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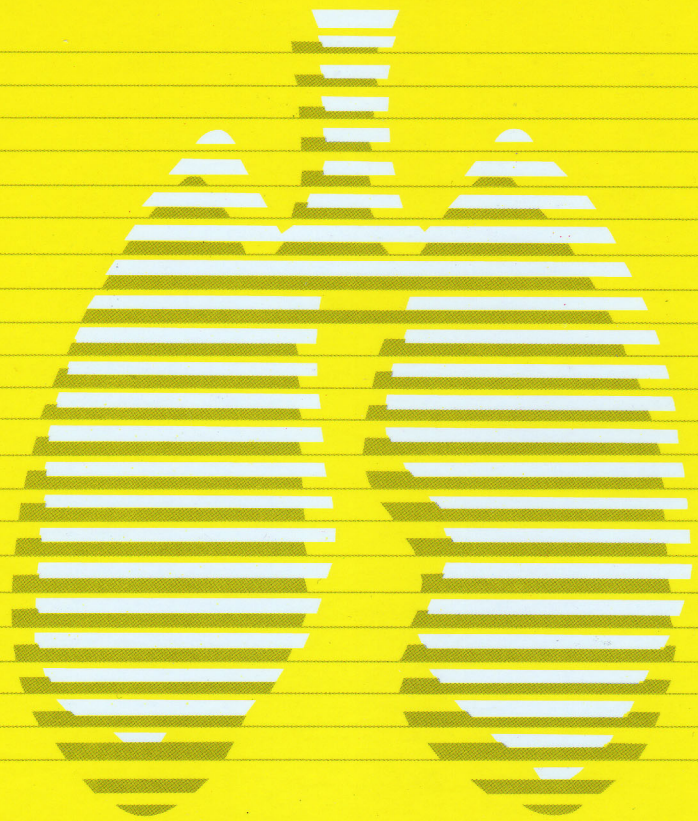

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Orginial Articles

Case Reports

“Non-Dipping” Blood Pressure and Excessive Daytime Sleepiness in Severe Obstructive Sleep Apnea

Che-Chia Chang*, Li-Pang Chuang*,**, Yu-Sheng Lin**,***, Shih-Wei Lin*,**, Chung-Shu Lee*, Chih-Hao Chang*, Ning-Hung Chen*,**

Background: Non-dipping blood pressure and obstructive sleep apnea both carry an increased risk of cardiovascular events and mortality. The relationship between non-dipping blood pressure and obstructive sleep apnea has been noted. However, data on the prevalence of sleep apnea with non-dipping hypertension and the relationship with excessive daytime sleepiness are limited.

Objective: The purpose of the present study was to determine the prevalence of non-dipping blood pressure and evaluate the relationship with excessive daytime sleepiness.

Patients and Methods: We prospectively enrolled adult patients with habitual snoring who visited our sleep clinics from November 2010 to May 2013. Polysomnography and 24-hour ambulatory blood pressure monitoring (ABPM) were used. Excessive daytime sleepiness was evaluated. The prevalence of non-dipping blood pressure and the relationship with excessive daytime sleepiness were evaluated.

Results: Thirty patients were dippers (57%) and 23 (43%) were non-dippers. Non-dippers had lower nighttime blood pressure and more excessive daytime sleepiness (Epworth sleepiness scale (ESS) ≥10) than dippers (p = 0.045). ESS was significantly negatively correlated with dipping of systolic and diastolic blood pressure and mean arterial pressure, R = -0.313, -0.304, -0.302, respectively (p < 0.05). Multivariate linear regression models for associations involving systolic blood pressure dipping showed that ESS was the only independent predictor of systolic blood pressure dipping [β = -0.005, p = 0.022, R^2 = 0.099, 95% confidence interval (CI) of β = -0.009-0.000] in stepwise linear regression analyses.

Conclusions: High prevalence of non-dippers was noted in severe obstructive sleep apnea patients. Non-dippers experienced more excessive daytime sleepiness. ESS was an independent predictor of dipping values. ABPM may play an important role in these high cardiovascular risk groups. ***(Thorac Med 2015; 30: 261-270)***

Key words: nocturnal blood pressure dipping, dipper, non-dipper, excessive daytime sleepiness, obstructive sleep apnea, hypertension, ambulatory blood pressure monitoring

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Introduction

Blood pressure (BP) falls 10-20% during sleep compared to awake time in normal subjects [1]. Those with an attenuated decline in nocturnal BP, with less than 10% nighttime BP decrease, are defined as "non-dippers" [2]. Hypertensive patients with non-dipping have been reported to have a worse cardiovascular prognosis and increased target organ damage, including left ventricular hypertrophy, microalbuminuria, ischemic stroke, and cardiovascular death [3-8].

Sleep-disordered breathing (SDB) has been associated with hypertension and cardiovascular disease [9-10]. High prevalence of non-dipping BP was noted in obstructive sleep apnea (OSA) patients. The relationship between severity of SDB and nocturnal non-dipping [11-12] and the dose-response causal role of SDB in systolic non-dipping has been reported [13]. Most studies on nocturnal non-dipping BP and SDB have had limited cases. The reason for the tendency of sleep apnea to become nighttime BP blunting is still unclear. Poor sleep quality is known to be associated with nocturnal BP blunting in normal adults [14], but the relationship cannot be well established in OSA patients [15].

Excessive daytime sleepiness (EDS) is an important clinical feature of SDB patients that may result from sleep fragmentation [16] and may lead to less daytime activity. Both are possible reasons for non-dipping BP. However, limited reports have discussed the relationship between EDS and non-dipping BP until now.

The purpose of this study was to determine the prevalence of non-dippers and to analyze the relationship between EDS and non-dipping BP in OSA patients with untreated hypertension.

Materials and Methods

Subjects

Each patient provided their informed consent to participate in the protocol, which was approved by the Research and Ethics Committee of Chang Gung Memorial Hospital in Taiwan. We prospectively included adult patients that visited the sleep clinic at Chung Gung Memorial Hospital between November 2010 and May 2013 due to habitual snoring. Patients had to have a history of hypertension without regular treatment confirmed by office BP readings obtained in the clinic (>140/90 mmHg). Patients then underwent both 24-hour ambulatory BP monitoring (ABPM) for hypertension and overnight polysomnography (PSG). Patients with a history of diabetes mellitus (DM), or those taking sleep apnea or anti-hypertensive therapy were excluded. Those with fasting blood sugar >126 mg/dl, or AHI <30 were also excluded.

Sleep Evaluation

All patients underwent conventional overnight PSG (Embla N7000; Medcare, Reykjavik, Iceland) in a sleep laboratory. Measures included airflow, chest and abdominal wall movements, snoring (by neck microphone), pulse oxyhemoglobin saturation (by pulse oximeter), electro-encephalogram channels (C3/A2 and C4/A1), bilateral electro-oculogram, chin and bilateral anterior tibial electromyograms, and electrocardiogram.

According to the recommendations of the American Academy of Sleep Medicine (2005) [17], cessation of airflow for more than 10 s was defined as an apnea. More than 30% reduction in airflow for ≥10 s and ≥4% oxygen desaturation or an arousal was defined as hypopnea. A desaturation episode was defined as a drop

of ≥4% in SpO_2 induced by an apnea-hypopnea event. The apnea-hypopnea index (AHI) was defined as apnea and hypopnea events per hour during sleep time. The desaturation index (DI) was defined as the number of desaturation episodes per hour during sleep time. Daytime sleepiness was assessed using the Epworth sleepiness scale (ESS) [18]; an ESS of more than 10 was considered as EDS.

Twenty-four-hour Ambulatory Blood Pressure Monitoring

Twenty-four-hour ambulatory BP was evaluated using a tonometric radial arterial wave capture wrist-bound BP measurement device (BPro®) [19]. Sphygmomanometer readings were calibrated with an arm-based oscillometric monitor according to the European Society of Hypertension (ESH) protocol [20] once before it was set on each patient. BP was measured every 15 minutes for 24 hours. Day time was defined as 6 AM to 24 PM and night time as 0 AM to 6 AM.

Normal day time and night time BP was considered to be <135/85 mmHg and <120/70 mmHg [21]. Patients were divided into dippers and non-dippers, based on more than 10% nocturnal systolic BP reduction.

Statistical analysis

Continuous variables were expressed as mean (± standard deviation), and categorical variables were shown as number (percentage). Various variables were compared between dippers and non-dippers using independent *t* tests for continuous variables or the chi-square test for categorical variables. The Pearson correlation test was used for evaluating the relationship between dipping values and selected variables. The linear relationship between ESS and BP dipping values was calculated. Stepwise linear regression was used to evaluate the relationship between dipping values and possible confounding values. SPSS for Windows version 17.0 was used for all data analysis. *P* values less than 0.05 were considered statistically significant.

Results

Eighty-five patients that visited the sleep clinics due to habitual snoring and that had hypertension were included. They were referred to the sleep study and 24-hr ABPM. After reviewing the medical records, 6 patients were excluded due to their undergoing antihypertensive agent(s) treatment. Sixteen patients were excluded because they did not complete the 24-hour ABPM (they did the ABPM only at night). Four patients had insufficient BP data on ABPM, according to the guideline [21-22], and were also excluded. Four patients with only habitual snoring (AHI<5) or mild to moderate OSA (AHI<30) were excluded. In the end, 53 patients were enrolled for analysis, and all had fasting sugar less than 126 mg/dl.

The subjects were mostly male, with only 4 females; their mean age was 43.9±9.4 years. The mean body mass index (BMI) in our population was 31.6±4.3 kg/m^2. The mean office systolic and diastolic BP (SBP and DBP) were 146.9±11.4 and 96±8.2 mmHg. According to the sleep study, the AHI was 68.5±24.6. Two-thirds of patients (n = 35) had EDS with an ESS ≥10 (Table 1).

Thirty patients were dippers (57%) and 23 (43%) had blunting nocturnal blood pressure as non-dippers. There was no difference in age, BMI, AHI, desaturation index (DI), and ESS between the dippers and non-dippers (Table 2). However, non-dippers had more EDS (ESS

Table 1. Subject Characteristics

Number	53
Age-years	43.9 (9.4)
Male-no. (%)	49 (92%)
BMI	31.6 (4.3)
Office blood pressure - mmHg	
Systolic blood pressure (SBP)	146.9 (11.4)
Diastolic blood pressure (DBP)	96.0 (8.2)
Apnea hypopnea index - events/h	68.5 (24.6)
Desaturation index - events/h	70.1 (25.6)
Arousal index - events/h	31.8 (26.1)
Lowest SaO_2 %	69.6 (12.8)
Mean SaO_2	85.6 (5.3)
Epworth Sleepiness Scale	12.8 (4.4)
≥10, N (%)	36 (68%)

≥10) than dippers ($p = 0.045$). Non-dippers also had higher night time BP (both systolic and diastolic) than dippers ($p = 0.016$ for SBP, $p = 0.007$ for DBP). The daytime BP and 24-hr BP of the 2 groups showed no difference. There was also no significant difference in sleep efficiency and sleep architecture (sleep stage percentage) between dippers and non-dippers (Table 3).

In addition to dividing patients into dippers and non-dippers, we also evaluated the relationship among age, gender, BMI, ESS, AHI, DI, lowest SaO_2, sleep efficiency, sleep stage, BP and continuous measures of dipping *[(daytime blood pressure-nighttime blood pressure)/ daytime blood pressure]*. ESS was significantly

Table 2. Characteristics of Hypertensive Obstructive Sleep Apnea Patients between Dippers and Non-Dippers

	Dippers	Non-Dippers	*p* value
Number (%)	30 (56.6%)	23 (43.4%)	
Age	43.2 (10.2)	44.7 (8.4)	0.567
Male (%)	28 (93%)	21 (91%)	0.782
BMI	31.4 (4.2)	31.9 (4.7)	0.707
Apnea hypopnea index	70.9 (23.0)	69.5 (23.6)	0.830
Desaturation index	71.6 (26.4)	71.2 (22.5)	0.948
Arousal index	33.5 (26.8)	29.5 (25.6)	0.580
Lowest SaO_2 %	70.3 (14.4)	68.8 (10.7)	0.669
Epworth Sleepiness Scale	11.9 (4.3)	14.0 (4.4)	0.102
≥10, No. (%)	17 (57%)	19 (83%)	0.045
Office BP mmHg			
SBP	148.5 (12.3)	144.8 (10.1)	0.241
DBP	94.3 (9.4)	97.7 (5.9)	0.145
ABPM mmHg			
24-hr SBP	136.9 (19.4)	140.0 (17.5)	0.549
24-hr DBP	92.5 (15.9)	95.3 (11.2)	0.488
Day time SBP	144.5 (19.9)	141.4 (17.9)	0.563
Day time DBP	97.5 (16.4)	96.3 (12.0)	0.762
Night time SBP	123.5 (17.8)	135.7 (17.6)	0.017
Night time DBP	83.4 (14.9)	92.4 (10.6)	0.017
Dipping, SBP %	14.4	4.0	<0.001

BMI: Body mass index, BP: Blood pressure SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 3. Sleep Efficiency and Sleep Architecture between Dippers and Non-Dippers

	Dippers	Non-Dippers	*p* Value
Sleep efficiency, %	69.2 (13.8)	73.5 (14.4)	0.265
Sleep stage			
Stage 1 %	56.5 (20.7)	52.2 (21.3)	0.933
Stage 2 %	25.5 (16.0)	30.2 (16.5)	0.305
Stage 3 %	3.9 (5.8)	3.6 (6.4)	0.845
Stage REM %	14.0 (7.5)	14.0 (7.8)	0.980

REM: rapid eye movement

Table 4. Pearson's Correlations between Blood Pressure Dipping Value and Patients' Clinical Data

	SBP Dipping	DBP Dipping	MAP Dipping
Age	-0.096	-0.100	-0.099
Gender	-0.058	-0.048	-0.052
BMI	-0.151	-0.140	-0.145
Apnea hypopnea index	0.009	0.028	0.019
Desaturation index	0.063	0.101	0.084
Arousal index	0.102	0.102	0.101
Lowest SaO_2	-0.010	0.010	0.002
Sleep efficiency, %	-0.162	-0.147	-0.154
Sleep stage			
Stage 1 %	0.132	0.133	0.133
Stage 2 %	-0.224	-0.227	-0.227
Stage 3 %	0.006	0.034	0.022
Stage REM %	0.113	0.095	0.103
Epworth Sleepiness Scale	-0.314*	-0.303*	-0.309*
Office SBP	0.027	-0.004	0.009
Office DBP	-0.161	-0.101	-0.185
24-hr SBP	-0.107	-0.115	-0.112
24-hr DBP	-0.055	-0.076	-0.067

*: $p < 0.05$

SBP: systolic blood pressure, DBP: diastolic blood pressure

negatively correlated with BP dipping in terms of SBP, DBP, and mean arterial pressure, R = -0.313, -0.304, -0.302, respectively, (all $p < 0.05$) (Table 4). The significant linear relationship between ESS and all kinds of dipping values are presented in Figure 1.

We used multivariate linear regression models for associations involving SBP dipping. Age, gender, BMI, AHI, arousal index, DI, lowest nighttime saturation, ESS, office BP, and 24-hour BP were all included in the analysis for adjustment of possible confounding factors. ESS was the only independent predictor of SBP dipping [$\beta = -0.005$, $p = 0.022$, $R^2 = 0.099$, 95%

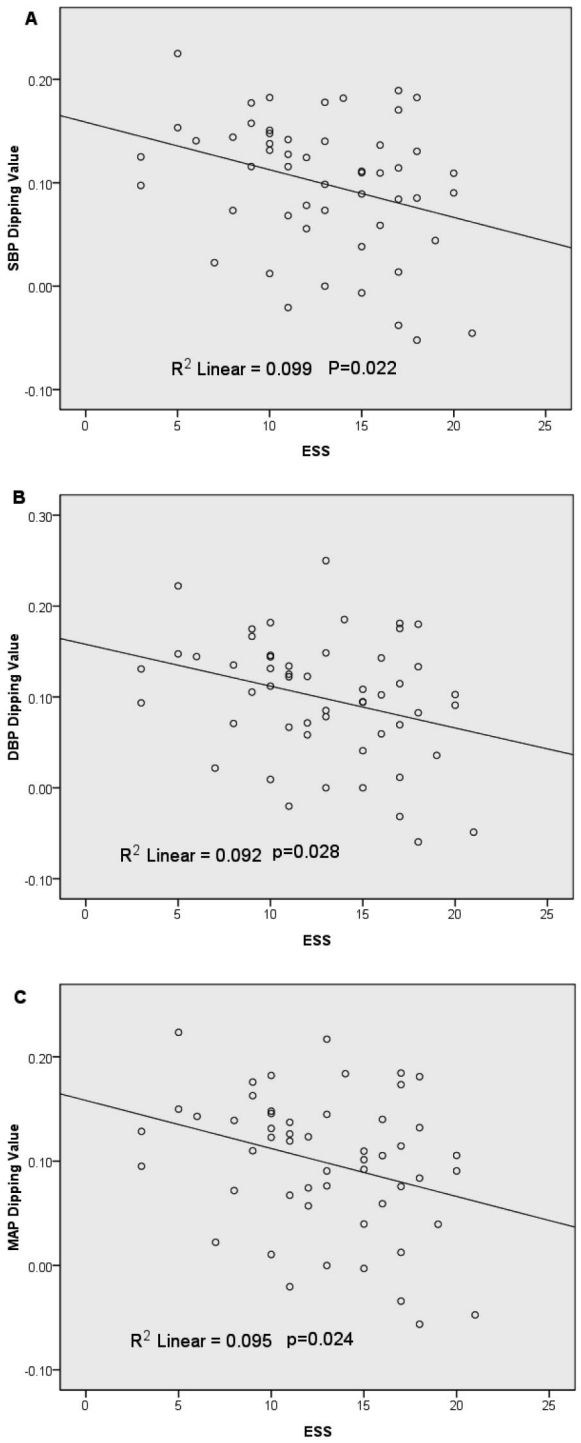

Fig. 1. Linear Relationships between Dipping Value and ESS. Significantly positive correlations are shown between ESS and (A) Systolic blood pressure dipping, (B) Diastolic blood pressure dipping, (C) Mean arterial pressure dipping.

confidence interval (CI) of β = -0.009-0.000] in stepwise linear regression analysis (Table 5).

Discussion

In our population, 43% of middle-age untreated hypertensive patients with severe OSA had blunted nocturnal BP. The non-dippers had more daytime sleepiness and higher BP at night. Our study is the first to describe the prevalence and characteristics of non-dipping BP in sleep apnea subjects in Taiwan. We also found a possible association between BP dipping and EDS, which has not been described before.

The Ohasama study in Japan, a cohort study on the relationship between nocturnal BP decline and mortality, found 16% of people in the general population had a loss of nocturnal BP dipping [7]. In the Wisconsin Sleep Cohort Study, 13% of non-dippers were patients without OSA [13]. Our study supported the higher prevalence of non-dipping BP in patients with both hypertension and OSA. Previous studies suggested a 30% to 50% rate of non-dippers in normo/hypertensive sleep apnea patients [11,13]. More than 80% of OSA patients had a reduction of nocturnal BP in studies that had a greater variety of sleep apnea severity than ours [15]. Other confounding factors for non-dipping BP, including ethnicity and psychosocial factors, should also be considered [23-24]. Most studies on SDB and non-dipping BP have had a limited sample size, so further work in this field is needed.

Sleep apnea severity has been reported to be associated with a non-dipping status [9,12], and the incidence of new non-dipping BP development has been associated with the severity of sleep apnea [13]. In our population, the AHI did not differ between the dippers and non-

Table 5. Stepwise Multivariate Linear Regression Models for SBP Dipping Values

Variables in the regression model		R_2	β	95% CI of β	*P*-value
For SBP dipping	ESS	0.099	-0.005	-0.009-0.000	0.022

SBP: systolic blood pressure, ESS: Epworth Sleepiness Scale

dippers, and was not correlated with dipping values. However, previous studies that found non-dipping was associated with sleep apnea severity had compared subjects with different degrees of sleep apnea. Our subjects all had severe sleep apnea, which may limit the finding of a relationship between OSA severity and a non-dipping BP condition.

In this study, we found EDS occurred more frequently in non-dippers. A correlation between ESS and SBP, and DBP and mean arterial pressure dipping values was also found. Limited studies have explored the relationship between EDS and a non-dipping pattern. Lloberes *et al* reported that only a diastolic non-dipping pattern occurred more frequently in people with EDS [25]. EDS may be related to sleep fragmentation and nocturnal hypoxemia [16], but there are many factors that could influence EDS, such as age, mood, sleep habits, diabetes and obesity [26]. We then attempted to adjust for confounding factors. DM patients were already excluded, and there was no difference in age, BMI, arousal index, desaturation index and lowest saturation during sleep between the dippers and non-dippers in our study. After adjusting for these factors, ESS was still a significant predictor of dipping values. It should be considered that patients with EDS may be less active during daytime, resulting in an attenuation of the difference in BP from day to night. The association between EDS and non-dipping BP may partially explain the higher prevalence of non-dippers among apnea patients. Heightened sympathetic nervous system activity was noted in both sleep apnea subjects and non-dippers [27-28]. This may be a causal link in the relationship between dipping and OSA, although this is not yet fully established. Therefore, the increasing incidence of non-dippers among OSA subjects may be due to multiple factors that require further study.

There were some limitation in our study. First, the study included only those with severe OSA; therefore, the results cannot be extended to mild or moderate sleep apnea. Second, we used tonometric ABPM instead of a conventional arm-cuff device, so there may be more missing data. The validation data for tonometric ABPM is limited, so further study may be needed to establish its reliability. However, compared with the conventional arm-cuff device, which may interrupt sleep [29], tonometric ABPM would have less influence on sleep.

Conclusion

In conclusion, patients with severe OSA and untreated hypertension had a high prevalence of loss of nocturnal BP reduction. The non-dippers also experienced more daytime sleepiness. EDS may play a role in non-dipping BP in sleep apnea patients. Since non-dippers and OSA patients both have a higher risk of cardiovascular events, ABPM should consider perform regularly to figuring out these high risk patients, especially patients with EDS.

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嚴重阻塞性睡眠呼吸中止症病人日間嗜睡以及夜間血壓下降幅度減少之關係探討

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前言：一般人夜間血壓會比日間降低至少 10%，夜間血壓下降幅度減少為心血管疾病的危險因子。阻塞性睡眠呼吸呼吸中止症也被廣泛認為是心血管疾病的危險因子。而夜間血壓降低幅度減少也有研究顯示與阻塞性睡眠呼吸中止症相關。然而針對阻塞性睡眠呼吸中止症病人中夜間血壓下降幅度減少的盛行率及可能發生原因之探討目前文獻資料仍然相當有限。而日間嗜睡為阻塞性睡眠呼吸中止症之常見表徵，但是與夜間血壓下降幅度減少之關係仍未被討論。因此本研究及針對阻塞性睡眠呼吸中止症病人日間嗜睡以及夜間血壓降低幅度減少之關係作探討。

方法：本研究為前瞻性研究，收集 2010 年 11 月至 2013 年 5 月間，因打呼至睡眠門診求診之高血壓之病人。病人皆安排接受完整睡眠檢查以及 24 小時活動式血壓計測量。排除高血糖及已接受高血壓治療之病人。探討病人夜間血壓降低幅度減少之盛行率，以及與日間嗜睡狀況之關係。

結果：共有 53 位高血壓之重度阻塞性睡眠呼吸中止症之患者加入研究。其中 23 人為夜間血壓降幅減少之病人，佔全體 43%。夜間血壓降幅減少與性別、體重、無呼吸－低呼吸指數（AHI）、夜間血氧狀態、日間血壓狀態無關。夜間血壓降幅減少之病人有較低的夜間血壓（p 值 =0.017）以及較高的比例有日間嗜睡的狀態（嗜睡問卷分數大於或等於 10 分）（p 值 =0.045）。夜間血壓降低之幅度也與嗜睡問卷分數呈線性負相關。經過回歸分析嗜睡問卷分數為夜間血壓降低之幅度之獨立的預測因子（p 值 = 0.022, R^2 = 0.099, 95 信賴區間 =-0.009-0.000）。

結論：夜間血壓降低幅度減少之情形於嚴重阻塞型呼吸中止症之病人中有較高的發生率。而這些病人有較多日間嗜睡之情形，日間嗜睡之問卷分數為夜間血壓降幅之獨立因子。於這些有較高之心血管風險之病人，24 小時活動式血壓計的血壓測量有重要臨床意義。*(胸腔醫學* ***2015; 30: 261-270)***

關鍵詞：夜間血壓下降，夜間血壓下降幅度正常者，夜間血壓下降幅度減少者，日間嗜睡，睡眠呼吸中止症，高血壓，動態血壓測量

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APACHE Score Used in Predicting Weaning Outcomes in an Intermediate Respiratory Care Center

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Background: This study explores the outcomes of patients with prolonged mechanical ventilation (PMV) treated in an intermediate respiratory care center (RCC), and assesses the effectiveness of the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system in predicting outcomes in this group of difficult-to-wean patients.

Methods: A prospective observational study was used to recruit consecutive PMV patients in an RCC. Demographics, patient source, time to weaning, and outcomes of weaning attempts were recorded. The APACHE II score was obtained within 24 hours after arriving at the RCC. Outcomes measured were successful weaning, mortality, transfer back to the intensive care unit, and transfer to the respiratory care ward.

Results: In all, 508 consecutive patients from among the 6820 ventilator patients screened were recruited. The mean duration of mechanical ventilation before entering the RCC was 31.1±18. 6 days. The mean APACHE II score was 19.3±6.2 on arrival at the RCC. The mean duration of RCC stay was 21.3±13.4 days. Of the recruited patients, 55.5% were successfully weaned, 20.3% failed to wean, 19.7% died, and 4.5% were transferred back to intensive care units; 40% of the successfully weaned patients were weaned by day 10. The APACHE II score was negatively correlated with successful weaning, and positively correlated with mortality, but bore no relationship with the duration of RCC stay.

Conclusion: The APACHE II score is moderately reliable in predicting outcomes of patients in an RCC. Our results offered some information that could be used in reforming services for PMV patients. ***(Thorac Med 2015; 30: 271-279)***

Key words: ventilator weaning, APACHE, intermediate care facilities, respiratory care center, long-term care

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Introduction

With the advances in medical therapy over the last few decades, critically ill patients are now more likely to survive the early stages of their illness. However, accompanying the improved survival rate and longevity of these patients is the challenge of prolonged mechanical ventilation (PMV). Medical costs related to PMV are substantial.

In order to minimize the medical costs without compromising the rate of successful weaning, specialized respiratory care units or so-called intermediate respiratory care units were set up in different countries. Several studies have found that patients treated in these units have had positive outcomes [1-7]. In Taiwan, an integrated delivery system (IDS) was initiated as part of the National Health Insurance Bureau (NHIB) program in Taiwan in 1998, to test the feasibility of setting up intermediate care units for post-acute care and weaning of PMV patients [8-10].

Scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II, have been designed to make quantitative statements regarding the severity of a disease and its prognosis, and have been well-established among intensive care unit (ICU) patients. Attempts at predicting the outcomes of PMV patients treated in intermediate care units and correlating disease severity by scoring systems are growing [11-12]. A higher APACHE II score generally is correlated with a higher likelihood of weaning failure and mortality with variable predictive values. Evolution of the scoring system is aimed at better prediction and calibration, with less lead time bias and broader disease subsets.

The purposes of this study are to explore the outcomes of patients requiring PMV treated in an intermediate respiratory care center (RCC), and to assess the reliability of the APACHE II scoring system in predicting outcomes in this group of difficult-to-wean patients.

Methods

The study protocol was approved by the Institutional Review Board of our hospital and the project was granted by the study hospital and National Science Council, Taiwan. As a part of an ongoing IDS, this study followed the protocols for weaning of patients on long-term ventilation in the study area [8]. Informed consents were obtained before the patients were transferred to the RCC.

There are 4 kinds of ICU accommodating severely ill patients: Respiratory ICU, treating patients mainly suffering from pulmonary diseases; Medical ICU, treating patients suffering from cardiovascular and other diseases; Neurologic ICU, treating mainly stroke-related patients and a lesser number of patients with neuromuscular diseases; other ICU, treating trauma patients along with surgical patients.

The inclusion and exclusion criteria for patients to be transferred to the RCC in this study were adopted from the national protocols of the IDS for ventilator-associated individuals in Taiwan. The inclusion criteria for RCC admission were: age greater than 17 years with prolonged mechanical ventilation of more than 21 days (>6 h/d ventilator use), and the physician's judgment that the patient would benefit from RCC treatment. The exclusion criteria for RCC admission were: hemodynamic instability requiring vasopressors, severe arrhythmias, massive gastrointestinal bleeding, plans for a second major surgery, and severe oxygenation failure

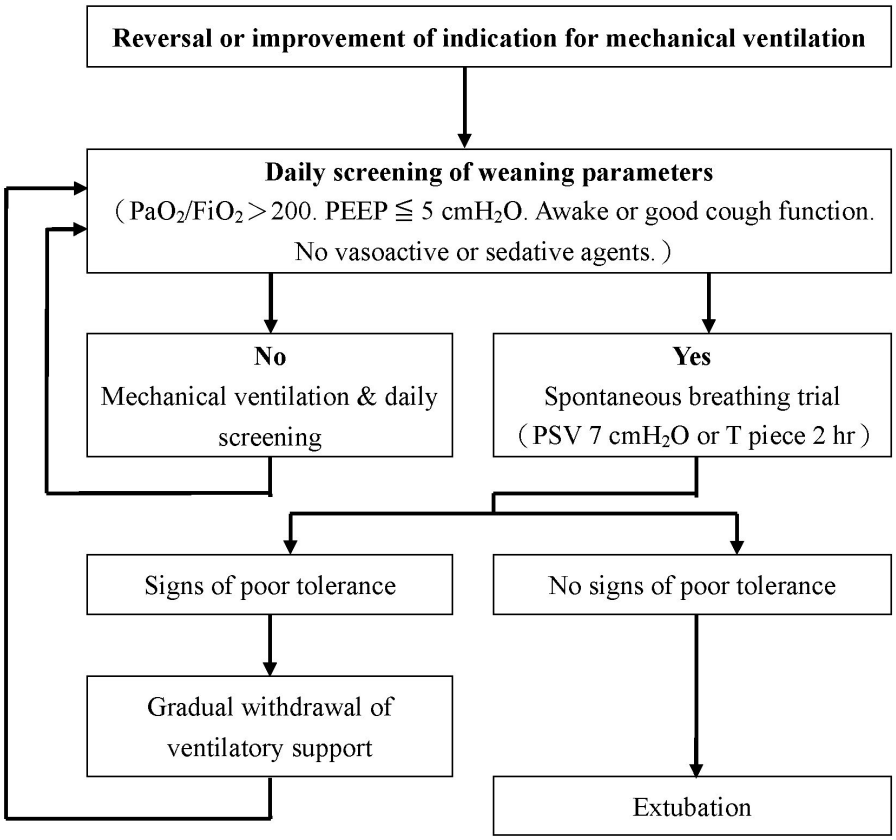

Fig. 1. Ventilator weaning protocol in the intermediate respiratory care center

requiring a fractional concentration of inspired oxygen (FiO_2) greater than 60% or positive end-expiratory pressure (PEEP) greater than 10 cmH_2O. The exclusion criteria should be re-evaluated every 7 days. Patients with or without tracheostomy would be eligible for transfer to the RCC if PMV was over 21 days. The criteria for transfer back to the ICU included acute myocardial infarction and a requirement of major surgery. Those patients transferred back to the ICU should be re-evaluated every 7 days for transfer back to the RCC. Successful weaning was defined as at least 3 days of complete ventilator independence. Patients who required partial support, such as nocturnal ventilation, were recorded as failure to wean. The maximum allowable RCC stay was 42 days.

A weaning protocol was used in the RCC in this study (Figure 1). The primary weaning method was pressure-support ventilation along with the use of a T-piece [13-18]. The weaning protocol used was generally agreed to by the chest medicine specialists involved in the IDS.

The following data were gathered prospectively for the consecutive post-ICU ventilator-dependent patients admitted from February 2005 through October 2006: demographic data, physiologic data on admission to the RCC, time to wean, outcome of weaning attempts, and discharge destinations from the RCC, all obtained from the patient database. The APACHE II score was obtained within 24 hours after arriv-

ing in the RCC [19].

Patients were categorized into 4 groups according to weaning outcomes. The successfully weaned group was defined as having at least 3 days of complete ventilator independence. The mortality group included patients who died in the RCC. The ICU group included patients who were transferred back to the ICU. Once a patient was transferred back to the ICU due to medical needs and then transferred to the RCC again after re-evaluations, they continued to use the maximal duration of RCC stay, so these patients would count only once. The respiratory care ward (RCW) group included patients who failed to wean in the RCC and were transferred to the RCW. Once a patient was transferred to the RCW, that patient was no longer eligible to be transferred back to the RCC.

Statistics

Demographics, APACHE II scores obtained within 24 hours after arriving in the RCC, duration prior to transfer, length of RCC stay in days, and patient source were compared between the groups of outcomes using the Kruskal Wallis rank test. Cutoff values for quartiles of APACHE II scores of all the patients included in the study were explored.

The cutoff value of APACHE II scores of the successful weaning/mortality groups obtained within 24 hours after arriving at the RCC were analyzed using receiver operating characteristic (ROC) curves, and the area under the curve. A value of 0.5 under the ROC curve indicated that the difference was no better than simply by chance, while a value of 1.0 indicated a perfect prediction.

All analyses were performed using the Statistical Package for the Social Sciences 10.0 for Windows (SPSS, Chicago, IL). Measured data were expressed as means ± SDs. A P value <0.05 was considered statistically significant.

Results

During the study period, 6,820 patients were treated with mechanical ventilation due to all causes in the study hospital. Among them, 508 (7.5%) PMV patients were transferred to the RCC consecutively, in accordance with the IDS protocols, and were thus enrolled in the study. The mean age was 71.0±13.5 (20-99) years, and 53% were men. The duration of PMV prior to transfer to the RCC was 31.0±18.6 days (Table 1).

The overall survival rate of the 508 recruited patients in the RCC was 80.3%. Patients who died had a higher APACHE II score and a shorter length of stay in the RCC. Patients who were transferred from the respiratory ICU had less chance of being successfully weaned (Table 1).

APACHE II scores were negatively correlated with successful weaning and positively correlated with mortality (Table 2). All the attempted multivariate analyses indicated that patients who were transferred from the neurological ICU or patients with lower APACHE II scores tended to have a higher likelihood of successful weaning. ROC curves were plotted by APACHE II scores versus successful weaning and mortality. The area under the curve was 0.622 for successful weaning and 0.703 for patients who died.

After being transferred to the RCC, 30% of patients stayed less than 10 days. Among those patients who were successfully weaned, 40% were weaned within 10 days and 70% by 18 days after transfer to the RCC. One-fourth of the mortalities was encountered within 10 days

Table 1. Characteristics According to Outcomes at RCC Discharge* (n = 508)

Characteristics	All n=508	Successfully weaned	Transferred to RCW	Returned to ICU	Mortality	*P* value‡
Number (%)		282 (56)	103 (20)	23 (5)	100 (20)	
Age (mean ± SD), yr	71.0 ±13.5	71.1 ±13.3	69.3 ±14.5	71.0 ±10.8	72.3 ±13.7	0.460
Gender: Male, n (%)	269 (53)	152 (54)	50 (49)	14 (61)	53 (53)	0.686
APACHE II score in RCC†	19 (15-23)	18 (14-22)	18 (15-23)	20 (16-22)	23 (18-27)	<0.001
1-15*	145 (29)	104 (72)	26 (18)	4 (3)	11 (8)	<0.001
16-19	123 (24)	65 (53)	31 (25)	6 (5)	21 (17)	
20-23	123 (24)	71 (58)	22 (18)	10 (8)	20 (16)	
24-40	117 (23)	42 (36)	24 (21)	3 (3)	48 (41)	
Ventilator days before RCC, days	31.1 ±18.6	30.6 ±18.9	34.2 ±21.9	29.2 ±17.0	29.0 ±12.5	0.532
Length of RCC stay†, days	18 (10-35)	13 (8-22)	41 (39-42)	32 (13-38)	15 (10-28)	<0.001
Patient source, n (%)						
Medical ICU	134 (26)	75 (56)	25 (19)	6 (5)	28 (21)	0.945
Neurological ICU	117 (23)	78 (67)	23 (20)	5 (4)	11 (9)	0.009
Respiratory ICU	142 (28)	55 (39)	35 (25)	9 (6)	43 (30)	<0.001
Others	115 (23)	74 (64)	20 (17)	3 (3)	18 (16)	0.162

‡Statistical analyses were compared between each subgroup.

†Values are median (25^{th}-75^{th} percentile).

*Cutoff values for quartiles of APACHE II score were 15, 19, and 23

after transfer to the RCC (Table 3).

Discussion

Apart from reporting outcomes of an intermediate care unit of a ventilator weaning center, this study explored the correlation of APACHE II scores obtained within 24 hours after arriving at the RCC to outcomes in the RCC. The APACHE II score may be used as a negative predictor for successful weaning, and a positive predictor for mortality.

Since the maximal stay in the RCC was set at 42 days, based on the IDS from the NHIB, the length of stay in the RCC in this study bore no significant relationship with the initial APACHE II score. Though the APACHE II score was not recommended as a predictor for mortality in these patients [11], our results supported its use as a positive predictor for mortality after long-term mechanical ventilation for all sorts of diseases. The discrepancy may be due to different study populations, as our patients were older (71.0±13.5 vs. 63.2±13.0 years, $P < .001$), fewer were male (53% vs. 65%, $P < .001$), there were higher APACHE scores (19.4±6.2 vs. 16.2±4.5, $P < .001$), and there was a larger difference in APACHE scores between survivors and non-survivors (4.7±1.1 vs. 0.9±0.25, $P < .001$).

In this study, 2 methods were used to assess the ability of the APACHE II score to predict outcomes of patients treated in the RCC. First, the different multivariate logistic regression models, which included variables of clinical interest (Table 2). Second, the predictions of

Table 2. Multivariate Logistic Regression of Those Successfully Weaned and Mortalities

	Odds ratio (95%CI)	*P* Value
Model of successful weaning		<0.001
Age	1.02 (1.00-1.04)	0.026
APACHE II score in RCC		
0-15	5.33 (2.84-9.97)	<0.001
16-19	2.85 (1.54-5.25)	0.001
20-23	2.95 (1.60-5.43)	0.001
24-40	1	
Lengths of RCC stay, days	0.92 (0.90-0.93))	<0.001
Patient source*		
Medical ICU	2.04 (1.15-3.60)	0.014
Neurological ICU	4.09 (2.20-7.58)	<0.001
Other ICU	2.77 (1.51-5.08)	0.001
Respiratory ICU	1	
(Constant)	0.39	0.164
Model of mortality		<0.001
APACHE II score in RCC		
0-15	0.12 (0.06-0.24)	<0.001
16-19	0.33 (0.18-0.61)	<0.001
20-23	0.25 (0.13-0.46)	<0.001
24-40	1	
Lengths of RCC stay, days	0.97 (0.95-0.99)	0.002
Patient source*		
Medical ICU	0.53 (0.29-0.95)	0.033
Neurological ICU	0.26 (0.12-0.55)	<0.001
Other ICU	0.44 (0.23-0.85)	0.015
Respiratory ICU	1	
(Constant)	2.32	0.012

*Reference group: Respiratory ICU

Variables of clinical interest in the model, including: demographics, APACHE II score, length of RCC stay and patient source.

successful weaning and mortality, which were evaluated by the ROC, with AUC 0.622 and 0.703, respectively. The possible causes for imperfect predictions may be the fact that this study included patients with respiratory failure from a variety of causes: nervous system lesions such as cerebrovascular diseases from the neurology ICU; thoracic cage problem such as traffic accidents from other admitting sources including the surgery ICU; cardiac pump failure such as congestive heart failure from the medical ICU; infection and/or pneumonia from the respiratory ICU. Also, for administrative reasons, the maximal time to be used in attempting to wean patients from the ventilator was set at 42 days when patients were entered into the

Table 3. Characteristics According to Length of Stay in the RCC (n = 508)

	Lengths of stay, days (quartiles)				
Characteristics	0-10	11-18	19-35	36-45	*P* value
Age (mean ± SD), yr	69.4±14.4	72.2±12.5	71.8±13.7	70.9±13.2	0.334
Gender: Male, n (%)	79 (55)	59 (51)	61 (50)	70 (56)	0.802
APACHE II score in RCC*	19 (13-23)	20 (15-23)	19 (15-23)	19 (16-23)	0.534
Ventilator days before RCC, days	30.5 ±19.0	30.6 ±20.2	29.2 ±17.1	34.1 ±18.1	0.578
Patient source, n (%)					
Medical ICU, 134	39 (29)	35 (26)	32 (24)	28 (21)	
Neurological ICU, 117	31 (27)	26 (22)	28 (24)	32 (27)	
Respiratory ICU, 142	37 (26)	32 (23)	30 (21)	43 (30)	
Others, 115	38 (33)	23 (20)	31 (27)	23 (20)	
Outcomes, n (%)					<0.001
Successfully weaned, 282	113 (40)	76 (27)	74 (26)	19 (7)	<0.001
Transferred to RCW, 103	3 (3)	2 (2)	9 (9)	89 (86)	<0.001
Returned to ICU, 23	4 (17)	6 (26)	3 (13)	10 (44)	0.126
Mortality, 100	25 (25)	32 (32)	35 (35)	8 (8)	<0.001

*Values are median (25^{th}-75^{th} percentile), *P* values from Kruskal-Wallis rank test.

APACHE II score in RCC indicated score obtained within 24 hours after arriving RCC.

IDS. This may further hamper the usefulness of APACHE II scores in predicting patients who may potentially be successfully weaned after 42 days.

As expected, patients suffering from respiratory diseases have the most difficulty weaning, due to there being a higher proportion with severe irreversible lung diseases, such as chronic obstructive pulmonary disease and bronchiectasis. Patients from the neurological ICU tend to have a greater chance of being successfully weaned, irrespective of age, sex and APACHE II scores. The postulated reason for the better outcome in patients with neurological disorders was that concomitant respiratory failures were frequently due to aspiration or ventilator–associated pneumonia causing PMV. The most common neurological disorders were severe acute stroke and repetitive strokes. Moreover, as the rate of successful weaning was 55% among all patients and 72% among patients with APACHE II scores of 1-15, stratification of patients for admittance to the RCC may be feasible. Further modification of the IDS may be possible, so as to benefit patients with neurological diseases and low APACHE II scores. An earlier screening phase of less than 21 days and a higher priority of transfer to the RCC may further help these types of patients, although validation studies are required.

There were several limitations in our study: (1) This cohort study was conducted in a single unit in a tertiary care hospital. (2) We did not investigate other possible factors that may influence outcomes, such as a major diagnosis, and important underlying diseases including chronic organ failure or cancer, dialysis, and a tracheostomy state. (3) The study period was almost a decade ago. The standards of critical care have continued to evolve during this period; the same

APACHE score will predict a higher weaning rate and lower mortality with advances in medicine. (4) Our ventilator days before transfer to the RCC were 31; this delay in RCC transfer may change patient characteristics. The reader should keep this in mind when using these data.

In conclusion, our study demonstrated that the APACHE II score is moderately reliable in predicting outcomes of RCC patients. The use of APACHE II scores in predicting outcomes in this group of PMV patients, who attempted weaning in the RCC, may be feasible. Further evolution of the scoring system by adding up variables of interest will be valuable. Our results offer some information for the reform of health services for PMV patients.

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APACHE 分數系統用來預測呼吸照護中心病患預後

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王金洲 * 林孟志 *

前言：本研究探討呼吸照護中心（RCC）長期使用機械通氣的病患，分析其結果與急性生理和慢性健康評估（APACHE）II 的相關性。

方法：這是一個前瞻性的觀察研究，在呼吸照護中心連續收錄長期使用機械通氣的病患。分析記錄其人口統計學、轉入來源、脫離呼吸器的時間、脫離呼吸器的結果及在 24 小時內抵達呼吸照護中心所測的 APACHE Ⅱ評分。脫離呼吸器的結果分為四組，成功脫離、死亡、重返重症加護病房、下轉到呼吸照護病房。

結果：我們篩選了 6820 位呼吸機使用患者，其中 508 例患者被收入本案。進入呼吸照護中心之前使用機械通氣的平均時間為 31.1±18.6 天，平均 APACHE Ⅱ評分為 19.3±6.2，停留在呼吸照護中心的平均時間為 21.3±13.4 天。脫離呼吸器的結果是 55.5% 成功脫離，20.3% 沒有脫離且下轉到呼吸照護病房，19.7% 死亡，4.5% 重返重症加護病房。在呼吸照護中心，10 天內死亡率為 4.9%，10 天內成功脫離率為 40%。APACHE Ⅱ評分與成功脫離呈負相關，APACHE Ⅱ評分與死亡率呈正相關，但與停留在呼吸照護中心的時間沒有相關。

結論：APACHE Ⅱ評分在預測呼吸照護中心患者的預後是中度可靠的。我們的研究結果在改革服務長期使用機械通氣的病患上，提供有價值的信息。*(胸腔醫學 **2015; 30: 271-279**)*

關鍵詞：呼吸器脫離，APACHE，中級照護機構，呼吸照護病房，長期照護

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Melioidosis Presenting as Splenic Abscesses and Suspected Septic Pulmonary Embolism – A Case Report

Tz-Yan Chang*,*****, Yuan-Ti Lee**,***, Tzu-Chin Wu*,***, Hsu-Chung Liu***,****

A 49-year-old man with newly-diagnosed type 2 diabetes and living in Kaohsiung presented with fever and chills for 1 month. On admission, physical examination revealed persistent abdominal tenderness in the region of the liver and spleen. Contrast-enhanced computed tomography of the abdomen disclosed multiple low attenuation lesions in the spleen, which were compatible with splenic abscesses. One week after admission, follow-up chest radiography revealed multiple alveolar and nodular infiltrates in both lungs. Splenectomy for infection control of the splenic abscess was performed at the suggestion of our infectious disease specialist. *Burkholderia pseudomallei* was isolated in cultures of the blood, splenic abscess, and sputum. The diagnosis of melioidosis with presentations of splenic abscesses, bacteremia, and suspected septic pulmonary embolism was made. Two weeks after admission, the patient expired due to refractory septic shock, even with adequate antibiotic treatment and aggressive resuscitative management. This case highlights the possibility that a patient with melioidosis and uncontrolled diabetes could present with splenic abscess, septic pulmonary embolism, and a poor prognosis. ***(Thorac Med 2015; 30: 280-285)***

Key words: melioidosis, pulmonary embolism, splenic abscess

Introduction

Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*, and is predominant in East Asia and Australia [1]. In Taiwan, outbreaks often occur from July to September, especially after the rainy days brought by typhoons [2]. Transmission is mainly through percutaneous inoculation during exposure to wet season soils or contaminated water. The risk factors for melioidosis include diabetes, alcohol use, and chronic renal disease [3]. Most individuals with *pseudomallei* infections have a subclinical disease course. However, bacteremia occurs in around half of those with clinical disease, and septic shock in up to 1/4 of cases. The

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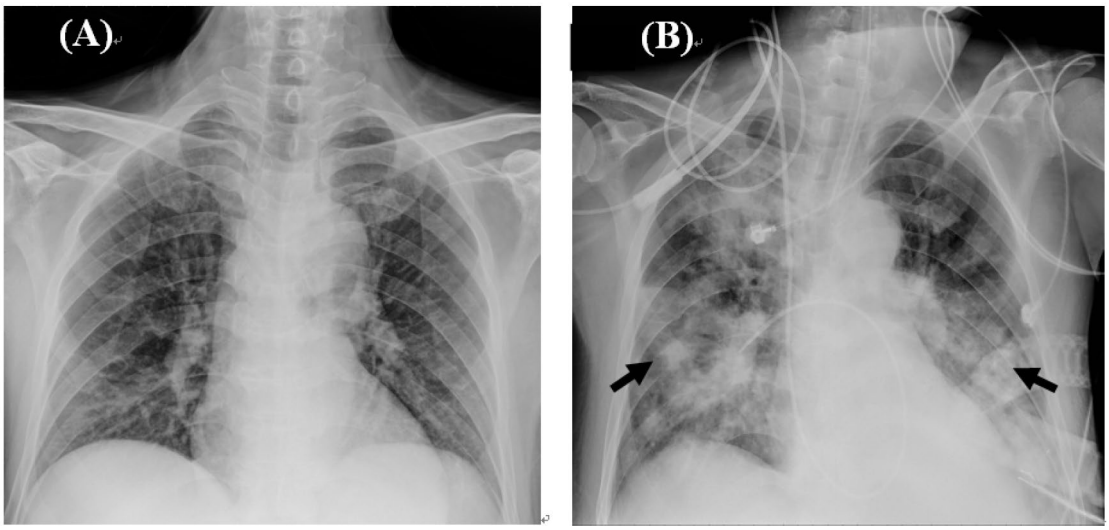

Fig. 1. (A) Chest radiograph on day 1 of admission showing no abnormal infiltrates in the bilateral lungs. (B) Chest radiograph on day 8 of admission showing multiple alveolar and nodular infiltrates predominantly at the bilateral lower lungs (as arrows).

most common clinical manifestations are pneumonia and localized skin infections. The findings in chest radiographs (CXR) include patchy or multi-lobar consolidations, nodules, necrotizing lesions, and pleural effusion [4]. Here, we present the case of a diabetic man with melioidosis presenting as splenic abscesses and suspected septic pulmonary embolism.

Case Report

A 49-year-old man living in Kaohsiung presented in September 2011 with intermittent fever and chills for 1 month. He denied having had any systemic disease. He was an ever-smoker, but had ceased smoking for 6 months. He initially visited a local clinic in Kaohsiung, and then went to a hospital in Changhua. Multiple splenic abscesses were discovered by serial infection surveys. Splenectomy was suggested, but his family hesitated to accept the operation. Thus, he turned to our hospital for further management. The CXR on admission showed no abnormal findings (Figure 1A). Physical examination revealed tenderness in the abdominal region of the spleen and liver. There was no muscle guarding or rebound pain. The initial blood test revealed a packed cell volume of 26.3%, a white blood cell count of 5.1×10^3/cumm (5% band forms, 83% neutrophils, 7% lymphocytes, 5% monocytes, and 0% eosinophils), a platelet count of 72×10^3/cumm, and C-reactive protein of 12.3 mg/dl. Splenic abscesses were suspected due to multiple low attenuation lesions found on the spleen in the venous phase of contrast-enhanced abdominal computed tomography (CT) (Figure 2A). Due to concern regarding the splenic abscesses and severe sepsis, an empiric antibiotic with doripenem was administered after admission. In addition, a new diagnosis of type 2 diabetes mellitus was made based on the patient's high serum blood sugar and glycated hemoglobin level (HbA1c = 12%). Insulin was also prescribed for blood sugar control.

During the hospital course, the patient's fever progressed with a spiking pattern, even

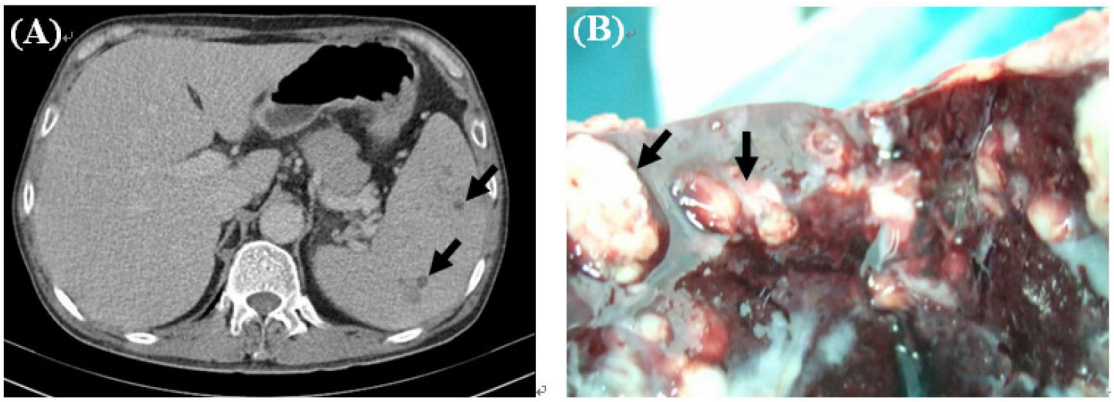

Fig. 2. (A) Contrast-enhanced abdominal computed tomography in the venous phase showing multiple low attenuation lesions on the spleen (as arrows). (B) The gross appearance of the resected spleen revealed many abscess formations (as arrows), which were confirmed by pathologic findings.

with the use of doripenem. One week after antibiotic treatment, the follow-up CXR showed a new appearance of multiple alveolar and nodular infiltrates in both lungs (Figure 1B). These CXR findings suggested the splenic abscesses had progressed to suspected septic pulmonary embolism. Due to his unstable hemodynamic status, he was transferred to the intensive care unit. This time, the blood cultures yielded *B. pseudomallei*. The antibiotic sensitivity test of the bacteria isolated from blood and sputum samples (from an endotracheal tube) exhibited susceptibility to imipenem, meropenem, levofloxacin, ceftazidime, piperacillin/tazobactam, and trimethoprim-sulphamethoxazole. The antibiotic was then changed from doripenem to imipenem, based on the drug susceptibility results. Splenectomy was performed for control of the infectious source, as suggested by our infectious disease specialist. The gross appearance of the resected spleen included pus formation (Figure 2B), and splenic abscesses were further confirmed by pathologic findings. Later, the culture of the splenic abscesses also isolated *B. pseudomallei*. A trans-esophageal echocardiogram was performed due to a suspicion of infectious endocarditis, and the result was negative. The follow-up CXR in the days after splenectomy showed no obvious improvement. Renal replacement therapy with continuous hemodialysis for the patient's acute renal failure was started on day 12 of admission. However, the patient later progressed to hepatic failure. Two weeks after admission, refractory septic shock developed, even with aggressive resuscitative management. He died of septic shock and multiple organ failure on day 15 after admission.

Discussion

Melioidosis is an infection caused by the Gram-negative bacterium, *B. pseudomallei* [1]. *B. pseudomallei* is known to be transmitted via percutaneous inoculation, inhalation, aspiration, and occasionally ingestion. The major mode of transmission is percutaneous inoculation during exposure to wet soils or contaminated water [3], and the infectious agents reach the lungs via the hematogenous route [5]. This patient

was living in Kaohsiung, in southern Taiwan, which has been reported to be an endemic area for *B. pseudomallei* infections [2]. The family denied that the patient had been exposed to wet soils or dirty water before disease onset. Agents from the Center for Disease Control in Taiwan investigated the patient's residence, but no contaminated areas or source of infection could be identified.

Melioidosis has the characteristic of being a predominantly seasonal outbreak, and about 75% to 81% of cases occur during the rainy season. Incidence is highest among those aged 40-60 years, although melioidosis has been well recognized to occur in children in Southeast Asia [6]. Northeastern Thailand and parts of northern Australia are major infection areas for melioidosis [7]. Fulminant melioidosis can occur in healthy individuals without underlying diseases and fatalities can occur in those without defined risk factors. Diabetes and renal failure are common risk factors for the development of clinical disease and bacteremia [8]. Most *B. pseudomallei* infections are asymptomatic, but an acute disease course is the most common presentation in patients with symptoms [9]. Fevers, chills, and rigors with and without hypotension are common, but localized symptoms are often absent. A prospective study of melioidosis in northern Australia found that 50% of cases presented as pneumonia, 46% as bacteremia, 15% as genitourinary tract infections, 13% as skin abscesses, and 4% as osteomyelitis or septic arthritis [10]. Melioidosis is also characterized by frequent formation of abscesses, which occur especially in the lungs, liver, spleen, skeletal muscle, and prostate gland [1]. The splenic abscesses in our case were compatible with a common presentation of melioidosis. However, the thoracic radiologic finding of suspected septic pulmonary embolism is not common among patients with pulmonary melioidosis [4]. Lee *et al*, reported a case of melioidosis with a presentation mimicking septic pulmonary embolism [11]. The cause of pulmonary infiltrates in our case may have been fulminant bacteremia and subsequent dissemination into the lungs. Bacteremic patients with melioidosis have a mortality rate as high as approximately 40% in northeast Thailand (35% in children) and 14% in Australia [9,12].

A delay in diagnosis of melioidosis can be fatal to patients, since empirical antibiotic regimens used for patients with bacterial sepsis often do not provide adequate coverage for *B. pseudomallei* [13]. The recommended treatment of melioidosis includes initial intensive therapy with intravenous ceftazidime, meropenem, or imipenem for at least 10-14 days, followed by oral eradication therapy, usually with trimethoprim-sulfamethoxazole for 3 to 6 months. The differential diagnosis of melioidosis in patients with pneumonia should always be kept in mind by clinical physicians in endemic areas. Delays in diagnosis or inadequate antibiotic treatment may be life-threatening to patients with melioidosis. This patient received antibiotics, initially with doripenem and then imipenem in the days after the identification of the bacterium. Both antibiotics used with this patient were considered to be adequate therapy for *B. pseudomallei* infections in previous reports [13-14]. In addition, the isolated *B. pseudomallei* in this patient was susceptible to imipenem *in vitro*. The reason for the poor prognosis of this patient may have been the poor blood sugar control of this diabetic patient and the fulminant infection.

In conclusion, melioidosis could present as pneumonia, bacteremia, hepatic or splenic abscesses, severe sepsis, or suspected septic

pulmonary embolism. The high mortality rate among patients with melioidosis suggests that early identification of *B. pseudomallei* infections and adequate antibiotic treatment are the keys to improved outcome. This case highlights the importance of clinical physicians keeping in mind the diagnosis of melioidosis when approaching a patient living in an endemic area.

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類鼻疽感染症以脾膿瘍及疑似敗血性肺栓塞表現－案例報告

張子晏 *,*****　李原地 **,***　吳子卿 *,***　劉旭崇 ***,****

49 歲男性病人新診斷的第二型糖尿病，住高雄地區，這次因為發燒及寒顫症狀持續一個月就診。住院理學檢查發現腹部肝脾部位有壓痛感。腹部電腦斷層顯示脾臟有多個低顯影病灶且符合脾膿瘍影像表現。住院一週後，追蹤胸部 X 光發現雙肺有新的多發性肺泡型及結節型浸潤。因感染科醫師建議及脾膿瘍的感染源控制，病人接受脾臟切除手術。之後，病人的血液、脾膿瘍、及痰液培養結果均檢出類鼻疽桿菌，確立診斷為類鼻疽感染症以及以脾膿瘍、菌血症、與疑似敗血性肺栓塞等表現。即使使用適當的抗生素治療及積極急救處置，病患仍在住院兩週後因敗血性休克死亡。這個案例顯示一個類鼻疽感染症和糖尿病控制不佳的病人，可能以脾膿瘍、敗血性肺栓塞、及不好的預後等表現。*(胸腔醫學 **2015; 30: 280-285**)*

關鍵詞：類鼻疽感染症，肺栓塞，脾膿瘍

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Pulmonary Amyloidoma Coexisting with Lung Adenocarcinoma: A Case Report and Literature Review

Po-Lan Su*, Chang-Yao Chu**, Jing-Jou Yan**, Han-Yu Chang*

Amyloidosis is characterized histopathologically by tissue infiltration with fibrillar protein with a β-sheet structural conformation. Clinical manifestations vary depending upon the type of amyloid and the distribution of deposition. Pulmonary amyloidosis may be localized to the respiratory tract or be part of a widespread process involving many organs. Primary pulmonary amyloidosis is classified into 4 major patterns, including parenchymal amyloidosis with a diffuse interstitial or nodular pattern, and tracheobronchial amyloidosis with submucosal plaques or luminal tumor-like masses. Pulmonary nodular amyloidosis, which is also referred to as "amyloidomas," develops mainly in the 6th to 7th decade without a gender predominance; it usually has a benign clinical course, and grows slowly. The nodules are, for the most part, rounded, sharply delimited, and located peripherally, with sizes ranging from 0.4 cm to 15 cm. The existence of multiple nodules is associated with cough, hemoptysis, and pleuritic pain. Calcification, and metaplastic bone or cartilage formation is usually found. Increased FDG uptake and an association with Sjögren's syndrome and pulmonary marginal zone lymphoma have been reported. No association with lung adenocarcinoma was reported in previous case series. ***(Thorac Med 2015; 30: 286-292)***

Key words: amyloidosis

Introduction

Amyloidosis, a building up of amyloid in the organs, is characterized histopathologically by tissue infiltration with fibrillar protein with a β-sheet structural conformation when stained specifically with Congo red dye with a yellow-green birefringence under polarized light [1]. The 2 major forms of amyloidosis are AL (primary) and AA (secondary). AL amyloidosis is formed by deposition of immunoglobulin light chain fragment, in association with multiple myeloma, Waldenström's macroglobulinemia or non-Hodgkin lymphoma. AA amyloidosis may complicate chronic diseases in which there is ongoing or recurring inflammation, such as rheumatoid arthritis, spondyloarthropathy, or inflammatory bowel disease; chronic infections;

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or periodic fever syndromes [19]. Clinical manifestations vary depending upon the type of amyloid and the distribution of deposition. Here, we present the case of a patient with pulmonary nodular amyloidosis.

Case Report

This 80-year-old male had a history of A-colon adenocarcinoma, stage C2 status post-right hemicolectomy with chemotherapy, type 2 diabetes mellitus, hypertension, and Parkinsonism. Five years after surgical intervention, chest X-ray (CXR) showed several lung nodules in the bilateral upper lung field, both of which were attached to the pleura. A faint opacity was also noted at the left upper lobe (Figure 1). Abdominal CT at that time showed no evidence of local recurrence, and primary pulmonary tumor was suspected. Further chest computed tomography (CT) showed ground glass opacity with suspicious solid parts, thought to be bronchoalveolar carcinoma. Multiple subpleural round nodules, including 2 at the right upper lobe and 3 at the left upper lobe, up to 2 cm in diameter,

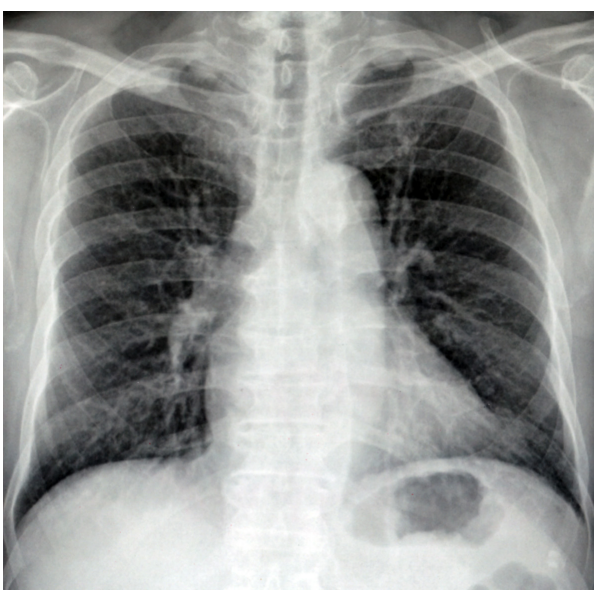
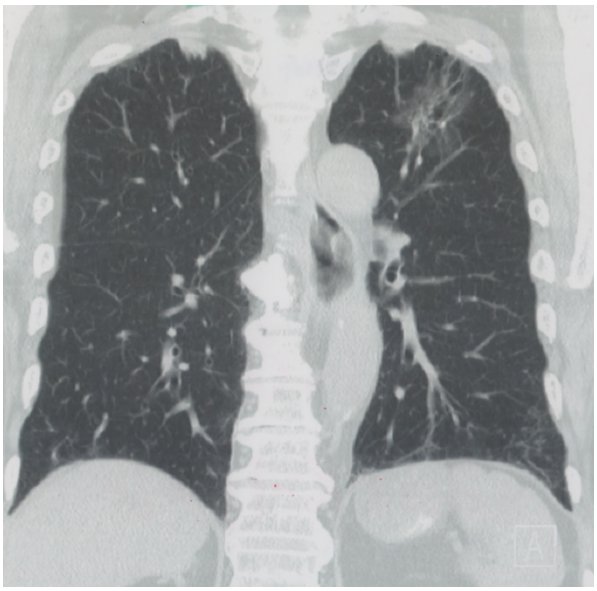
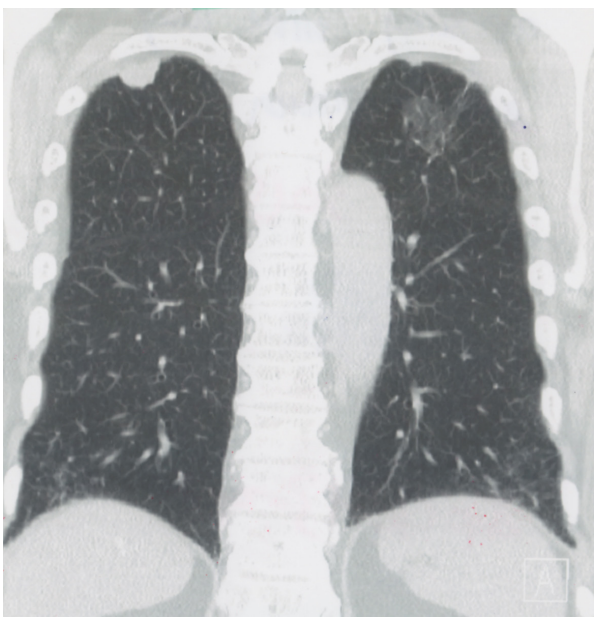


Fig. 1. CXR showed several lung nodules attached to the pleura in the bilateral upper lung field. Faint opacity was also noted at the left upper lobe.

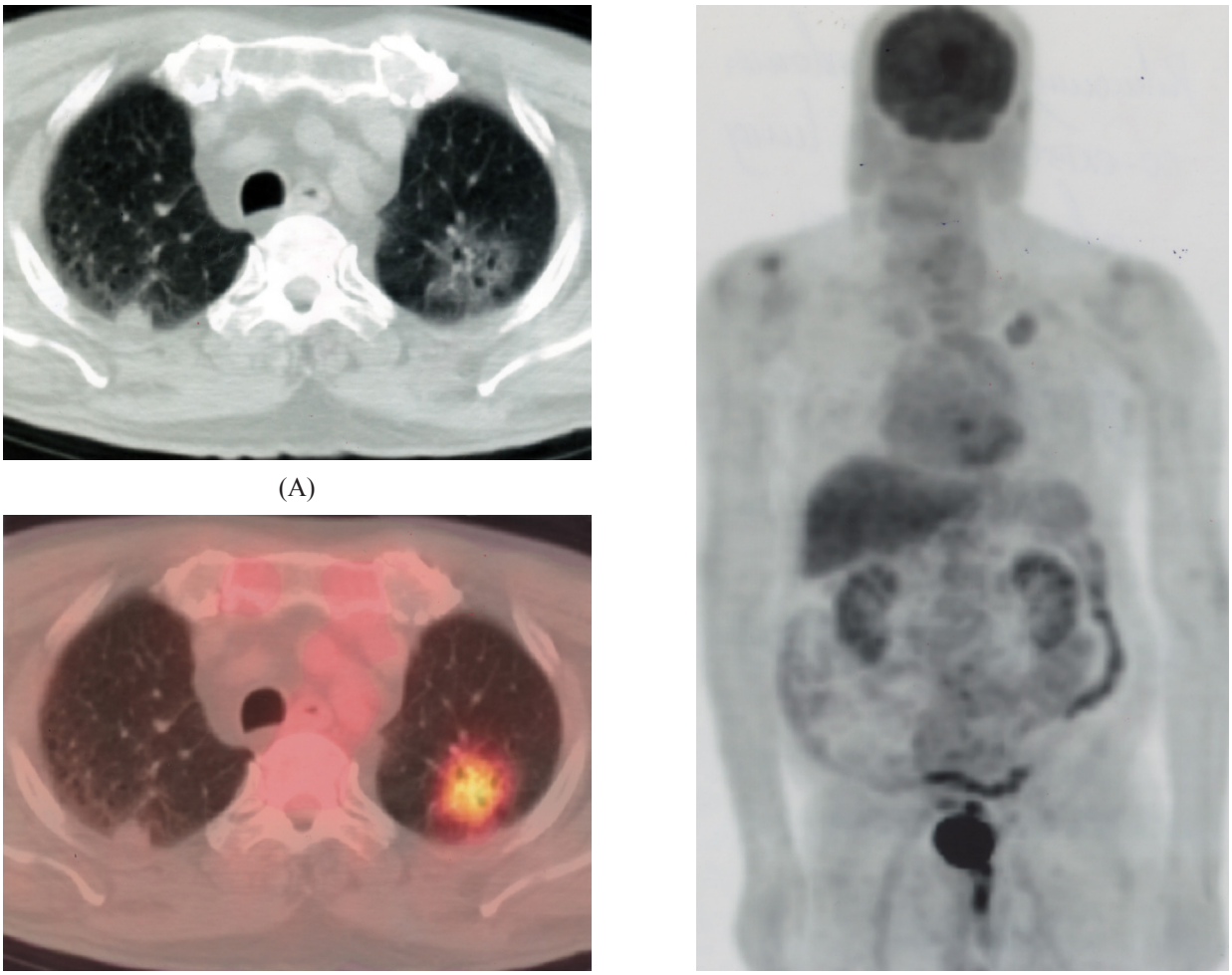


(A)



(B)

Fig. 2. Coronal reformation in the chest CT series showed ground glass opacity with central solid parts, highly suspicious of bronchoalveolar carcinoma (A-B). Moreover, multiple subpleural round nodules, up to 2 cm in diameter, were noted in the bilateral apex of the lung (A-B).



(A) (B) (C)

Fig. 3. PET-CT revealed a hypermetabolic lesion within the ground glass lesions (A-B); there was no FDG uptake at the bilateral subpleural lung nodules (C).

were noted (Figure 2A-B). PET-CT revealed a hypermetabolic lesion within the ground glass lesions and no FDG uptake of subpleural nodules at all (Figure 3A-C). Based on the current imaging study, lung malignancy with T2a N0M0, stage Ib, was suspected. Thus, left upper division segmentectomy and mediastinal lymph node dissection were arranged and the final pathologic report showed stage IA well-differentiated adenocarcinoma and bilateral nodular amyloidoma (Figure 4A-D).

Discussion

Pulmonary amyloidosis may be localized to the respiratory tract or be part of a widespread process involving many organs [2]. Most cases of pulmonary amyloidosis are associated with systemic AL amyloidosis [3], and 88% of patients with systemic amyloidosis are found to have pulmonary involvement at autopsy [4]. Systemic amyloidosis with a propensity for the lung could be primary in relation to multiple

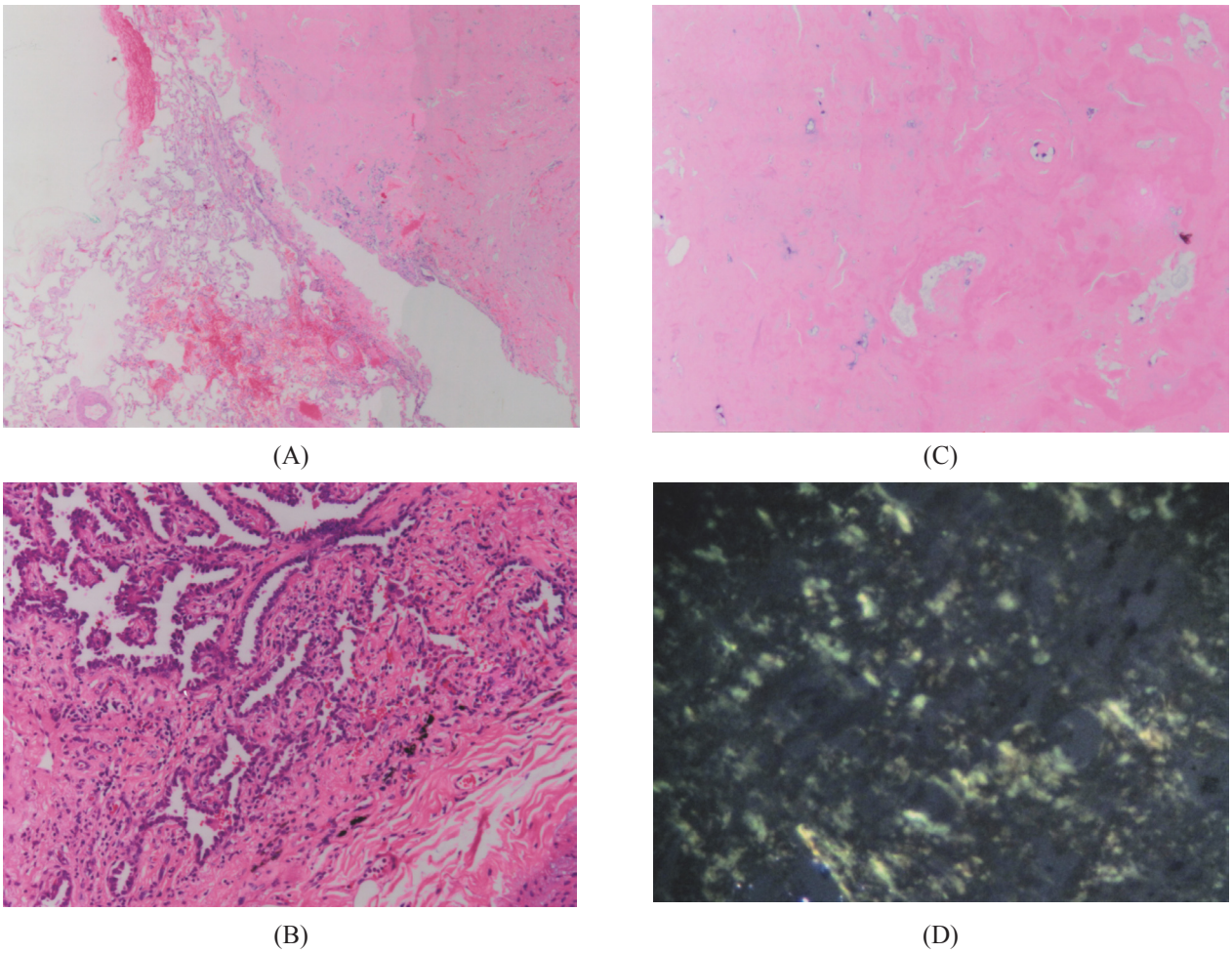


Fig. 4. Pathological examination of the surgical specimen showed both bronchoalveolar carcinoma and amyloidosis (A). Detailed examination showed bright-pink hyaline material with an apple-green appearance under Congo-red stain at the amyloidosis part (B-C). Acinar type of bronchoalveolar carcinoma was also revealed (D).

myeloma; secondary to tuberculosis, chronic renal disease, syphilis, osteomyelitis, inflammatory bowel disease, bronchiectasis, rheumatoid arthritis, leprosy, and lung myeloma; or familial. Most of these patients have diffuse interstitial infiltration as seen in imaging studies of the chest [3-4].

Patients without systemic amyloidosis were thought to have primary pulmonary amyloidosis, also known as isolated pulmonary amyloidosis [3-4]. There are 4 major patterns of isolated pulmonary amyloidosis [2-4,7,20,21] (Table 1). Parenchymal amyloidosis occurs in either a diffuse interstitial or nodular pattern, and tracheobronchial amyloidosis may produce submucosal plaques or luminal tumor-like masses. Different patterns of localized pulmonary amyloidosis have distinct clinical manifestations and disease progression. Amyloid of a diffuse parenchymal form is a serious disease, frequently associated with plasma cell dyscrasia. Patients have a median survival of 2 years after diagnosis [3,11].

Pulmonary nodular amyloidosis, which is

Table 1. Incidence of Different Forms of Pulmonary Amyloidosis

		Tracheobronchial		Parenchymal	
Series	Case Numbers	Tumor-like	Submucosal	Interstitial	Nodular
Cordier *et al*. [2]	7	0	5	0	2
Utz *et al*. [3]	11	0	4	0	7
Smith *et al*. [4]	3	0	0	0	3
Hui *et al*. [7]	48	10	4	6	28
Thompson *et al*. [20]	126	10	57	4	55
Pitz *et al*. [21]	6	1	1	1	3
Total	201	21 (10.3%)	71 (35.3%)	11 (5.6%)	98 (48.8%)

also referred to as "amyloidomas," is frequently seen in older patients in their 6th to 7th decade, without a gender preference [7-8]. It can develop as single or multiple nodules [10-11], and has a benign clinical course and slow growth, as reported in previous case series [2-3,5-6,10-11,13,20-21]. The nodules are usually rounded and sharply delimited, and located peripherally with sizes ranging from 0.4 cm to 15 cm [14]. Solitary nodules are usually asymptomatic. Multiple nodules are frequently associated with cough, hemoptysis, and pleuritic pain [12]. Transbronchial biopsy and percutaneous lung biopsy have been used as diagnostic tools [13]. Pathology findings usually show the amyloid is either AL or AA, although AL deposition accounts for 63~80% of cases [7,20]. Calcification, metaplastic bone or cartilage formation is usually found [2,7,9].

FDG-PET has been widely used as an important diagnostic tool to evaluate possible malignancy. Several conditions that could also cause increased uptake of glucose and mimic malignancy have been reported [15-16]. FDG-PET is a sensitive imaging modality for metabolically active lesions that include inflammatory infiltrates. Several case reports have shown increased FDG uptake in pulmonary nodular amyloidosis [15-17]. Despite its rarity, pulmonary nodular amyloidosis should also be considered as a differential diagnosis of pulmonary opacities with high FDG uptake on PET. Recurrence is frequent after surgery [18]. In our case, there was no increased FDG uptake.

Only 10% of patients with nodular amyloidosis have an underlying plasma cell dyscrasia [10]. There are also case reports of coexisting pulmonary marginal zone lymphoma and parenchymal deposition of amyloid [23-24]. Association with Sjögren's syndrome has been reported [22]. No evidence of pulmonary lymphoma was noted in our patient by pathology evaluation, and no evidence of Sjögren's syndrome was noted by laboratory study. To the best of our knowledge, there has been no case report on the association between adenocarcinoma and pulmonary nodular amyloidosis.

In conclusion, we reported a case of pulmonary nodular amyloidosis without increased FDG uptake, and that was not associated with autoimmune disease or underlying hematologic malignancy. Since there was no association between pulmonary amyloidoma and lung adenocarcinoma in this case, we believe that the amyloidoma probably coexisted with lung adenocarcinoma.

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肺部類澱粉瘤合併肺腺癌：個案報告與文獻回顧

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類澱粉沉積症於病理學切片上會呈現纖維狀蛋白以β摺疊的方式沉積，一般可以使用剛果紅染色後在偏光顯微鏡下呈現黃綠折射來診斷。臨床上表現取決於沉積的器官位置，以肺部為例，類澱粉的沉積可以區分為四大類。在肺實質以瀰漫性間質沉積或結節沉積、在氣管以黏膜下腫瘤或環狀沉積。其中結節沉積又被稱做是類澱粉瘤，常見於 60~70 歲病患，男女比大約 1:1，大多數是良性變化，可能以單一或事多發結節來表現。在影像分析上大多邊緣清晰，大小分布於 0.4~15 公分不等。多發性結節通常會合併咳嗽、血痰或是肋膜疼痛的情況。在病理切片下有時會合併有鈣化或軟骨生成的情形。曾有文獻指出類澱粉瘤與乾燥症以及邊緣區淋巴瘤有相關性，也容易在正子造影過程會呈現類惡性腫瘤的表現。目前沒有文獻指出與肺腺癌有相關性。*(胸腔醫學* ***2015; 30: 286-292)***

關鍵詞：多發性肋膜下類澱粉瘤

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A Rapidly Lethal Primitive Neuroectodermal Tumor of the Mediastinum in a 27-Year-Old Male

Yi-Hsuan Tsai*, Chih-Jen Yang*,****, Shan-Yin Tsai***, Ming-Shyan Huang*,**

A 27-year-old male with an unremarkable medical history presented with progressive dyspnea for about 2 weeks. He also complained of mild fever, exertional dyspnea, paroxysmal nocturnal dyspnea, dry cough and chest tightness. Chest radiograph in the chest clinic of our hospital revealed a large opacity at the left lower lung field, suggesting a large mass with massive pleural effusion. Computed tomography revealed a huge posterior inferior mediastinal mass, and positron emission tomography revealed high fluorodeoxyglucose uptake in the mass. A pathological examination of the specimens from a computed tomography-guided biopsy showed a small blue round cell tumor, positive for CD99, and fluorescence in situ hybridization revealed a Ewing' sarcoma breakpoint region 1 22q12 rearrangement, favoring a primitive neuroectodermal tumor. Despite aggressive palliative chemotherapy, the patient died 3 months later due to uncontrolled malignant disease. Through this case and a review of similar cases in the literature, we highlight the difficulty in making a timely diagnosis and discuss the challenges of treatment. ***(Thorac Med 2015; 30: 293-299)***

Key words: primitive neuroectodermal tumor

Introduction

A primitive neuroectodermal tumor (PNET) is a nerve-derived small round cell tumor that mainly affects the long bones. Nearly 80% of patients are younger than 20 years [1]. The similar chromosomal translocation occurring in both Ewing's sarcoma and PNET lesions suggests that these tumors are closely related. Most Ewing's sarcomas/PNET have a stereotypical immune phenotype, with CD99 expression found in all cases and no expression of cytokeratins or desmin [1]. The 2 tumor types also show Homer-Wright pseudorosettes and a Ewing' sarcoma breakpoint region 1 (EWSR1) 22q12 rearrangement [1]. PNET are invasive and usually lethal, although aggressive surgical resection with additional radiation therapy has been reported to result in disease-free survival.

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Case Report

A 27-year-old male with an unremarkable medical history presented with progressive dyspnea for about 2 weeks. He complained of mild fever, dyspnea on exertion, paroxysmal nocturnal dyspnea and dry cough, and also chest tightness at the left anterior upper chest area. He had suffered from these symptoms for 2 weeks before he visited our chest clinic. He denied any contact history before the development of the symptoms and no similar symptoms were noted in his family. He also denied body weight loss and other gastrointestinal or genital symptoms.

A chest radiograph in the chest clinic of our hospital revealed a large opaque lesion at the left lower lung field, suggesting a huge mass with massive pleural effusion (Figure 1). After the fluid had been drained out, computed tomography (CT) revealed a huge posterior inferior mediastinal tumor with pulmonary extension and rib invasion (Figure 2A). Positron emission tomography (PET) revealed that the mass had high fluorodeoxyglucose (FDG) (standardized uptake value maximum [SUVm]:18) uptake (Figure 2B). A CT-guided biopsy showed a primitive small blue round cell tumor with extensive tumor necrosis. The tumor cells had coarse chromatin and scanty cytoplasm, and mitotic figures were occasionally seen. Immunohistochemistry showed that the tumor cells were positive for CD99 (Figure 3A), and a fluo-

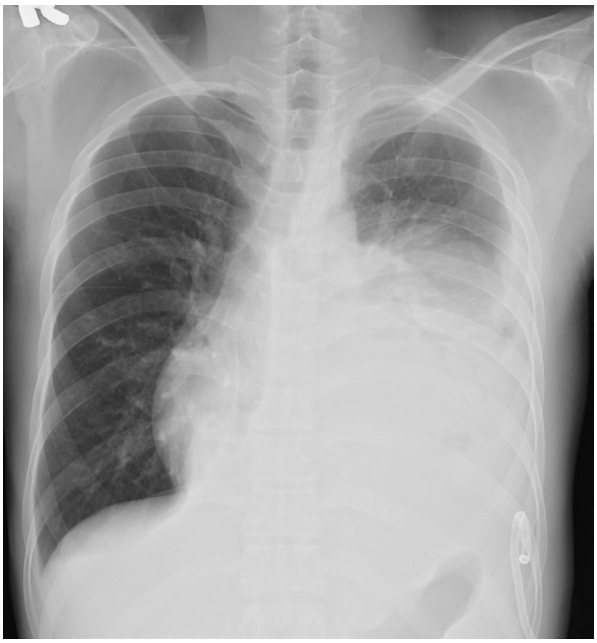

Fig. 1. Chest film showed a large opacity at the left lower lung field, suggesting a huge mass with massive pleural effusion.

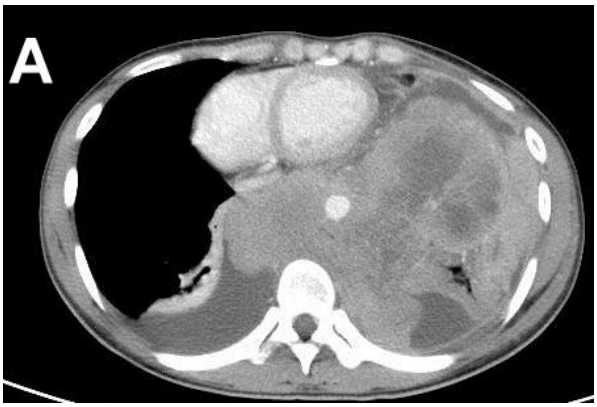

Fig. 2A. CT revealed a huge heterogeneous posterior inferior mediastinal mass.

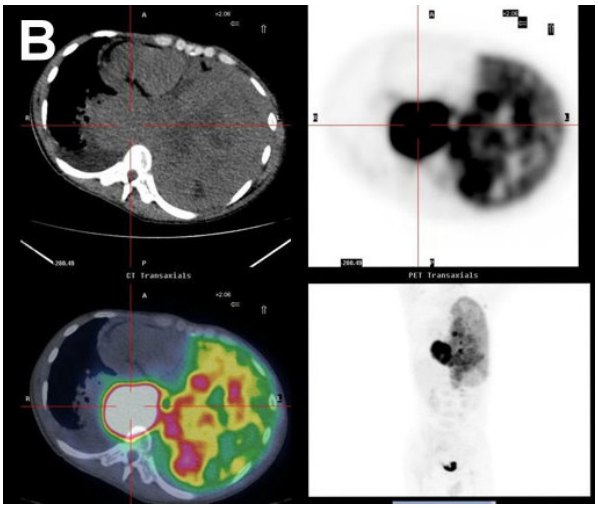

Fig. 2B. High FDG (SUVm 18) uptake in the mass, which was located in the posterior inferior mediastinum.

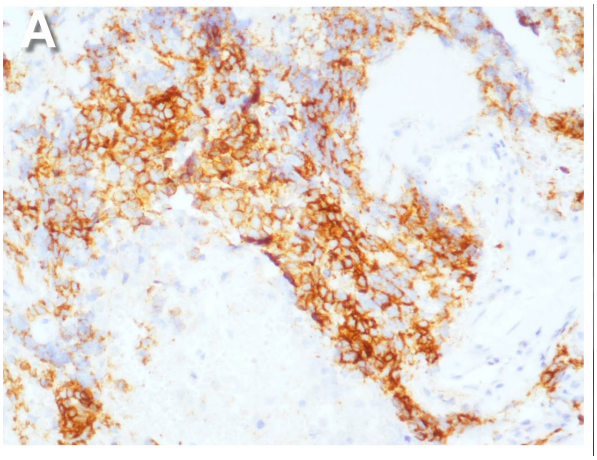

Fig. 3A. Section expression of CD99

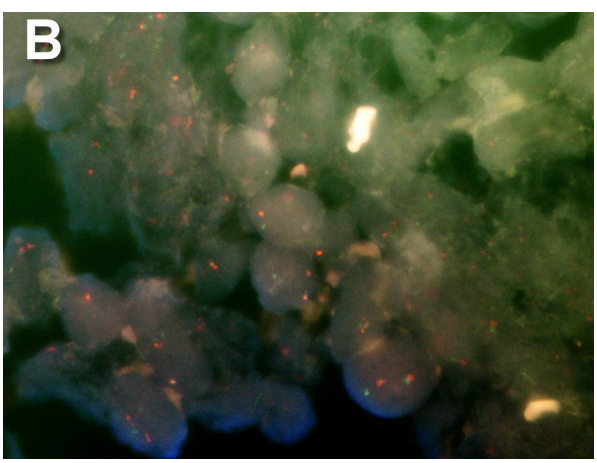

Fig. 3B. FISH revealed a EWSR1 22q12 rearrangement

rescence in situ hybridization (FISH) study of the specimens revealed a EWSR1 22q12 rearrangement (Figure 3B). Taken together, a PNET of the mediastinum was suspected. However, the patient hesitated to undergo surgery because the tumor was too large to be completely resected. Thus, we initiated chemotherapy with cyclophosphamide, vincristine-TEVA and epirubicin. Nevertheless, 3 months later the patient died due to uncontrolled malignant disease.

Discussion

Small blue round cell tumors are rare, and include Ewing's sarcoma, melanoma, esthesioneuroblastoma, desmoplastic small round cell tumor (DSRCT), PNET, small cell lymphoma and neuroblastoma [1]. PNET belongs to the highly aggressive Ewing's sarcoma family of tumors [2]. These tumors most commonly occur in long bones, but they also have been reported to originate from extra-skeletal sites such as the kidneys [3], bladder [4], penis [5], brain [6], intrathoracic area [7-11] and chest wall [12-14]. In a Medline search, reported cases of intrathoracic PNET were very rare (Table 1).

In the histological examination, PNET often shows a uniform population of small cells with round-to-oval nuclei, fine chromatin, scant cytoplasm, and indistinct cytoplasmic borders [7,15]. Immunohistochemical staining, such as CD99/MIC2, vimentin, desmin, LCA, neuron-specific enolase, epithelial membrane antigen, and cytokeratins [16], has been used for the differential diagnosis of small round cell tumors. CD99/MIC2 is expressed by 90% of Ewing's sarcoma family tumors [17], and it is regarded to be the most reliable marker for the Ewing's sarcoma family of tumors and PNET. However, it is difficult to make a definite diagnosis merely based on cytomorphology. Furthermore, most Ewing family tumors have a balanced translocation involving chromosomes 11 and 22, which fuse portions of the Ewing's sarcoma (EWS) gene on 22q12 with the Friend leukemia integration 1 gene on 11q24 [18]. Reverse transcriptase-polymerase chain reactions or molecular analysis by FISH have been proposed to be reliable diagnostic tools. In the current case, FISH revealed a EWSR1 22q12 rearrangement, which favored a PNET (Figure 3B) [18-21].

Table 1. List of Published Cases of Primitive Neuroendocrine Tumors of the Chest in a PubMed Search

Study/year	Case Number	Age/Sex	Initial Site	Therapy	Chemotherapy	Outcome
Ann Thorac Surg/2001 [10]	1	26/F	Lung	surgery + chemotherapy	isophosphamide, etoposide, cyclophosphamide, doxorubicin, vincristine	8 months
J Korean Med Sci/2007 [11]	1	67/M	Lung	surgery + chemotherapy + radiation therapy		
Cardiovascular Pathology/2007 [9]	1	16/M	Lung	chemotherapy	vincristine, isophosphamide, doxorubicin, etoposide, VIDE	
Journal of Thoracic Oncology/2009 [25]	25	mean age: 27.2 years	Thorax	surgery + chemotherapy + radiation therapy		4~108 months
European Journal of Cardio-thoracic Surgery/2009 [14]	1	26/M	Chest wall	surgery + chemotherapy	cyclophosphamide, vincristine, doxorubicin, ifosfamide, and etoposide	>5 years
Chest/2010 [16]	1	21/M	Chest wall	surgery + chemotherapy		>3 years
Asian Cardiovascular & Thoracic Annals/2010 [13]	1	48/M	Chest wall	surgery + chemotherapy + radiation therapy	vincristine-adriamycin-cyclophosphamide and ifosfamide-etoposide	>23 months
Pathol Oncol Res/2011 [8]	1	15/M	Lung	chemotherapy	vincristine, ifosfamide, doxorubicin, and etoposide.	1 year
Interactive Cardiovascular and Thoracic Surgery/2011 [12]	1	13/M	Chest wall	surgery + chemotherapy	ifosfamide, vincristine and doxorubicin, and etoposide	>1 year
Med Onc/2012 [7]	1	28/M	Lung	chemotherapy	ifosfamide, dacarbazine and cisplatin	4 months

Image findings of PNET of the thorax are rarely reported. Calcification and hemorrhagic necrosis have been described in some reports [9-12,14,16,22]. The common differential diagnoses are lymphoma, primary intrathoracic sarcomas such as leiomyosarcoma, angiosarcoma and rhabdomyosarcoma, chondrosarcoma, synovial sarcoma, malignant fibrous histiocytoma, fibrosarcoma, and osteosarcoma [16]. FDG/PET has been reported to be a diagnostic tool that complements CT in the staging of sarcomas [23], with the potential to discriminate between

sarcomas and benign tumors [23]. However, the role of PET-CT using FDG in the diagnostic work-up of PNET of the lung has not yet been clearly established [23]. The FDG heterogeneous uptake of PNET indicates the differences in biological behavior and metabolic profile of PNET at different sites [23]. Four case reports of patients who underwent PET showed prominently increased FDG uptake in PNET [7,12,23-24]. In our case, PET showed high FDG (SUVm:18) uptake in the mass, which was located in the posterior inferior mediastinum.

Since PNET and Ewing's sarcoma are considered to be the same family of tumors with different degrees of neuroectodermal differentiation, the chemotherapy regimens are similar for both diseases, and include vincristine-based chemotherapy [1] in combination with ifosfamide, doxorubicin, etoposide; and vincristine, actinomycin D, and cyclophosphamide [1].

However, there are currently no established regimens for PNET because of the rarity of these tumors. Some studies have reported that tumor resection with adjuvant chemotherapy may provide a better outcome [13,25-26]. In these studies, the most common adjuvant chemotherapy regimens were the combination of vincristine-TEVA, actinomycin D (or doxorubicin) and cyclophosphamide [25-26]. Alternative regimens with isophosphamide, etoposide and epirubicin have also been reported in some studies [6,25-27]. In the largest case series of PNET of the thorax, the median survival time was 13 months, and most cases received chest wall resection [25]. In addition, the patients who underwent definitive surgery after initial chemotherapy had a higher success rate for complete thoracic PNET resection and better disease-free survival [25]. Only 3 cases received chemotherapy alone: 1 died after 6 months, another died after 17 months, and the third patient was alive after more than 28 months [25]. In the present case, the tumor was too large for complete resection, and the patient hesitated to undergo surgery. Thus, we used cyclophosphamide, vincristine and epirubicin as palliative chemotherapy. The patient unfortunately died 3 months later. Poor prognostic factors include a large tumor size, metastasis at the time of diagnosis, and incomplete resection [13].

In conclusion, PNET is rare in adults, and the diagnosis and treatment are challenging. Combined imaging, pathology, immunohistochemistry and molecular analysis may help in making an early diagnosis. Neo-adjuvant chemotherapy [16,25] with complete tumor resection or complete tumor resection with adjuvant chemotherapy [8,13-14,25] has yielded a more than 1 year disease-free survival rate in some case reports. However, some patients who received both chemotherapy and surgery showed poor outcomes [7,10,12]. Therefore, further studies are needed to determine the optimal therapy for these patients.

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在一個 27 歲的男性出現快速致命的縱膈腔原始性神經外胚層腫瘤

蔡怡萱 *　楊志仁 *,****　蔡善茵 ***　黃明賢 *,**

27 歲男性，無過去病史，這兩周來有呼吸喘加劇的情況，伴隨著發燒，運動後喘，夜喘，乾咳和胸悶的現象，來門診求診。胸腔 X 光攝影發現左側肺野有大片不透光區塊，懷疑有巨大腫瘤伴隨積水。電腦斷層證實有一個巨大的後縱膈腔腫瘤。核磁共振顯示腫瘤攝取氟代去氧葡萄糖（FDG）並顯影。電腦斷層定位切片的病理顯示小藍圓細胞瘤，免疫染色 CD99 有反應，螢光原位雜和技術（FISH）顯示 EWSR1 22g12 基因重置，診斷為原始性神經外胚層腫瘤。雖然我們給予了積極的化學治療，病人仍在三個月後因腫瘤惡化死亡。透過整理這個案例，我們回溯過去一系列相似的個案，也突顯此疾病診斷的相當困難且治療極富挑戰。*(胸腔醫學 **2015; 30: 293-299**)*

關鍵詞：原始性神經外胚層腫瘤

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Microscopic Polyangiitis in a Patient with Diffuse Alveolar Hemorrhage and No Biochemical Renal Impairment

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Microscopic polyangiitis (MPA) is an autoimmune disease characterized by inflammation of the small vessels and the presence of circulating anti-neutrophil cytoplasmic antibodies (ANCA). Resulting from an injury orchestrated by ANCA, MPA usually manifests as necrotizing glomerulonephritis (GN) and necrotizing pulmonary capillaritis. The major clinical feature of MPA is rapidly progressive GN; however, diffuse alveolar hemorrhage (DAH) that originates from pulmonary capillaritis is often the main reason for hospitalization. The clinical presentation of DAH is highly variable, ranging from asymptomatic radiographic abnormalities to fatal respiratory failure. Some patients may experience a variable degree of hemoptysis, accompanied by dyspnea, chest tightness and anemia. Early diagnosis and prompt therapy will lead to a good prognosis for patients with MPA. We describe a 44-year-old male with MPA presenting with hemoptysis for 1 month. DAH was detected by the presence of numerous hemosiderin-laden alveolar macrophages in bronchoalveolar lavage. The renal function at diagnosis was normal though microscopic hematuria was observed. The patient was successfully treated with rituximab, a monoclonal chimeric antibody targeting CD20, a cell-surface protein expressed on B-lymphocytes. ***(Thorac Med 2015; 30: 300-306)***

Key words: microscopic polyangiitis, anti-neutrophil cytoplasmic antibodies, diffuse alveolar hemorrhage

Introduction

Diffuse alveolar hemorrhage (DAH), a clinicopathologic syndrome characterized by widespread extravasation of red blood cells into pulmonary alveolar spaces, may be life-threatening and poses an important challenge for clinicians [1-2]. DAH can occur as a manifestation (or a complication) of various diseases, or present in isolation [3-4]. Most cases of DAH, however, are caused by pulmonary capillaritis associated with autoimmune diseases. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) represents the most common cause of pulmonary vasculitis [1-2].

AAV is an idiopathic multisystem vasculitides that is associated with necrotizing inflammation of small- and medium-sized blood vessels and the presence of autoantibodies to neutrophil constituents, particularly proteinase

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3 (PR3) and myeloperoxidase (MPO). It mainly comprises 3 different disease entities: Churg–Strauss syndrome, granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis) and microscopic polyangiitis (MPA) [5-6]. MPA is defined as necrotizing vasculitis with few or no immune deposits in the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides [7], and mostly affects small vessels in the respiratory tract and in the kidneys (pauci-immune necrotizing glomerulonephritis) [8-9]. Differing from kidney involvement that is typically detected well after the onset of disease [9-13], the incidence of DAH in MPA is around 30%. Subclinical DAH may be common, as more than half of patients were found to have iron-positive alveolar macrophages in excess of 20% in a bronchoalveolar lavage (BAL) fluid examination in a previous study [14]. The presence of DAH in MPA is associated with a poor prognosis [8]. However, early diagnosis and early initiation of a tailored therapy are believed to improve outcomes [15-16]. Here, we describe a case of MPA that manifested with DAH only, and no biochemical evidence of renal failure on diagnosis.

Case Report

A 44-year-old male current smoker was admitted to the hospital because of progressive dyspnea on exertion, blood-tinged sputum, body weight loss (8 kg during 6 months) and intermittent chest tightness for 1 month. He underwent thyroidectomy 17 years previous to this visit and was treated with thyroid hormone supplements. Any history of respiratory diseases such as sinusitis, asthma or bronchiectasis were denied, and he did not use anti-platelet agents, anticoagulants, illicit drugs, herbs or alcohol. Any recent travel history or occupational exposure was also denied. His vital signs were normal on admission. On physical examination, the conjunctiva was pale and auscultation of the chest revealed crackling sounds in bilateral lower lung fields. The laboratory test results were: white blood cell count (WBC), 7000/cumm, hemoglobin 9.9 g/dL, platelet count 464000/cumm, albumin 3.0 gm/dL, blood urea nitrogen (BUN) 21 mg/dL, and creatinine 1.34 mg/dL. The levels of prothrombin time and activated partial thromboplastin time were both within normal range. Urinalysis showed 2+ for protein and 3+ for blood by dipstick, and a red blood cell count of 11-20 per high power field. Chest radiograph (CXR) showed bilaterally diffuse interstitial infiltrates in middle-to-lower zones and alveolar infiltrates in bilateral lower lobes (Figure 1). Chest computed tomography (CT) revealed multiple interlobular

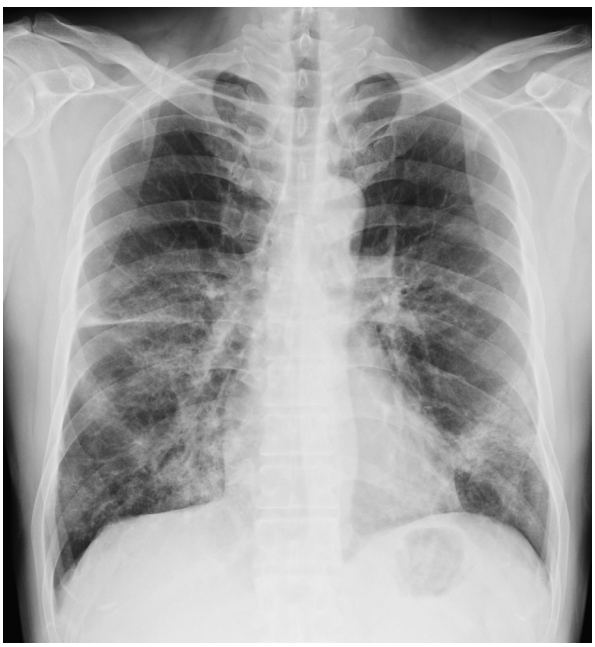
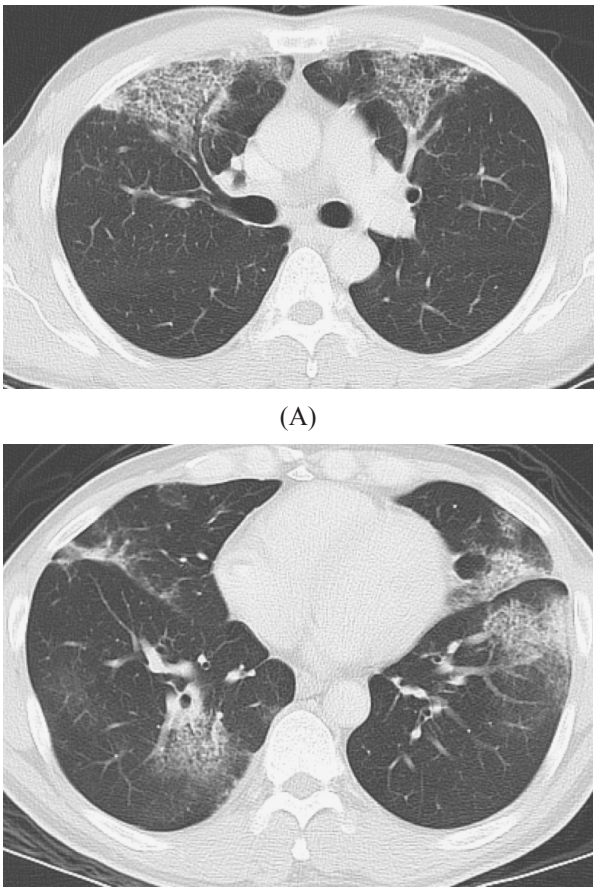


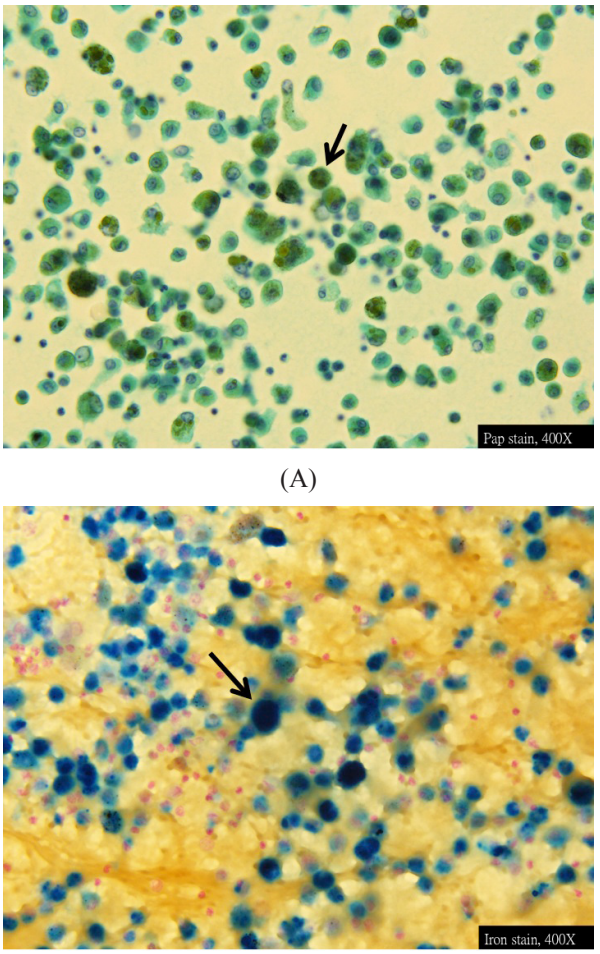
Fig. 1. CXR showed bilaterally diffuse interstitial infiltrates in middle-to-lower lung zones and alveolar infiltrates in lower lobes.



(A)

(B)

Fig. 2. Chest CT revealed multiple interlobular septal thickening and ground-glass opacities in upper (A) and lower lobes (B).



(A)

(B)

Fig. 3. Papanicolaou stain showed the presence of numerous hemosiderin-laden macrophages (A) that were positive for iron stain (B) in BAL fluid (400X).

septal thickening and ground-glass opacities in bilateral lung fields (Figure 2). The sputum examinations were negative for bacteria, *Mycobacterium tuberculosis* or malignant cells, and serological tests were negative for *Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Legionella pneumophila*. He then underwent flexible bronchoscopy followed by BAL. There were no visible bleeding sources grossly, but sequential lavage aliquots were progressively more hemorrhagic. The cytological analysis of BAL fluid showed the presence of numerous hemosiderin-laden macrophages (Figure 3A), which were histologically reactive with "Prussian-blue" stain (Figure 3B). The BAL fluid was negative for malignant cells. The GMS stain was negative and there was no growth in the bacterial culture. Since the BAL findings were compatible with DAH, additional laboratory studies were performed. The levels of complement 3 and 4 were normal, and the anti-nuclear antibodies and antibodies to double-stranded DNA, cardiolipin and glomerular basement membrane were all negative. Of note, the titer

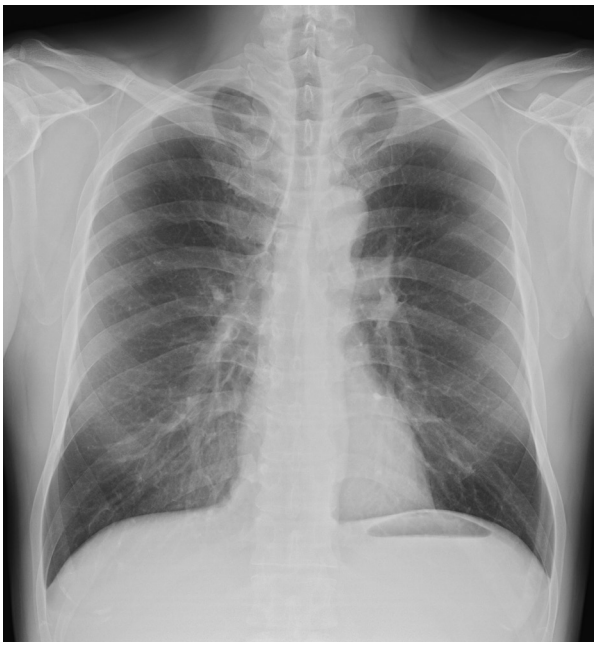


Fig. 4. The follow-up CXR 2 months after treatment showed regressive change.

of perinuclear ANCA (p-ANCA) was reported to be 114 IU/mL (reference range, 0-5 IU/mL). We consulted a rheumatologist. MPA was diagnosed based on the presence of DAH, microhematuria, positive p-ANCA, absence of upper airway involvement, and no clinical evidence of granulomatous inflammation. Immunotherapy with rituximab (RTX) was initiated quickly for this patient. The hemoptysis and dyspnea resolved gradually. After 2 months of rituximab therapy, the CXR showed remarkable regressive change (Figure 4). The urinalysis revealed less microhematuria. The titer of p-ANCA 1 year after diagnosis was reduced to 6.7 IU/mL.

Discussion

MPA is an idiopathic ANCA-associated autoimmune vasculitis with little or no immune complex deposition that commonly affects the kidneys, lung, nerves, skin, and joints [8-9]. There is a slight male predominance (male-to-female ratio of 1.5:1) and the age at onset is approximately 50 years. The prevalence of MPA is higher than that of GPA in southern Europe, Japan and China [17-18].

Although the exact mechanisms remain unclear, a growing body of evidence suggests that ANCA, especially ANCA against myeloperoxidase (MPO-ANCA), may be involved in the pathogenesis of MPA [19-21]. It has been reported that serum MPO-ANCA titers decrease as pulmonary abnormalities improve after treatment, which suggests the role of MPO-ANCA in DAH associated with MPA [22]. Nevertheless, further investigations are required to validate the value of serial measurements of ANCA titers in the follow-up of MPA patients.

The symptoms and clinical course of MPA have varied widely. About 70% of patients may have constitutional symptoms such as fatigue, fever or body weight loss at diagnosis, but patients may present acutely (with symptoms from days to weeks) or insidiously [8-9]. MPA is the most common cause of renal-pulmonary syndrome, which presents as the coexistence of glomerulonephritis (GN) and DAH sequentially or simultaneously [9]. Renal involvement, characterized by rapidly progressive glomerulonephritis (RPGN), is observed in 78-100% of patients with MPA [14]. Although cases with asymptomatic abnormalities in urinalysis (proteinuria, microscopic hematuria, and red blood cell casts) have been reported, most patients will progress to end-stage renal disease [15]. DAH, the classic pulmonary manifestation of MPA, occurs in approximately 30% of patients and is the major factor contributing to morbidity and mortality, especially when bleeding is abundant [9]. DAH is usually detected by

the presence of hemoptysis, diffuse alveolar infiltrates, and a drop in the hematocrit level. However, the diagnosis of DAH remains a challenge for physicians because hemoptysis, the cardinal sign of DAH, may occur late or even be absent when alveolar bleeding is significant. In addition, the radiographic findings of DAH are non-specific and vary from vague ground-glass opacity (GGO) to intense consolidation [11]. CXR in DAH frequently reveals patchy or diffuse airspace opacities, more prominent in perihilar areas and in the middle and lower lung zones. The lesions are mostly bilateral, but sometimes unilateral infiltrates can be found. The initial feature of DAH in chest CT is a GGO lesion. Then, interlobular septal thickening in association with GGO may be seen within days when the hemosiderin-laden macrophages begin to accumulate in the interstitium. Complete clearing of GGO and/or interstitial opacities may happen within 2 weeks. However, it may progress to a reticular pattern or honeycombing if bleeding occurs repeatedly. Of note, pulmonary fibrosis is not uncommon in MPA; it may precede other manifestations by a variable length of time and has a worse prognosis [23-24]. The incidence of DAH in MPA may be underestimated because some patients may present with subclinical alveolar hemorrhage or asymptomatic pulmonary infiltrates [23].

BAL is a valuable diagnostic test for DAH. It confirms the presence of intra-alveolar blood and excludes occult infections and bleeding from the large airways. Findings that suggest DAH include an increasingly hemorrhagic appearance of consecutive BAL aliquots and the presence of greater than 20% hemosiderin-laden macrophages as demonstrated by Prussian blue staining of lavage specimen centrifugates [4]. Transbronchial biopsy is unlikely to establish a diagnosis because of limited specimens. Open lung biopsy is not indicated since the pathologic findings of MPA are non-specific [2]. For this reason, lung biopsy is not recommended in MPA when the diagnosis can be made by serum ANCA assays [1].

In the past, MPA, as well as other AAV, would be almost fatal. However, the use of glucocorticoids with/without cyclophosphamide has resulted in a dramatic decrease in morbidity and mortality during past decades [15]. RTX is a monoclonal chimeric antibody targeting CD20, a cell-surface protein expressed on B-lymphocytes. Since B cells are the precursors for ANCA-producing plasma cells, antibody-mediated modification and/or depletion of B lymphocytes is the proposed mechanism for this approach to decrease autoantibody production and control disease activity [25]. RTX is highly effective in patients with refractory and/or relapsed AAV and is also considered as the treatment of choice for MPA [26].

Conclusion

DAH may occur before overt renal insufficiency in MPA. The clinical presentations of DAH are highly variable. BAL is suggested for hemoptysis patients with diffuse infiltrates in CXR. The availability of ANCA testing and enhanced awareness of the disease will make early diagnosis and prompt treatment of MPA possible.

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無臨床腎功能異常之顯微性多血管炎合併瀰漫性肺泡出血

丁文穎　林芳綺　賴信良

顯微性多血管炎是一種自體免疫疾病，其特徵為全身小血管發炎，且血清中存在抗嗜中性球細胞質抗體。在顯微性多血管炎，抗嗜中性球細胞質抗體引發的壞死性血管炎常常造成壞死性腎絲球腎炎以及肺部微血管炎。雖然急進性腎絲球腎炎是顯微性多血管炎最重要的臨床表現，但是肺部微血管炎造成的瀰漫性肺泡出血才是患者需要住院的主要原因。瀰漫性肺泡出血臨床症狀變異很大，可能只有胸部 X 光異常卻無症狀，也可能呼吸衰竭。及早診斷及時治療可以改善顯微性多血管炎患者的預後。我們報告一名 44 歲男性，住院主訴咳血一個月，尿液鏡檢發現血尿，生化檢查卻無明顯的腎功能異常。經由支氣管肺泡灌洗術發現瀰漫性肺泡出血，隨後抗嗜中性球細胞質抗體陽性，診斷為顯微性多血管炎。之後病人接受 anti-CD20 單株抗體 rituximab 治療，臨床症狀及胸部 X 光異常顯著改善。希望藉此病例提醒臨床醫師，凡疑似瀰漫性肺泡出血之病人，無論其腎功能是否有顯著異常，仍應將顯微性多血管炎列入鑑別診斷。*(胸腔醫學* ***2015; 30: 300-306)***

關鍵詞：顯微性多血管炎，抗嗜中性球細胞質抗體，瀰漫性肺泡出血

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Myxoma as a Rare Cause of Posterior Mediastinal Masses

Chiao-Hung Wang*,**, Hsiu-Ling Cheng***, Tzu-Hsiu Tsai**, Jin-Yuan Shih**

Myxomas are rare benign mesenchymal tumors that most frequently occur within the myocardium. Myxoma with mediastinal localization is extremely rare, and few cases have been described in the medical literature. Here, we present a 54-year-old man with a mediastinal mass found incidentally by chest radiography. He complained only of vague chest pain at the right-side chest wall. Computed tomography scan of the chest revealed a well-encapsulated, homogenous and non-enhanced lesion at the posterior mediastinum, with a content density higher than water and normal fat. He received video-assisted thoracoscopic surgery for tumor excision, and pathology revealed spindle cells set in a loosely fibrillar stroma, compatible with the histological diagnosis of myxoma. During follow-up for 2 years after the surgical resection, there was no recurrence. Our case reminds us that myxoma may be a rare cause of mediastinal tumors, and complete resection of the tumor is recommended in order to avoid recurrence. ***(Thorac Med 2015; 30: 307-313)***

Key words: myxoma, mediastinal mass, mediastinal myxoma

Introduction

The term myxoma was first introduced by Virchow in 1863 to describe a tumor that mimics the mucinous substance of the umbilical cord [1]. Diagnostic criteria for myxomas were proposed in 1948 by Stoute, who described the myxoma as a lesion of primitive mesenchymal origin. Myxoma is composed of stellate cells, which disperse within a myxoid mucopolysaccharide stroma. These stellate cells originate from multipotent mesenchyme that are capable of neural and endothelial differentiation [2]. Myxomas are rare benign mesenchymal tumors. The most frequent site of occurrence is within the myocardium, especially the right atrium, but it is now recognized that myxomas can occur in skin, bone, somatic soft tissues, and other sites [3-4]. Few cases of myxoma with pulmonary localization have been described in the medical literature, and present as either parenchymal or endobronchial lesions [5]. Mediastinal myxoma is also extremely rare and, to the best of our knowledge, the last case was reported in 1974. This report presents another case of myxoma found in the mediastinum, and reminds us that

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myxoma may be a rare cause of mediastinal tumors.

Case Report

A 54-year-old man without a smoking history came to our hospital for help due to an abnormal chest X-ray during a regular health examination. He had diabetes mellitus under medical control and a history of pulmonary tuberculosis with completed treatment. We reviewed the chest X-ray and found a well-defined soft tissue shadow superimposed at the lower mediastinal area (Figure 1). The patient complained only of vague chest pain at the right-side chest wall, but denied dyspnea, dysphagia, cough, wheezing, hemoptysis, or body weight loss. On examination, he was afebrile and had stable vital signs. No physical abnormalities were found after physical examination, and no abnormalities were detected through biochemical and hematological analysis.

To further investigate the suspicious mediastinal mass, computed tomography (CT) scan of the chest was arranged 4 days later, and revealed a well-encapsulated, homogenous and non-enhanced lesion, 5.3×7×8.5 cm in size, at the posterior mediastinum and adjacent to the esophagus (Figure 1). The CT density of the lesion content was slightly higher than water and much higher than subcutaneous fat. This feature of the mediastinal mass on CT scan was not typical of a pure cystic lesion, such as a bronchogenic cyst, that is commonly seen in the

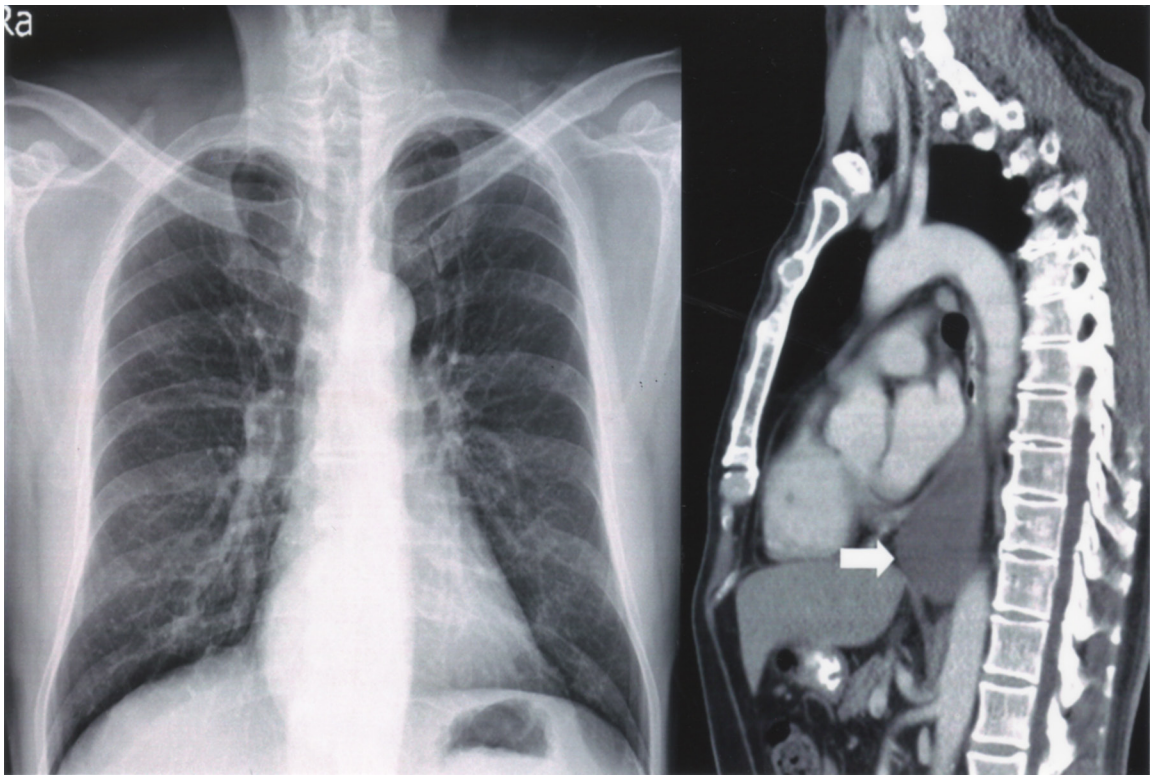

Fig. 1. Chest images of the mediastinal myxoma. Chest X-ray reveals a well-defined soft tissue shadow superimposed at the lower mediastinal area. Computed tomography scan of the chest with intravenous contrast reveals a homogenous and non-enhanced mass lesion at the posterior mediastinum, with content density higher than water and normal fat. The lesion is indicated by the arrow.

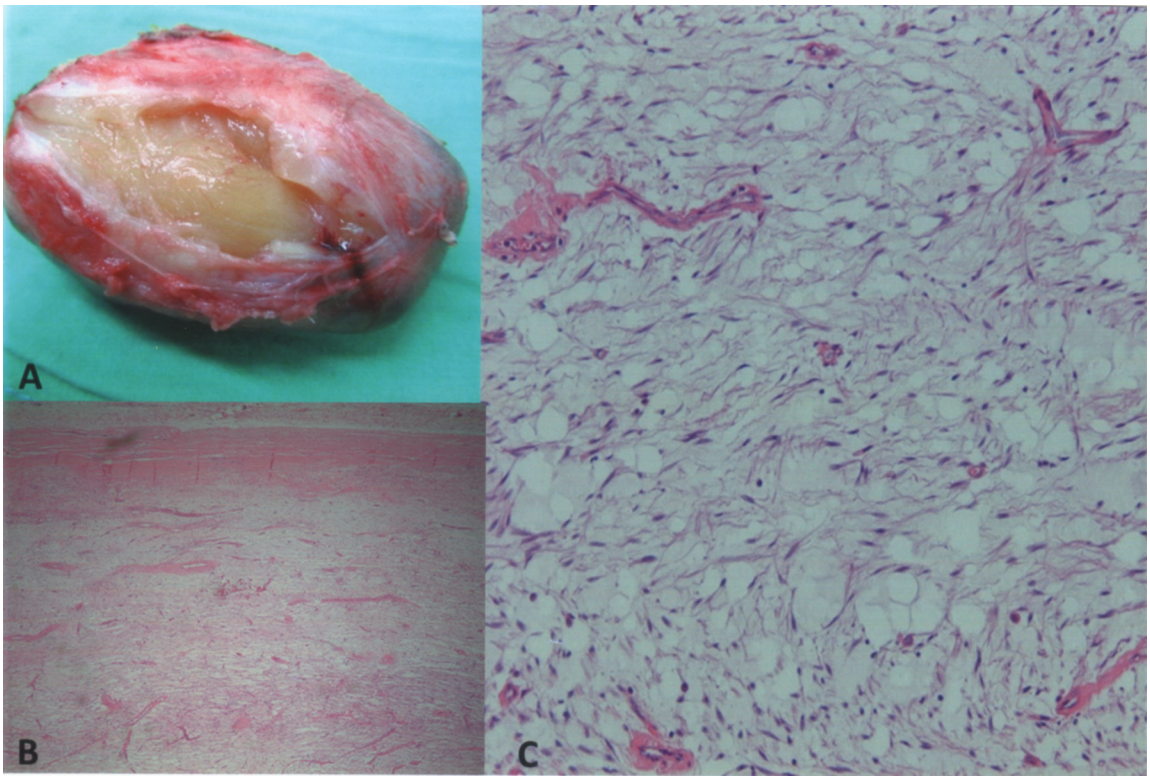

Fig. 2. Gross and microscopic appearance of the tumor. A: After removal at surgery, the tumor is grossly well-encapsulated, with a myxoid content appearing yellowish tan in color and soft in consistency. B: Histological examination at low magnification demonstrates a well circumscribed lesion, with pseudo-encapsulation of the tumor. Hematoxylin and eosin stain, magnification × 100. C: The tumor is composed of scattered spindle cells set in a myxoid stroma, and has low cellularity and hypovascular features. No cellular pleomorphism, mitotic activity, or lipoblast is observed. Hematoxylin and eosin stain, magnification × 400

middle mediastinum.

To clarify the nature of the mediastinal mass, video-assisted thoracoscopic surgery for tumor excision was arranged after discussion with the patient. During the operation, esophageal laceration, due to severe adhesion between the mass and the esophagus, was noted when the mediastinal mass was dissected from the esophagus. Afterward, the mass was removed, and it was found to be grossly well-encapsulated on the surface. The cut surfaces revealed a solid tumor with a myxoid content, which appeared yellowish tan in color and soft in consistency (Figure 2).

In the microscopic examination, the mass was seen as a well circumscribed lesion with fibrous septum, and was composed of stellate spindle cells scattered within a loosely fibrillar stroma. The cells exhibited long cytoplasmic processes set in a myxoid background, made up of a loose matrix of fibers (Figure 2). Neither cellular pleomorphism nor mitotic tumor cell activity was observed, and no lipoblast was found in it. This excluded the diagnosis of liposarcoma for the lesion, and led to the pathological diagnosis of mediastinal myxoma in this case.

The patient soon recovered from the surgery. Esophagography performed afterwards revealed no extravasation of contrast, suggesting

that the esophageal laceration healed well. Due to the benign nature of the mediastinal mass, the patient was discharged after postoperative care. During the 2-year follow-up post-surgical resection, the patient was well, and there was no evidence of recurrence of the mediastinal myxoma.

Discussion

The mediastinum is a space demarcated by the pleural cavities laterally, the thoracic inlet superiorly, and the diaphragm inferiorly. It can be conceptually compartmentalized into anterior, middle, and posterior divisions based on structural landmarks seen on the lateral radiograph. This conceptual compartmentalization has important implications for the differential diagnosis of mediastinal masses found by chest imaging. The most common causes of an anterior mediastinal mass include thymic tumor, teratoma and germ cell tumor, intrathoracic goiter and malignant lymphoma. Masses of the middle mediastinum are typically congenital cysts, including foregut and pericardial cysts, while those that arise in the posterior mediastinum are often neurogenic tumors [6]. However, some unusual tumors may also appear within the mediastinum, as in the case reported here. Myxoma is a rare cause of mediastinum masses.

Myxomas are benign mesenchymal tumors that may occur in many locations. The most common form is the primary cardiac myxoma, which occurs mostly in adults and accounts for 30-50% of all cardiac tumors. Although most cardiac myxomas are sporadic, familial cardiac myxomas are associated with an autosomal-dominant transmission, and constitute approximately 7% of cases with cardiac myxoma. The clinical consequences of cardiac myxoma depend on its location within the heart, as well as the size and mobility of the tumor. Patients with cardiac myxomas may be asymptomatic, but intra-cardiac obstruction and embolization may occur catastrophically. Myxomas in locations other than the heart are rare [5]. The extracardiac origins of myxoma include the bones (particularly facial bones), skin and subcutaneous tissue, head and neck, genito-urinary tract, and skeletal muscles [3-4]. As seen in the cases of myxoma reported in the literature, the mediastinum is an extremely rare origin of myxoma.

Symptoms of mediastinal mass can be categorized into 2 groups: localizing effects and systemic symptoms. Localizing presentations are secondary to tumor compression or invasion, and may include chest pain, dyspnea (due to airway compromise) and dysphagia (due to esophageal compression), and palsy of the diaphragm and/or vocal cords (due to the influence of the effectors on the innervated nerves). Systemic symptoms are typically due to the release of excess hormones, antibodies, or cytokines [6]. The localizing presentation of mediastinal myxoma is related to the size, location and consistency of the tumor. In our case and that reported by Jaituni, the patients were asymptomatic or minimally symptomatic, probably because of the slow growth rate and soft consistency of the tumor. However, it is worth noting that myxoma may expand suddenly after trauma [7]. Moreover, myxoma may grow with local infiltration into the adjacent soft tissues or produce osteolytic lesions in bones [7]. Systemic presentations of myxoma, including labial skin pigmentation, Cushing's syndrome and acromegaly, have been observed in patients with cardiac and head and neck myxomas, and are considered to be associated with autosomal-dominant transmission [8]. However, such sys-

temic presentations have never been reported in cases of mediastinal myxoma.

To our knowledge, very few cases of mediastinal myxomas have been described in the literature. The most recent report, describing a 51-year-old male with a large mediastinal myxoma, was that by Jaituni in 1974 [7]. Our case and that reported by Jaituni are almost the same in clinical presentations. Both patients remained asymptomatic for a prolonged time and their laboratory data were unremarkable. The treatment and final diagnosis were realized by surgical excision of the tumor [7].

CT scan of myxoma typically shows a homogenous and marginated mass without contrast enhancement, with a content density slightly higher than water, much higher than normal fat, and less than the surrounding muscle [9]. MRI may reveal a sharply defined lesion with lower intensity than muscles on the T1-weighted image and a higher signal than fat on the T2-weighted image, with homogeneity of signals on both images [10]. However, because of the lack of characteristic radiographic features, establishing the diagnosis of myxoma based on imaging findings before operation is difficult.

Microscopic examination of the tumor discloses stellate cells in a myxoid stroma containing thin-walled vessels. Microcystic architecture, nuclear pleomorphism and mitotic activity of the stellate cells are absent. Also, no epithelial, cartilage or other mesenchymal differentiation showed up in immunohistochemical studies [5]. Myxoma can be pathologically confused with myxoid changes within other lesions, both benign and malignant. Differential diagnoses for a myxoma usually include benign and malignant neural lesions, liposarcoma, rhabdomyosarcoma, and chondrosarcoma. Each of these lesions has specific criteria for the pathological diagnosis. For example, liposarcomas exhibit lipoblasts within the specimen. Chondrosarcomas exhibit chondroid tissue with chondroblasts, chondrocytes, increased mitotic activity, pleomorphism, and tumor giant cells [4].

Treatment for myxoma is surgical excision. Several cases of recurrence have been reported when the tumor is incompletely resected [11]. To ensure complete resection, it is recommended to extract the whole tumor with a part of the surrounding tissue if the boundary of the tumor is not clear. Myxomas usually do not metastasize, but long-term follow-up for surveillance of recurrence is usually suggested for a patient with myxoma that has been resected.

In conclusion, myxoma is a benign mesenchymal tumor that is frequently located in the heart, but it may very rarely appear in the mediastinum. The presence of myxoid stroma, thin-walled vessels and stellate cells, and the absence of epithelial, condroid, lipomatous and neural differentiation, are the histological hallmarks of myxoma. Treatment for myxoma is surgical excision, and complete resection of the tumor is recommended in order to avoid recurrence.

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罕見的後縱膈腔腫瘤－黏液瘤

王喬弘 *,** 鄭秀玲 *** 蔡子修 ** 施金元 **

黏液瘤是一種常出現在心臟的間質細胞瘤。然而在縱膈腔的黏液瘤是相當罕見的，只有非常少數的縱膈腔黏液瘤曾在過去的文獻被提及。在此，我們報告一位 54 歲男性於健康檢查接受胸部 X 光檢查時，意外發現的縱膈腔黏液瘤。病人僅抱怨輕微的右側胸痛，其電腦斷層顯示在縱膈腔出現一個均質、未顯影，且被完整包覆的腫瘤。病人之後接受胸腔鏡手術切除腫瘤。病理切片上發現在鬆散的纖維基質中散布著一些紡錘狀細胞。病理診斷最終確定是縱膈腔的黏液瘤。而在術後的兩年追蹤也沒有發現復發的情形。本病例提醒我們，黏液瘤仍舊可能是造成縱膈腔腫瘤的原因，而治療上則是建議完全的切除以避免再度復發。*(胸腔醫學 **2015; 30: 307-313**)*

關鍵詞：黏液瘤，縱膈腔腫瘤，縱膈腔黏液瘤

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Multiple Diaphragmatic Defects Complicated with Acute Hydrothorax in a Peritoneal Dialysis Patient – A Case Report

Huan-Wei Chen*,**, Kai-Huang Lin*,**, Hsiao-Hua Liu*,***, Huang-Chi Chen*,**

Peritoneal dialysis, a renal replacement therapy, is being increasingly used for patients with end-stage renal disease. Of all the complications related to peritoneal dialysis, hydrothorax is rather less common. Hydrothorax related to peritoneal dialysis has its unique presentation. We report a 51-year-old woman who received peritoneal dialysis for her end-stage renal disease and presented to our hospital with non-productive cough and progressive deteriorated shortness of breath for 1 week. The chest X-ray showed a massive amount of right-side pleural effusion, and the pleural fluid analysis revealed it was transudative with a high glucose content. We arranged peritoneal scintigraphy with a technetium-99m Phytate shunt scan and the result showed increased activity in the right lung field, suggestive of the existence of pleuro-peritoneal communication. Video-assisted thoracoscopy was arranged, and showed multiple diaphragmatic defects. Surgical diaphragmatic repair was then performed with endoscopic suture. Thereafter, the patient changed her renal replacement therapy to hemodialysis. No recurrent hydrothorax was found in the subsequent follow-up course. For the diagnosis of hydrothorax related to peritoneal dialysis, biochemistry and imaging studies are indicated, and video-assisted thoracoscopy with endoscopic suture would be a reasonable treatment choice. ***(Thorac Med 2015; 30: 314-320)***

Key words: hydrothorax, pleuro-peritoneal communication, peritoneal dialysis

Introduction

The use of peritoneal dialysis is expected to increase, since it allows patients more freedom in daily activities. Hydrothorax related to peritoneal dialysis, a less common complication when compared with the others, has a unique presentation. The "sweet" pleural fluid is of diagnostic value in certain circumstances. Peritoneal scintigraphy is helpful when there are findings of possible pleuro-peritoneal communication. We herein report the case of a patient with the initial presentation of shortness of breath and massive right-side pleural effusion. The patient was diagnosed as having multiple diaphragmatic defects via video-assisted tho-

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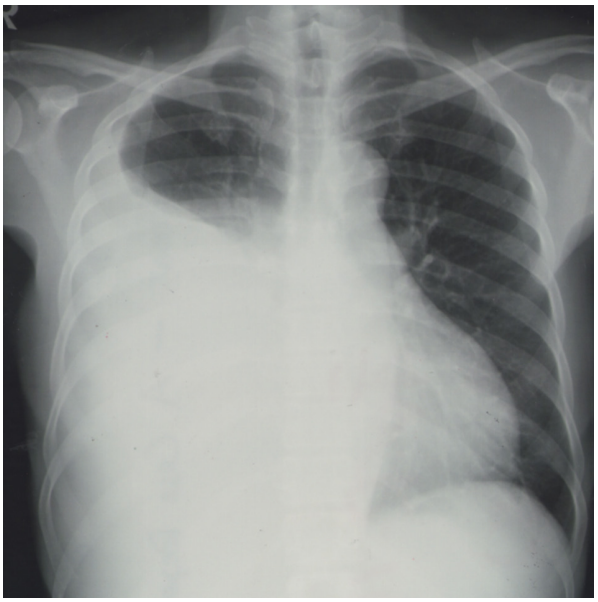

Fig. 1. Chest X-ray showed a massive amount of right-side pleural effusion.

racoscopy. The surgical outcome was ideal and there was no recurrence.

Case Report

A 51-year-old woman had a history of type 2 diabetes mellitus (DM), hypertension and end-stage renal disease. The renal replacement therapy for her was peritoneal dialysis for about 1 year. She presented to our hospital with non-productive cough and progressively deteriorating shortness of breath for 1 week, and denied other symptoms such as fever, chest pain or chest tightness. The hemogram data showed no leukocytosis. Chest X-ray revealed massive pleural effusion on the right side (Figure

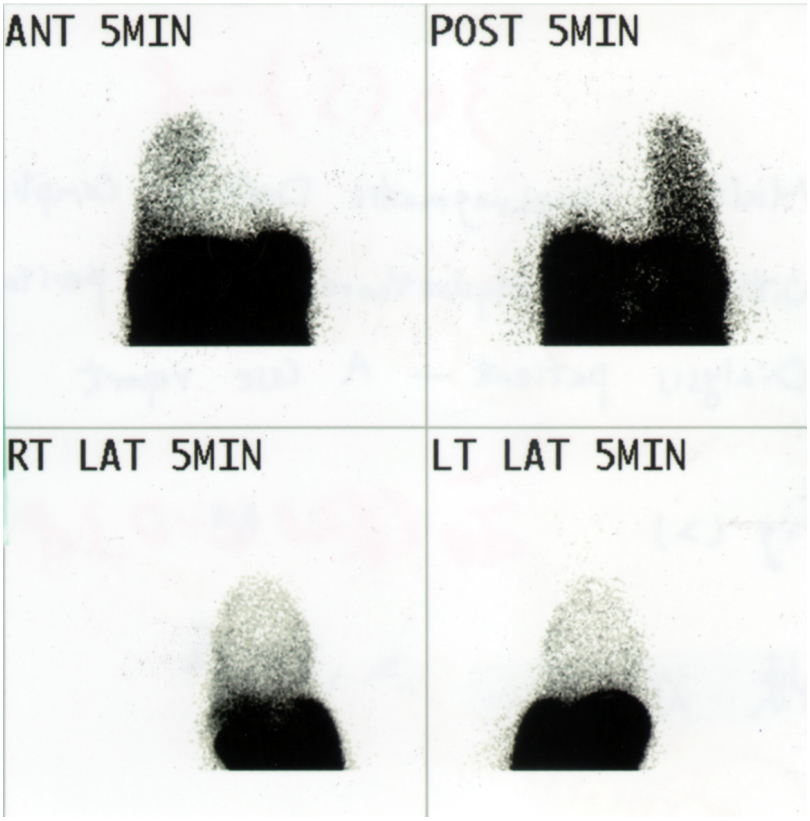

Fig. 2. Peritoneal scintigraphy was performed following injection of 5 mCi of technetium-99m Phytate through the peritoneal dialysis route. Images were taken 5 minutes later. The picture showed increased activity in the right lung field.

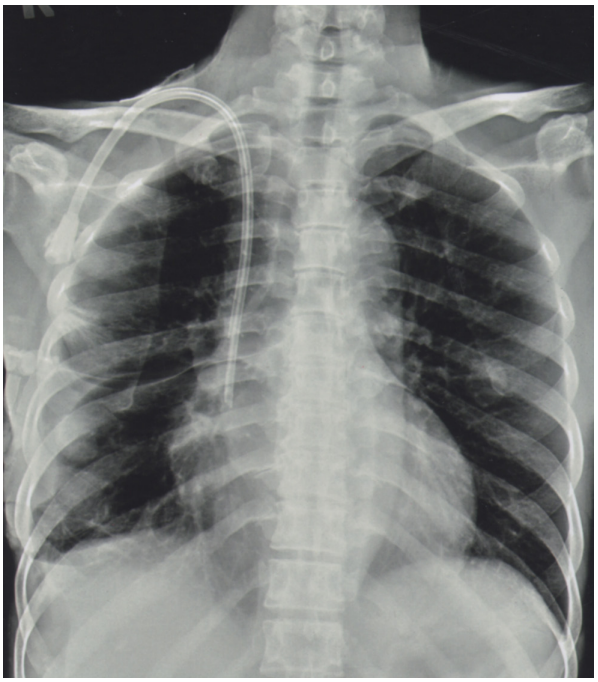

Fig. 3. After video-assisted thoracoscopy with endoscopic sutures for the diaphragmatic defects, the patient chose hemodialysis as a renal replacement. Chest X-ray follow-up showed the Hickman catheter in situ without recurrence of hydrothorax.

1). Thoracocentesis was performed for symptomatic relief and about 1000 ml of clear light straw-colored pleural fluid was drained out. The pleural fluid was submitted for further analysis and the results showed glucose 223 mg/dl, total protein less than 1.0 g/dl, lactate dehydrogenase 11 unit/l, WBC count 19/μl and RBC count 32/μl. The cytology study showed no evidence of malignant cells, and no microorganisms grew in the pleural fluid culture. Although she was diagnosed with type 2 DM, the patient had fair blood glucose control, with HbA1c 5.6%. During the thoracocentesis, serum glucose was 101 mg/dl and ascites glucose was 331 mg/dl.

As pleuro-peritoneal communication was still highly suspected, we arranged peritoneal scintigraphy with a technetium-99m Phytate shunt scan. This procedure was performed following injection of 5 mCi of technetium-99m Phytate through the peritoneal dialysis route. Images were taken 5 minutes later. The result showed increased activity in the right lung field, suggestive of the existence of pleuro-peritoneal communication (Figure 2). We consulted the chest surgeon for further survey. Video-assisted thoracoscopy was performed, and showed multiple diaphragmatic defects. Surgical diaphragmatic repair was then done with endoscopic sutures. Thereafter, the patient changed her renal replacement therapy to hemodialysis. No recurrent hydrothorax was found in the subsequent follow-up course (Figure 3).

Discussion

Peritoneal dialysis is a renal replacement therapy for patients with end-stage renal disease. The use of peritoneal dialysis is expected to increase, for it allows patients more freedom in daily activities. In terms of infectious complications, bacterial peritonitis is the most common [1]. Of the non-infectious complications, ultrafiltration failure is considered to be the most common, followed by hernia and exit site leak [2]. Van Dijk *et al*. reported that in peritoneal dialysis patients, the anatomic complication rate for the peritoneal cavity boundary is about 10%, and for hydrothorax, it is less than 1% [3].

The first description of pleuro-peritoneal leakage causing pleural effusion in a peritoneal dialysis patient was in 1967 [4]. The clinical presentations included respiratory distress, especially dyspnea or shortness of breath. The severities of discomfort depend on the rate of pleural fluid accumulation and lung collapse. About 25% of patients is symptomless [5]. Due to fluid accumulation in the pleural space, these

patients may be identified as having decreased ultrafiltration of the dialysis.

The possible mechanisms include lymphatic drainage disorder, pleuro-peritoneal pressure gradient and a congenital diaphragmatic defect [6]. The congenital diaphragmatic defect theory seems to be able to explain the preponderance of right-side hydrothorax, because the left-side defects are covered by the heart and pericardium. Others have proposed that an embryonic remnant, the pneumatoenteric recess and the infracardiac bursa, provides a route connecting the peritoneal cavity to the right pleural space [7]. Clinical observation and a large multicenter study in Japan have shown that the majority of acute hydrothorax has developed on the right side [5]. Furthermore, more right-side hydrothorax was observed in females [8]. The patient that we reported was also a female with right-side hemithorax involvement.

Diagnostic approaches to peritoneal dialysis-related hydrothorax could be divided into biochemical and imaging studies. We generally perform thoracocentesis and pleural fluid analysis for further survey of those patients with pleural effusion. These approaches are believed to be helpful and sometimes diagnostic in peritoneal dialysis-related hydrothorax. Pleural fluid analysis can reveal a transudate with a very high glucose concentration [9]. Some researchers believe that a pleural fluid glucose concentration greater than 300 mg/dl is diagnostic [10]. Chow *et al*. suggested that a glucose concentration gradient of pleural fluid to serum greater than 50 mg/dl has nearly 100% sensitivity and specificity in confirming the diagnosis of pleuro-peritoneal communication [11].

However, the interpretation should be very careful, particularly for patients with hyperglycemia. With its low molecular weight, glucose could move from blood to pleural fluid across the endothelial and mesothelial membranes by simple diffusion. Therefore, simultaneously checking the glucose levels in pleural fluid, ascites and serum is indicated.

Imaging studies include intraperitoneal infusion of contrast material via the catheter with plain abdominal X-ray, computed tomography, or intraperitoneal infusion of a radioisotope (technetium-tagged macro-aggregated albumin) followed by peritoneal scintigraphy. In general, the most commonly used method would be peritoneal scintigraphy [9,12].

After the diagnosis is confirmed, the next issue is treatment. Interruption of the peritoneal dialysis should be the initial management to avoid further deterioration. Therapeutic thoracocentesis and pleural fluid drainage are indicated for acute or persistent symptoms. Interruption of peritoneal dialysis for 2 to 6 weeks is recommended [6,13]. Although spontaneous closure of the pleuro-peritoneal communication with resumption of peritoneal dialysis has been documented [14-15], whether to temporarily or permanently shift to hemodialysis depends on the patient's condition and inclination.

Pleurodesis via instillation of sclerosing agents is another way to treat recurrent pleural effusion. The instillation agents include talc, tetracycline, autologous blood and OK-432. The choice of agent depends on effectiveness, cost, convenience and possible side effects. However, due to the anticipated adhesion, performing thoracoscopy after failure of conventional pleurodesis would be a problem [15].

Video-assisted thoracoscopy is less invasive than conventional thoracotomy, and is widely used to resolve thoracic problems. This procedure permits excellent visualization of the entire parietal pleura and diaphragm surface with

minimal incisions. Not only can video-assisted thoracoscopic pleurodesis be performed, but the surgeon can also directly repair the diaphragmatic defects. More and more encouraging results have been reported that support the use of video-assisted thoracoscopy with endoscopic suture in treating peritoneal dialysis patients who have diaphragmatic defects [16-18]. The patient we reported received this kind of treatment and used hemodialysis before and after surgical intervention. Thereafter, she permanently switched to hemodialysis. Video-assisted thoracoscopy with endoscopic sutures can repair diaphragmatic defects and prevent subsequent possible diaphragmatic hernia. Our patient had a good outcome without recurrence.

We would like to conclude here that more similar cases will probably be reported because of the increasing use of peritoneal dialysis. The majority of cases will probably be on the right side. "Sweet" pleural fluid obtained from thoracocentesis will be helpful in the diagnosis of these patients. Simultaneous checking and careful interpretation of the glucose levels of pleural fluid, ascites and serum are indicated. Imaging studies, such as peritoneal scintigraphy, can provide more evidence for confirmation. Interruption of peritoneal dialysis for 2 to 6 weeks is usually recommended, and whether to temporarily or permanently shift to hemodialysis depends on the patient's condition and inclination. We think that video-assisted thoracoscopy with endoscopic sutures is a reasonable choice for peritoneal dialysis patients who have diaphragmatic defects.

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腹膜透析患者併發橫膈缺損及急性水胸－病例報告

陳煥威 *,** 林楷煌 *,** 劉小華 *,*** 陳皇吉 *,**

腹膜透析是末期腎病的患者，在接受腎臟替代療法中的一種選擇，目前來說確實愈來愈被廣為使用。在所有與腹膜透析相關的併發症中，水胸這個併發症的發生比例相對較低，而且這個疾病也有其特殊的表現。我們所提的這個病例報告是一位 51 歲因為末期腎病而接受腹膜透析的女性患者，她就醫主要的問題是一個禮拜的乾咳以及愈來愈厲害的呼吸喘促。胸部 X 光顯示有大量的右側肋膜積液，而且肋膜積液的分析顯示出有高的葡萄糖含量。我們安排腹部的鎵 -99m 閃爍攝影檢查，發現在右邊肺野的放射線活性增高，顯然有胸腔腹腔交通的問題存在。影像輔助的胸腔內視鏡檢查發現有多處橫膈缺損，因此接著做內視鏡橫膈修補。之後，這個患者將她的腎臟替代療法改為血液透析，也不再有水胸的這個問題復發。針對這樣一個腹膜透析相關的水胸，生化和影像方面的檢查都有助於診斷的確立。而且影像輔助的胸腔內視鏡檢查合併內視鏡修補，理應是一個適當的治療選項。*(胸腔醫學 **2015; 30: 314-320**)*

關鍵詞：水胸，胸腔腹腔交通，腹膜透析

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Amenorrhea in a Patient with Pulmonary Tuberculosis

Yu-Cheng Chen, Jann-Yuan Wang

Menstrual abnormalities may occur in women with pulmonary tuberculosis (TB). The association between non-genital TB and amenorrhea is not well understood. We present the case of a 22-year-old unmarried woman who suffered from secondary amenorrhea before and during anti-TB treatment, and who recovered spontaneously thereafter. This case demonstrates that gynecologists should always consider pulmonary TB as a possibility in women presenting with menstruation abnormality in a TB endemic area, and physicians should pay attention to menstruation issues when treating women with TB who are of reproductive age. Gynecologist consultation may be necessary in order to prevent permanent infertility. ***(Thorac Med 2015; 30: 321-325)***

Key words: infertility, *menstruation*, *Mycobacterium tuberculosis*, secondary amenorrhea, *tuberculosis*

Introduction

Tuberculosis (TB) remains a major medical problem, regardless of whether it is a pulmonary or extra-pulmonary-based disease. In cases of air transmission, the lung is the most common site of involvement. With hematogenous or lymphatic spread, TB can result in a variety of extra-pulmonary symptoms and conditions. Urogenital TB has long been responsible for intra-uterine adhesion, causing hypomenorrhea, secondary amenorrhea (defined as cessation of regular menses for 3 months) and even infertility. As a result, TB is the leading cause of female infertility in developing countries [1-2].

Other causes of secondary amenorrhea include unexpected pregnancy, hyperthyroidism, adrenal tumor, pituitary gland disease, ovarian disease, uterus disease, medication use and stress [3]. Even without urogenital involvement, approximately 2/3 of women in their child-bearing years still complain of menstrual problems when they suffer from TB [4]. The presentations may be secondary amenorrhea, spotting during menstrual periods, hypomenorrhea, shorter duration of the menstrual period, and pelvic pain. The mechanism remains unclear, but patients with more advanced pulmonary involvement and prolonged courses were more susceptible. After completing anti-TB treatment, most patients resumed their normal menstrual cycles [4]. Here, we report a woman with pulmonary TB, but not urogenital TB, complicated with amenorrhea, and review the

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related literature.

Case Report

A 22-year-old unmarried woman with the chief complaint of an irregular menstrual cycle for 4 months and no menstruation for 2 months, visited our gynecologic outpatient clinic. Her menarche was at the age of 14. She had neither abdominal pain nor abnormal vaginal discharge. She had begun to be sexually active at the age of 18 and had no prior history of pregnancy. A urine pregnancy test was ordered and the result was negative. She did not take oral contraceptive pills (OCP) and denied any underlying medical condition. Her weight was 58 kg. There was no goiter, excessive hair growth, or galactorrhea upon physical examination. Transvaginal sonography (TVS) reported no uterine or ovarian lesion. Her serum hormone profile revealed elevated follicle-stimulating hormone (FSH, 112 IU/mL, normal range 5 to 20 IU/mL), normal estrogen (E2, 37 pg/mL, range 20 to 145 pg/mL), and normal TSH (2.22 uIU/mL, range 0.4 to 4 uIU/mL). Serum cancer antigen 125 (CA-125) was borderline (23.7 u/mL, range 0 to 35 u/mL). She refused hysterosalpingography, laparoscopy and hysteroscopy, and simply received close clinical follow-up. However, fever and productive cough developed 1 month later. The symptoms persisted for 2 months and were refractory to antitussives and antipyretics, so she was referred to a pulmonologist for further evaluation.

In the examination, neither palpable lymph nodes nor crackles were found. Laboratory tests revealed leucocytosis (leucocyte 19700 /mL) with a predominance of neutrophils with differential (93.3%) and mild anemia (hemoglobin 10.8 g/dL). Serology testing for human immunodeficiency virus infection was found to be negative. Chest radiography (Figure 1) revealed a nodule with an adjacent infiltrate in the right upper lung field. One of the 3 sputum samples was smear-positive for acid-fast bacilli (1+). The diagnosis of pulmonary TB was later confirmed by the positive result on her nucleic acid amplification test (NAAT) for *Mycobacterium tuberculosis* complex. Standard and supervised anti-TB treatment with daily isoniazid 300 mg, rifampin 600 mg, ethambutol 1200 mg, and pyrazinamide 1500 mg was then started. All 3 of the initial sputum samples were culture-positive for susceptible *M. tuberculosis* complex.

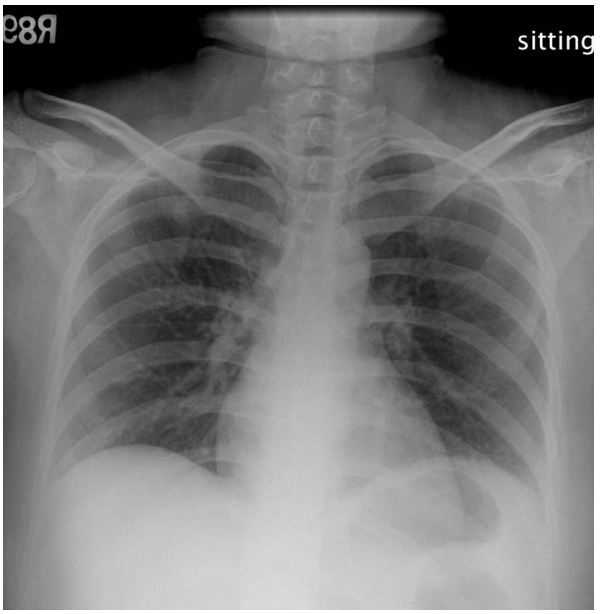

Fig. 1. Chest radiography showing a nodule with adjacent infiltrate in the right upper lung zone

At the time of starting anti-TB treatment, she had already had no menstruation for 5 months. Two months later, her menstrual period began spontaneously, and again after 2 more months. Follow-up TVS still revealed negative findings for the uterus and adnexa. Her FSH and E2 were normalized (11.8 mIU/mL

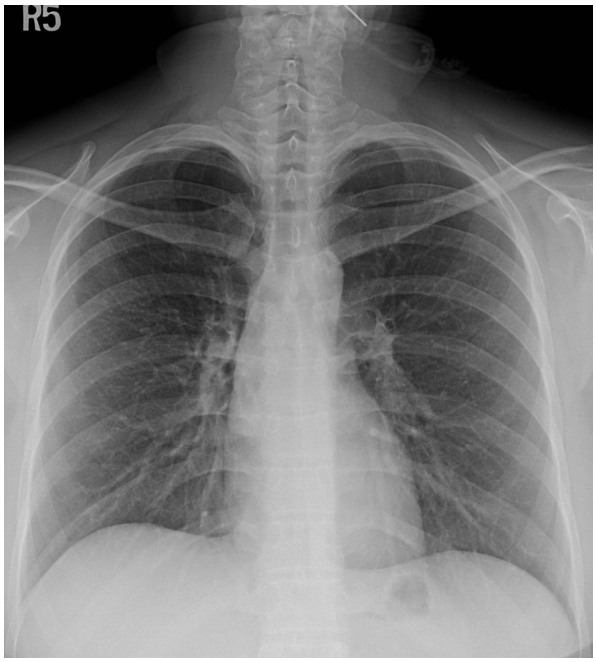

Fig. 2. Chest radiography after completion of anti-tuberculosis treatment showing resolution of the right upper lung nodule and infiltrate

and 78.8 pg/mL, respectively) at the end of the anti-TB treatment. No major adverse reactions developed during the 6-month treatment course. Chest radiography showed resolution of the right upper nodule and infiltrate (Figure 2). She was regularly followed up at our gynecologic clinic without any further menstruation problems.

Discussion

This case demonstrates the impact of TB on menstruation. Genital TB, which is notorious for its poor prognosis with regard to fertility, can cause direct injury to the urogenital tract, resulting in TB salpingitis, TB endometritis and ovarian TB [1-2]. In a study, approximately 13% of women with pulmonary TB had genital TB concomitantly [5]. Pulmonary TB without urogenital involvement may play a role in women with menstrual problems [4], but is seldom regarded as the cause in surveillance.

Investigations on menstrual disorder rely on careful clinical history-taking and physical examination focused on hirsutism, galactorrhea, thyroid goiter, sexual experience, surgery and medication. Urine pregnancy test (β-human chorionic gonadotropin, thyroid-stimulating hormone, prolactin, FSH, and luteinizing hormone measurements) is always the first line of testing. Serum androgen level exam can be arranged if adrenal tumor is suspected in women with symptoms of hirsutism and acne. Hysterosalpingography and hysteroscopy are indicated if anatomic abnormality or intra-uterine infection and adhesions are clinically suspect. After common causes are excluded, the physician might as well review respiratory and constitutional symptoms of TB. Chest radiography can be arranged for screening for pulmonary TB if abnormal opacity or miliary lesions are present.

Since only TVS was performed, genital TB may have been under-diagnosed in this reported case. However, a few studies have observed menstrual abnormalities in patients with pulmonary TB [6-8]. In a retrospective cohort study, menstrual abnormalities were noted in 66% of women with non-genital TB and 28% of normal individuals ($p<0.001$) [4]. It is worth noting that the incidence of secondary amenorrhea was significantly higher in the former group (26.5% vs. 20%, $p<0.001$). However, the underlying pathophysiology remains unclear. Non-genital TB may affect menstrual function with a complex number of inter-related mechanisms regarding hypothalamic-pituitary-ovarian function [9]. Hypo-estrogenic menstrual abnormality has been described in patients with a long duration of symptoms and serious/advanced stages of

disease [4,10-11]. The anti-gonadotrophic action of mycobacterial endotoxin on the ovarian granulosa cells may also play a role [12].

The treatment course for menstrual abnormality is usually benign, and excessive or prolonged vaginal bleeding is not observed [4,7]. Timely and appropriate treatment for the underlying disease, TB, will usually restore the patient's menstrual cycle back to normal [4,7]. Approximately 3/4 of women with pulmonary TB and menstrual abnormalities resume a normal menstrual cycle after the completion of anti-TB treatment [4-5,7]. Those women whose normal menstrual cycle is restored can conceive and give birth to normal babies.

In summary, this case highlights the importance of appropriate cooperation between chest specialists and gynecologists for women with TB. In TB endemic areas, gynecologists should consider pulmonary TB as a possible etiology for menstruation abnormality. Pretreatment counseling of women with pulmonary TB should include information on these reversible changes. Persistence of menstrual abnormalities or presence of infertility after completion of treatment should raise immediate concern and prompt an investigation into the possibility of genital tract involvement.

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一位肺結核病人的閉經症

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經期異常可以發生在有肺結核但沒有生殖器結核病的婦女，但其與閉經症之間的關聯性並未明確。我們報告一位 22 歲的婦女在接受肺結核治療前及治療中罹患次發性閉經症之後自然痊癒。本案例說明醫師在對生育年齡的婦女治療肺結核時，需留意其月經問題。為防止永久性不孕症的發生，婦產科醫師的諮詢可能是必要的。*(胸腔醫學 **2015; 30: 321-325**)*

關鍵詞：不孕症，月經，結合分枝桿菌，次發性閉經症，結核

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