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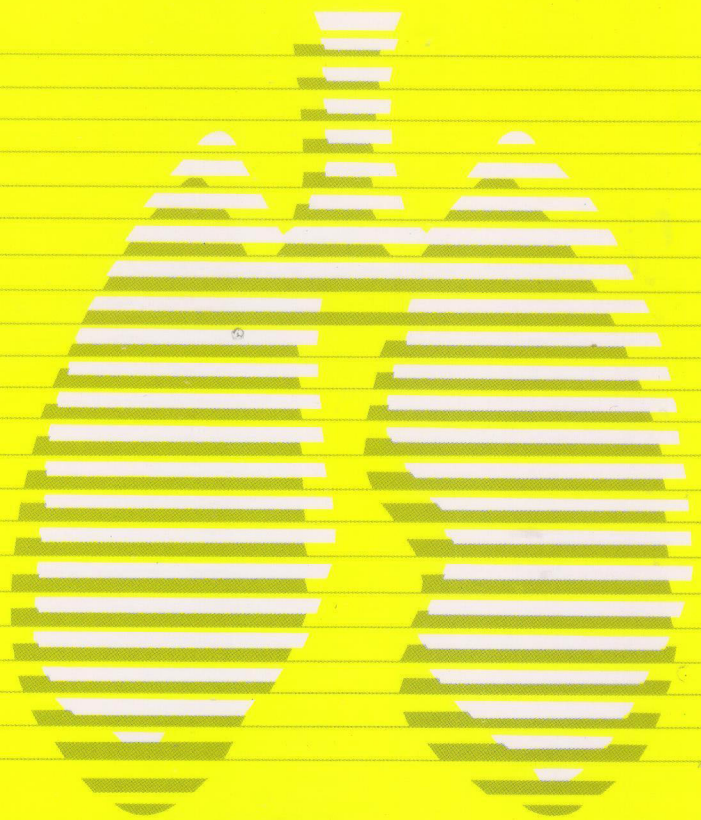

台灣胸腔暨重症加護醫學會

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原著

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Orginial Articles

Case Reports

Use of a Rapid Shallow Breathing Index from a Commercially Available Respiratory Monitor in Predicting Weaning of Ventilated Patients

Chieh-Jen Wang*, Fung-J Lin**,***, Chien-Liang Wu*,**

Objective: Frequency-to-tidal volume ratio (f/Vt) has been widely used as a weaning predictor for years. A method using a hand-held monitor with an automatic f/Vt calculation was tested in this study to verify its clinical application.

Design: This was a prospective study of 102 respiratory failure patients ready for weaning in a 15-bed adult medical intensive care unit (ICU). Two f/Vt measurements were taken daily: 1 by the standard manual calculation (Yang's method) and the other by the VentCheck™ monitor. Weaning was considered successful if the patient tolerated 2-hour trials without distress and remained free from mechanical ventilation for at least 48 hours. The patients were divided into successfully and unsuccessfully weaned groups. The sensitivity, specificity, and likelihood ratio of these predictors were calculated and the data were analyzed with an ROC curve to examine accuracy.

Results: The overall weaning success rate was 67.6%. There were no significant differences in the APACHE II score, age, gender, and diagnosis between the 2 groups. Sensitivity and accuracy were higher for Yang's method (traditional) than the 1-minute f/Vt (91.3% vs. 81.2% and 82.4% vs. 79.4%, respectively), but the areas under the ROC curve were similar for both measurements (0.86).

Conclusions: The 1 minute f/Vt using the VentCheck™ monitor is comparable to Yang's method in predicting successful weaning of ICU patients. ***(Thorac Med 2009; 24: 186-192)***

Key words: rapid shallow breathing index, weaning predictors, mechanical ventilation, spontaneous breathing trial

Introduction

Frequency-to-tidal volume ratio (f/Vt) [1], also known as the rapid shallow breathing index (RSBI), has long been used as a predictor for weaning. Although several potential weaning predictors, like the weaning index (WI) [2] and airway occlusion pressure ($P_{0.1}$) [3] have been proposed, f/Vt remains the most widely used. Ely *et al*. [4] first integrated the "wean-

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ing predictor", f/Vt, into his "daily screen" to select patients for spontaneous breathing trials. In such cases, respiratory therapists performed f/Vt measurements several times in the morning. Although the measurements are simple, the method is entirely manual, and therefore time-consuming. A computer-aided device can lower the workload and increase accuracy. We used a hand-held device, VentCheck™, with differential pressure and single-patient-use flow sensors to provide the breath-by-breath status of the patient's respiration, including f/Vt. The positioning of its measurement is the same as in the traditional method, but without the manual calculation. We therefore conducted this prospective study to compare the accuracy of automatic f/Vt measurement with that of manual measurements in predicting successful weaning.

Materials and Methods

Patients

This study was conducted in a 15-bed adult medical intensive care unit (ICU) of a 450-bed regional referral hospital from March 1, 2005 to May 31, 2005. The study design was approved by the hospital's Institutional Review Board and informed consent was waived because all of the procedures were considered routine clinical practice.

All of the patients admitted to the ICU and on mechanical ventilation for more than 48 hours were enrolled, except those not breathing spontaneously. When a patient's clinical condition improved and the causes of respiratory failure had been controlled or stabilized, daily screening of weaning based on the protocol of Ely *et al*. [4] was performed each morning. In addition, the respiratory therapists would perform 2 measurements of f/Vt: 1 by the traditional method [1] and the other by VentCheck™, a handheld respiratory mechanical monitor with breath-by-breath f/Vt display, at 15-minute intervals.

The order of each measurement was arranged using a random digit chart. Patients were returned to the previous ventilation mode during the period between the 2 methods of measurement. After the measurement, if there was a measured f/Vt value (by either method) below 105, a spontaneous breathing trial (SBT) using a T-piece was conducted by the respiratory therapists. The ICU physicians assigned to perform SBT evaluation were blinded to the method of f/Vt measurement. SBT was not conducted if all measurements were higher than 105.

SBT was considered a success if none of the following occurred within 120 minutes of the test: respiratory rate >35 breaths/min; oxygen saturation by pulse oximeter <90%; heart rate >140 beats/min or a sustained increase or decrease in the heart rate by more than 20%; systolic blood pressure >200 mmHg or <80 mmHg; and agitation, diaphoresis, or anxiety [5]. If the patient did not pass the daily screening or the SBT, the previous mechanical ventilation mode was resumed until the next morning. Screening was repeated daily until either the patient passed the SBT or worsened clinically. Weaning was classified as successful if the patient could maintain spontaneous breathing for 48 hours (with or without extubation). Weaning was defined as failure if the patients could not tolerate SBT for 48 hours or if f/Vt remained higher than 105 after 1 week. Otherwise, weaning was classified as unsuccessful.

Equipment

The traditional f/Vt measurements were the same as those described by Yang and co-worker

[1]. New predictors were obtained using a portable lung mechanical monitor (VentCheck™, Novametrix, Wallingford, CT). According to the operating manual, the displayed value of f/Vt was the real-time measurement. The machine automatically renewed the data breath by breath. The measurement procedure for this device was similar to the traditional method: after disconnection, the patient breathed room air spontaneously for 1 minute. The monitor was attached to the end of the endotracheal tube by a flow sensor (dead space 8 ml). The displayed value at the end of 1 minute was defined as the 1-minute f/Vt.

Statistical Analysis

Results are presented as means ± standard deviation (SD). For analysis, the patients were divided into 2 groups: those patients successfully weaned and those who failed. The paired t-test or Chi-square test was used to compare differences between the groups. Measurements of the area under the receiver operating characteristic (ROC) curves were performed with MedCalc, ver. 9.2 (MedCalc Software, Mariakerke, Belgium).

Differences in diagnostic accuracy between the 2 methods were estimated using the difference in the area under the ROC. Sensitivity, specificity, and positive and negative likelihood ratios for each method were also calculated at the recommended cut-off (f/Vt <105). All of the other statistical analyses were performed with SPSS, ver. 13.0 (SPSS Inc, Chicago, Ill). All p values and confidence intervals (CIs) were 2-sided. A p value <0.05 was considered statistically significant.

Results

A total of 102 consecutive patients (72 males and 30 females) were enrolled in the study. The main reasons for ICU admission were pulmonary disorders (66%), followed by cardiovascular disorders (25%) (Table 1). The distributions were not significantly different between the 2 groups. There was no significant difference in disease severity and gender distribution (Table 1).

Two hundred ninety-four SBTs were conducted in this study. Only the last SBT measurement from each patient was used for the final analysis. Of the 102 patients, 69 (68%) were classified as having been successfully weaned

Table 1. Baseline characteristics of patients successfully and unsuccessfully weaned

	Successful Weaning (n=69)	Unsuccessful Weaning (n=33)	*p* value
Age, years	68.5 ± 16.1	73.4 ± 16.2	0.15
Gender, male (%)	53 (77%)	19 (58%)	0.078
APACHE II Score	20.4 ± 7.2	20.4 ± 6.8	0.98
Causes of ICU admission			0.073
Respiratory disorders	45 (65%)	22 (67%)	
Cardiovascular disorders	20 (29%)	5 (15%)	
Others	4 (6%)	6 (18%)	

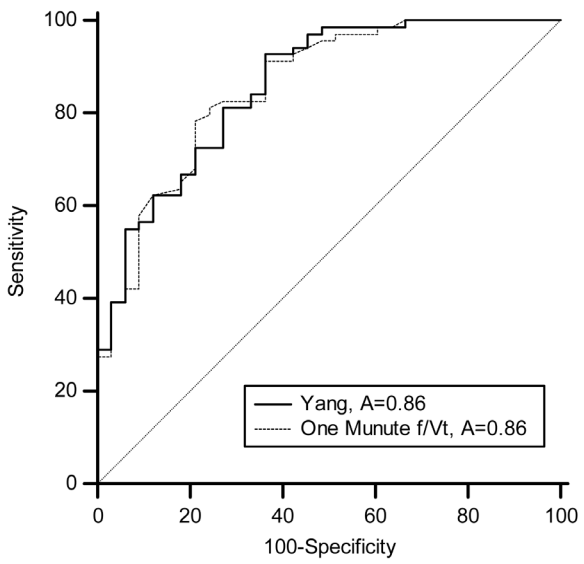

Fig. 1. ROC curves for the Yang's and VentCheck™ methods in predicting successful weaning (use "1-minute f/Vt" below)

(Table 1). Those who underwent successful weaning had fewer SBT trials (successful: 2.5 ± 2.0 vs. unsuccessful: 3.6 ± 3, p=0.027). The 1-minute f/Vt and Yang's f/Vt in the successfully weaned group were 77.6 ± 32.1, 78.4 ± 25.8, respectively (Table 1).

For all of the patients, the ROC areas were 0.858 (95% CI, 0.78-0.94) for Yang's method, and 0.856 (95% CI, 0.78-0.93) for the 1-minute f/Vt by VentCheck™, (Figure 1). The areas under the ROC curve were not significantly different between the 1-minute f/Vt and Yang's method. As shown in Table 2, sensitivity was higher for Yang's method, while specificity was higher for the VentCheck™ method at the traditional cut-off value. The 1-minute f/Vt also had the higher positive likelihood ratio for predicting successful weaning compared with Yang's method.

Discussion

Our findings showed that the 1-minute f/Vt by VentCheck™ has a higher positive likelihood ratio for predicting successful weaning

Table 2. Area under the ROC curve and test characteristics of the 3 different measurement methods

Methods	Yang's method	One minute f/Vt
AUC	0.858	0.856
(95% CI)	(0.781 to 0.935)	(0.778 to 0.934)
Sensitivity	91.3%	81.2%
(95% CI)	(82.0 to 96.7)	(69.1 to 89.6)
Specificity	63.6%	75.8%
(95% CI)	(45.1 to 79.6)	(57.7 to 88.9)
Positive LR	2.51	3.35
(95% CI)	(1.59 to 3.97)	(1.81 to 6.18)
Negative LR	0.14	0.25
(95% CI)	(0.06 to 0.31)	(0.15 to 0.42)
Accuracy	82.4%	79.4%
(95% CI)	(75.0 to 90.0)	(71.6 to 87.3)

AUC=Area under the curve; 95% CI=95% confidence interval; Positive LR=positive likelihood ratio; Negative LR=negative likelihood ratio.

than the traditional Yang's method, and that the 2 methods were comparable in predicting weaning outcome, based on the ROC curve analysis (Figure 1). But advantage of the 1-minute f/Vt is its automatic calculation, which reduces measurement errors and decreases time consumption. Its higher positive likelihood ratio also suggests fewer futile trials.

In the original report on the use of indexes, a threshold value of f/Vt <105 was used to provide the best discrimination between weaning success and failure [1]. In subsequent years, several studies used different cut-off values (60-105) and yielded varied likelihood ratios (0.84-4.67) [6]. McIntyne *et al*. [6] concluded that clinicians might conduct a carefully monitored SBT without any predictor measurements. However, Stoetz *et al*. [7] showed that clinical judgment alone might not be reliable. The argument surrounding these results might be due to deviations in methodologies [8]. If we tried to apply a diagnostic test to clinical practice, we would have to perform and interpret it in the manner described in the reference study.

Tobin *et al*. [10] pointed out that failure to consider the effects of spectrum and test-referral bias on pre-test probability might lead to misinterpretation of the reliability of weaning-predictor tests. In their study, the Bayesian model was used to evaluate the varied performances of weaning-predictor tests in previous trials and found that the original f/Vt value was still a reliable screening test. Our 1-minute f/Vt was compatible with the original f/Vt in terms of accuracy. Its calculation was automatic, time-saving, and accurate. Furthermore, a useful weaning index should have a higher conditional probability (a high likelihood ratio) [11-12]. From this standpoint, our 1-minute f/Vt was advantageous, in that futile trials were avoided compared with the original f/Vt.

Our study had some limitations, however. First, it was a single hospital study. The enrolled patients might not be representative of the entire patient population. Moreover, male patients accounted for 70% of the study population. Epstein *et al*. [13] reported that female patients had a higher f/Vt than men, especially when breathing through small endotracheal tubes. Patients in this study had to meet the criteria of f/Vt <105 before undergoing an SBT trial, which might have delayed the SBT trial for female patients. Also, we did not record the length of stay in the ICU and the number of mechanical ventilation days because the original purpose of this study was to "validate" the VentCheck method as an f/Vt calculator. However, the missing data obviously weakened the power of differentiating the efficacy between the methods.

Secondly, the definition of weaning in our study focused on spontaneous breathing, not on extubation. The main reason for this was that some patients had had previous tracheostomy, or delayed extubation had been ordered by the primary care physicians for airway protection. However, as Tobin *et al*. [10] have reported, if tolerance for extubation was used as the gold standard in evaluating the reliability of a weaning-predictor test, the study population would be skewed towards less severely ill patients because some patients would be too weak to tolerate extubation.

We conclude that single breath f/Vt (1-minute f/Vt) obtained by a hand-held monitor has an accuracy comparable with the original method, but is faster and easier to perform. The higher likelihood ratio of this index (1-minute f/Vt) suggests it is a more useful weaning predictor than the original one. However, the application of this new weaning index requires more inves-

tigation for further validation.

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以單一呼吸測量的淺快呼吸指數對加護病房的呼吸器離脫預測的正確性

王玠仁* 林芳杰**,*** 吳健樑*,**

前言：淺快呼吸指數（f/Vt）被運用來預測呼吸器離脫已經有許多年的歷史。我們發現了一種掌上型監測裝置可快速且自動計算出此參數，然而其測量方式有異於傳統的方法。為了驗證其臨牀可用性，我們因此設計了這個研究。

方法：這是一個前瞻性研究，在一地區後送醫院15床的內科加護病房進行；共有102個準備離脫呼吸器的病人被納入。每個病人以隨機次序接受兩次淺快呼吸指數的量測，一種是傳統的手動測量，另一種（one-minute f/Vt）則以掌上呼吸參數監測器VentCheck™獲得。離脫成功的定義為病人成功的通過兩小時的自主呼吸測試且在後續48小時內不再接受呼吸器的輔助呼吸。病人自主呼吸測試的結果被分入成功及失敗組，各參數的敏感性，特異性及離脫可能性都分別計算出來並以ROC曲線來分析它們的正確性。

結果：整體病人的離脫成功率是67.6%。在離脫成功及失敗組間病人的疾病嚴重度（APACHE II score），年紀，性別，及疾病形態並無統計學上差異。這兩個參數都能正確的區分出成功和失敗組的病人（$p < 0.001$）。敏感性與正確性仍以傳統方式較1-minute f/Vt為高。分別為（91.3% vs. 81.2% and 82.4% vs. 79.4%），但以ROC曲線來檢測時兩者並無差異（0.86）。

結論：以掌上型呼吸監測器VentCheck™取得的one-minute f/Vt和傳統方式測得的f/Vt一樣有效。*(胸腔醫學* ***2009; 24: 186-192)***

關鍵詞：淺快呼吸指數，離脫參數，機械性通氣輔助，自主呼吸測試

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Transudative Chylothorax: Two Case Reports and Review of the Literature

You-Lung Chang, Chao-En Huang, Chien-Tung Chiu, Yu-Feng Wei, Yung-Fa Lai

Chylothorax is uncommon and transudative chylothorax is even rarer. In contrast to exudative chylothorax, the most common etiologies of transudative chylothorax are liver cirrhosis, congestive heart failure, nephrotic syndrome and superior vena cava thrombosis. We present 2 case reports of transudative chylothorax: The first case describes a man who had shortness of breath and orthopnea for 3 days, mimicking congestive heart failure. After a series of workups, nephrotic syndrome-related chylothorax was diagnosed, and diuretics and a low-salt diet were prescribed. No recurrence of dyspnea was noted during 1 year of follow-up. The second case involved a woman that suffered from progressive dyspnea for 2 months. After a thoracentesis study, we ruled out congestive heart failure and nephrotic syndrome. Liver cirrhosis-related chylothorax was later confirmed. However, the patient's symptoms recurred, even after receiving diuretic treatment and with low-salt diet control. We also reviewed the medical literature to remind clinicians of the importance of avoiding unnecessary workups if chylothorax is transudative. ***(Thorac Med 2009; 24: 193-198)***

Key words: transudate, chylothorax, nephrotic syndrome, cirrhosis

Introduction

Chylothorax forms when the thoracic duct is disrupted and the chyle leaks into the pleural cavity [1]. Medical staff generally associates chylothorax with malignancy, trauma and surgery. However, the etiologies differ if chylothorax is transudative. We report 2 cases of transudative chylothorax, and stress the importance of avoiding unnecessary workups if chylothorax is transudative.

Case Reports

Case 1

A 60-year-old man was admitted due to progressive dyspnea and orthopnea for 3 days. Paroxysmal nocturnal dyspnea and exertional dyspnea were also noted. On physical examination, his jugular vein was engorged. Pulmonary auscultation revealed bilateral crackles, with the left lower lobe louder than the right. On cardiac auscultation, a regular heart beat with grade 2 systolic murmur was noted. Abdominal

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examination revealed mild ascites and the lower extremities were edematous.

Chest radiography revealed right-side pleural effusion and increased infiltrates (Figure 1). ECG showed a normal sinus rhythm without STT change. Hemogram showed a leukocyte count of 14.8 x 10^9/L (neutrophils 89.5%, lymphocytes 6.7%), hemoglobulin of 11.0 g/dL and a platelet count of 219 x 10^9/L. The biochemistry study revealed blood urea nitrogen/creatinine of 28.8/2.5 mg/dL, troponin-I of 0.025 ng/mL and blood glucose of 101 mg/dL. The thoracentesis study revealed milk-like pleural effusion, and transudative chylothorax was confirmed (Table 1). A chest and abdominal computed tomography scan showed no solid tumor or lymphadenopathy, but right pleural effusion with atelectasis, mild ascites and congestive mesenterium (Figures 2A and 2B) was noted. The bronchoscopic study showed no endobronchial lesions. The results of the serum tumor marker study were within normal limits. The 24-hour creatine clearance rate was 26.3 mL/min and 24-hour urine total protein loss was 10.4 g/day. The workup for nephrotic syndrome showed negative antinuclear antibody, rheumatic factor and VDRL activity, C3/C4 of 139/40.8 mg/dL, negative hepatitis B and hepatitis C virus activity, and no monoclonal gammopathy activity of serum-immune electrophoresis and urine-immune electrophoresis. Kidney biopsy

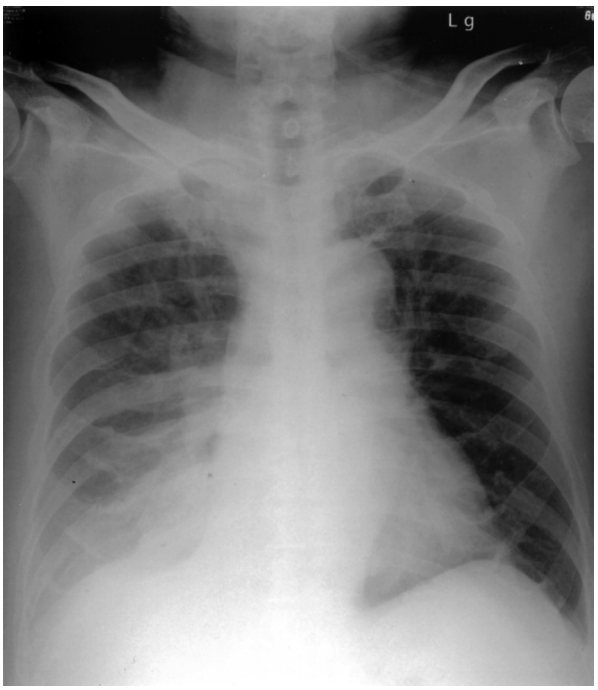

Fig. 1. Chest radiography, posteroanterior view, shows right lower increased infiltrates and pleural effusion (case 1)

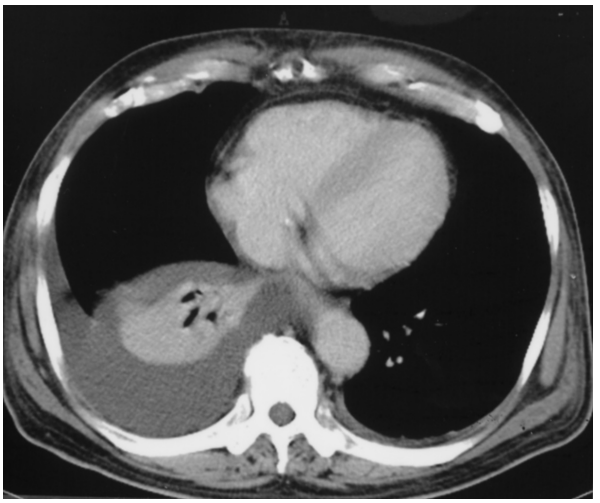

Fig. 2A. Chest computed tomography shows right pleural effusion and atelectasis (case 1)

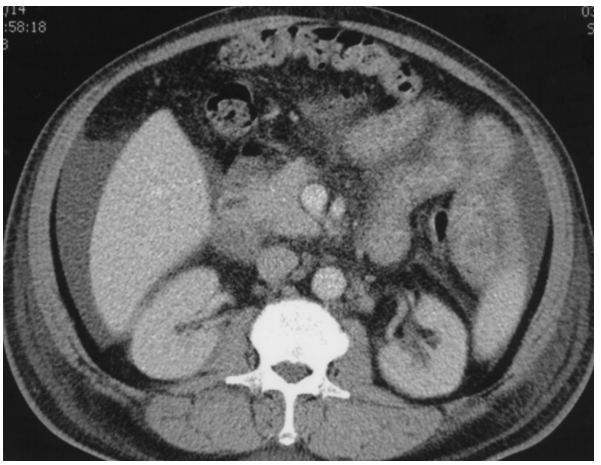

Fig. 2B. Abdominal computed tomography shows mild ascites and congestive mesenterium (case 1)

Table 1. Laboratory features of the pleural effusions

	Case 1	Case 2
Leukocyte (mm^{-3})	300	12
Lymphocyte (%)	30	34
Neutrophils (%)	18	14
Mesothelial cells (%)	23	7
Cytology	(-)	(-)

was suggested, but the patient refused.

Under the diagnosis of nephrotic syndrome-related chylothorax, the patient received diuretic treatment and low-salt diet control. The patient's body weight showed a reduction from 96 kg to 85 kg in 12 days. No recurrence of dyspnea or bilateral leg edema during the 1 year of follow-up at the outpatient department was noted, but an elevated serum creatinine level up to 3 mg/dL was documented.

Case 2

A 52-year-old woman presented with progressive dyspnea on exertion for 2 months. She had hepatitis B-related liver cirrhosis, Child-Pugh B grading, and was regularly followed up at the gastroenterology clinic. She visited the chest medicine clinic for shortness of breath. On physical examination, she looked thin and weak. Pulmonary auscultation revealed decreased breathing sounds at the right lower lung field. On cardiac auscultation, a regular heart beat without murmur was noted. Abdominal examination revealed a small liver size and no ascites, but splenomegaly. The lower extremities were dry and the patient had poor skin turgor.

The chest radiography showed right-side massive pleural effusion. The thoracentesis study revealed milk-like fluid, and transudative chylothorax was almost confirmed by the high pleural fluid triglyceride and low cholesterol levels (Table 2). Six months later, thoracentesis was performed again for repeated accumulation of pleural effusion, and the study results (Table 2) confirmed the diagnosis of transudative chylothorax. Echocardiography showed good left ventricle contractility without regional wall abnormality, and an injection fraction of 57%. Because there were no symptoms or signs of nephrotic syndrome, liver cirrhosis-related chylothorax was suspected. The patient continued to suffer repeated dyspnea on exertion during the 8-month follow-up, even under diuretics treatment and low-salt diet control, and was admitted to the hospital 3 times, presenting with hepatic encephalopathy and re-accumulation of chylothorax. A pig-tail catheter was placed for symptom relief, but the patient refused further management and was lost to follow-up.

Table 2. Laboratory features of the pleural effusions vs. serum

	Case 1		Case 2	
	Pleural fluid	Serum	Pleural fluid	Serum
LDH (U/L)	113	253	46	363
Total protein (g/dL)	0.33	3.9	0.9	6.6
Triglyceride (mg/dL)	199	381	125	34
Cholesterol (mg/dL)	32	578	13	137

LDH= lactate dehydrogenase

Discussion

Most pleural fluid with chylothorax is exudative [1]. According to a study of 203 cases of chylothorax at the Mayo clinic, surgery or trauma was the leading etiology (49.8%), followed by malignancy (16.7%) [2]. But patients with transudative chylothorax have different etiologies. Diaz-Guzman *et al*. reviewed the medical literature from 1966 to 2003 using Medline and found that liver cirrhosis, congestive heart failure, nephrotic syndrome, systemic amyloidosis and superior vena cava thrombosis were the main causes in such instances [3]. The incidence of chylothorax varied by etiology and was approximately 0.5% to 5.6% of all cases of pleural effusion [1, 4-5]. Transudative chylothorax is much less common, but Romero *et al*. [4] revealed that 20% of 24 cases of chylothorax were cirrhotic in origin, and suggested previous studies had underestimated the prevalence; only 5% of 203 cases of chylothorax were related to liver cirrhosis in another study [2]. We agree with the findings of Romero *et al*. because the appearance of chylothorax is not always milky. Clinicians may not put chylothorax into their differential diagnosis if the pleural effusion is not milk-like. Staats *et al*. reported 53% of 38 cases of chylothorax did not have a chyle-like appearance [6]; congenital chylothorax was serous in appearance before milk feedings started in another study [1].

Of all cases of transudative chylothorax, around 40% were due to liver cirrhosis and 20% were secondary to congestive heart failure [3-4]. The pathophysiology of transudative chylothorax is not clear. The possible mechanism is that elevated portal pressure along with degenerative changes in the lymphatics in liver cirrhosis and malabsorption and bowel edema in nephrotic syndrome produce chylous ascites fluid, which is then translocated across the diaphragm into the pleural cavity [4, 7-8]. To our surprise, 52% of 30 patients with nephrotic syndrome had chylous ascites in a retrospective study [7]. We believe that this mechanism fits our first case, though no radiolabeled tracer was injected into the peritoneum. To our knowledge, this is the 7th reported case of chylothorax from chylous ascites in nephrotic syndrome [3, 9-10].

The diagnostic criteria of chylothorax are the pleural fluid triglyceride levels. Pleural fluid triglyceride levels >110 mg/dl and a pleural fluid to serum cholesterol fluid level <1 make the diagnosis. In our first case, the pleural fluid to serum triglyceride ratio was <1 (199 mg/dl over 381 mg/dl). Some authors have suggested that the pleural fluid to serum triglyceride level ratio should be >1 to establish the diagnosis, but there was no relationship between the pleural and serum triglyceride levels in patients without chylothorax [1, 4, 7, 13]. We believe the phenomenon is more common in patients with nephrotic syndrome because of the tendency toward hyperlipidemia.

The prognosis of cirrhotic chylothorax is worse than that of chylothorax secondary to malignancy or trauma [4, 14]. The median duration from diagnosis to death is 5 months [4]. Poor liver function and old age may explain the poor outcome [4]. Successful conservative treatment, such as with a low-fat diet with medium-chain triglycerides and pleurodesis, or invasive treatment, for example, a transjugular intrahepatic portosystemic shunt, have been reported [15-16]. In our second case, the patient refused further treatment and was lost to follow-up. A poor prognosis was predicted in that case.

In summary, transudative chylothorax is a rare entity. In contrast to exudative chylothorax,

the etiologies are liver cirrhosis, congestive heart failure, nephrotic syndrome, amyloidosis and superior vena cava thrombosis. Unnecessary workup should be avoided if chylothorax is transudative.

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滲出液乳糜胸：兩例病例報告及文獻回顧

張祐綸　黃照恩　邱建通　魏裕峰　賴永發

乳糜胸是少見的病例而滲出液乳糜胸更是少見。不同於漏出液，滲出液乳糜胸最常見的病因是肝硬化、充血性心衰竭、腎病症候群及上腔靜脈阻塞。在此我們報告兩例滲出液乳糜胸：第一位是男性主述氣喘及端坐性呼吸三日，經過一系列檢查後發現是腎病症候群引起的乳糜胸。經低鹽飲食及利尿劑治療後，病患的情況好轉。第二位是主述漸近性氣喘兩個月的女性，在經肋膜穿刺及排除掉充血性心衰竭後，確定是肝硬化引起的乳糜胸。然而在經低鹽飲食及利尿劑治療後，病患的症狀仍然反覆發作。在此我們回顧滲出液乳糜胸的文獻並提醒臨床醫師在發現乳糜胸是滲出液時，勿作無謂的檢查。*(胸腔醫學* ***2009; 24: 193-198)***

關鍵詞：滲出液，乳糜胸，腎病症候群，肝硬化

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Therapeutic Bronchoscopic Segmental/Lobar Lavage for Unilateral Pulmonary Alveolar Proteinosis – A Case Report

Ming-Ji Tsai *, Shi-Chuan Chang*,**

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by an accumulation of periodic acid-Schiff-positive materials in the alveolar space. The typical image findings are bilateral diffuse interstitial and parenchymal infiltrates shown on chest radiographs and/or computed tomography (CT) of the chest. We report a case of unilateral PAP in a 51-year-old woman with unilateral emphysema. Chest radiographs and thoracic CT demonstrated findings that were highly suggestive of PAP in the right lung and emphysema in the left lung. Bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) were performed and a diagnosis of idiopathic PAP (iPAP) was made based on the gross appearance of retrieved BAL fluid (BALF), cytological examination of the BALF, and the pathologic findings of TBLB specimens. Because the patient had significant hypoxemia, therapeutic bronchoscopic segmental-lobar lavage was performed under sedation and endotracheal tube intubation. After 4 cycles of lobar lavage, the clinical symptoms improved remarkably and the patient was discharged and followed up at the outpatient department. Therapeutic bronchoscopic segmental/lobar lavage may be effective in patients with iPAP, especially in those who are at high risk for therapeutic whole lung lavage. ***(Thorac Med 2009; 24: 199-205)***

Key words: bronchoscopic segmental/lobar lavage, pulmonary alveolar proteinosis

Introduction

Pulmonary alveolar proteinosis (PAP) characterized by the accumulation of periodic acid-Schiff (PAS)-positive materials in the alveolar space and terminal airways was first described by Rosen and colleague in 1958 [1]. The clinical features and routine blood examinations are nonspecific, although elevation of the serum lactate dehydrogenase (LDH) level alone is reported to be characteristic for idiopathic PAP (iPAP) [2]. The findings of iPAP on chest radiographs are nonspecific, except in advanced cases. The diagnosis of iPAP can be typically made by transbronchial lung biopsy (TBLB) or open-lung biopsy. However, the gross appearance of

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bronchoalveolar lavage fluid (BALF) and characteristic cytological findings of BALF may be diagnostic [3-4]. Therapeutic lung lavage for iPAP includes whole-lung lavage (WLL) [5], WLL through a bronchospirometry catheter [6], segmental irrigation through a catheter [7], catheter lobar lavage [8], or segmental/lobar lavage by fiberoptic bronchoscopy (FOB) [9-12]. WLL is the mainstay treatment of iPAP currently, although administration of granulocyte/macrophage colony-stimulating factor (GM-CSF) may be of help in iPAP patients with mild to moderate diseases [13]. However, for a patient who is at high risk with WLL, bronchoscopic segmental/lobar lavage may be the alternative treatment. We report a patient with an unusual presentation of unilateral PAP subjected to bronchoscopic segmental/lobar lavage with a good response.

Case Report

A 51-year-old woman had been diagnosed with asthma and allergic rhinitis since she was a teenager. Pulmonary tuberculosis was diagnosed 40 years ago and was adequately treated. She had worked as a cook for more than 10 years and was retired for several years. She never smoked, but was often exposed to a cigarette-smoking environment. She had no known exposure to industrial dusts in the past.

In November 2007, the patient had mild dyspnea on exertion, dry cough, and occasionally audible wheezing. Abnormal findings were shown on chest radiographs (CXR), and lung biopsy was suggested by a physician at another hospital after a poor response to empiric treatment. In March 2008, progressive worsening of the dyspnea and cough developed. She visited our outpatient department (OPD) and CXR (Figure 1) showed mixed interstitial and alveolar infiltrates in the right lung, especially in the lower lung field, and reticular opacity with emphysematous change in the left lung. An empiric antibiotic was administered, and no response was noted on the serial follow-up CXR. The patient was admitted in April 2008. Physical examinations at admission revealed normal vital signs. Rales were heard in the right lower chest and diminished breathing sounds in the left chest on chest auscultation. The results of pulmonary function testing (PFT) were as follows: forced expiratory volume in 1 second (FEV_1), 0.80 liter (35% of the predicted value); forced vital capacity (FVC), 1.16 liter (41% of the predicted value); FEV_1/FVC, 68%; diffusing capacity for carbon monoxide (DLCO), 6.24 ml/min/mm Hg (26% of the predicted value). The complete blood count was normal. The serum LDH level was 218 IU/L (95-213 IU/L), which was the sole abnormality of the blood biochemistries. High-resolution computed tomography (CT) of the chest (Figure 2) showed ground glass opacity and a crazy-paving pattern in the right upper lobe (RUL), right middle lobe

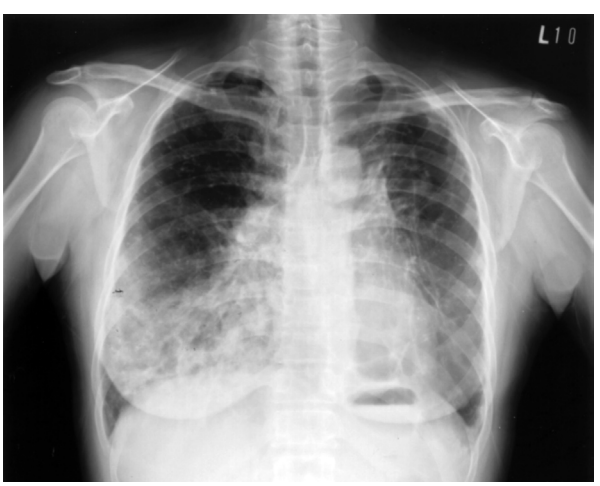

Fig. 1. Chest radiograph showing consolidation in the right middle and lower lobes, and emphysematous change in the left lung.

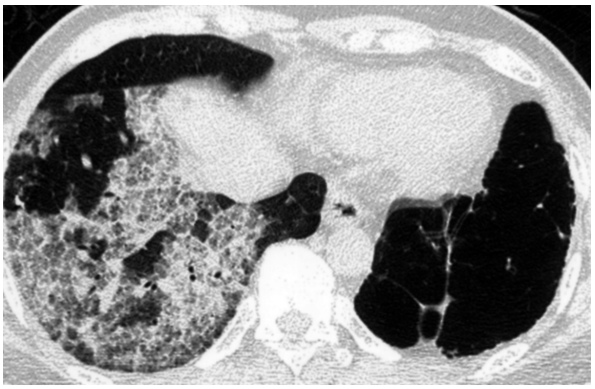

Fig. 2. High resolution computed tomography of the chest showing patchy areas of ground glass opacities with prominent septal thickening in the RLL. Bullous emphysema in the left lung is noted.

(RML), and right lower lobe (RLL) of the lung. Bullous emphysema in the left lung was noted.

FOB with diagnostic BAL was performed and the gross appearance of the retrieved fluid was white, turbid and milky. TBLB was done after the BAL. The cytological examination of the BALF (Figure 3) and pathological examination of the TBLB specimens (Figure 4) showed findings compatible with PAP.

The results of arterial blood gas (ABG) analysis obtained in room air before therapeutic BAL were as follows: pH, 7.43; $PaCO_2$, 45 mmHg; and PaO_2, 56 mmHg; the PaO_2 obtained at FiO_2 100% was 72 mmHg. Therapeutic bronchoscopic segmental/lobar lavage was performed at the respiratory intensive care unit. The patient was sedated and an endotracheal tube was indwelled. The RLL was selected for the first cycle of therapeutic BAL based on the chest CT findings. Each segmental bronchus of the RLL was lavaged with 200 ml warm saline solution sequentially. The procedure was suspended temporally while the saturation was below 90%. Therapeutic BAL was stopped when the returning fluid gradually clarified. During the first cycle of therapeutic lavage, 2300 ml sterile normal saline was used and 1532 ml fluid was retrieved. The entire procedure lasted approximately 60 minutes. The endotracheal tube was extubated a few hours later. Therapeutic segmental/lobar BAL was done every 3 or 4 days to complete 4 cycles. The 2nd cycle of BAL was performed for the RUL and RML sequentially. During the secondary cycle, 1485 ml normal saline was instilled into the RUL and 920 ml fluid was retrieved and 1500 ml normal saline was infused into the RML and 1150 ml

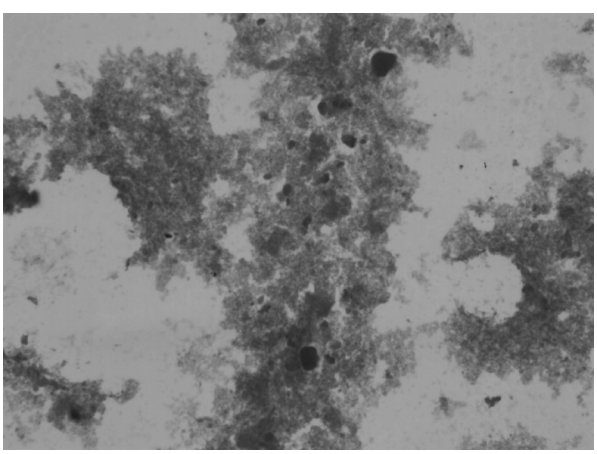

Fig. 3. Cytological smear of bronchoalveolar lavage fluid (BALF) shows strong PAS (periodic acid-Schiff) -positive for extracellular materials (x 40).

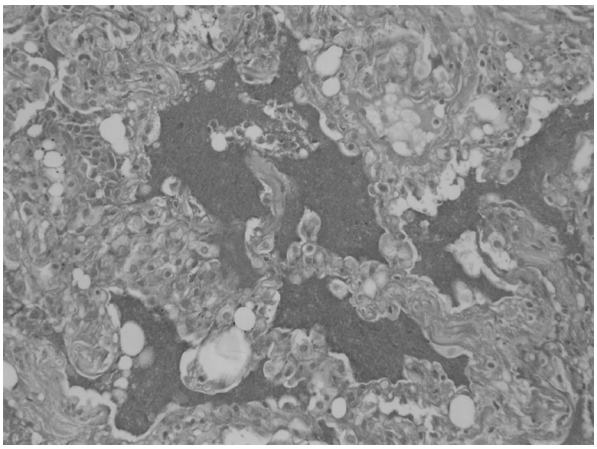

Fig. 4. The histopathology of the transbronchial lung biopsy specimen shows alveoli filled with PAS stain positive material (x 200).

fluid was retrieved, respectively. In all, 3135 ml normal saline was instilled and 2120 ml of fluid was retrieved. The whole procedure took 60 minutes. The 3rd cycle of lavage was performed with 2450 ml of normal saline for the RLL and 1784 ml of fluid was retrieved. The 4th cycle of lavage was performed with 3300 ml of normal saline for the RUL and RML, and 2293 ml of fluid returned. After 4 cycles of lavage, she was transferred to the general ward. Subjective improvement of dyspnea was noted after the therapeutic lung lavage. The results of the follow-up ABG analysis in room air were: pH, 7.46; $PaCO_2$, 40 mmHg; PaO_2, 59 mmHg; and PaO_2 obtained at FiO_2 100% was 404 mmHg. The serum LDH was 180 U/L. The patient was discharged and followed up at the OPD. In June 2008, she reported that the dyspnea and cough had improved markedly. The results of follow-up PFT were: FEV_1, 0.93 liter (40% of the predicted value); FVC, 1.61 liter (57% of the predicted value); FEV_1/FVC, 57%. The ABG data obtained at room air showed: pH, 7.42; $PaCO_2$, 36 mmHg; PaO_2, 62 mmHg. The CXR in October 2008 disclosed a regressive change in the infiltration of the right lung (Figure 5).

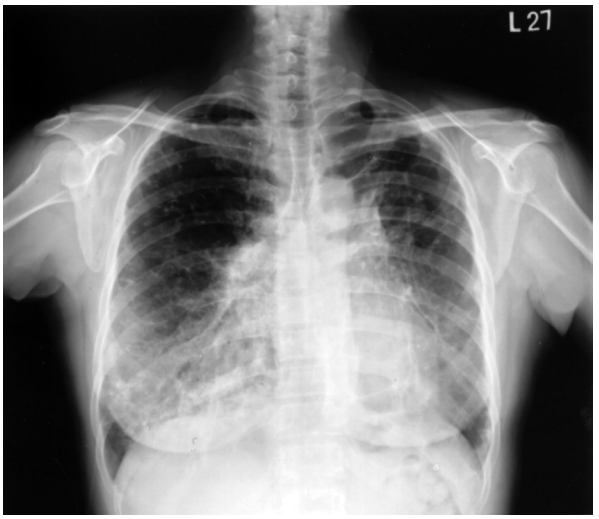

Fig. 5. Chest radiograph shows improvement of consolidation in the right middle and lower lobes after lavage 6 months later.

Discussion

The etiology and pathogenesis of iPAP remain unknown. The clinical features and laboratory findings are nonspecific, although isolated elevation of the serum LDH level may be suggestive. Bilateral diffuse patchy infiltrates and asymmetrical airspace consolidation shown on the CXR may be the typical findings for iPAP [14]. In a report from a single institute, unilateral alveolar infiltrates were reported in 15% of patients with iPAP [15], however, unilateral lung involvement of iPAP based on chest CT is very rare, except in those with secondary PAP. In our reported case, the cause of emphysema involving the left lung remains unknown. However, this might explain the reason why iPAP occurred in the right lung only. The unusual presentation of the image findings shown on CXR and CT in iPAP patients may provide a further challenge to clinical physicians because iPAP is a rare disease. For a definite diagnosis of iPAP, open lung biopsy is the gold standard, but nowadays is less commonly required [2, 16]. The characteristic appearance of milky white BALF grossly and the characteristic cytological findings of BALF showing alveolar macrophages containing PAS-positive material and a granular acelluar material background may be diagnostic for iPAP [2, 17]. Further diagnosis can be supported by pathological examination of TBLB and/or open lung biopsy specimens and/or the presence of anti-GM-CSF antibodies in BALF and/or peripheral blood [18].

The initial therapies for iPAP were empirical. In 1964, Ramirez-Rivera proceeded with

a trial WLL with a total of 3 liters of normal saline under local anesthesia [5]. The technique was modified to the use of general anesthesia, increased lavage volume [19], concomitant use of chest percussion [20], and completion of bilateral sequential WLL in the same treatment session [16]. Although, several other methods of lavage have been proposed, WLL appears to be the mainstay of treatment for iPAP.

Those patients who undergo lavage at any time during the course of their disease have a superior survival to those who have not received the treatment. Patients often experience dramatic improvement within 3 months after the therapeutic lung lavage [14]. The major adverse effect of WLL is severe hypoxemia during the procedure [19]. Double lumen endotracheal tube intubation and general anesthesia are mandatory for therapeutic WLL. In such cases, an anesthesiologist, physician for respiratory care, and surgical room are required, and a longer time for the procedure is needed. Segmental and/or lobar lavage by FOB has been reported, but the procedures seemed complicated [10-12]. Therapeutic segmental/lobar lavage by FOB was reported by Cheng *et al*. to have a fair response in 3 iPAP patients with mild severity under local anesthesia [9]. In the report, lavage was done only in the bilateral lower lobes. However, the disease in most of the iPAP patients who need therapeutic lung lavage will not be limited to the lower lobes only. Severe cough and hypoxemia were the major complications reported. The only benefit was that the volume of the lavage fluid was about 2 liters, much less than the volume of WLL, which was reported to be 9 liters or more [15]. Nevertheless, a few cycles of segmental/lobar lavage may be needed because the volume of lavage fluid and the treatment effect were limited in the previous study [9], and may not be suitable for iPAP patients with moderate to severe hypoxemia. Actually, 1 of the 3 patients who failed to improve still had to return for WLL 6 months later [9].

Administration of recombinant GM-CSF was reported to have a therapeutic response in 48% of patients with iPAP [14]. However, the treatment effect was limited to mild to moderate cases. In addition, a patient who fails to respond to GM-CSF will still need WLL. The treatment duration of GM-CSF therapy is long and shows no effect in severe cases. Therapeutic lung lavage is not needed in only 37% of iPAP patients at 5 years [14]. The median interval between the diagnosis of iPAP and the first WLL was about 2 months [14]. About 79% of patients require WLL within 12 months after the diagnosis of iPAP [14]. The median duration of response to WLL was 15 months, and less than 20% of patients who were followed beyond 3 years remained free of recurrence [14]. There was no reliable factor to predict the treatment response to lung lavage, although younger age was reported to be a risk factor for non-response [14].

In our reported case, severe emphysematous change occurred mainly in the left lung. As a consequence, WLL or Cheng's method [9] was not suitable or not without hazard in our patent. Based on our clinical experience, we chose to perform modified therapeutic segmental/lobar lavage via FOB under sedation, to diminish the cough and the patient's anxiety. The patient was intubated with a single lumen endotracheal tube, which could be removed shortly after therapeutic lung lavage. The entire procedure required about 1 hour for each cycle, less than that for WLL, and was able to prevent the occurrence of severe hypoxemia and unstable hemodynamics. The modified therapeutic segmental/lobar lavage is quite simple and can be

performed in the hospital with a qualified chest physician and respiratory care team.

In summary, our reported case highlights the potential value of therapeutic segmental/lobar lavage in treating the patient who has unilateral iPAP due to severe emphysema involving the contralateral lung. This modified therapeutic lung lavage may be a safe procedure for patients with iPAP, in particular, those for whom WLL may be hazardous or those with advanced disease.

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支氣管鏡肺葉灌洗術在單側肺泡蛋白質沉著症的治療——病例報告

蔡明吉* 張西川*,**

肺泡蛋白質沉著症是一罕見的疾病，其特徵是肺泡中堆積periodic acid-Schiff染色陽性物質，病因目前仍不明。我們報告一位51歲女性，於住院前五個月出現乾咳及漸進性呼吸困難。胸部X光片顯示，右肺中葉及下葉有實質化病灶，左肺有肺氣腫變化。胸部電腦斷層攝影呈現，毛玻璃樣的病灶以及不規則石板拼鋪型態（crazy-paving pattern）。經支氣管鏡檢查暨診斷性支氣管肺泡灌洗術和經支氣管肺切片檢查，確診為肺泡蛋白質沉著症。基於病人有嚴重低血氧症以及左肺部呈現肺氣腫變化，在給予鎮靜劑及置放氣管內管下，為病人施行經支氣管鏡肺葉灌洗術。治療後，病人症狀明顯改善而出院，五個月後的門診追蹤顯示病人的復原情形良好。經支氣管鏡肺葉灌洗術之施行難度不高，可在大多數醫院執行，特別是針對接受全肺灌洗術可能具有較高風險的肺泡蛋白質沉著症病人。*(胸腔醫學* ***2009; 24: 199-205)***

關鍵詞：肺泡蛋白質沉著症，支氣管鏡肺葉灌洗術

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Primary Pulmonary Mucosa-associated Lymphoid Tissue Lymphoma with Amyloidosis and Lymphoid Interstitial Pneumonitis – A Case Report

Ming-Wei Weng*,**, Hong-Chung Wang**,****, Chin-Hung Chang**,****, Shong-Ling Lin***,****, Ruay-Sheng Lai**,****

Pulmonary mucosa-associated lymphoid tissue lymphoma (MALToma) is rare, especially when combined with lymphoid interstitial pneumonitis (LIP). We report the case of a 66-year-old man who was admitted because of severe hemoptysis for 3 days. Computed tomography (CT) scan of the chest showed a mass-like lesion (8 x 8 x 6 cm^3) in the left lower lobe and diffuse cystic lesions in both lungs. Pathologic study of the specimens after left lower lobectomy revealed diffuse infiltration of lymphoid cells and plasma cells positive for CD20. Congo red stain also showed amyloid deposition. Lymphoepithelial cells had infiltrated throughout the cystic area of the pulmonary parenchyma in the left lower lobe. These findings were compatible with the diagnosis of MALToma, with amyloidosis and LIP. Since LIP may be a presentation of MALToma, primary pulmonary MALToma should be considered for cases of nodular or mass lesion combined with diffuse cystic lung disease. ***(Thorac Med 2009; 24: 206-211)***

Key words: MALToma, amyloidosis, lymphocytic interstitial pneumonia

Introduction

Most of the primary pulmonary non-Hodgkin's lymphomas are low-grade, small B-cell lymphomas that originate from mucosa-associated lymphoid tissue [1]. High-resolution computed tomography (HRCT) findings of primary pulmonary mucosa-associated lymphoid tissue lymphoma (MALToma) include consolidation, nodules, reticular shadowing/fibrosis and bubble-like radiolucencies in the tumor [2]. Although cystic lesions in lymphocytic interstitial pneumonia (LIP) have also been described [3], the relationship of LIP to pulmonary MALToma has been rarely investigated [4-5]. Amyloidosis is also associated with systemic lympho-proliferative disorders such as lympho-plasmacytic lymphoma with kappa light chains [6-7]. We

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present herein a case with diffuse cystic lesions in both lungs, as shown on chest computed tomography (CT), that were characteristic of LIP. Pathology studies revealed primary pulmonary MALToma with amyloid deposition and LIP.

Case Report

A 66-year-old man was admitted to our hospital due to severe hemoptysis during the preceding 3 days. He had had mild dyspnea on exertion, intermittent hemoptysis, and non-productive cough for 2 years. He had no joint pains, malar rash, dry eyes, dry mouth, or gastrointestinal complaints. Complete blood count (CBC), blood chemistry, and thyroid functions were within normal limits, except a reversed albumin/globulin ratio (2.8/4.2 g/dl). His serum immunoglobulin (IgG and IgA) levels were likewise within the normal range, although his IgM was 580 mg/dl, which is above the normal range (46-304 mg/dl). Immuno-electrophoresis of serum proteins revealed IgM polyclonal hypergammaglobulinemia. Serum tests for antibodies against nuclear antigens, extractable nuclear antigens, and human immunodeficiency virus (HIV) were negative.

A panendoscopy showed chronic gastritis, and the chest radiogram revealed a mass-like lesion in the left lower lobe and diffused reticular infiltrations in both lungs (Figure 1). Chest CT scan demonstrated a homogeneous enhanced mass lesion with some calcification spots, measuring about 8 x 8 x 6 cm^3 in size, in the left lower lobe, and multiple lung cysts of variable size but with slightly irregular walls (Figure 2).

Surgical intervention with lobectomy of the left lower lobe was performed for the repeated hemoptysis. The resected tumor showed a white-tan fleshy appearance, and was 8 x 5.5 x 3 cm^3 in size. Histopathology demonstrated diffuse infiltration of small to medium-sized centrocyte-like and monocytoid lymphoid cells (Figure 3). The lymphoid cells had infiltrated

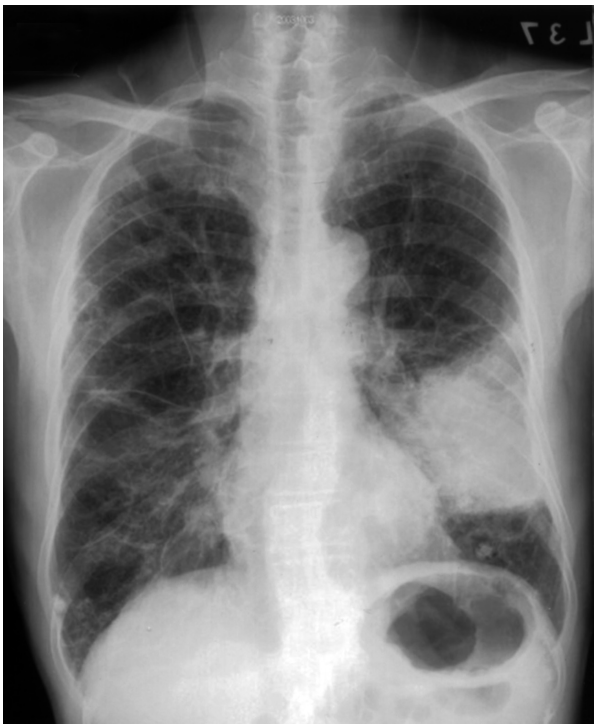

Fig. 1. Chest radiography showing a mass (10 x 6 cm) in the left lower lobe and diffuse reticular infiltrations in both lungs

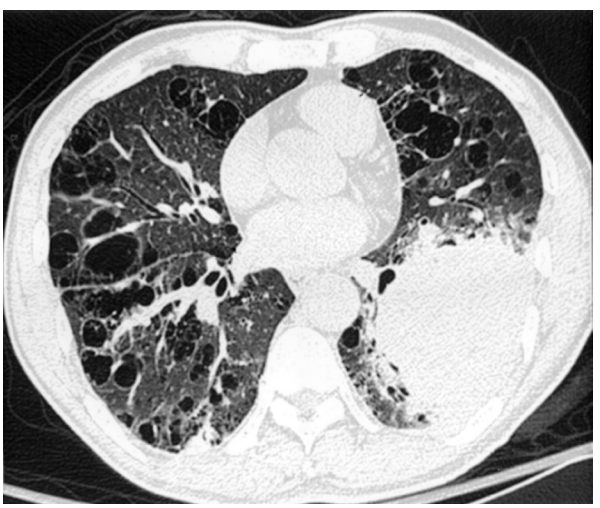

Fig. 2. Diffuse cystic lesions found in both lungs in the HRCT scan, along with a huge mass in the left lower lobe

the bronchiole and presented with the features of a lympho-epithelial lesion (Figure 4). Congo red stain was performed and a diagnosis of amyloid deposition was confirmed by apple green birefringence under polarized light. The lymphoid cells were positive for CD20 and negative for CD3. These cells were also distributed along the alveolar septa and around the formation of the variable size cysts. Pulmonary MALT lymphoma with amyloidosis and LIP were diagnosed.

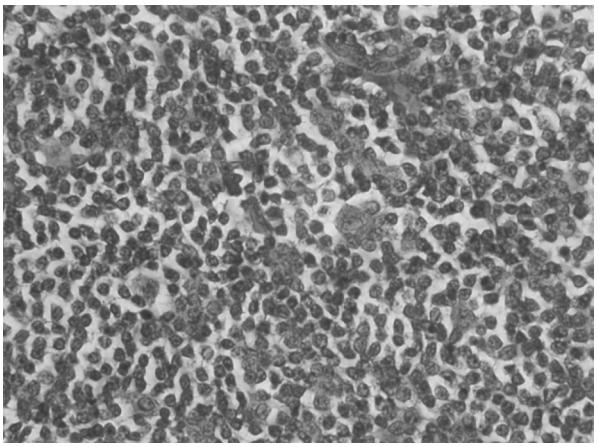

Fig. 3. Lobectomy specimen showing diffuse infiltration of centrocyte-like monocytoid lymphoid cells and low-grade malignancy. (Hematoxylin and Eosin x 100)

Fig. 4. Lymphoepithelial and plasma cells within interstitial tissue were found in the remaining parenchyma distant from the consolidation mass (Hematoxylin and Eosin x 100)

Hemoptysis resolved after surgery, and the patient was then treated with prednisolone at the outpatient department.

Discussion

MALT is a primary site for B-cell mediated immunity and is usually absent from organs but reactive to chronic bacterial infection, inflammation or B-cell dysfunction, such as Sjogren's syndrome and rheumatoid arthritis [8]. These tumors have been described in a variety of non-gastrointestinal mucosal extra-nodal and non-mucosal sites, such as the breasts, conjunctiva, genitor-urinary tract, liver, lung, salivary glands, skin, and thyroid. The tumor is usually indolent and appears in the form of a chronic alveolar opacity. Clinical symptoms include cough and dyspnea, and less commonly, chest pain and hemoptysis. The prognosis is excellent, but the treatment regimens (simple monitoring, surgery or single-agent chemotherapy) are still controversial [9].

LIP is considered to be a benign lymphoproliferative disorder characterized by a diffuse and exquisitely interstitial proliferation of small lymphocytes and plasma cells. It occurs most commonly in patients with Sjögren's syndrome, autoimmune thyroid disease, acquired immunodeficiency syndrome (AIDS), or Castleman disease [10]. On histologic examination, LIP is characterized by a diffuse interstitial cellular infiltration composed of a mixture of mature small lymphocytes and plasma cells that widen the alveolar septa [11]. CT findings include areas of ground-glass attenuation, thin-walled cystic airspaces, focal airspace consolidation, centri-lobular or peri-bronchiolar small nodules and bronchiectasis, and must be differentiated from pulmonary Langerhans histiocytosis and

lymphangioleiomyomatosis [3]. Progressive dyspnea, non-productive cough, fever, anorexia, weight loss, and arterial hypoxemia are common symptoms. Corticosteroid therapy is generally the treatment of choice.

LIP has subsequently been recognized to be low-grade B cell lymphoma and is currently classified as MALToma [11]. The relationship of LIP to pulmonary MALToma has been described by Teruya-Feldstein *et al*. [4]. Julie *et al*. reported that LIP may present as an early stage of MALToma or an immunologic response to a chronic antigenic stimulus that may provide a milieu or microenvironment for the evolution of a monoclonal B-cell population [5]. Hence, LIP may be a presentation of MALToma.

Pulmonary amyloidosis has been recognized in 3 forms: alveolar septal, nodular, and tracheobronchial. Nodular amyloidomas are well-circumscribed consolidated masses of dense, amorphous eosinophilic amyloids, often associated with inflammatory cell infiltrates, and consist of clusters of plasma cells and lymphocytes [6]. Calcification and metaplastic ossification are common. Amyloidomas are associated with systemic lympho-proliferative disorders and plasma cell dyscrasias, primarily multiple myeloma, and lympho-plasmacytic lymphoma [12-13]. Primary pulmonary lymphomas may contain amyloid deposits, but this finding is rare, occurring in less than 1% of cases, and usually have serum lambda light chain deposits and positive immunostains for CD20 and a kappa light chain of the pulmonary parenchyma [6-7, 14].

In summary, MALToma is a low-grade malignancy that is usually asymptomatic, slowly progressive, and with a good prognosis. LIP, with its characteristic cystic lesion, may be a presentation of MALToma, so primary pulmonary MALToma should be considered in cases of nodular or mass lesions combined with diffuse cystic lung disease.

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原發性肺部黏膜相關類淋巴組織之淋巴瘤合併類澱粉沉積及淋巴球間質肺炎——病例報告

翁銘偉*,** 王鴻昌**,**** 張慶宏**,**** 林秀玲***,**** 賴瑞生**,****

原發性黏膜相關類淋巴組織之淋巴瘤（MALToma）在肺部是相當罕見的，尤其是合併有淋巴球間質肺炎。在此我們報告一位66歲男性病患因嚴重咳血三天而住院。胸部電腦斷層呈現左下肺部有一8 x 8 x 6公分腫瘤病灶及雙側肺野廣泛囊狀浸潤。左下肺葉切除術後病理報告顯示有廣泛淋巴細胞及漿細胞增生且CD20染色呈陽性反應。另外剛果紅染色也發現類澱粉沉積。淋巴上皮細胞已滲透至左下肺實質的囊狀部位。以上病理變化符合黏膜相關類淋巴組織之淋巴瘤合併類澱粉沉積及淋巴球間質肺炎的診斷。因淋巴球間質肺炎可能為黏膜相關類淋巴組織之淋巴瘤的一個表徵，所以廣泛性囊狀病灶的病人需考慮原發性肺部黏膜相關類淋巴組織之淋巴瘤的可能。*(胸腔醫學 2009; 24: 206-211)*

關鍵詞：類澱粉沉積，淋巴球間質肺炎，黏膜相關類淋巴組織之淋巴瘤

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Acute Respiratory Distress Syndrome Following Scrub Typhus

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Scrub typhus is a zoonotic disease caused by *Orientia tsutsugamushi* and is an acute febrile illness. Clinically, the manifestations and complications of scrub typhus are protean. Severe complications of this disease have been very rare since the introduction of specific antibiotic therapy. The most serious clinical manifestations are pneumonitis with acute respiratory distress syndrome (ARDS), myocarditis, pericarditis, meningoencephalitis, and acute tubular necrosis with acute renal failure. We encountered a case of ARDS associated with scrub typhus. The case was proven by the finding of skin eschars, and the laboratory diagnosis at the Center for Disease Control, Department of Health, Taiwan, confirmed scrub typhus using a serum antibody. The patient recovered dramatically and was successfully weaned from ventilator support after an appropriate antibiotics course. ***(Thorac Med 2009; 24: 212-217)***

Key words: Scrub typhus, acute respiratory distress syndrome, *Orientia tsutsugamushi*

Introduction

Tsutsugamushi fever, or scrub typhus, is a zoonotic disease caused by *Orientia tsutsugamushi*. It is transmitted to humans by the bite of the larval thrombiculid mite, known commonly as a chigger. Scrub typhus is an acute febrile illness in which respiratory abnormalities are common. It is distributed widely in the Asia-Pacific region and is common in some parts of Taiwan, especially in Kinmen, Nantou, Penghu, Hualien, and Taitung Counties [1]. Pulmonary involvement of scrub typhus usually reveals a pattern of interstitial pneumonia, interstitial edema, and hemorrhage caused by vasculitis [2-3]. Acute respiratory distress syndrome (ARDS) has rarely been seen since the introduction of specific antibiotic therapy [4-6]. We describe the case of a patient with life-threatening adult respiratory distress syndrome with multiple organ failure complicating scrub typhus. After intensive supportive care and intravenous minocycline therapy, the patient dramatically recovered.

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Case Report

A 46-year-old woman was transferred to our hospital via emergency ambulance from a local hospital on November 21, 2008, because of progressive dyspnea associated with skin eschar. She had rheumatoid arthritis under treatment with immunomodulatory and immunosuppressive agents (prednisolone 5 mg qd, hydroxychloroquine 200 mg bid, methotrexate 10 mg qw) for 10 years. She was a housekeeper and lived in the rural area of Penghu, which is an endemic area for scrub typhus. She had had a febrile sensation for a few days, along with headache, cough, and generalized myalgia since about November 12. She visited a local hospital and was admitted on November 17 due to a suspicion of scrub typhus, community-acquired pneumonia or viral infection of unknown etiology. Intravenous aqueous penicillin 24 million units/day and minocyclin 200 mg/day were started; however, her condition worsened. She was referred to us following the gradual development of more dyspnea and progressive pneumonia.

At the emergency room, the patient's vital signs were: blood pressure 119/78 mmHg, body temperature 37.3°C, heart rate 87/min and respiratory rate 30/min. One 1.5-cm black-crusted shallow ulcer (eschar) was found on the anterior chest wall and another 1-cm eschar was located on the right ankle. Chest auscultation revealed fine crackles in both lower lung fields. Laboratory data revealed a white blood cell count (WBC) of 8,460/μL, with 95% neutrophils and 3% lymphocytes. The serum aspartate aminotransferase (AST) (423 IU/L), alanine aminotransferase (ALT) (378 IU/L), erythrocyte sedimentation rate (ESR) (60 mm/hr) and C-reactive protein (CRP) (7.0 mg/dl) levels were all elevated. While the patient was on supplemental oxygen with a non-rebreathing mask, the arterial blood gas study revealed pH 7.43, $PaCO_2$ 40.6 mmHg and PaO_2 55 mmHg. Chest radiography showed heterogenous airspace infiltrates in the right lung with pleural effusion and opacification of the left lower chest (Figure 1). Mechanical ventilatory support for ARDS was started in the emergency department, and the patient was then admitted to the respiratory intensive care unit. With a tentative diagnosis of ARDS due to scrub typhus (tsutsugamushi disease) and with bacterial pneumonia, the patient was started on intravenous minocyclin 200 mg/day, piperacillin/tazobactam 13.5 g/day and hydrocortisone 200 mg/day.

Sputum examination showed normal throat flora, and no acid-fast bacilli or fungus was found. Bronchofiberscopy revealed fresh blood at the orifice of the right middle lobe bronchus and lower division of the left upper lobe bronchus. Comprehensive microbiological testing of bronchoalveolar lavage (BAL) fluid and protected specimen brushing proved negative, as did cultures of urine, blood, and pleural fluid. Sero-

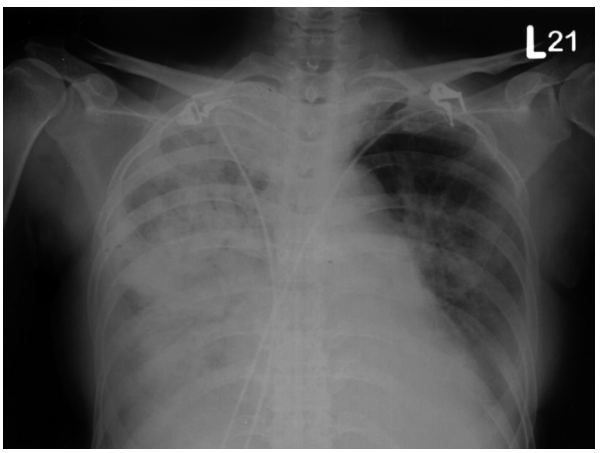

Fig. 1. Chest X-ray showing heterogenous airspace infiltrates in the right lung with pleural effusion and opacification in the left lower chest.

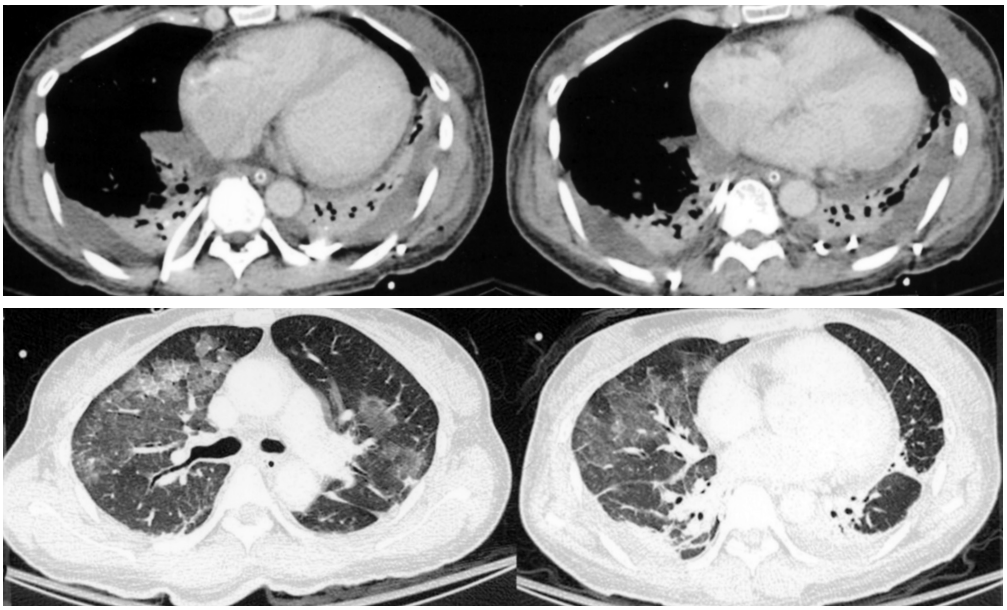

Fig. 2. CT of the chest showing multifocal ground-glass opacity in the bilateral lungs, predominate at the right side, atelectasis of the bilateral basal lungs and a small amount of residual bilateral pleural effusion post-pigtail drainage.

logical tests for *Legionella* species, *Chlamydia* species, *Mycoplasma* species, human immunodeficiency virus (HIV), and hepatitis B and C were negative. Nasal swab for influenza A and B antigen were negative. Rheumatoid factor, antinuclear antibody and anti-double stranded deoxyribonucleic acid (DNA) antibody were negative. High-resolution computed tomography (CT) showed multifocal ground-glass opacity at the bilateral lungs and atelectasis of the bilateral basal lungs on the 4th day of admission (Figure 2). Serologic testing by the Center for Disease Control (Taiwan) for indirect microimmunofluorescent antibody (IFA) of *O. tsutsugamushi* was negative on day 1 and positive 6 days later (lgG $\geq$ 640 and lgM $\geq$ 160). Six days later, the patient's critical condition had improved markedly and she was successfully weaned from the ventilator. She recovered fully and was discharged on day 13 (Figure 3).

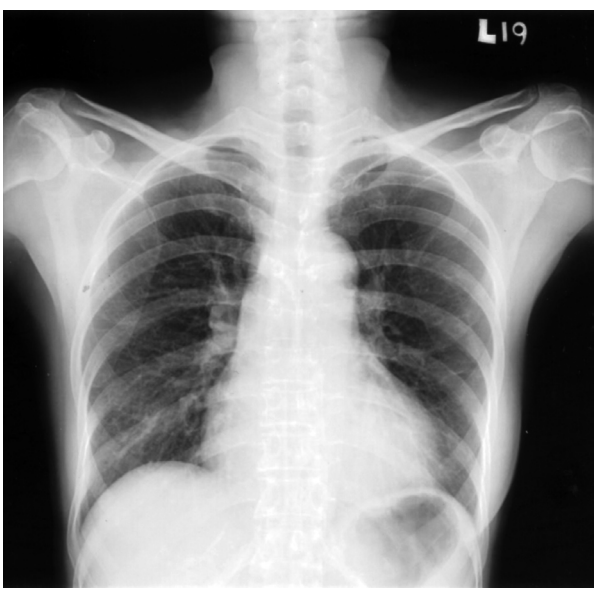

Fig. 3. Chest X-ray showing no obvious lesion.

Discussion

Scrub typhus is an acute febrile illness characterized by a typical primary lesion (eschar), regional or generalized lymphadenopathy, rash, and nonspecific symptoms, such as fever, chills,

cough, abdominal pain and myalgia. Clinical symptoms occur 6-18 days after exposure, with an average incubation period of 10 to 12 days. Choi *et al*. documented the most common clinical symptoms as fever (73/75, 98%), myalgia (61/75, 81%), and headache (60/75, 80%), and the most common signs as rash (59/75, 79%) and eschar (56/75, 75%) [2]. In another report, the 5 major clinical symptoms, fever, headache, eschar, rash, and lymphadenopathy, were observed in 90.1%, 61.9%, 23.1%, 21.6%, and 10.7% of cases, respectively [1]; 83% of the cases showed 1-3 clinical symptoms and 10% showed 4-5 symptoms [1].

Systemic involvement of various organs results in conditions such as myocarditis, meningoencephalitis, acute renal failure, and interstitial pneumonia, which can progress to ARDS and even catastrophic multi-organ failure [4-10]. ARDS is a rarely reported but serious com-plication of scrub typhus. It is important to know that ARDS may develop in scrub typhus, and to be aware of the possible risk factors, because ARDS is treatable if considered and diagnosed early. Tsay and Chang reported 5 cases of ARDS in 33 cases of serious complications with scrub typhus; patients with ARDS were older than those without ARDS (39 ± 22 vs. 23 ± 9 years, $p = 0.009$), and thrombocytopenia (100% vs. 50%, $p = 0.049$) and early pneumonitis (100% vs. 25%, $p = 0.003$) were more frequently noted in patients with ARDS than in those without ARDS [5]. In another report, 8 of 72 scrub typhus patients with ARDS showed initial symptoms of dyspnea and cough, a higher WBC count, lower hematocrit, and higher total bilirubin count; these symptoms and delayed treatment with appropriate antibiotics were significantly predictive variables associated with scrub typhus patients with ARDS [4]. Multivariate analysis showed that low albumin levels, prolonged prothrombin time, and delayed treatment with appropriate antibiotics were independent predictive variables associated with scrub typhus complicated by ARDS [4].

Pathologic findings of scrub typhus have been characterized by vasculitis of the microvasculature of the involved organ resulting from a direct invasion by *O. tsutsugamushi* [11]. After bronchoscopy, there was hemorrhaging from the bilateral bronchus in our patient, and the pathologic report of the biopsy showed nonsignificant findings. We believed there was a vasculitis-related pulmonary hemorrhage, so we began intravenous steroid. The symptoms and imaging improved soon thereafter. The reported incidence of chest radiographic abnormalities in patients with scrub typhus varies from 59% to 72% [2, 12]. Bilaterally diffuse areas of reticulonodular opacity, hilar lymph node enlargement, and septal lines are the most common findings. Airspace consolidation is relatively uncommon and generally appears in the lower zone of both lungs. Unilateral or bilateral hilar enlargement and pleural effusion are common radiographic features, found in 25%-27% and 12%-43% of patients, respectively [2, 12]. Ground glass opacity and interlobular septal thickening were common findings in thin-section CT, whereas centrilobular nodules and axial interstitial thickening were less common [3]. Contrast-enhanced chest CT images in most cases depicted mediastinal (10/11, 91%), axillary (8/11, 73%), and hilar lymphadenopathy (5/11, 45%). The lymph nodes were typically large and did not have necrotic centers [3].

In summary, we reported a case of scrub typhus that resulted in the serious complication of ARDS. Early diagnosis is important because there is usually an excellent response to treat-

ment, and timely antimicrobial therapy may help prevent complications. Although the radiologic findings of scrub typhus are nonspecific, an awareness of the related findings at imaging, especially CT, may facilitate an accurate diagnosis.

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恙蟲病併發急性呼吸窘迫症候群

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恙蟲病是一種會引起發燒的蟲媒病，是由名為*Orientia tsutsugamushi*的立克次體所導致的一種傳染性疾病。恙蟲病的臨床表現及併發症是變化多端的。自從特定抗生素使用後，此類疾病所引起之併發症就很少見。罕見的嚴重併發症包括肺炎合併急性呼吸窘迫症候群、心肌炎、心包膜炎、腦膜腦炎、及急性腎小管壞死合併急性腎衰竭。我們在此報告一位恙蟲病合併急性呼吸窘迫症候群個案。臨床檢查發現患者身上有焦痂且血清抗體經由衛生署疾病管制局證實為恙蟲病感染。經過適當的抗生素治療後，此病患症狀迅速改善並成功脫離呼吸器使用。*(胸腔醫學* ***2009; 24: 212-217****)*

關鍵詞：恙蟲病，急性呼吸窘迫症候群，*Orientia tsutsugamushi*

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Short-term Deployment of Self-expanding Metallic Stent for Healing of Tracheal Laceration after Esophagectomy in an Esophageal Cancer Patient Requiring Mechanical Ventilation – Case Report

Ho-Yiu Wong, Chia-Hung Chen, Yi-Heng Liu, Te-Chun Hsia, Chuen-Ming Shih, Wu-Huei Hsu, Chih-Yen Tu

Laceration of the posterior tracheal wall is 1 of the risks of transhiatal esophagectomy (THE). Conservative treatment of tracheal injury in patients with positive pressure mechanical ventilation is, according to current opinions, ineffective. We describe a feasible method to treat an esophageal cancer patient requiring mechanical ventilation who suffered a posterior tracheal wall tear with a persistent air leak after a THE, and who was successfully weaned after a self-expanding metallic stent placement. Three months later, the stent was electively removed after adequate healing of the tracheal laceration. ***(Thorac Med 2009; 24: 218-222)***

Key words: esophagectomy, complications, tracheal injury, metallic stents

Introduction

Esophagectomy is always used as an operative technique for benign or malignant esophageal disease; 2 methods, transthoracic esophagectomy and transhiatal esophagectomy (THE), are used for approaching the lesion. The major complications include anastomosis leak, lung collapse, pneumonia, chylothorax and tracheal laceration. THE has greater safety with lower morbidity than transthoracic esophagectomy for benign and malignant esophageal disease [1]. The rate of complications, including tracheal injury or laceration, with the THE procedure was reported to be around 1.8% [2]. Tracheal injury or laceration usually heals without surgical intervention, although sometimes the tracheal laceration requires the use of pericardial or pleural tissue to cover the defect. However, healing the tracheal laceration spontaneously and without intervention in a patient receiving positive pressure ventilation is difficult. We report a case of tracheal laceration successfully treated using a self-expanding metallic stent implant to cover the laceration, in an esophageal cancer patient requiring mechanical ventilation who suffered a posterior tracheal wall tear with a persistent air leak after a THE for esophageal

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cancer. The air leakage and tidal volume were improved after the metallic stent implant. Three months later, the stent was electively removed and granulation tissue formation was observed in the follow-up bronchoscopy, with no residual tracheal laceration noted.

Case Report

A 51-year-old man had presented at the hospital with dysphagia and body weight loss 2 months before this admission. Although a physical examination and laboratory data showed no significant abnormalities, panendoscopic observation revealed a tumor-like lesion located 27 cm from the upper incisors of the esophagus. Tissue specimens were obtained and revealed squamous cell carcinoma. He was diagnosed as having esophageal carcinoma (clinical stage T2N1M0, stage IIB), and underwent a THE in the middle third of the esophageal carcinoma (pathological stage T1N1M0, stage IIB) with a gastric pull-up. The patient was admitted to the intensive care unit (ICU) and extubated smoothly on the first postoperative day. On postoperative day 7, he experienced postoperative atelectasis with acute respiratory failure requiring a positive pressure mechanical ventilator. He was ventilated at a tidal volume of 600 mL and with 6 cm H_2O positive end-expiratory pressure (PEEP) levels using a volume-guaranteed ventilation mode. However, the ventilator showed a persistent air leak (150 mL per cycle), so we changed to a pressure control ventilation mode to maintain his tidal volume of 450 mL. On postoperative day 14, we performed bronchoscopy for the patient because of difficulty in weaning from the ventilator. Bronchoscopic observation revealed a tear in the membranous trachea near the carina (Figure 1). A diagnosis of tracheal laceration with persistent air leak under positive pressure ventilation after THE was made, and we inserted a 14 mm x 3 cm (length x diameter) covered Ultraflex bronchial stent (Boston Scientific; Natick, MA) into the left main bronchus under flexible bronchoscopic guidance to cover the tracheal laceration. Six hours after the metallic stent implantation, the clinical parameters were greatly improved: the tidal volume increased from 450 mL to 600 mL without an air leak, and the respiratory rate decreased from 24 breaths/min to 16 breaths/min. The patient was successfully weaned from the ventilator on postoperative day 16. Three months later, the follow-up bronchoscopy showed partial granulation tissue formation into the proximal and distal end of the metallic stent. Therefore, we electively removed the metallic stent by flexible bronchoscope under local anesthesia and granulation tissue formation was observed by bronchoscopy, which revealed that the tracheal laceration was healed (Figure 2).

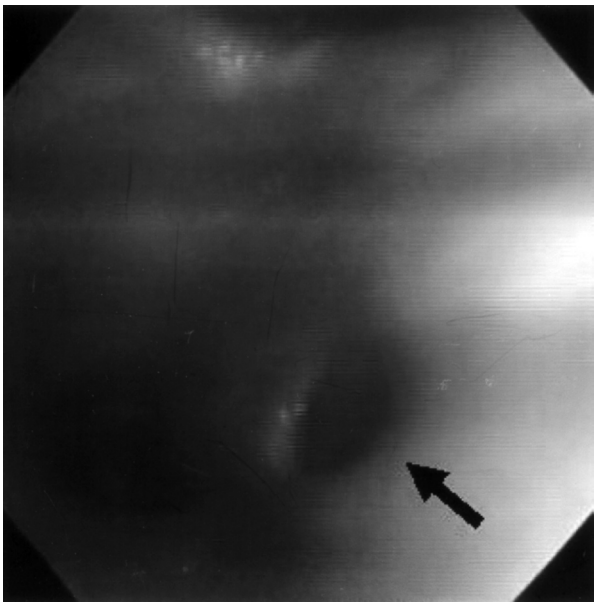

Fig. 1. A tear (arrow) in the membranous trachea near the carina seen on bronchoscopy

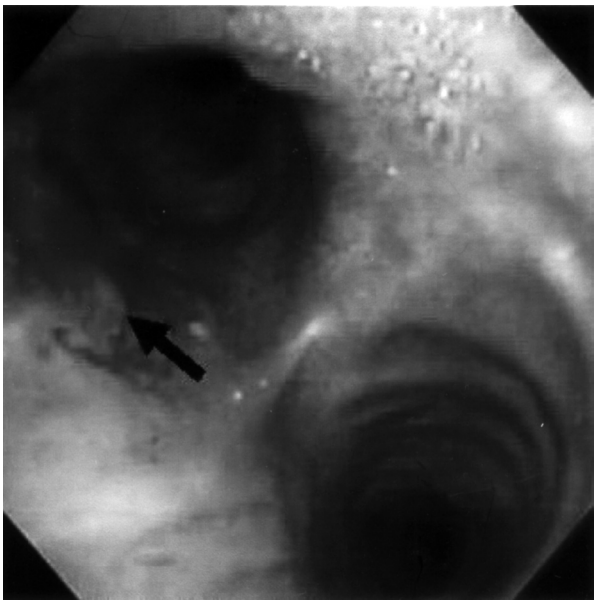

Fig. 2. The membranous tracheal tear was filled with granulation tissue formed by the metallic stent (arrow)

Discussion

THE is a feasible technique and has recently been popularized for use in most patients requiring esophageal resection for benign or malignant disease [1-2]. However, the complication of tracheal injury associated with THE has been described. The incidence of this complication is reported to be from <1% to 1.8% [1, 3]. Patients with tracheal injury require artificial ventilation for a longer period and stay longer in the ICU than patients without such injury [3]. Most of these airway injuries can be approached and repaired by a partial sternal split, pericardial patch or thoracotomy. Only a few therapeutic alternatives are available for those patients judged unsuitable for surgery. Furthermore, in intubated patients with tracheal laceration, concern has been raised that conservative treatment may be less effective and practical than primary closure. In our case, the patient suffered postoperative atelectasis with acute respiratory failure, and flexible bronchoscopy confirmed the diagnosis of a membranous tracheal tear with persistent air leak. The patient did not undergo operation for the injury because of his critical condition and possible postoperative scarring of surrounding tissues.

Stent placement has been proven to be a successful modality in patients with airway obstruction as a result of both malignant and benign airway conditions present with disabling symptoms [4-6]. Stents are generally of 2 types, metallic and silicone, with each having its own advantages and disadvantages. A major drawback to metallic stents is their propensity to promote excessive granulation tissue formation, which can lead to airway obstruction [7-8]. However, this property of promoting granulation tissue may be desirable in patients with airway dehiscence [9]. Based on this reasoning, we used the covered self-expanding metallic stent for our patient who had a tracheal laceration after THE, and who was not suitable for primary closure or conservative therapy under positive pressure ventilation.

It is reasonable to conclude that the covered self-expanding metallic stent provided a platform for healing the tracheal laceration in our patient, because the patient's respiratory rate and air leak improved 6 hrs after the stent was implanted. Moreover, we were able to wean our patient off mechanical ventilation 2 days after the procedure, as a result of the appearance of granulation tissue formation.

In conclusion, from our experience it appears that temporary placement of a covered self-expanding metallic stent in a ventilated patient with tracheal laceration and persistent air leak after THE may be of value. To our knowledge, this is the first case of tracheal injury after THE successfully treated by a metallic airway

stent implant.

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使用呼吸器的食道癌病人接受食道切除所發生氣管撕裂後短期運用金屬支架使撕裂處成功癒合

黃浩堯　陳家弘　劉奕亨　夏德椿　施純明　徐武輝　涂智彥

穿洞式食道切除的危險率是氣管後壁的撕裂。保守治療對於病人有氣管受傷同時使用正壓呼吸器，以目前的看法是沒用的。我們討論一位使用呼吸器的食道癌病人接受橫膈裂孔食道切除導致氣管後壁撕裂所產生持續性的漏氣，放置金屬支架後病人就成功脫離呼吸器。三個月後，撕裂處癒合然後選擇性移除支架。*(胸腔醫學* ***2009; 24: 218-222)***

關鍵詞：食道切除，併發症，氣管受傷，金屬支架

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A Case of Septic Shock due to *Mycobacterium tuberculosis*: An Uncommon and Forgotten Disease Entity?

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Septic shock caused by *Mycobacterium tuberculosis* has rarely been reported following the advent of effective anti-tuberculous drugs. Since the emergence of human immunodeficiency virus (HIV) infection, there have been several reports regarding septic shock due to *M. tuberculosis* in these immunocompromised patients. Recently, this presentation has also been found in non-HIV patients. We described a non-HIV patient presenting with a rapidly fatal course; *M. tuberculosis* was the only causative micro-organism identified. Pulse contour cardiac output (PiCCO) was used for the first time to document the hemodynamic change in septic shock due to *M. tuberculosis*. ***(Thorac Med 2009; 24: 223-229)***

Key words: *Mycobacterium tuberculosis* septic shock

Introduction

Septic shock is mostly caused by Gram-negative, Gram-positive, anaerobic bacterial or fungal infections. Septic shock due to *Mycobacterium tuberculosis* is rarely reported. A syndrome reminiscent of septic shock, "*sepsis tuberculosis gravissima*", has been attributed to disseminated tuberculosis (TB). Most cases have been reported in patients with proven human immunodeficiency virus (HIV) infection. The hemodynamic characteristics of this syndrome are usually measured by pulmonary artery catheterization. We describe a non-HIV patient in whom *M. tuberculosis* was the only documented cause of septic shock. The patient's septic shock hemodynamic data was confirmed by transpulmonary thermodilution using the pulse contour cardiac output (PiCCO) method (Pulsion Medical Systems. Munich, Germany).

Case Report

A 43-year-old female software engineer presented at the emergency department with fever for 2 weeks. She had had productive cough for 1 year, and malaise with weight loss (2 kg) for 2 months. She was diagnosed with pulmonary TB 4 years ago, and had received a 6-month course of anti-tuberculous therapy. She never smoked

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or drank.

On physical examination, the patient was in a state of acute distress. Her temperature was 38.5°C, respiratory rate 26/min, pulse rate 120/min, and blood pressure 109/42 mmHg. She had bilateral crackles, more prominent on the right side. The laboratory test revealed an elevated white cell count (24980/mm^3), neutrophilia (92%), anemia, (hemoglobin 10 g/dL), and thrombocytosis (platelet count 642000/mm^3). Arterial blood gas analysis performed while the patient was breathing 5 L/min of oxygen through a nasal cannula showed respiratory alkalosis with a pH of 7.49, a PCO_2 of 34 mmHg, a PO_2 114 mmHg and an HCO_3 of 25 mEq/L. Urinalysis revealed no pyuria. Chest radiograph showed a destroyed right lung with multiple large cavities and reduced volume, and mottling infiltrates at the left upper lobe (Figure 1). Chest computed tomography (CT) further depicted a destroyed right lung with large cavities and cystic bronchiectatic changes, and peribronchial consolidations with cavities at the left upper lung (Figure 2). Her sputum stained positive (4+) for acid-fast bacilli and later grew *M. tuberculosis*. Isoniazid, ethambutol, rifampicin, and pyrazinamide were started after the acid-fast stain results on day 1. We also started intravenous ceftazidime and levofloxacin immediately, and intravenous streptomycin 3 days later, but fever persisted and the hypoxemia deteriorated. Meanwhile, blood, urine, and sputum cultures sampled at the emergency department for bacteria and fungi all yielded no growth. Hypotension and hypoxemic respiratory failure developed on day 8. She was intubated, transferred to the intensive care unit (ICU), and treated with high-dose dopamine and norepinephrine. We connected her to a PiCCO device, and the hemodynamic data showed a profile suggestive of septic shock (Table 1), with normal central venous pressure, a normal cardiac index, normal end-diastolic volume and intrathoracic blood volume indexes, and reduced systemic vascular resistance. Repeated sputum smears from the endotracheal tube revealed >25 polymorphonuclear leukocytes per low power field without bacteria, except that the sputum acid-fast stain was persistently positive. Labo-

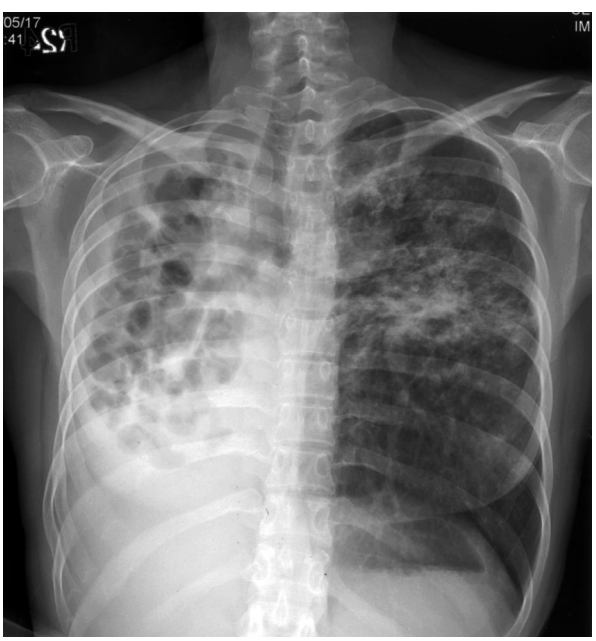

Fig. 1. Chest radiograph showing a destroyed right lung with multiple cavities, and infiltrates at the left upper lung.

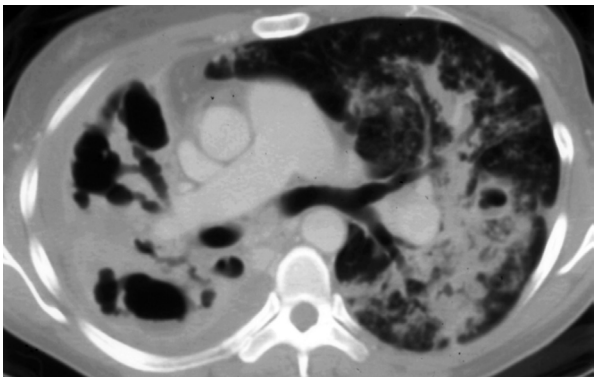

Fig. 2. Computed tomography of the chest depicts peribronchial consolidations at the left upper lung and right-side destroyed lung with cavities and bronchiectasis.

Table 1. Hemodynamic data measured by pulse-induced contour cardiac output (PiCCO) during the first 4 days in the ICU

	Day 1	Day 2	Day 3	Day 4
Heart rate (rate/min)	136	143	127	122
Blood pressure (mmHg)	107/98	126/79	116/78	120/82
Central venous pressure (mmHg)	7	12	13	12
Cardiac Index (3.0-5.0 l/min/m^2)	4.85	3.3	3.63	2.97
Global end-diastolic volume index (680-800 ml/m^2)	741	510	703	621
Intrathoracic blood volume index (850-1000 ml/m^2)	927	537	879	776
Systemic vascular resistance index (1970-2390 dyne seconds/cm^5/m^2)	1600	1986	1672	2210
Extravascular lung water index (<10 ml/kg)	12.4	10.2	11.9	9.6
Dopamine (ug/kg/min)	5	3	3	0
Norepinephrine (ug/min)	23	23	17	11

ratory test for HIV antibody was negative. Her shock state improved, but on day 13 her anemia suddenly worsened, and the serum creatinine level suddenly increased. On day 19 high fever and profound shock developed, along with progressive anemia, thrombocytopenia and renal insufficiency. Bone marrow aspirate showed findings of hemolytic anemia and thrombocytopenia. The direct Coombs' test was positive. Multiple organ failure ensued. She died on day 21. Autopsy was not performed. After her death, blood culture for mycobacteria was negative. Isolates of *M. tuberculosis* from her sputum were sensitive to isoniazid, ethambutol, rifampicin, streptomycin and ofloxacin.

Discussion

Dissemination of *M. tuberculosis* leading to severe infection can occur with or without formation of miliary tubercles. Miliary TB is widely known, while TB without miliary tubercles, which is much less common and less well known, is referred to as *sepsis tuberculosa acutissima*. Both can progress to septic shock with multiple organ failure, termed *sepsis tuberculosa gravissima* [1], and Landouzy septicemia in Europe.

Sepsis tuberculosa acutissima was described in 31 cases before 1951 [1], but seemed to be left unnoticed after the advent of effective chemotherapy, which, along with improved diagnostic methods, had lowered the incidence of this syndrome in TB non-endemic areas. However, It has been reported again in conjunction with HIV infection since 1990 [2-5] (Table 2), and has been found in non-HIV patients since late 1990 [6-9]. Patients relatively young in age and without HIV infection, as in our case, seem to be an unexplained major characteristic of these cases (Table 2). Our patient, like several of those reported before, had a history of pulmonary TB. However, she never smoked or drank, in contrast to previously reported cases who were often heavy smokers and alcoholics.

Clinical features included altered mental status, dyspnea, under-nutrition, loss of body weight, and renal insufficiency [8-9]. But rap-

Table 2. Case reports of septic shock due to *Mycobacterium tuberculosis*

Author	Number of patients	Age/Gender	Culture site	Autopsy findings	HIV status	AFS/Sputum culture	CXR	Diagnosis	TB medication and outcome
Gachot B *et al*.; 1990 [2]	4	NA	3: blood culture 1:NA	NA	All +	NA/NA	NA	NA	NA/expired
Ahuja SS. *et al*.; 1992 [13]	2	34/M	NA	miliary TB in multple organs	NA	NA/NA	bilateral alveolar pattern	postmortem	-/expired on day 4
		27/F	NA	miliary TB in multiple organs	NA	+/NA	clear→ left lower infiltrates	antemortem	HERZ since day 23/ expired on day 32
Vadillo M. *et al*.; 1994 [3]	1	63/M	bronchial washin and bone marrow	caseating granuloma in multiple organs.	+	+/+	normal	antemortem	RE since day 2/ expired on day 3
George S *et al*.; 1996 [4]	1	32/F	NA	caseating granuloma in multiple organs.	+	NA/NA	normal	postmortem	-/expired on day10
Clark TM *et al*.; 1998 [5]	1	34/M	blood	AFB in multiple organs.	+	+/NA	bilateral reticulonodular shadowing	antemortem	HRAC since day 2/ expired on day 4
Angoulvant D *et al*.; 1999 [6]	1	44/M	BAL	-	-	+/+	bilateral pulmonary infiltrates	antemortem	HER since day ?/ Expired on day 3
Pene F *et al*.; 2001 [7]	1	69/F	sputum and ascites	-	-	-/+	bilateral interstitial infiltrates	postmortem	-/expired on day 4
Michel P *et al*.; 2002 [8]	3	47/M	sputum	-	-	NA/+	bilateral alveolar and interstitial pattern	antemortem	HERZ since day ?/ Expired on day 17
		41/M	Sputum and pleural effusion	lung cavitation with Gram-negative bacilli	-	+/+	right pneumothorax	antemortem	HERZ since day ?/ Expired on day 20
		73/F	bronchial sampling	-	-	NA/NA	NA	postmortem	- /expired on hour 28
Bridges DA *et al*.; 2006 [9]	1	50/M	sputum	-	-	+/+	multiple cavities	-	HERZ since D1/ Survive

NA: not available; H: isoniazid; E: ethambutol; R: rifampicin; Z: pyrazinamide; A: amikacin; C: levofloxacin; AFB: acid-fast bacillus

idly progressive septic shock leading to respiratory and eventual multiple organ failure is almost the rule. One characteristic rarely observed in the commonly occurring cases of septic shock is the presence of a preceding chronic illness, such as cough, malaise or weight loss. Chest radiographs and CT usually show diffuse alveolar-interstitial infiltrates (Table 2), compatible with acute respiratory distress syndrome (ARDS), but may disclose cavities, as in our case, that may suggest TB.

Similar to lipopolysaccharide in bacterial septic shock, lipoarabinomannan or other mycobacterial products were believed to play a role in septic shock due to *M. tuberculosis*. *In vitro* studies have shown that human monocytes and activated peritoneal macrophages release tumor necrosis factor (TNF) after being stimulated by lipoarabinomannan from *M. tuberculosis* [10].

The problem left unresolved is the high mortality rate of such cases. Despite early recognition and institution of anti-tuberculous drugs in most of the cases and in our patient, the infection has proved fulminant and refractory to

treatment, and victims usually succumbed within days. Miliary granuloma formation has been suggested to imply a more adequate inflammatory response that may confine disseminated *M. tuberculosis*, as compared with no granuloma formation in *sepsis tuberculosa acutissima*. Thus a poorer outcome could be expected in patients without miliary lesions, such as our patient [3]. In our case, the high mycobacterial load was also an important factor contributing to the fulminant course. Another probable contributing factor was her hemolytic anemia, which occurred after experiencing an improved clinical course for a short period. Autoimmune hemolytic anemia has been associated with miliary TB [11]. However, because her anemia occurred after initiation of anti-tuberculous therapy, it could have been caused by rifampicin, which could also have caused the progressive renal failure [12].

In the majority of reported cases, *M. tuberculosis* septic shock was confirmed by hemodynamic data from pulmonary artery catheterization [2, 4, 13]. The lack of these data in some cases was due to either failed attempts at catheterization [5] or the doctor's preference for 2-dimensional echocardiography [6]. With controversies over the safety and benefits of pulmonary artery catheterization in critical patients [14], many intensivists have raised concerns about its use. PiCCO is a device requiring a central venous line and an arterial catheter with a thermister. PiCCO quantifies several parameters, including cardiac output, cardiac preload, systemic vascular resistance and extravascular lung water. Using the pulse-induced contour cardiac output method, PiCCO offers a less invasive yet accurate method for continuous monitoring of patients with septic shock [15]. However, several disadvantages exist, such as the inaccuracy under certain conditions (intracardiac shunts, aortic aneurysm, aortic stenosis, pneumonectomy, etc.), the need for frequent calibrations, and the cost. The hemodynamic data of our patient using PiCCO were in line with those of case reports, showing a normal to high cardiac output and low systemic vascular resistance index (SVRI), suggestive of septic shock. It seemed that a less depressed cardiac performance and a less edematous lung were observed in such patients. We deduced that these patients had endured fever and undernutrition for a period before the catastrophic finale. The subacute or chronic course could have made them more hypovolemic than patients with acute bacterial septic shock. Such large volume deficits in young patients with good heart performance could contribute to their dry lung, despite rapid fluid resuscitation.

In conclusion, we report a case with septic shock due to *M. tuberculosis*, in which hemodynamic data were documented by PiCCO for the first time. In endemic TB areas, *M. tuberculosis* should be listed as a possible causative microorganism of septic shock, especially when the episode is preceded by a subacute or chronic illness.

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結核敗血性休克及其在脈搏波形分析心排出量監測（PiCCO）的血行動力學表現

林倬漢　鄭之勛　王振源　李麗娜

結核敗血性休克在有效的抗結核藥物問世後就不再被注意，而1990年代開始，有人類免疫不全病毒感染的病患併結核敗血性休克的病例被報導，然而，1990年代末期，開始也有無人類免疫不全病毒感染的病患併結核敗血性休克的病例被注意，我們相信結核敗血性休克因之前有效結核藥物的發明，及診斷的進步，而在結核盛行的地區被忽視。

我們報告一位43歲女性患者，發生結核敗血性休克，其人類免疫不全病毒血清學檢查為陰性，在加護病房中，運用脈搏波形分析心排出量監測（PiCCO），並和文獻的資料作印證。*(胸腔醫學* ***2009; 24: 223-229)***

關鍵詞：結核敗血性休克

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Malignant Solitary Fibrous Tumor of the Pleura with Concurrent Thymoma: A Case Report

Yo-Ju Chen, Wen-Hu Hsu

Solitary fibrous tumors of the pleura (SFTP) are extremely rare. In the past, the origin of these tumors was thought to be mesothelial cells. With the development of immunohistochemical stain, we have found that SFTPs are subpleural mesenchymal tumors. Clinical preoperative diagnosis of the disease is difficult due to the absence of specific symptoms. Usually, SFTPs cannot be distinguished from other pleural tumors or lung tumors with pleural involvement, based on the image studies. Although the majority of these tumors have a benign course, the malignant form still remains enigmatic. The behavior of these tumors is often unpredictable and not correlated with the histologic findings. Surgical resection is a better treatment modality. The risk of recurrence is high after resection of a malignant sessile SFTP. Herein, we present the case of a mass in the left lower thorax with a concurrent anterior mediastinal tumor, which were simultaneously treated by excision of the mass in the pleura with wedge resection of the left lower lobe of the lung, and removal of the mediastinal tumor via an ipsilateral thoracotomy approach. The final pathologic diagnosis of the tumor was malignant SFTP and minimally invasive thymoma, WHO type B1. There was no evidence of recurrence of either disease in the 7-month follow-up after surgery. The related literature is also reviewed. ***(Thorac Med 2009; 24: 230-236)***

Key words: solitary fibrous tumors of the pleura (SFTP), thymoma, surgical resection

Introduction

Localized pleural tumor was initially reported by Wagner in 1870. Klemperer and Rabin, in 1931 published the first pathologic description and classified mesothelioma as "localized" or "diffuse" [1]. In 1942, Stout and Murray claimed that localized mesothelioma had a mesothelial origin [2]. However, other investigators thought that the mesothelial cells could have been trapped within growing fibrous mesenchymal tumors [3]. The controversy on the origin of these tumors persisted for decades. In recent years, immunohistochemical studies have provided strong evidence for a mesenchymal origin of these tumors. Clinically, solitary fibrous tumors of the pleura (SFTP) are extremely rare, and preoperative diagnosis is usually dif-

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ficult. Sometimes, the tumor might simulate a mediastinal tumor, according to the findings of computed tomography (CT) scans of the chest. There have been no reports of SFTP with concurrent thymoma in the English literature. Herein, we reported a case of SFTP with a concurrent small mediastinal tumor, a thymoma.

Case Report

A 66-year-old female has lived in Taiwan for more than 60 years. She denied any systemic disease in the past. She didn't smoke cigarettes or drink alcohol. One month before admission, a huge tumor mass in the left lower lung field was found incidentally on the CXR during a routine health check-up. After admission, the CXR (Figure 1A & Figure 1B) demonstrated a well-defined round mass, measuring 6.7 cm in size, in the left lower lung field, with incomplete border signs. Pleural tumor or lung tumor with pleural involvement was highly suspected.

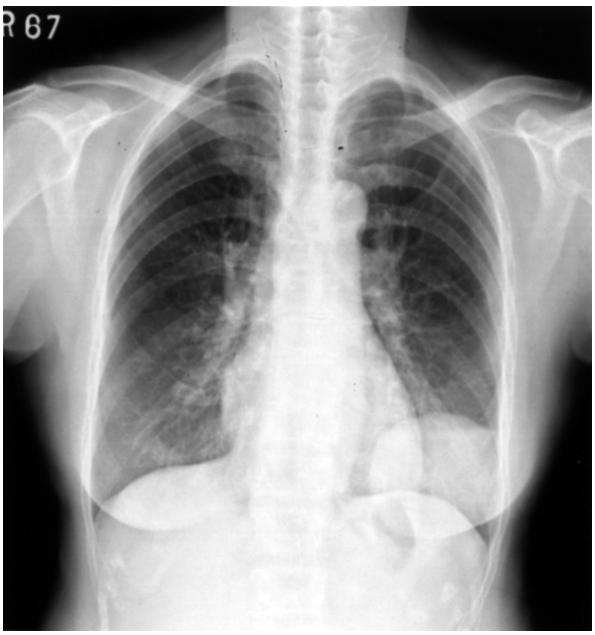

Fig. 1A. Chest radiography (PA view) demonstrating a well-defined round mass in the left lower lung field with incomplete border signs.

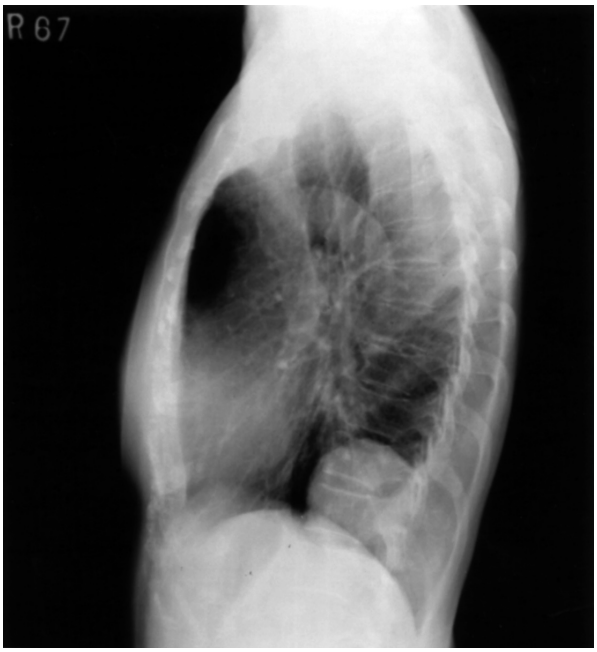

Fig. 1B. Chest radiography (lateral view) demonstrating a well-defined tumor in the left lower thorax, near the C-P angle.

The CXR also showed degenerative change of the T-spine and bilateral acromio-clavicular joints. Further CT scan of the chest confirmed a well-defined soft tissue mass, about 7.2 cm x 5.5 cm x 7.5 cm in size, in the left lower thorax, with an inhomogenous component and areas of necrosis in the tumor (Figure 2A). Fibrous tumor with probable lung parenchymal invasion was suspected. Meanwhile, the CT scan of the chest revealed a small homogenous soft tissue mass, about 1.5 cm in diameter, abutted to the aortic arch (Figure 2B). Under the impression of pleural tumor and concurrent thymoma, the patient was referred to a thoracic surgeon for surgical intervention. Further sonography of the whole abdomen, a radionuclide whole body bone scan, and a CT scan of the brain concluded no evidence of distant organ metastasis. The serum level of CEA was within normal limits. All of the preoperative work-up examinations, such as blood cell count, biochemistry, and pulmo-

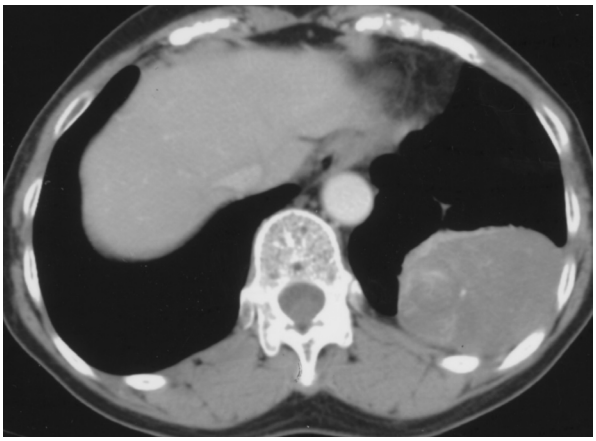

Fig. 2A. CT scan of the chest revealing a soft tissue mass with a heterogenous component in the left lower lung field.

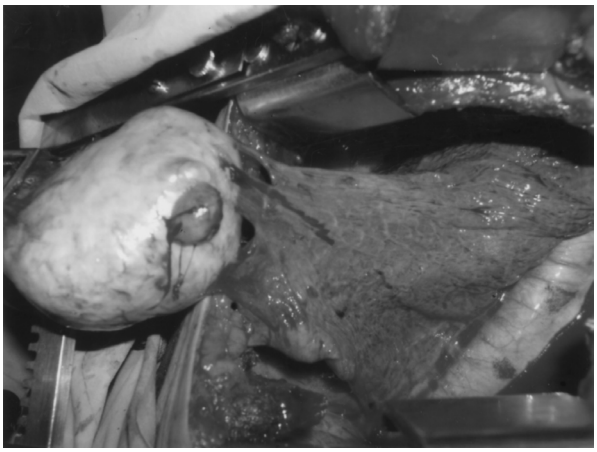

Fig. 3A. Specimen: tumor arising from the visceral pleura of the left lower lobe of the lung.

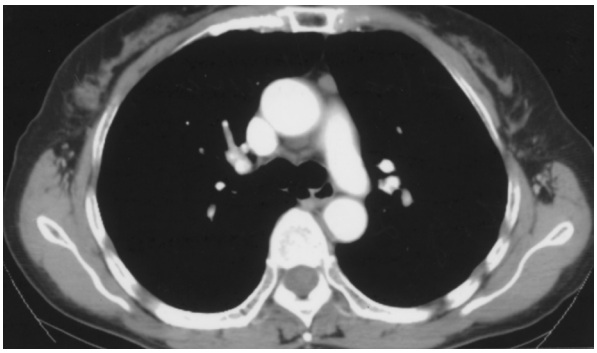

Fig. 2B. CT scan of the chest revealing a small homogenous soft tissue nodule in the anterior mediastinum abutting the ascending aorta.

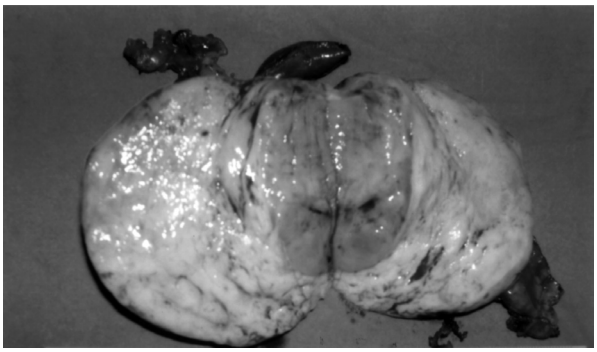

Fig. 3B. Specimen: an encapsulated yellowish-white rubbery tumor, measuring 8 cm x 7.2 cm x 4.6 cm, with central necrosis foci.

nary function tests, were within normal limits. Physical examinations disclosed normal breathing sounds, and she did not have clubbing fingers or hypoglycemia. Thereafter, she underwent operation. The parts of the fibrous tumor tightly attached to the parietal pleura in small areas were resected first, and then the tumor could be taken out from the patient's thorax easily. The tumor also abutted the left lower lung parenchyma (Figure 3A). Stapler resection was performed on the healthy lung parenchyma, at 1 cm away from the tumor. Meanwhile, the small mediastinal tumor was removed via an ipsilateral thoracotomy approach. The postoperative course was smooth, and the patient was discharged 8 days after surgery.

The specimens consisted of an encapsulated yellowish white rubbery tumor, measuring 8 cm x 7.2 cm x 4.6 cm (Figure 3B), with central necrosis foci and attached lung parenchyma, and a small, tan-gray soft tissue, measuring 1.5 cm x 1.5 cm x 1.2 cm with attached fat tissue. Microscopically, the sections of tumor revealed fibrovascular proliferation composed of neoplastic fibroblastic cells with a background of loose or dense fibrous stroma and ropy collagen. Severe pleomorphism, atypical mitotic figures, and tumor necrosis were observed (Figure 4A).

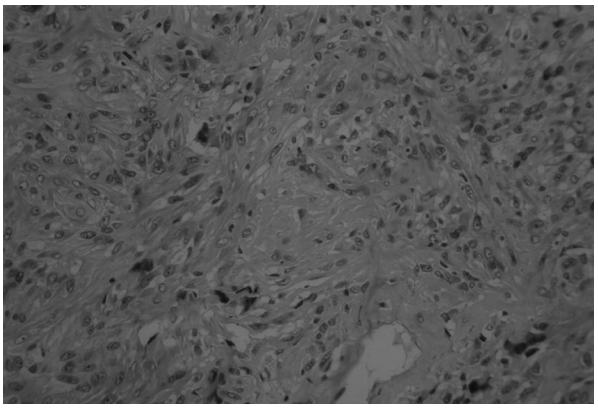

Fig. 4A. H&E stain: sections of the malignant solitary fibrous tumors of the pleura showing severe polymorphism, atypical mitosis, and necrosis.

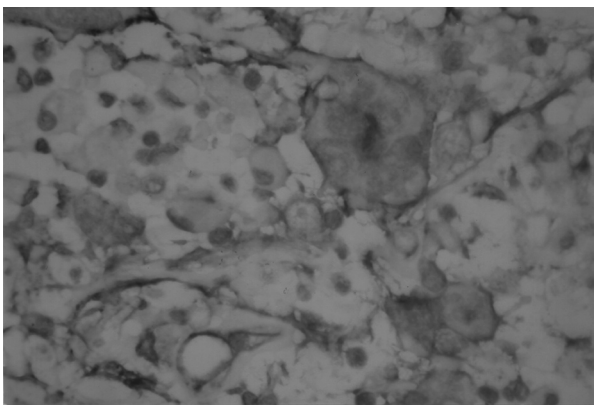

Fig. 4B. Immunohistochemical stain: sections of specimen showing CD34 positive stain on the plasma membrane of the tumor cells.

The results of immunohistochemical staining showed that the tumor cells were positive for CD34 (Figure 4B), but negative for cytokeratin. No tumor invasion was observed in the attached lung parenchyma and involved parietal pleura. Sections of the small mediastinal tumor revealed WHO type 1 thymoma morphologically. The tumor had invaded through the fibrous capsule and reached the perithymic soft tissue. The tumor cells were positive for cytokeratin, and CD-3-positive small T lymphocytes were identified within the tumor. The final diagnosis was malignant solitary fibrous tumor of the pleura and concurrent minimally invasive thymoma, WHO type B-1. The patient had received regular follow-up for 7 months, as of this writing, and no recurrence of either disease was found.

Discussion

SFTPs have been described in all age groups from 5 to 87 years, but they typically peak in the sixth and seventh decades of life [5, 8]. They have an even distribution between men and women [5, 8], and often have an indolent clinical course, being asymptomatic for several years [6]. The majority of patients with malignant SFTP are symptomatic and have large tumors [6, 8, 10]; they often present with cough, chest pain, and dyspnea. When there are no specific symptoms, the preoperative diagnosis is extremely difficult. Hypertrophic arthropathy or hypoglycemia may help in establishing the diagnosis, but they only occurred in 4% and 2% of patients respectively, as reported by Magdeleinat [7]. Digital clubbing and hypertrophic pulmonary osteoarthropathy (Pierre-Marie-Bamberg syndrome) have been described in 10%-20% of patients with either benign or malignant SFTP [6, 8]. On the other hand, in less than 5% of patients, SFTP can secrete insulin-like growth factor II, causing refractory hypoglycemia [8, 11] Pleural effusion developing in 6-8% of patients with localized fibrous tumor of the pleura has been reported [8]. The computed tomography scan of the chest demonstrates a well-circumscribed round tumor with a homogenous density in the most cases [9]. However, the CT scan findings are not specific, and cannot differentiate benign from malignant SFTP. In addition, it is very difficult to distinguish these tumors from others originating from the mediastinum or chest wall. If the component of the

tumor is heterogenous, bronchogenic carcinoma should be included in the differential diagnosis, especially for those patients with a smoking history. Nuclear magnetic resonance has benefit in confirming the fibrous character of the tumor [9]. The diagnostic accuracy of CT-guided biopsy is not satisfactory, reaching only about 45% in the Magdeleinat study [7]. Our patient was 66 years old--the typical peak age; she did not have any obvious symptoms, and all of the biochemistry tests were normal, without hypoglycemia or hypertrophic arthropathy. The CT scan of the chest showed a well-circumscribed round tumor with heterogenous foci and a concurrent small mediastinal tumor. So far, no obvious significant relationship between fibrous tumor of the pleura and thymoma can be concluded.

Macroscopically, the most benign SFTP are small or huge pedunculated tumors, while the malignant tumors are often larger than 10 cm in diameter on presentation [12]. Both small and large are encapsulated by a thin, translucent membrane, containing a reticulated vascular network. Firm adhesion without invasion between the visceral surface and parietal pleura may be seen. The cut surface occasionally shows hemorrhagic and necrotic areas, which usually predominate in the malignant form, and are caused by their large size [8, 10]. Microscopically, SFTSs are characterized by a proliferation of uniform elongated spindle cells intimately intertwining with various amounts of connective tissue. Histologic signs of malignancy include high cellularity and mitotic activity (more than 4 mitoses per 10 high-power fields), pleomorphism, and the presence of necrotic or hemorrhagic zones [8, 13]. The immunohistochemical staining demonstrated that SFTPs express vimentin, which is a marker of mesenchymal cells, and do not express cytoplasmic keratins, which are found in mesotheliomas [4]. In addition, CD34 is a useful marker in the diagnosis of a solitary fibrous tumor, but its expression can be loose in high-grade tumors [13]. Our patient's specimen had a benign appearance grossly, less than 10 cm, with a shiny and intact capsule; the portion attached to the lung parenchyma was pedunculated. However, necrosis, which usually predominates in malignant SFTP, was noted on the cut surface. Firm adhesion between the visceral surface and the parietal pleura was noted, but there was no tumor infiltration in the parietal pleura. Microscopically, there were cells with pleomorphism and atypical mitotic figures, and the presence of tumor necrosis in our patient's specimen. The immunohistochemical stain demonstrated evidence of SFTP, positive to CD34 and negative to cytokeratin.

Surgical intervention provides not only a definite diagnosis, but also a curative modality for the disease. It is well known that the best treatment is complete surgical resection. A distance of 1 cm to 2 cm from the tumor is usually recommended to reach healthy tissue [10]. Magdeleinat [7] reported complete resections in all of the 38 patients with benign SFTP, and 21 complete resections in 22 patients with malignant SFTP. There were only 2 local recurrence cases during a mean 88-month follow-up period. Thoracoscopic approaches can be safely used to remove small pedunculated tumors located on the visceral pleura [14]. The role of adjuvant therapy in SFTP has not been systematically explored because of the limited numbers of patients. Based on several studies, the administration of adjuvant therapy after resection of malignant sessile tumors is recommended, especially for recurrent tumors [10]. Additional therapies, such as brachytherapy and

photodynamic therapy, have been developed for malignant mesothelioma, but their use in SFTP has rarely been reported, and their utility remains unproven [15]. Our patient underwent en-bloc surgery, and the safe margin was more than 1 cm. There was no tumor recurrence for 7 months postoperatively.

Solitary fibrous tumor is a rare mesenchymal tumor, and not a mesothelial tumor. The clinical diagnosis may be difficult, because patients with SFTP often have nonspecific symptoms. The microscopic findings of malignant SFTP include high cellularity and mitotic activity, pleomorphism, and the presence of necrotic or hemorrhagic zones. Immunohistochemical staining provides a diagnostic modality for SFTP. The majority of these tumors have a benign course, but the behavior of malignant SFTP is unpredictable and doesn't correlate with histologic findings. Only surgical resection of the tumor provides the opportunity to cure SFTP. The role of adjuvant therapy is still unproven.

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孤立性肋膜纖維瘤合併胸腺瘤：病例報告及文獻回顧

陳右儒　許文虎

孤立性肋膜纖維瘤是一種相當罕見的疾病。在過去認為這種腫瘤是由肋膜生長出，但藉由免疫組織化學染色技術的進步，我們瞭解事實上孤立性肋膜纖維瘤是由肋膜下肺間葉所生長出之腫瘤。臨床上並沒有特定的症狀增加術前診斷的困難度。常常單靠影象學並不能區分孤立性肋膜纖維瘤及其他肋膜腫瘤或肺癌合併肋膜侵犯。大多數此類腫瘤的病程緩和，但若為惡性形式則其病程難以預估。另外此類腫瘤的行為與組織學形態常不一致。手術切除應該是較好的治療方式。若是為非梗狀之惡性孤立性肋膜纖維瘤，手術切除後之復發率較高。今天我們提出一個病例，腫瘤位於左下胸腔內，同時合併有一前縱膈腔腫瘤。這位病人接受了經由開胸手術同時切除胸腺瘤及肋膜纖維瘤。最後的病理診斷為惡性孤立性肋膜纖維瘤及胸腺瘤，WHO type B1。目前術後七個月追蹤中且兩種疾病皆無復發現象。同時我們也進行一些文獻回顧。*(胸腔醫學* ***2009; 24: 230-236)***

關鍵詞：孤立性肋膜纖維瘤（SFTP)，胸腺瘤，手術切除

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Lambert-Eaton Myasthenic Syndrome Associated with Small Cell Lung Cancer – A Case Report

Bo-Lung Ho, Shinn-Liang Lai

Lambert-Eaton myasthenic syndrome (LEMS) is a rare neuromuscular disorder characterized by the defective release of neurotransmitters from pre-synaptic nerve terminals. It is an autoimmune condition associated with autoantibody immunoglobulin G (IgG) targeted at voltage-gated calcium channels (VGCCs). It is also associated with small cell lung cancer (SCLC) in about 60% of cases. We report a patient with SCLC initially presenting with LEMS. This 63-year-old-male first experienced progressive weakness of the 4 limbs within about a 1-year period; LEMS was diagnosed with electrophysiologic studies. Chest computed tomography (CT) then revealed a mass shadow at the subcarinal area. Cytology study of the bronchoscopic transbronchial fine needle aspiration revealed SCLC, limited in stage.

The carcinoma responded to a chemotherapy regimen of cisplatin and etoposide. The weakness of the 4 limbs improved significantly within 1 month after the first cycle of chemotherapy. The subcarinal mass also regressed significantly with chemotherapy. ***(Thorac Med 2009; 24: 237-242)***

Key words: Lambert-Eaton syndrome, small cell lung cancer, voltage-gated calcium channels

Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is a rare disease characterized by muscle weakness and autonomic dysfunction. It was reported for the first time in 1956 by Lambert *et al*. [1]. The diagnostic repetitive nerve stimulation tests and electromyography were first reported in 1957 [2]. This manifestation resulted from a presence of immunoglobulin G (IgG) auto-antibody targeted to presynaptic voltage-gated calcium channels (VGCCs) that induced an abnormality of presynaptic acetylcholine release [3]. LEMS usually occurs together with small cell lung cancer (SCLC); it is associated with SCLC in about 60% of cases [4], and the incidence of LEMS in SCLC is approximately 6% [5]. In this report, we present a case of LEMS with SCLC and discuss the etiology, diagnosis and treatment of the condition.

Case Report

This 63-year-old male had a history of hy-

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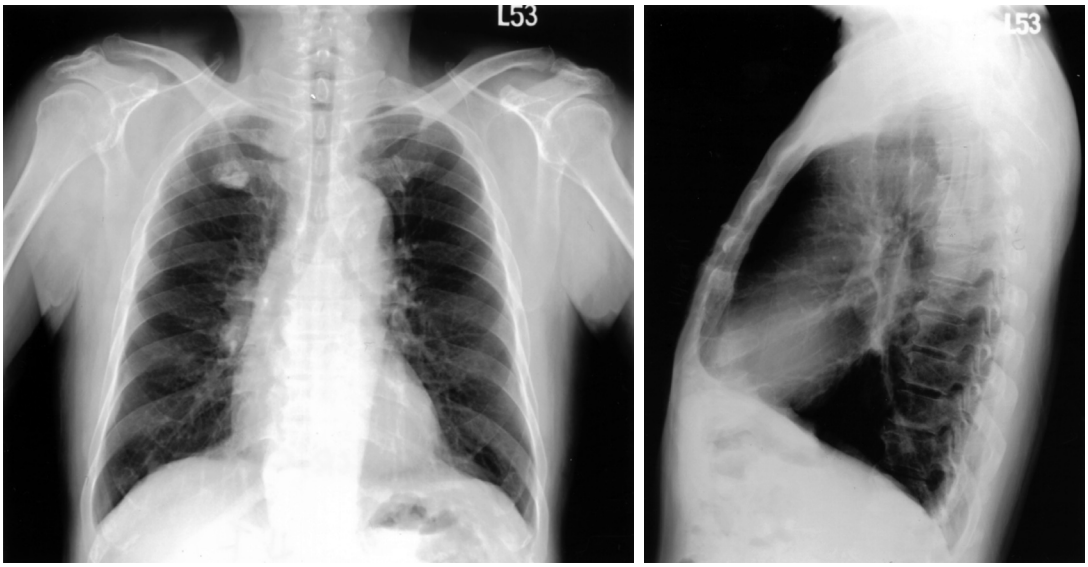

Fig. 1. Chest radiograph showing carinal widening and a subcarinal lesion

pertension, and no other disease history. He was a taxi driver. He had smoked 2 packs of cigarettes per day for 30 years, and quit for 20 years. He began feeling a weakness of the proximal muscles of all limbs around January 2007. The weakness progressed gradually. In June 2007, he could not drive his car due to muscle weakness. Ptosis, dry eye and dry mouth were also noted. Body weight loss of about 10 kilograms was noted during a 6-month period. In July 2007, he visited a neurologist at Taipei Municipal Hospital, where chest X-ray film revealed a subcarinal mass (Figure 1). Operation was suggested by the surgeon there, but he refused and came to our hospital, instead. He visited our neurologist and chest medicine specialist in Oct 2007. Chest computed tomography (CT) scan revealed a 5.8 x 4 x 3 cm subcarinal soft tissue mass (Figure 2). Some small lymph nodes were noted at the right hilar area, aorta-pulmonary artery window area, and lower paratracheal area. SCLC at a limited stage was diagnosed. The nerve conduction velocity study revealed sensory-motor polyneuropathy. The

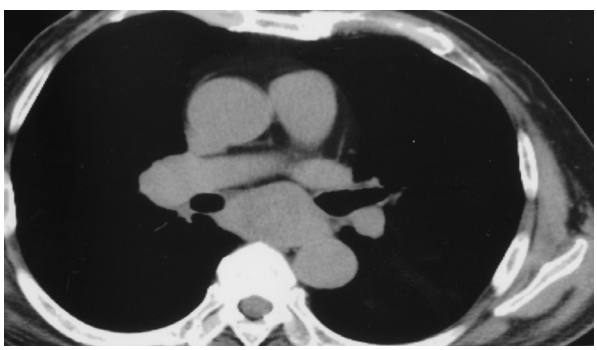

Fig. 2. Computed tomography of the chest showing the subcarinal soft tissue mass lesion

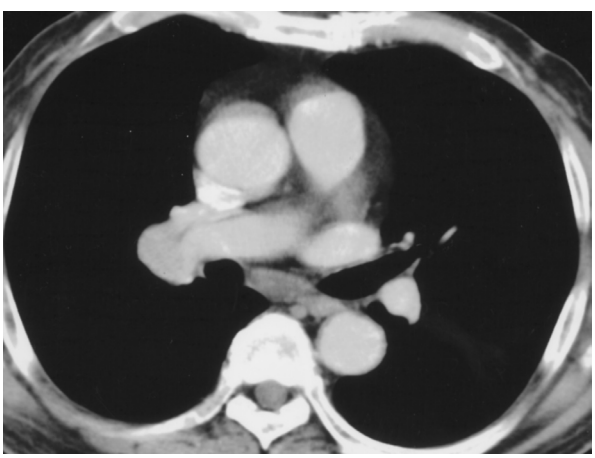

Fig. 3. After 4 months of chemotherapy, the subcarinal tumor size decreased significantly, to about 2 x 2 x 1.5 cm

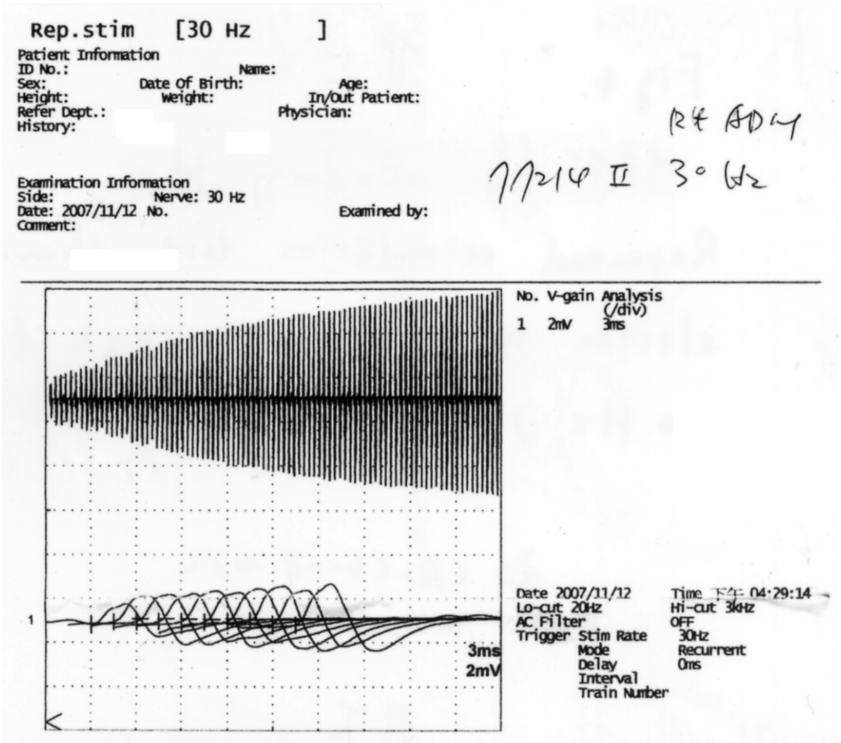

Fig. 4. Repeated stimulation tests showing electrical stimulation at a high frequency (30 Hz), in a 30 x 10^{-3} seconds period (30 msec); the compound muscle action potentials of the right digiti minimi increased from about 2 x10^{-3} volts (2mV) to about 6 mV, or approximately 300% of the initial response.

CEA was 2.44 ng/ml.

He was admitted to our ward in Nov 2007. Physical examination revealed ptosis of the bilateral eyelids. Neurological examination revealed grade III muscle power in the proximal muscles of the 4 limbs. The deep tendon reflexes were generally decreased. With the exception of the elevated serum lactate dehydrogenase (431 U/L), all other laboratory results, including complete blood counts, electrolytes, and urine and stool routine tests, were within normal limits. Scanning studies, including brain CT and whole body bone scan, found no metastasis.

The compound muscle action potentials (CMAPs) of the right abductor digiti minimi muscle were low (only about 2 mV). During the repetitive nerve stimulation test at a frequency of 30 Hz, the CMAPs increased in amplitude to about 300% of the initial response (Figure 4), which was compatible with LEMS.

Initial treatment with chemotherapy using cisplatin and etoposide was given. The first chemotherapy treatment began in Nov 2007. In consideration of the patient's malaise, and his will and inclination, we did not perform concurrent chemoradial therapy. One month later, the quadriparesis improved significantly, and he could walk quite well without help. The muscle power of the proximal limbs increased to more than grade IV. The patient had received 6 cycles of chemotherapy up to March 2008. Chest CT follow-up in April 2008 revealed the subcarinal mass had significantly decreased in size, to 2 x 2 x 1.5 cm (Figure 3).

Discussion

LEMS is characterized by a reduction in the Ca^{2+}-dependent quantal release of acetylcholine in pre-synaptic motor nerve terminals [4]. The release of neurotransmitters at pre-synaptic nerve terminals depends on the influx of calcium ions via VGCCs [3]. This release results in depressed tendon reflexes and muscle weakness.

There are at least 5 types of VGCCs (L, N, P/Q types, R, T). The P/Q type VGCCs appear in almost 100% of LEMS, which implies the pathophysiological role of this specific VGCC [6].

Several previous studies implicated SCLC in triggering LEMS. SCLC may be of neuroectodermal origin, and express VGCCs [7]. There is marked macrophage and lymphocyte infiltration in LEMS-associated SCLC, and it is significantly more aggravated than non-LEMS-related SCLC. This raises the possibility that it is the tumor in LEMS that provokes the immune response [8].

The clinical characteristics of LEMS are proximal muscle weakness, especially weakness of the legs, and depressed tendon reflexes, usually with a gradual onset. The muscle strength may increase transiently with voluntary exercise.

The most common alternative and differential diagnosis is myasthenia gravis (MG) [9]. Decreased tendon reflex and autonomic dysfunction are features of LEMS, but not of MG [4]. Clinically, it may be difficult to differentiate MG from LEMS, because the distribution of muscle weakness may be similar in these 2 diseases [9], but there still exists some differences in symptoms between the 2 diseases.

In most patients with MG, the first symptom is ptosis, but it is virtually excluded in LEMS patients. Limb weakness confined to the upper limbs is only found in MG patients, but is absent in LEMS. Muscle weakness in MG tends to develop in a cranio-caudal direction, which is the opposite of LEMS [9].

The diagnosis of LEMS is made with electrophysiologic tests. It is characterized by greatly reduced amplitudes of CMAPs that increase by over 100% during repetitive nerve stimulation with a stimulation frequency as high as 15 Hz or 30 Hz [9].

Once the diagnosis of LEMS is confirmed with electrophysiologic tests, an exhaustive search for an underlying malignancy must be undertaken. Chemotherapy for small cell carcinoma is the cornerstone strategy and will be expected to improve the muscle weakness symptoms [10].

Plasmaphoresis and intravenous immunoglobulin can improve symptoms, but the effects are short-lived unless immunosuppressive agents are employed, as well. Cholinester inhibitors, in the same dose as used in MG, may produce some improvement in LEMS, but not as dramatically as that in MG. In patients with significant weakness, prednisolone (60-80 mg/d) and azathioprine (2-3 mg/kg/d) are the most frequently used drugs, given alone or together. Cyclosporine (5-6 mg/d) can be used in those who do not respond to azathioprine [10].

This case may have been a case of extrapulmonary small cell cancer (EPSCC), because there was no visible intrapulmonary cancer. But of course, we cannot totally exclude the possibility that the tumor was a metastasis to the mediastinal lymph nodes from invisible SCLC. EPSCC is rare; it behaves aggressively, and is often associated with paraneoplastic syndromes. The overall 5-year survival of EPSCC patients

was reported to be 13% [11].

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Lambert-Eaton氏肌無力症候群合併小細胞肺癌——病例報告

侯伯龍　賴信良

Lambert-Eaton氏肌無力症候群為一少見的神經肌肉疾病，其在病理生理上的特性為一自體免役機制，自體分泌的G型免役球蛋白（IgG）與節前神經末稍上的電位制動鈣離子通道（voltage-gated calcium channels, VGCCs）結合，其引發的一序列生化反應致使節前神經元末稍無法順利釋放乙醯膽鹼（Acetylcholine)，導致肌肉無力以及肌腱反射下降。約有60%的Lambert-Eaton氏肌無力症候群病人合併有小細胞肺癌。我們在此報告一位63歲男性病患在Lambert-Eaton氏肌無力症候群發生後約一年由胸部斷層掃瞄發現主氣管分枝（Carina）下腫塊，經支氣管鏡細針穿壁抽吸，細胞學檢查確診為小細胞肺癌，局限期。經以Cisplatin和etoposide（PVP）化學治療，一個月後肌無力已顯著改進，癌腫塊也明顯縮小。*(胸腔醫學* ***2009; 24: 237-242)***

關鍵詞：Lambert-Eaton氏肌無力症候群，小細胞肺癌，電位制動鈣離子通道（voltage-gated calcium channels, VGCCs）

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