓	128 mEq/L	135-148 mEq/L
[K+] ↓	3.4 mEq/L	3.5-5.1 mEq/L
Aspartate transaminase ↑	81 IU/L	10-42 IU/L
Troponin I ↑	0.761 ng/mL	<0.16 ng/mL
Creatine phosphokinase (CPK) ↑↑↑	4,605	39-308 IU/L
Creatinine	1.1 mg/dL	0.7-1.2 mg/dL
Blood urea nitrogen	17.1 mg/dL	5.0-24.0 mg/dL
Urine dipstick RBC ↑	6-9 /HPF	0-5 /HPF

ing, diarrhea, abdominal discomfort, myalgias, arthralgias, or symptoms indicating infections in the central nervous or urinary systems. He denied any recent travel or contact with any ill persons. Although he may have recently had contact with pigeons, he never kept pets in his residence. His past medical history was remarkable only for diabetes mellitus, which had been controlled well with glimepiride.

On initial physical examination, he had a respiratory rate of 20 breaths per minute, temperature of 40.1°C (104.2°F), pulse rate of 93 beats per minute, blood pressure of 197/87 mmHg, and an oxygen saturation of 92% in ambient air. The remainder of his physical examination, including chest auscultation, was unremarkable.

The results of his laboratory testing on admission are shown in Table 1. His chest radiographs revealed a consolidative opacity of the right lower lung and bilateral gynecomastia, which could have been explained by his being mildly overweight (BMI=25.2 kg/m^2) (Figure 1, Panel A). The electrocardiography was unremarkable and echocardiography found no regional wall motion abnormalities.

In summary, the patient manifested pneumonia, rhabdomyolysis, hyponatremia, impaired liver function, and probable myocardial injury. Given that the patient's minor falls did not cause any significant muscular crashing injury, and that *Legionella pneumophila* is the most commonly cited pathogen that causes rhabdomyolysis in the setting of CAP, he was treated with preemptive, intravenous levofloxacin. Although his creatine phosphokinase (CPK) level increased to 10,112 U/L on the day of admission, his renal function remained within the normal range with aggressive, careful intravenous hydration. His urinary antigen test for Legionella came back positive on hospital day 2. On hospital day 3, azithromycin was added to the antibiotic regimen because of the patient's persistent high fevers; however, the fever subsided abruptly on hospital day 4. The patient made a full recovery and was discharged on day

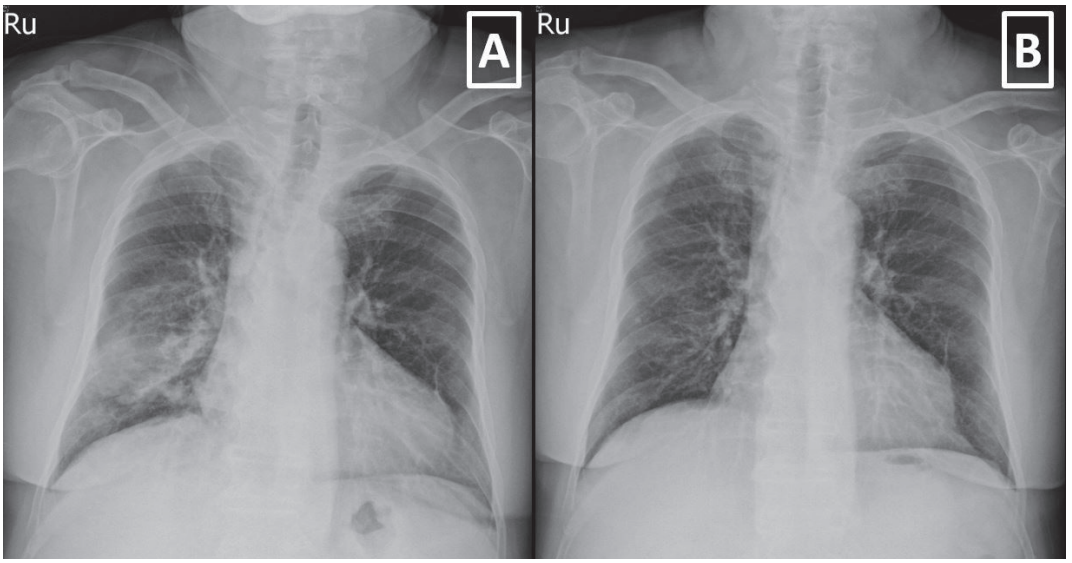

Fig. 1. Chest Radiographs. Panel A: Chest radiograph demonstrating a consolidative opacity of the right lower lung. Panel B: Resolution of the opacity after 4 weeks.

12 after admission. His follow-up chest radiograph at about 4 weeks after his initial presentation showed a complete resolution of the consolidative opacity of the right lower lung (Figure 1, Panel B).

Discussion

Rhabdomyolysis is a rare complication of CAP. An early retrospective study reported that *L. pneumophila* infection was responsible for 50% of patients who were diagnosed with both CAP and rhabdomyolysis [3]. Among those patients infected with *L. pneumophila*, males were much more likely than females to develop rhabdomyolysis. In addition, while *L. pneumophila* tends to cause disease in older patients, those who developed rhabdomyolysis were relatively young. The study also indicated that, in the setting of pulmonary infection, patients infected with *L. pneumophila* were found to have higher CPK levels than those infected with other pathogens. The mortality rate of patients with Legionnaires' disease was generally reported to be 15%; however, it rose to 40% in the study when both rhabdomyolysis and renal failure presented as complications of the disease.

A definitive diagnosis of rhabdomyolysis is made based on the presence of myoglobinuria. However, myoglobin released after muscle injury has a short half-life in the circulation because of its rapid excretion into the urine, making it a test with a low sensitivity value for the diagnosis of rhabdomyolysis. CPK levels are generally used as an indirect marker of muscle damage and correlate well with the severity of rhabdomyolysis [4]. A marked elevation of serum myoglobin that results in biopsy-proven renal failure has been reported at a CPK level as low as 519 IU/L [5].

The exact pathophysiology of muscle injury associated with Legionnaire's disease remains unknown. Two probable, hypothetical mechanisms that have been proposed are direct invasion and toxin generation of *L. pneumophila*. However, as researchers have not found any

evidence for the presence of *L. pneumophila* in muscle specimens from infected patients, muscle injury by the organism's endotoxin or exotoxin seems to be a more likely mechanism of rhabdomyolysis at present [6]. In addition, although sepsis accounted for 2% of cases of rhabdomyolysis [6], the case presented here demonstrates that rhabdomyolysis can develop in patients with Legionnaire's disease whose presentation does not fit the most recent definition of sepsis.

Complications associated with rhabdomyolysis include electrolyte abnormalities, acute kidney injury, hepatic dysfunction, compartment syndrome, and disseminated intravascular coagulation [7]. As a result of muscle cell lysis, hyperphosphatemia, hypocalcemia, hyperkalemia, and hyperuricemia can develop. Renal insufficiency or injury may also play a role in the development of abnormal electrolyte levels. While the mechanisms of renal injury associated with rhabdomyolysis are multifactorial, the main pathogenesis of the condition is the formation of myoglobin casts that occlude the distal tubules, causing acute tubular necrosis or acute tubulointerstitial nephritis [8]. However, in cases of Legionnaires' disease, renal dysfunction can arise without preceding rhabdomyolysis, suggesting that legionellosis-associated renal injury can be caused directly by *L. pneumophila* or indirectly by its other complications, such as sepsis [8].

Suspicion of the disease and effective antibiotic therapy (with a newer quinolone and/or newer macrolide) at an early stage of the disease course can significantly improve patient outcomes. However, the diagnosis of Legionnaires' disease is often a difficult one to make because of the nonspecific nature of the disease's clinical features. Legionella urinary antigen testing is a noninvasive, rapid, and commonly used tool for diagnosing Legionnaires' disease. Even so, given the low incidence of the disease, the test must be conducted only with high-risk patients who present with characteristic clinical features, particularly extrapulmonary ones. While we accentuated the presence of rhabdomyolysis in our case because of its rarity, it is of significant importance in the diagnosis of Legionnaires' disease to scrutinize the presence of other extrapulmonary features (Table 2) [9-14]. These features, compared to pulmonary symptoms, usually present in the early stage of the infection. Still, none of them, when presenting separately, is specific or diagnostic for Legionnaires' disease. Therefore, clinicians should not ascribe rhabdomyolysis, developing in the setting of CAP, to Legionnaires' disease, unless other causes of rhabdomyolysis, such as alcohol ingestion, trauma, statin intake, hypokalemia, hypernatremia, and hypophosphatemia [5-6], are excluded and/or the coexistence of other characteristic extrapulmonary features is also evident.

In conclusion, in reporting this case, we recommend preemptive antibiotic therapy against Legionella bacteria when patients present with a combination of pneumonia and unexplainable rhabdomyolysis.

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Table 2. Extrapulmonary Features of Legionnaires' Disease

Organ System	Clinical features	Laboratory features
Nervous system	• mental confusion • headache (40~48%) • lethargy, stupor, dizziness • impaired cognition • ataxia	• mild pleocytosis in the CSF
Head, eyes, ears, nose and throat	• vertigo	
Heart	• relative bradycardia or Faget's sign • QTc prolongation • high-grade AV block • "culture negative" perimyocarditis and endocarditis	• troponin ↑
Gastrointestional system	• watery diarrhea/loose stools (21~50%) • abdominal pain • nausea, vomiting, anorexia (8~49%)	
Hepatic manifestations	• hepatomegaly	• AST/ALT ↑ • ALK-P ↑ or ↓ • total bilirubin ↑
Kidney & urinary system	• glomerulitis • acute kidney injury	• microscopic hematuria • proteinuria • myoglobinuria • + legionella urinary antigen • BUN ↑ • creatinine ↑
Musculoskeletal system	• myalgia/arthralgia (20~40%) • rhabdomyolysis	• CPK ↑
Endocrine system	• SIADH	• hyponatremia
Serology & immune system	• disseminated intravascular coagulation	• WBC ↑ • severe relative lymphopenia (<10%) • lymphocytosis • platelet level ↓ • prothrombin Time (INR) ↑ • LDH ↑ (>400) • + direct and/or indirect fluorescent antibody • + charcoal yeast agar culture
Skin	• rash • Raynaud's phenomenon	
Others	• fever (usually >38.9°C [88~90%]; can be up to 40°C [20~62%]) • dehydration • rigors • chills (42~77%) • fatigue • shock/hypotension	• K+↓ • $[PO4]^{3-}$↓ • ferritin↑ (often >2 times of normal value) • ESR and/or CRP ↑ • procalcitonin ↑

CSF: cerebrospinal fluid; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALK-P: alkaline phosphatase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CPK: creatine phosphokinase; SIADH: syndrome of inappropriate antidiuretic hormone secretion; WBC: white blood cell count; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; INR: international normalize ratio; AV: atrioventricular; QTc: corrected QT interval

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退伍軍人病與橫紋肌溶解症：一個案例報告與文獻回顧

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退伍軍人病 (Legionnaires' disease) 是造成嚴重社區型肺炎 (community-acquired pneumonia) 的重要原因之一。患者經常只在被診斷肺炎時，同時表現出肺外特徵 (extrapulmonary features) 時才會被懷疑遭到此症感染。本文報告一位肺炎患者，因為同時出現一群少見且獨特之肺外特徵，包括橫紋肌溶解症 (rhabdomyolysis)、相對性心搏過緩 (relative bradycardia)、肝功能與肌鈣蛋白 (troponin I) 升高、低血鈉、輕微低血鉀，而被診斷患有退伍軍人病。基於過去文獻指出退伍軍人病為最常造成橫紋肌溶解症之細菌性肺炎，患者於快速尿液抗原確診退伍軍人病之前，便開始接受靜脈注射 levofloxacin 治療。患者最終亦完全康復。根據病人的臨床表現與本文中針對退與軍人病與橫紋肌溶解症之相關文獻回顧，我們建議當肺炎患者同時併有無法解釋之橫紋肌溶解症時，應該高度懷疑退伍軍人病的可能。*(胸腔醫學* ***2019; 34: 126-132****)*

關鍵詞：退伍軍人病，橫紋肌溶解症，肺外特徵

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Uterine Myoma ─ Induced Venal Thrombosis and Acute Pulmonary Thromboembolism: 2 Case Reports

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Acute pulmonary thromboembolism is a catastrophic disease that could lead to sudden death. The overall average annual incidence of acute pulmonary embolism is approximately 70 per 100,000, and that of venous thrombosis approximately 124 per 100,000. According to Virchow's theory, 3 conditions (stasis, vessel injury and hypercoagulopathy) are the major causes of pulmonary thromboembolism. Most cases (80–95%) of pulmonary embolism occur as a result of thrombus originating in the lower extremities due to stasis. Several predisposing factors, such as economic class syndrome, have been mentioned in previous reports. In rare cases, a huge uterine myoma can cause compression of the pelvic venous system leading to deep venous thrombosis and pulmonary embolism. The high prevalence of myoma (the most common benign neoplasm) among women of reproductive age indicates the need to evaluate the associated risk of deep venous thrombosis/pulmonary embolism secondary to uterine myoma in female patients with abnormal menstruation. This would help clinical physicians accurately determine the correct etiology of venous thromboembolism and avoid unnecessary thrombophilia workup. ***(Thorac Med 2019; 34: 133-138)***

Key words: myoma, pulmonary embolism

Introduction

Uterine leiomyomas are the most common pelvic tumor in women. They have a higher prevalence in reproductive-age women and typically present with symptoms of abnormal uterine bleeding and/or pelvic pain/pressure. As a uterine myoma grows, it compresses the surrounding structures (the myometrium and connective tissue), causing a compartment effect [1]. Sometimes, a uterine myoma leads to pelvic venous system stasis and causes formation of deep venous thrombosis (DVT). Subsequent pulmonary embolism (PE) is a rare but life-threatening complications [2]. Only a few reports have described this association in patients without other risk factors for venous thromboembolism (VTE) [2-6]. Thirty-one cases were found in a review of cases reported since 1992. The race of these patients was not reported in 19 cases, but 6 cases were reported as black, 5 as white and only 1 as Asian [5-6]. The lower

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number of myoma- induced thrombophilia cases amoug Asians may be related to the lower incidence rates of diagnosed venous thrombosis among Asians [7-8]. Therefore, we would like to report the cases of 2 Taiwanese patients with PE due to iliac venous thrombosis secondary to extrinsic compression by a uterine myoma.

Case Report

Case 1

A 45-year-old female patient had a significant history of uterine myoma once since June 2011. The myoma was intramural with an initial size of 4.4 x 3.9 cm. The tumor continued growing to 7.9 x 6.9 cm within 1 year (June, 2012) (Figure 1).

She visited our emergency department on 2013/01/02 due to progressive dyspnea lasting for months. She initially experienced dyspnea while walking or during activity. However, the symptoms worsened gradually, and she could not deal with her daily activities. Physical exam showed normal blood pressure at 114/51 mmHg, but tachypnea and tachycardia were also noted. Oxygen saturation was 89% under nasal cannula at 3L/min. Right leg mild swelling was also noticed. Bedside echocardiogram (ECG) showed right ventricular (RV) enlargement with left ventricular (LV) compression and D shape of the small LV, with a normal LV ejection fraction (61.6%).

Computed tomography (CT) pulmonary angiogram revealed diffuse hypodensities involving the branches of the bilateral pulmonary arteries, suggestive of PE. The standard CT angiography to evaluate DVT identified a right iliac vein obstruction caused by the intramural myoma (Figure 2).

The patient denied a pregnancy loss or a thrombosis event. No contributory family history was identified. Thrombophilia workup showed normal homocysteine, protein C, protein S, and antithrombin III levels. Lupus anticoagulant, and anticardiolipin were negative.

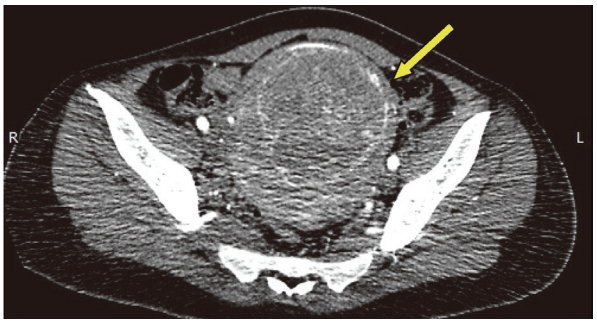

Fig. 1. Large intramural myoma from the first patient in June, 2012 (arrow)

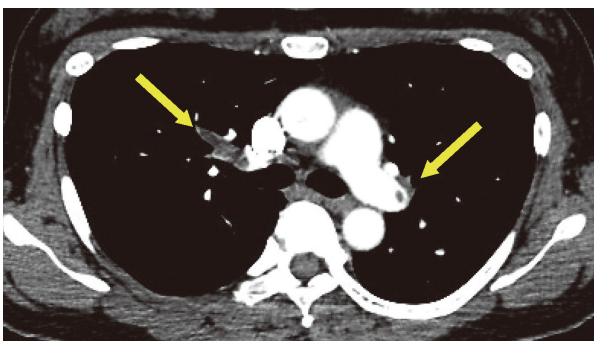

Fig. 2. Computed tomography pulmonary angiogram revealing mass filling defects in several bilateral pulmonary artery segments (arrows)

The patient was suffering from menorrhagia before our initial treatment, so we used short half-life intravenous heparin as initial therapy. During treatment, the patient's menstrual flow increased significantly and iron deficiency anemia was detected. An oxytocin IV pump was used to improve the massive menstrual flow. We also administered blood transfusion with packed RBC and provided oral iron supplements, but the anticoagulant was not withheld. As the menorrhagia had improved, we shifted heparin to subcutaneous enoxaparin and then oral anticoagulation therapy with warfarin.

Eight months later, laparotomy with myomectomy was performed. Warfarin was discontinued 1 week before operation and never used after that. The patient was followed up for 1 year after discontinuing anticoagulation therapy and there were no more thromboembolic events.

Case 2

A 45-year-old female patient had uterine myoma and followed up at a local medical clinic for years. She began suffering from left leg pain a few days before admission. On 12 June 2016, she suddenly collapsed at the metro station due to cardiac arrest. Cardiopulmonary resuscitation was performed when the emergency medical technician arrived. After 29 minutes' resuscitation, spontaneous circulation returned. ECG disclosed sinus tachycardia, a right bundle branch block and an S1Q3T3 pattern. The initial arterial blood gas data were pH: 6.716, $PaCO_2$: 99.5 mmHg, PaO_2: 73.8 mmHg, HCO_3: 12.5 mmol/L and SaO_2: 71.3, the D-Dimer level was more than 10,000 ng/mL.

CT revealed pulmonary arterial thromboembolism in the superior and inferior major branches of the right pulmonary artery and in an inferior branch of the left pulmonary artery (Figure 3). Two uterine myoma, 1 at least 13 x 9 cm and another about 3.5 cm, causing inferior vena cava (IVC) and right common iliac artery compression, were noted (Figure 4). We prescribed anticoagulant therapy with subcutaneous enoxaparin for 2 days, combined with rivaroxaban. The patient was transferred to the general ward and discharged with a good neurologic outcome after 9 days in the ICU. The lung ventilation/perfusion scan was normal at 1 year follow-up. We discontinued rivaroxaban therapy and there were no more thromboembolic events.

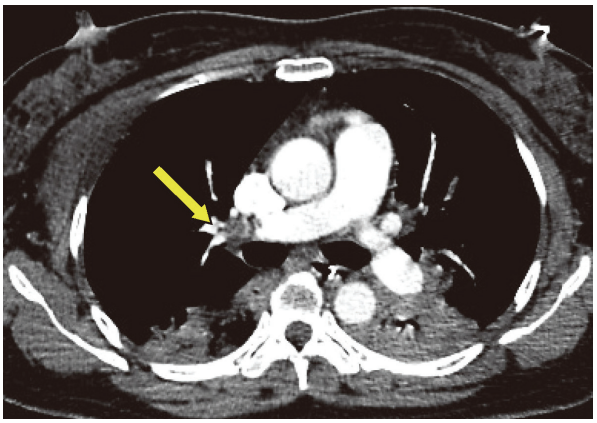

Fig. 3A. Pulmonary arterial thromboembolism in the superior and inferior major branches of the right pulmonary artery near the pulmonary trunk (arrows).

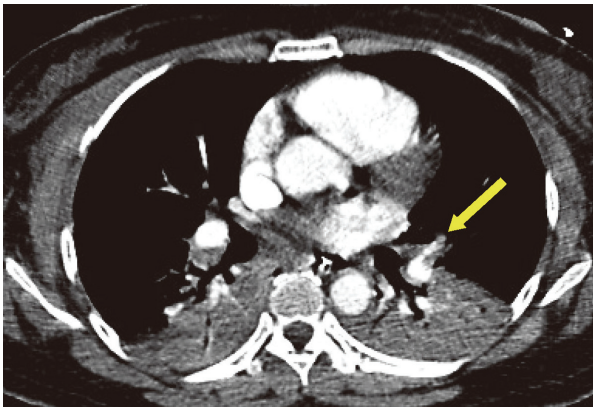

Fig. 3B. Pulmonary arterial thromboembolism in an inferior branch of the left pulmonary artery (arrow).

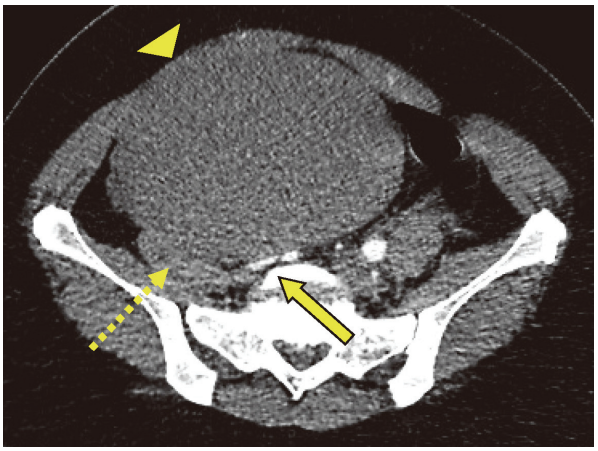

Fig. 4. Large uterine myoma (arrowhead) with inferior vena cava (dashed arrow) and right common iliac artery compression (arrow).

Discussion

Venous thrombosis, including DVT and PE, occurs with an incidence of approximately 1 per 1,000 annually in adult populations. The incidence rate increases rapidly after around age 45, and is slightly more prevalent among males. Major risk factors other than age include exogenous factors such as surgery, hospitalization, immobility, trauma, pregnancy and hormone use, and endogenous factors such as cancer, obesity, and inherited and acquired hypercoagulation disorders [7].

PE results from a venous blood clot that dislodges, travels through the venous system, and obstructs the pulmonary artery. This can cause acute RV failure and is life-threatening. The most common sources of blood clots (up to 85%) are DVT of the iliac and renal veins, and the IVC [8]. Early recognition and anticoagulation treatment can reduce complications and mortality [2].

Many reports of intra-peritoneal organ compression by uterine myoma have been published. The clinical presence and degree of symptoms depend on the myoma size, location and orientation. Larger myomas carry a higher risk of pelvic venous congestion with lower limbs edema and venous stasis/thrombosis formation. DVT occurs from ovarian vein to the pulmonary vein. The most frequent site of venous compression is the common iliac vein. Compressions on the left, right, and both pelvic sides have all been described, but the left side is more common than the right. In some cases, no specific DVT territory is reported at all [3-6].

In previously described cases, most patients survived after proper treatment such as anticoagulation, thrombolysis, IVC filter, or pulmonary embolectomy, and received hysterectomy or myomectomy as a final treatment. But before the operation, these patients should receive an anticoagulant to prevent another embolism. The duration of anticoagulant treatment has varied between 1 and 6 months. [3-5]. However, a major challenge in these cases is managing menorrhagia. Because of the anticoagulation therapy, the intensity of menstrual bleeding increases and usually causes anemia. Anemia related to menorrhagia can be controlled by blood transfusion, and oral or intravenous iron supplements until the surgery, which should be scheduled as soon as the clinical status is stable [3-5]. In the first case we presented, our treatment strategy was a short half--life anticoagulant with heparin as initial treatment due to the large amount of menstrual bleeding. Blood transfusion and an iron supplement were given. We also prescribed oxytocin to control the menstrual bleeding. The menorrhagia was under control after intervention so we shifted heparin to enoxaparin and warfarin.

In cases of uncontrolled menorrhagia or a high risk with anticoagulant use, there are some alternative treatments, such as vena cava filter, embolectomy or thrombectomy, which are all effective [3-6].

Hysterectomy was performed as the final treatment for most patients [3-6]. Since the mechanism of deep venous thrombosis and subsequent PE was stasis due to direct iliac vein compression, removal of the myoma was a definitive treatment to prevent further emboli. In a previous study [6], the prognosis was generally good, except for 2 cases, 1 suffered from massive PE and subsequently expired, and the other, who did not undergo myoma removal, had recurrent venous thrombosis and lower limbs symptoms.

Since the early diagnosis of myoma--related

thrombophilia is important, compression ultrasound could be considered for patients with a large myoma and at a high risk of VTE. Prophylactic anticoagulation might be of benefit for lowering the VTE risk until surgery, but clinicians should be aware of the bleeding risk [5].

There are some unanswered questions, such as the optimal treatment for PE, the true indication of vena cava filters, and the duration of anticoagulant use in the patients. More clinical experience is needed to answer these questions.

Conclusion

Thromboembolic disease due to venous stasis from external compression has been reported in the literature, but rarely is uterine myoma the cause. Early diagnosis could be difficult due to the limited case number. Physicians should keep in mind the rare complications of uterine myoma, prevent thromboembolism and initiate proper therapy as soon as possible based on the patient's condition.

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子宮肌瘤導致靜脈血栓形成及急性肺栓塞：病例報告

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急性肺栓塞症 (Pulmonary thromboembolism) 是一種嚴重的疾病，且可能導致猝死。急性肺栓塞症的平均每年發生率約為十萬分之七十，靜脈血栓形成的平均每年發生率約為十萬分之七十。根據 Virchow 的理論，三種臨床狀況：血液瘀滯 (stasis)、血管損傷 (vessel injury) 和高凝血狀態 (hypercoagulopathy) 是導致急性肺栓塞的主要原因。大多數病例 (80-95%) 的肺栓塞是源於下肢的靜脈血栓所造成的。根據以前的報告中曾經提到過幾種誘發因素 (predisposing factors)，如經濟艙症候群 (economic class syndrome)。偶有案例報導，巨大的子宮肌瘤可導致骨盆靜脈系統受壓迫，從而導致下肢靜脈血栓 (Deep venous thrombosis, DVT) 和急性肺栓塞症。由於子宮肌瘤常見於育齡婦女 (最常見的良性腫瘤)，女性患者若患有子宮肌瘤相關症狀如月經過多，應該評估繼發性下之靜脈血栓和急性肺栓塞的風險。這將有助於臨床醫生準確地診斷血栓的病因，避免不必要的檢查。*(胸腔醫學* ***2019; 34: 133-138****)*

關鍵詞：子宮肌瘤，急性肺栓塞

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