Comparison of Tuberculous Empyema and Tuberculous Pleurisy in Terms of Risk Factors, Radiographic Findings and Biochemical Characteristics

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Background: Tuberculous empyema and tuberculous pleurisy are caused by different pathogenic mechanisms, and are 2 distinct types of tuberculous pleural effusion that require different treatments. No previous study has analyzed the risk factors, biochemical characteristics and radiological features of the 2 entities.

Methods: We studied the medical records of 84 patients with a diagnosis of tuberculous pleural effusion, who were treated between January 2002 and January 2005 in a tertiary-care hospital. There were 56 (66.7%) men and 28 (33.3%) women, with a mean age of 61.29 years. We further divided all patients into 2 groups: tuberculous empyema (n=23) and tuberculous pleurisy (n=61). We compared the risk factors, biochemical characteristics, and radiological features between these 2 groups.

Results: Among the 84 patients, the most common risk factors were diabetes mellitus (n=11), neoplasia (n=6), and alcoholism (n=4). There were no statistically significant differences in risk factors and radiographic findings between the 2 groups. The similar biomedical characteristics of tuberculous pleurisy and tuberculous empyema were the high LDH level (322.80 ± 190.42, 530.88 ± 71.79 U/L, respectively, p=0.14), high adenosine deaminase (ADA) activity (53.50 ± 21.6, 54.6 ± 11.6 U/L, respectively, p=0.942) and high percentage of lymphocyte counts (82.71 ± 21.62, 76.34 ± 18.22 %, respectively, p=0.538). The only statistically different biomedical characteristic between the 2 groups was the red blood cell (RBC) count in the pleural fluids, which was significantly higher in tuberculous empyema than in tuberculous pleurisy (41.28 ± 123.52 vs. 9.68 ± 27.36 10^3/UL, respectively, p<0.05).

Conclusion: When a patient presents with tuberculous pleural effusion that is lymphocyte-predominant, and has a high ADA activity and bloody appearance, tuberculous empyema should be highly suspected. ***(Thorac Med 2006; 21: 1-8)***

Key words: tuberculous pleural effusion; tuberculous empyema; tuberculous pleurisy

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Introduction

Tuberculosis (TB) is one of the most common causes of death, especially in developing countries [1]. Tuberculous pleural effusion (TPE) occurs in approximately 30% of patients with TB [2] and constitutes the major portion of extrapulmonary TB morbidity. There are 2 distinct types of TPE: tuberculous pleurisy and tuberculous empyema, which are caused by different pathogenic mechanisms. The formation of tuberculous pleurisy is mainly due to the entry of *Mycobacterium tuberculosis* into the pleural space, provoking an intense hypersensitivity reaction [3]. Tuberculous empyema is usually caused by a subpleural caseous focus or cavity rupture into the pleural space [4]. Management for these 2 distinct types of TPE is different. Treatment for tuberculous pleurisy requires only antituberculous chemotherapy alone, but tuberculous empyema may require further surgical intervention, and its optimal duration of treatment has not been established [4]. It is crucial to diagnose tuberculous empyema as soon as possible; however, it takes 2 to 6 weeks to confirm *M. tuberculosis* growth in Lowenstein-Jensen (L-J) media. Thus, finding the special or characteristic risk factors, radiographic features or biochemistry presentation of tuberculous empyema appears to be imperative for an earlier diagnosis. To our knowledge, there have been limited studies of the difference in the risk factors, and radiographic or biochemical characteristics between tuberculous empyema and tuberculous pleurisy. Therefore, we undertook a 3-year retrospective study of patients with tuberculous pleural effusion, and herein report the results.

Materials and Methods

Patients

We reviewed the medical records of 627 patients with a diagnosis of pulmonary tuberculosis between January 2002 and January 2005, as found in the TB Register at the China Medical University Hospital, a tertiary-care hospital in Taiwan. Among this group, 84 patients with tuberculous pleural effusion were enrolled into this study. There were 56 (66.7%) men and 28 (33.3%) women, with a mean age of 61.29 years (range, 20 to 92 years).

Case Definition of Tuberculous Pleurisy and Tuberculous Empyema

The diagnosis of tuberculous pleural effusion (TPE) should meet at least 1 of the following criteria: (1) positive Ziehl-Neelsen (Z-N) stains for pleural fluid or tissue, or cultures of pleural effusion or biopied tissue specimens positive for *M tuberculosis*, (2) histopathologically demonstrated caseous granulomatous inflammation in pleural biopsied tissue specimens, or (3) positive Z-N stains from sputum or bronchoalveolar lavage (BAL) fluid or cultures of sputum or BAL fluid positive for *M tuberculosis*, if the pleural effusion was accompanied with pulmonary infiltration. All patients that failed to meet 1 of the above criteria were excluded from the study. We further divided all the enrolled patients into 2 groups: tuberculous empyema and tuberculous pleurisy. Tuberculous empyema was defined as patients who only met the first criteria, and tuberculous pleurisy was defined as patients who met the second or third criteria [4]. Therefore, tuberculous pleurisy was diagnosed in 61 patients: 9 patients by Z-N stain of the sputum, 38 patients by cultures of the sputum, 11 patients by the pathology of the pleural biopsy, 2 patients by the BAL cultures, and 1 patient by video-assisted thoracoscopic biopsy. Tuberculous empyemas

were diagnosed in 23 patients: 20 patients by the culture of the pleural fluid and 3 patients by Z-N stain of the pleural fluid.

Chest Radiograph Analysis

Chest radiographs of all enrolled patients were reviewed and the data of their initial presentation recorded carefully. The location and amount of pleural effusion were recorded. A massive amount of pleural effusion was defined as a hemithorax completely opacified; a moderate amount of pleural effusion was defined as more than one-third of the hemithorax opaque, without its complete obliteration; and a mild amount of pleural effusion was defined as less than one-third of the hemithorax opaque.

Analysis and Collection of the Characteristics of Pleural Fluids

All specimens from routine diagnostic thoracentesis were sent for laboratory tests, including pH, specific gravity, bacterial cultures, Gram stain, mycobaterial smear and cultures, lactate dehydrogenase (LDH), adenosine deaminase (ADA), total protein, and differential total leukocyte counts.

Statistical Analysis

Statistical calculation was performed using a statistical software package (SPSS, version 10.0; SPSS, Inc; Chicago, IL). The 2 groups of continuous variables were compared with a *t*-test analysis of variance. Chi-square analyses of contingency tables were used to compare the correlation of 2 categorical variables. A level of less than 0.05 was considered significant for all statistical tests.

Results

Risk Factors

Among the 84 enrolled patients with TPE, 61 had tuberculous pleurisy and 23 had tuberculous empyema. As shown in Table 1, the 84 patients comprised 56 (66.7%) men and 28 (33.3%) women, with a mean (± SD) age of 61.29 (± 20.03) years (range, 20 to 92 years). The mean (± SD) body mass index (BMI) was 21.36 (± 5.12) kg/m^2 and 27.3% of the patients were current smokers. A current smoker was defined as a person one who had smoked at least 1 cigarette a day during the past year. Possible risk factors for tuberculosis were detected in 28 patients (33.3%), including diabetes mellitus (DM), 12 patients; neoplasia, 6 patients; alcoholism, 4 patients; uremia, 2 patients; human immunodeficiency virus (HIV), 2 patients; liver cirrhosis, 2 patients; and rheumatoid arthritis (RA), 1 patient. However, no statistically significant difference was found between the 2 groups (Table 1).

Findings on Chest Radiographs

Pleural effusions of 37 patients (44.1%) were accompanied with pulmonary lesions, which were at the right upper lobe in 15 patients, right middle lobe in 4 patients, right lower lobe in 1 patient, left upper lobe in 9 patients, and bilateral upper lobes in 8 patients. Six of these 37 (16.2%) patients exhibited pulmonary cavitation, as shown in Table 2. Chest radiographs showed effusion on the right side in 46 patients (54.8%), on the left side in 35 patients (41.7%), and on both sides in 3 patients (3.6%). Chest radiographs showed a completely opacified hemithorax in 6 patients (7.1%), opacity of more than one-third of the hemithorax without complete obliteration in 44 patients (52.4%), and opacity of less than one-third of the hemithorax in 34 patients (40.5%). There were no significant differences in the

Table 1. Demographic Features of Patients with Tuberculous Pleural Effusion

	Total (n=84) n (%)	Tuberculous pleurisy (n=61) n (%)	Tuberculous empyema (n=23) n (%)	*P* value
Age	61.29 ± 20.03	63.44 ± 19.67	50.57 ± 15.29	0.601
Male	56 (66.7)	43 (70.5)	13 (56.5)	0.226
Female	28 (33.3)	18 (29.5)	10 (43.5)	
BMI	20.11 ± 5.12	22.41 ± 6.12	19 ± 3.64	0.461
Smoking	23 (27.3)	16 (26.2)	7 (30.4)	0.331
Underlying	12 DM	10 DM	2 DM	0.216
disease	6 neoplasia	5 neoplasia	1 neoplasia	
	4 alcoholism	3 alcoholism	1 alcoholism	
	2 uremia		2 uremia	
	2 HIV	2 HIV		
	2 L/C	2 L/C		
	1 RA	1 RA		

Abbreviations

BMI: body mass index DM: diabetes mellitus HIV: human immunodeficiency virus

RA: rheumatic arthritis L/C: liver cirrhosis

Table 2. Comparison of Tuberculous Pleurisy and Tuberculous Empyema in Terms of Radiographic Findings

	Total (n=84) n (%)	Tuberculous pleurisy (n=61) n (%)	Tuberculous empyema (n=23) n (%)	*P* value
APL*	37	29	6	0.109
Cavitation	6	4	2	
Side of effusion	46 (54.8)	31 (50.8)	15 (65.2)	0.942
Right	35 (41.7)	27 (44.3)	8 (34.8)	
Left	3 (3.6)	3 (4.9)	0	
Bilateral			0.256	
Amount**	6 (7.1)	4 (6.6)	2 (8.7)	
Massive	44 (52.4)	29 (47.5)	15 (65.2)	
Moderate Mild	34 (40.5)	28 (45.9)	6 (26.1)	

APL*: associated pulmonary lesions

**Definition of amount of effusions

Massive: hemothorax complete opaque

Moderate: more than one-third of the hemithorax opaque without complete obliteration

Mild: less than one-third of the hemithorax opaque

percentage of associated pulmonary lesions, cavitation, and location and amount of pleural effusion between the 2 groups.

Characteristics of Pleural Fluids

The analysis of the characteristics of the pleural fluids is summarized in Table 3. Tuberculous empyema had higher LDH activity than tuberculous pleurisy (530.88 ± 71.79 vs. 322.80

Table 3. Comparison of Tuberculous Pleurisy and Tuberculous Empyema in Terms of Biochemical Characteristics

	Total Number n=84	Tuberculous Pleurisy n=61	Tuberculous Empyema n=23	*P* value
LDH, U/L	383.39 ± 471.71	322.80 ± 190.42	530.88 ± 71.79	0.14
Glucose, mg/dL	125.92 ± 72.91	131.67 ± 66.88	114.17 ± 84.20	0.496
Protein, g/dL	4.15 ± 1.22	4.22 ± 1.25	4.02 ± 1.19	0.902
ADA, U/L*	54.32 ± 24.15*	53.50 ± 21.6*	54.6 ± 11.6*	0.942
RBC Count cells 10^3/μL	19.50 ± 71.01	9.68 ± 27.36	41.28 ± 123.52	<0.05
Leukocyte Count cells 10^3/μL	1.68 ± 1.98	1.77 ± 2.21	1.48 ± 1.35	0.242
Lymphocyte (%)	81.51 ± 20.18	82.71 ± 21.62	76.34 ± 18.22	0.538

* All parameters, except ADA activity, were obtained in the 84 patients. ADA activity was obtained in only 56 patients: 38 patients with tuberculous pleurisy and 18 patients with tuberculous empyema.

TPE: tuberculous pleural effusion ADA: adenosine deaminase

LDH: lactate dehydrogenase RBC: red blood cell

± 190.42, p=0.14), however, it did not reach statistical significance. ADA activity was high in both groups (54.6 ± 11.6 vs. 53.50 ± 21.6), but with no statistical significance. No significant differences in other biochemical parameters were noted between the 2 groups. Interestingly, only the level of RBC counts was significantly lower in tuberculous pleurisy than in tuberculous empyema (9.68 ± 27.36 vs. 41.28 ± 123.52 10^3/UL, respectively, p<0.05).

Discussion

The global prevalence of TB infection is estimated to be 32% (1.86 billion people), with approximately 8 million new symptomatic cases and an estimated fatality rate of 23% (1.87 million people die of TB annually) [5]. The prevalence of TB is high in Taiwan and mortality trends have not declined as expected over the past decade, especially in aboriginal areas [6-7]. TPE accounts for 20~30% of all patients with tuberculosis [8], which is the most common cause of exudative pleural effusion in the world. TPE usually occurred in children and young adults [9], but the mean patient age has gradually risen in recent years due to an increase in a reactivated form of tuberculosis [10]. In this study, the mean (± SD) age at occurrence was 61.29 ± 20.03 years, and a relatively high association with pulmonary lesions (44.1%) was demonstrated, which indicated that the major forms of tuberculosis in our region may be mostly related to reactivation [9].

In comparison with never-smokers, current smokers had an excessive risk of pulmonary TB [11]. Pulmonary TB in current smokers may have more cavitary lesions and more severe progression [12]. However, no previous study has described the relationship between smoking and tuberculous empyema. About 30.4% of patients with tuberculous empyema were current smokers in this study, which showed no statistically significant difference compared to patients with tuberculous pleurisy. The severity of injury to the lung was potentially related to the amount of smoking the lung was exposed to, however, we lacked the precise numbers of cigarettes smoked in this study.

The severity of lung disease in adults with pulmonary tuberculosis is associated with the

extent of malnutrition, as reflected by the body mass index (BMI) [13], which is known to interfere with cell-mediated responses. Generally BMI less than 19 kg/m^2 is associated with increased risk for tuberculosis [13]. In our series, the value of mean (± SD) BMI in the tuberculous empyema group was smaller than that in the tuberculous pleurisy group, but did not reach statistical significance. Risk factors for developing tuberculosis include alcoholism, infection with HIV, malignancy, liver cirrhosis, and uremia. DM was the most common risk factor in this study, which is significantly different from previous reports, in which alcoholism was the predominant risk factor [9]. In particular, we described a patient in this report with RA controlled by immunosuppressive therapies, and who subsequently developed tuberculous pleurisy. Recent studies have supported the evidence that newer therapies for RA may lead to increased rates of infection by opportunistic pathogens such as *M. tuberculosis* [14].

The high mean patient age, together with the relatively high association with pulmonary lesions (44.1%), suggests that TPE in our region may be caused by reactivated tuberculosis rather than primary tuberculosis. Pulmonary cavitations were seen in 6 (16.2%) of 37 patients with associated pulmonary lesions, which is similar to that in a previous report (14.6%) [9]. The incidence of the involved site of pleural effusion was approximately equally distributed between the left and right sides in our study, nevertheless, tuberculous empyema had a right-side predominance (65.2%), but did not reach statistical significance. A moderate amount of pleural effusion was the most common presentation in the chest radiographs in our study, and this was the same in the 2 groups. In our series, only 6 patients (7.1%) demonstrated complete hemithorax opacity on plain film, which was similar to the finding in a previous study, in which 7.9% was reported [15]. LDH in pleural fluid is a good marker to distinguish bacterial empyema or complicated parapneumonic effusion from simple parapneumonic effusion [16]. In this study, although tuberculous empyema had higher LDH levels than tuberculous pleurisy, there was no statistical significance (530.88 ± 71.79 vs. 322.80 ± 190.42 U/L, respectively). The higher pleural fluid LDH level of bacterial empyema may result from the stronger toxic effect of tumor necrosis factor-α, interleukin-1, lipopolysaccharide, and other bacterial products [17]. However, tuberculous empyema is mainly caused by activated T lymphocyte immunity. As previous studies have reported, the glucose level is typically very low in TPE. However, 11 patients (13.1%) in this study had DM, which may have interfered with the glucose level in the pleural fluids. The levels of ADA, a marker of the activation of T lymphocytes, increased in TPE. This determination has acquired popularity in areas of high incidence for TPE because it is not invasive, not expensive, and readily accessible. The reported cutoff value for ADA varies from 47 to 60 U/L, with a sensitivity of 90% to 100% and a specificity of 89% to 100% [18]. In our study, the mean (± SD) ADA activity was 54.32 (± 24.15) U/L in all TPE, and there was no statistically significant difference between tuberculous empyema and tuberculous pleurisy.

Interestingly, tuberculous empyema showed higher median RBC counts than tuberculous pleurisy, and the empyema was often hemorrhagic. The probable mechanism for higher RBC counts in tuberculous empyema may result from a subpleural caseous focus or cavity ruptures into the pleural space, which lead to serious capillary injury.

There were some limitations to our study. First, it was a retrospective study, including only bacteriologically or pathologically proved TPE; therefore, some patients with a successful therapeutic trial or partially treated patients with negative cultures were not included. Second, pulmonary cavitations were detected by chest radiographs, which are less sensitive than chest computed tomography. This may account for the relatively low incidence of cavitation in the study.

In conclusion, tuberculous empyema differs from bacterial empyema, and has a markedly higher level of LDH in the pleural fluid. The only significant difference between tuberculous empyema and tuberculous pleurisy is the level of the RBC count in the pleural fluid. Thus, if the pleural effusions are exudative, lymphocyte-predominant, and with a high ADA activity and bloody appearance, tuberculous empyema should be highly suspected.

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結核性膿胸與結核性肋膜炎在危險因子、影像學發現與生化檢查的比較

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前言：結核性膿胸與結核性肋膜炎為兩個臨床表現的結核性肋膜積液，分別由不同的致病機轉所造成，也需要不同的處理方式。目前沒有相關的研究來分析這兩種不同型式的積液在危險因子，影像學發現與生化檢查的差異性。

方法：我們從 2002 年 1 月到 2005 年 1 月間，收集了 84 位診斷為結核性肋膜積液的病人。我們進一步將這些病人分為結核性膿胸(n=23)與結核性肋膜炎(n=61)兩組，並比較這兩組在危險因子，影像學發現與生化檢查的差異性。

結果：在 84 個病人中，最常見的危險因子分別為糖尿病(n=12)，腫瘤(n=6)，和酒精依賴(n=4)。危險因子和影像學發現在這兩組病人間並無明顯的差異。結核性膿胸與結核性肋膜炎皆有相同之高數值的乳酸脫氫酶(LDH)(322.80 ± 190.42, 530.88 ± 71.79 U/L, p=0.14）高數值的腺甘脫胺酶活性(ADA)(53.50 ± 21.6, 54.6 ± 11.6 U/L, p=0.942）與高比率的淋巴球（82.71 ± 21.62, 76.34 ± 18.22 %, p=0.538)。唯一在生化檢查上的不同點是結核性膿胸在紅血球數目(RBC count)明顯高於結核性肋膜炎(41.28 ± 123.52 vs. 9.68 ± 27.36 10^3/UL, p<0.05)。

結論：不管在在危險因子，影像學發現與生化檢查方面，結核性膿胸和結核性肋膜炎大部分沒有明顯的差異。唯一的差異性是結核性膿胸比結核性肋膜炎在肋膜積液中有明顯較高的紅血球數。因此當一個肋膜積液為淋巴球佔多數，具有高數值的 ADA ，和血樣的外觀時，結核性膿胸必須被高度懷疑。*(胸腔醫學* ***2006; 21: 1-8)***

關鍵詞：結核，結核性胸腔積液，結核性膿胸，結核性肋膜炎

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Surgical Treatment of Metastatic Pulmonary Tumors

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Background: Metastasectomy has been proved to be an opportunity for long-term survival for patients with various neoplasms with pulmonary metastases. A retrospective study was performed to analyze the results and identify the prognostic factors of surgical treatment for pulmonary metastases.

Methods: From 1991 to 2003, a total of 73 patients who underwent surgical treatment for pulmonary metastases at the Kaohsiung Veterans General Hospital were enrolled for analysis.

Results: The overall 5-year survival rate was 25.1%. The operation-related mortality rate was 2.74%. Gender, origins of the primary cancers, number of pulmonary metastases, and surgical procedures had no significant effect for those patients who underwent pulmonary metastasectomies. However, patients who had a disease-free interval longer than 36 months had a better 5-year survival rate than those who had a shorter disease-free interval (29.6% vs. 10.5%).

Conclusion: Pulmonary metastasectomy is a safe and potentially curative procedure. The disease-free interval is an important prognostic factor for patients with pulmonary metastases. ***(Thorac Med 2006; 21: 9-15)***

Key words: secondary tumors of the lung, metastasectomy

Introduction

The curative potential of metastasectomy for patients with pulmonary metastases has been increasingly recognized lately. Clinically, neoplasms with pulmonary metastatic lesions have been regarded as distant metastases, and suggested a dismal long-term survival. In autopsy studies, approximately one-third of patients died of various cancers co-existing with pulmonary metastases, and the lung was the only organ of metastases in a small percentage of patients that died of cancer [1-2]. Early attempts at resecting pulmonary metastases were described, in 1947, by Alexander, who reviewed 25 patients with pulmonary metastatic carcinoma and sarcoma. The result suggested that a survival advantage was possible for cancer patients with pulmonary metastases [3]. Martini *et al.* also demonstrated the value of multiple pulmonary resections for patients with osteogenic sarcoma with pulmonary metastases [4]. McCormack reviewed the results of surgical excision for pulmonary metastases of various carcinomas and demonstrated a 27% overall 5-

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year survival rate for patients who underwent pulmonary metastasectomies [5]. A recent review of the long-term results of pulmonary metastasectomy in a large number of series found in the International Registry of Lung Metastases also demonstrated that pulmonary metastasectomy is a safe and potentially curative procedure for cancer patients with pulmonary metastases [6].

These beneficial results encouraged us to review our experience in the surgical treatment of secondary lung tumors and to identify any valuable prognostic factors for patients with pulmonary metastatic lesions.

Material and Methods

Between September 1991 and June 2003, 73 patients who underwent pulmonary resections for metastatic lung cancers at the thoracic surgery division of Kaohsiung Veterans General Hospital were enrolled for retrospective analysis. The inclusion criteria were 1) the primary tumor under control, 2) metastatic disease confined to the lung, 3) complete resection in the planned surgery, and 4) adequate post-operation pulmonary function reserve [5-7]. Patients were excluded if the planned resections were not accomplished or the operations were only for diagnosis. All patients were thoroughly evaluated, including the clinical history, physical examination, chest CT scan, whole body bone scan, and sonography of the upper abdomen before the pulmonary resection for metastatic lesions. The entities of the pulmonary metastatic lesions were confirmed by pathologic diagnosis. When the lesions were difficult to distinguish from primary neoplasms of the lung, such as squamous cell carcinoma and adenocarcinoma, a comparison of the primary lesions with the lung lesions was performed by pathologists under light microscopy.

Complete data of the primary neoplasms, surgical procedures, number and size of pulmonary metastatic lesions, and survival were available for all patients. However, the disease-free interval (DFI) data was available for only 53 patients. The DFI was the period of time from the date of surgery for the primary tumor to the date of recognition of the pulmonary metastases or the treatment of pulmonary metastases. Operative mortality was defined as deaths occurring within 30 days of surgical resection, and all deaths beyond 30 days but during the same hospitalization.

The categorical data were compared by chi-square or Fisher's exact tests. Analysis of variance (ANOVA) was used for comparing continuous data within different subgroups. The overall survival curve was constructed using the Kaplan-Meier method, and log-rank statistics were used for comparisons. All statistical manipulations were performed with the SPSS for Windows software system (SPSS, Inc., Chicago, IL). All reported probability values were two-tailed and p values less than 0.05 were considered as statistically significant in this series.

Results

Thirty-eight male and 35 female patients were enrolled for analysis. The mean age of these 73 patients was 52 years (range, 15 to 82 years). At the end of the follow-up period (July 1, 2003), 25 (34.2%) of 73 patients were still alive. The follow-up time ranged from 0.5 to 84 months (mean, 23.4 months). The demographic data of the patients are shown in Table 1. Twenty-five patients had metastasis from the colorectal area, 12 from the gynecological system, 9 from the urinary tract, 10 from sarcoma, and 17 from other original areas. Colorectal cancer is a common

Table 1. Characteristics of patients who underwent pulmonary metastasectomy

Characteristic	No. of patient	%
Gender		
Male	38	52.0
Female	35	48.0
Origins of the primary neoplasms		
Colorectal carcinoma	25	34.2
Gynecological carcinoma	12	16.4
Urinary tract carcinoma	9	12.3
Sarcoma	10	13.7
Others	17	23.3
Surgical procedure		
Pneumonectomy	2	2.7
Lobectomy	25	34.2
Segmentectomy or wedge resection	46	63.1
No. of metastases		
Single	40	57.0
Multiple	33	45.0
Tumor size		
≤ 3 cm	44	60.0
> 3 cm	29	40.0
Disease-free interval (months)		
≤ 36	29	50.9
> 36	28	49.1

origin for patients undergoing pulmonary metastasectomy. The median survival time for colorectal cancer, gynecological cancer, urinary tract cancer, sarcoma, and other cancers was 31.13 months, 18.01 months, 25.10 months, 27.00 months, and 23.20 months, respectively (p = 0.733).

Postero-lateral thoracotomy was the preferred approach for pulmonary resections. A segmental resection or wedge resection was performed in 63.1% (46/73) of patients, and was the most common procedural choice for resection of metastatic lesions in the present series. Lobectomy and pneumonectomy were performed in 34.2% and 2.7% of the cases, respectively. Fifty-six patients underwent single thoracic surgery; 17 patients received sequential operations for ipsilateral or bilateral metastatic lesions; 2 patients combined chest wall resection with pulmonary resection; 40 (57%) patients had a single metastatic lesion in the lung; and 33 (43%) patients had multiple metastatic lesions. Forty-four (60%) patients had a tumor size smaller than 3 cm and 29 (40%) had a tumor size larger than 3 cm.

Two patients died during hospitalization, at 36 and 44 days after pulmonary resection, respectively. The overall hospital mortality rate was 2.7%. The median survival of all patients was 24.9 months, and the estimated overall 5-year survival rate was 25.1%. (Figure 1) Gender, origins of the primary tumors, numbers of metastases (single vs. multiple), tumor size (≤3 cm vs. >3 cm), and surgical procedures were not significant prognostic indicators in our study (Table 2). There was no significant statistical difference in disease-free interval between patients with different tumor origins in the ANOVA test (p = 0.5). However, the 10.5% 5-

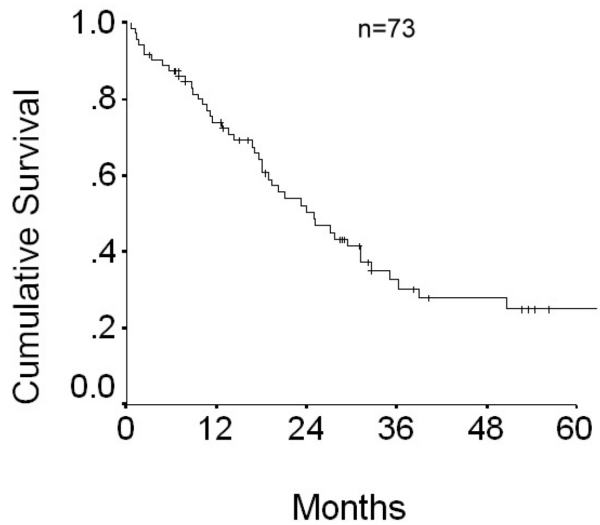

Fig. 1. The survival curve of all patients who underwent pulmonary metastasectomy. The overall 5-year survival rate was 25.1%. The median survival time was 24.90 months.

Table 2. Analysis of survival according to prognostic factors

Prognostic factors	Median Survival (months)	*P*
Gender		
(male vs. female)	21.03 vs. 27.00	0.427
Surgical procedures		
(pneumonectomy/lobectomy vs. wedge/ segmental resection)	18.87 vs. 31.10	0.209
No of metastases (Solitary vs. multiple)	24.90 vs. 25.10	0.830
Size (>3 cm vs. <3 cm)	21.03 vs. 31.10	0.236
DFI (>36 months vs. <36 months)	31.10 vs. 17.63	0.036

year survival rate of patients with a DFI shorter than 36 months was significantly poorer than the 29.6% 5-year survival rate of those patients whose DFI was longer than 36 months (p = 0.036) (Figure 2).

Discussion

Metastatic dissemination is frequent in neoplastic disease and is the principal cause of death. Many subsequent retrospective studies have demonstrated the significant benefits of pulmonary metastasectomy in a small number of patients. In carefully selected cases, using well-defined selection criteria, surgical resection together with adjuvant therapy can significantly increase the survival of patients with a metastatic neoplasm restricted to the lung. Although its benefits are still controversial, pulmonary metastasectomy has been gradually accepted as a therapeutic procedure for patients with metastatic pulmonary tumors of various histologies. In our study, the mortality rate for pulmonary metastasectomy was 2.74%, which is comparable with the surgical mortality rate of conventional surgical resections for primary lung cancer. The overall 5-year survival rates of the patients who underwent pulmonary resection for secondary pulmonary malignancy in our study was 25.1%, which is also in line with previously reported results of 25% to 35% 5-year survival rates [5, 8].

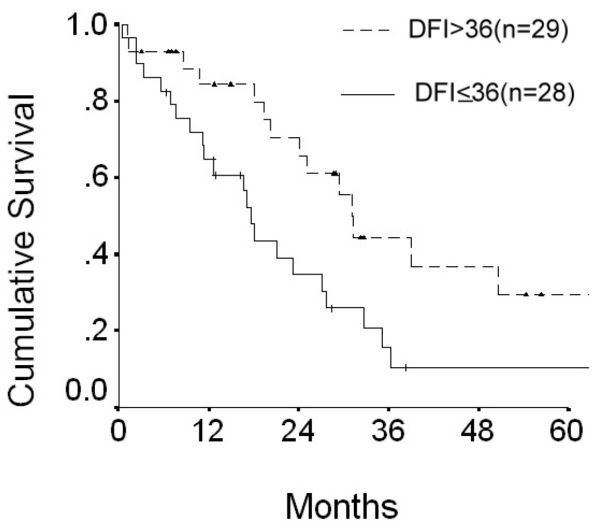

Fig. 2. The Kaplan-Meier survival curve of patients with different disease-free intervals. The 5-year survival rates were 29.6% and 10.5% for DFI >36 months and DFI <36 months respectively (p=0.036).

Although several types of surgical approaches have been advocated for pulmonary metastasectomy, postero-lateral thoracotomy has been the most common approach for the resection of lung metastases. Since mediastinal lymph node involvement could be detected in approximately 26% of metastatic lung cancer patients, lobectomy with lymph node dissection was suggested in several reports as a survival-improving procedure for patients with pulmonary metastases [9].

However, in retrospective studies of pulmonary metastasectomy for colorectal cancer, wedge resection yielded better survival than lobectomy [10-11]. Recently, video-assisted pulmonary resection has also been suggested as an acceptable surgical procedure for patients with small, solitary and peripherally located pulmonary metastases [12]. Clearly, the beneficial effects of different surgical procedures are still controversial. However, in this study, no significant survival difference could be observed between patients who underwent different types of surgical procedures, such as wedge resection, lobectomy or pneumonectomy.

Besides surgical procedures, the resectability of all metastases [6, 13-14], patient age, gender, histological type of primary neoplasm, number and size of metastases, and disease-free interval have also been considered as important prognostic factors for patients with pulmonary metastatic neoplasms. However, in previous series analyzing the influence of histological type on pulmonary metastasectomy, similar survival benefits after pulmonary metastasectomy were observed in soft tissue sarcoma, osteosarcoma, kidney, colon, breast, head and neck cancers [15-20]. However, a series investigating metastatic melanoma demonstrated a worse survival benefit after pulmonary resection [21]. In our study, colorectal cancer, gynecological cancer, genitourinary tumor, and sarcoma were included, and no significant survival difference could be observed among the histological entities.

Although, the number of metastases has been suggested to influence the survival of patients who have undergone metastasectomy, the findings regarding the influence of numbers of metastases on survival are still diverse and equivocal in different studies [6, 8]. Our studies also did not disclose a significant difference in survival between solitary and multiple metastases. While it is noteworthy that the number of nodules estimated by pre-operative tests, such as CT of the chest, is often inaccurate, not all the nodules detected by pre-operative image studies are malignant lesions. The accurate number of metastatic lesions can only can be determined by pathologic examination after surgery.

A short DFI may indicate a more virulent tumor with a poor prognosis. A longer DFI may indicate less aggressive tumor biology and correlate with a longer post-resection survival. Zheng *et al.* concluded the DFI is an important prognostic factor for pulmonary metastases [22]. In a retrospective analysis of 5206 cases from the International Registry of Lung Metastases, DFI longer than 36 months was demonstrated as an independent predictor of survival for patients with pulmonary metatasis [6]. A similar result also was found in a study of osteosarcoma patients with pulmonary metastases, which demonstrated a survival advantage with DFI of more than 6 months [8]. However, in 2 studies of patients with colorectal cancer, no survival advantage could be demonstrated [5, 23]. In our study, a DFI longer than 36 months provided a significant survival benefit for patients with pulmonary metastasis who had undergone pulmonary metastasectomy.

In conclusion, pulmonary metastasectomy is a safe procedure with a low surgical mortality rate. It is also a potentially curative procedure, and a 5-year survival rate can be reached in appropriately selected patients. In our present study, patient gender, origin of primary tumor, surgical procedure for metastasectomy, number of pulmonary nodules, and tumor size did not have an effect on the prognosis of patients who had undergone metastasectomy. However, a DFI longer than 36 months had a significant prognostic effect on long-term survival for patients who have

undergone pulmonary metastasectomy.

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轉移性肺部腫瘤之外科治療

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轉移腫瘤切除術已證實是對於肺部轉移腫瘤的治療方式之一。為了研究其結果及其預後因子，作回溯性研究分析。於 1991 年至 2003 年在高雄榮民總醫院，共七十三位患者因肺部轉移腫瘤接受外科性治療。五年存活率為 25.1%，手術死亡率為 2.74%。在預後因子統計分析中發現，就病患性別、原發腫瘤種類、手術方式、肺部轉移腫瘤數目、腫瘤大小，對手術後生存並無影響。而原發腫瘤切除治療後至出現肺臟轉移時間小於或大於 36 個月之五年存活率分別為 10.5% 及 29.6%。原發腫瘤切除治療後至出現肺臟轉移時間為一個重要預後因子。同時轉移腫瘤切除術是安全且有治癒可能的方法。*(胸腔醫學* ***2006; 21: 9-15)***

關鍵詞：次發性肺部腫瘤、轉移腫瘤切除

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Outcomes of Patients after Discharge from the Respiratory Care Center

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Background: Since little attention has been given to the long-term outcomes of patients in hospital-based ventilator weaning units, we sought to evaluate the outcomes of patients discharged from the Respiratory Care Center (RCC) in a university medical center in southern Taiwan.

Methods: A prospective data collection was performed with the patients who were admitted to the RCC during a 3-year period, from December 2001 to December 2004. These data included age, gender, underlying disease, total ventilator days, ICU and RCC stay days, ICU and RCC ventilator days, hospital discharge status, and disposition. Long-term outcomes after discharge from the RCC were ascertained using a review of hospital medical records and/or direct inquiry of patients and/or family members through telephone interviews.

Results: Totally, 240 prolonged mechanical ventilator-dependent (≥21 days) patients were admitted to the RCC during the study period. Sixty-eight patients (28.3%) were unsuccessfully weaned, and transferred to the RCW, and 133 patients (55.4%) were successfully weaned from the ventilator and left the RCC; the overall hospital mortality rate was 16.3% (39 patients). The weaning rates for the 3 periods of RCC stay were: early weaning (within 14 days) at a rate of 26. 7%, mid-term weaning (15-28 days) at a rate of 33.3%, and late weaning (>28 days) at a rate of 16.7%. Those patients who stayed in the RCC for more than 28 days had a statistically significantly lower rate of successful weaning. The Kaplan-Meier (KM) survival curve estimates of 240 patients after discharge from the RCC were as follows: 1 month, 70% (95% confidence interval [CI], 65% to 75%); 3 months, 58% (52% to 66%), 6 months, 54% (46% to 62%); 1 year, 43% (36% to 50%); 2 years, 35% (28% to 43%). The KM survival estimates of the unsuccessfully weaned patients after discharge were performed, and there were significant differences in the outcomes of these 2 groups. Within the group of 133 successfully weaned patients, those who underwent early, mid-term, and late successful weaning did not differ in their outcomes, including survival rate and the ventilator-independent rate, after discharge from the RCC.

Conclusion: About half of the patients were successfully weaned at our RCC. Patients discharged from the RCC had poorer outcomes if they were ventilator-dependent. And, early or late ventilator weaning in the RCC did not have an impact on the long-term survival or ventilator-independence of the patients. ***(Thorac Med 2006; 21: 16-24)***

Key words: outcomes; survival; weaning; prolonged mechanical ventilator-dependent

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Introduction

Patients were conventionally defined as prolonged mechanical ventilator-dependent if they had received mechanical ventilation for more than 21 days [1]. The short-term outcomes in the respiratory care center (RCC) have been assessed in several studies [2-4], while little attention has been given to the long-term outcomes of these individuals after discharge from the RCC. In this study, we sought to evaluate the long-term outcomes of patients who had undergone prolonged mechanical ventilation and were discharged from the RCC.

Materials and Methods

Those patients who were admitted to the RCC with prolonged mechanical ventilation for more than 21 days, from December 2001 to December 2004, were enrolled into this study. Their data, including age, gender, underlying disease, total ventilator days, ICU and RCC stay days, ICU and RCC ventilator days, hospital discharge status, and disposition, were recorded. Long-term outcomes after discharge from the RCC were ascertained using a review of hospital medical records and/or direct inquiry of the patients and/or family members through telephone interviews.

The causes of respiratory failure leading to mechanical ventilation and ultimately to RCC admission were classified into a 10-category classification scheme, as follows: group 1, COPD; group 2, pneumonia and empyema; group 3, underlying chronic lung disease other than COPD (pulmonary fibrosis, obesity); group 4, heart failure with pulmonary edema (AMI and CHF); group 5, post-thoracic surgery (hemothorax, hemoptysis, thymic cancer, esophageal perforation); group 6, post-CV surgery (CABG, aortic aneurysm, pericardial effusion); group 7, following any other surgery (PPU, pancreatic cancer, DU bleeding, acute cholecystitis, HCC, ischemic bowel, rectal or colon cancer, abdominal stabbing injury, bone fracture, ovarian cancer); group 8, neuromuscular disease (CVA, ICH or SAH, brain tumor, seizure, tentanus); group 9, sepsis-related; and group 10, miscellaneous causes (EV bleeding, DOA, hypoglycemic with hypoxemic encephalopathy, lung cancer, etc.).

Patients who were discharged from the RCC were divided into 2 groups, namely, the successfully weaned group and the unsuccessfully weaned group, based on ventilator use during discharge. Within the successfully weaned group of patients, 3 subgroups of patients were defined: the early, mid-term, and late weaning groups, based on weaning times of < 14 days, 15-28 days, or > 28 days, respectively, in the RCC.

Kaplan-Meier (KM) survival analysis to estimate overall survival and the ventilator-independent rate in the 2 groups and 3 subgroups of patients was performed. Statistical analysis to compare mortality between those who were successfully weaned and unsuccessfully weaned was evaluated by Student's t test. Comparison of the 3 subgroups of successfully weaned patients was performed by analysis of variance.

Results

Totally, 240 individuals with prolonged mechanical ventilation were admitted to and discharged from the RCC during the study period. The demographic data are shown in Table 1. The mean age was 73.3 ± 12.7 years, and 42.5% of these patients were women. The mean ICU length of stay before RCC admission was 31.5 ± 19.4 days; The ventilator days before RCC admission were 30.1 ± 18.1; the successfully weaned group

Table 1. Demographic data of 240 patients with prolonged mechanical ventilation in the RCC.

Weaning	AAD & Expired	Unsuccessful	Successful	Total
Patients	39 (16.3%)	68 (28.3%)	133 (55.4%)	240
Gender: Female	16	29	57	102 (42.5%)
Male	23	39	76	138 (57.5%)
Age (mean± SD) y/0	73.5 ± 14.8	74.7 ± 10.2	72.1 ± 13.2	73.3 ± 12.7
RCC stay days	21.7 ± 18.1	30.4 ± 13.3	16.9 ± 10.9	21.5 ± 14.2
ICU stay days	35.8 ± 22.0	30.8 ± 21.0	30.6 ± 17.6	31.5 ± 19.4
ICU ventilator days	35.8 ± 22.0	30.4 ± 21.2	28.3 ± 14.6	30.1 ± 18.1
RCC ventilator days	21.4 ± 18.3	30.1 ± 13.7	10.5 ± 8.6	17.8 ± 14.9

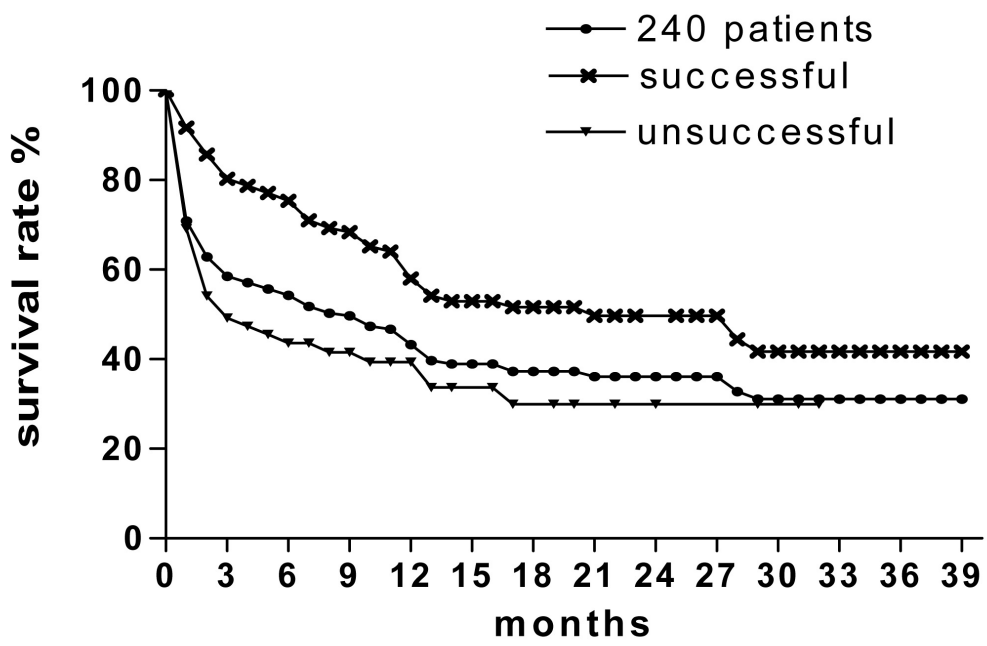
Table 2. The cause of respiratory failure and admission to the RCC, and the condition at discharge.

Causes	Total patients	Ventilator-independent	Ventilator-dependent	Death
COPD	8 (3.3%)	3 (38%)	3 (38%)	2 (24%)
Pneumonia & empyema	116 (48.3%)	60 (52%)	33 (28%)	23 (20%)
Other lung disease (non-COPD)	6 (2.5%)	3 (50%)	3 (50%)	0 (0)
CHF with pulmonary edema	22 (9.2%)	11 (50%)	8 (36%)	3 (14%)
Post-thoracic surgery	4 (1.7%)	3 (75%)	1 (25%)	0 (0)
Post-CV surgery	13 (5.4%)	8 (62%)	2 (15%)	3 (23%)
After any other surgery	18 (7.5%)	11 (61%)	4 (22%)	3 (17%)
Neuromuscular disease	21 (8.8%)	17 (81%)	4 (19%)	0 (0)
Sepsis	11 (4.6%)	7 (64%)	3 (27%)	1 (9%)
Other	21 (8.7%)	10 (48%)	7 (33%)	4 (19%)
Total	240	133 (55%)	68 (28%)	39 (16%)

(133 patients; 55.4%) had 28.3 ± 14.6 days, the unsuccessfully weaned group (68 patients; 28.3%) had 30.4 ± 21.2 days, and the expired group (39 patients; 16.3%) had 35.8 ± 22.0 days of pre-RCC admission ventilator use. In terms of total ventilator days after admission to the RCC, the successfully weaned group had 10.5 ± 8.6 days, the unsuccessfully weaned group had 30.1 ± 13.7 days, and the expired group had 21.4 ± 18.3 days. Among the hospital survivors (201 patients; 84%), 42% (84 patients) were discharged to a RCW, 0.5% (1 patient) was discharged home, 5% (10 patients) were discharged to a nursing home, 52.2% (105 patients) were discharged to a general care ward, and 3.5% (7 patients) were returned to the ICU. Thirty-nine of the 240 patients (16.3%) died during the RCC stay.

The causes of respiratory failure leading to prolonged mechanical ventilation and the need of RCC admission, and the mortality rate of each group of patients among the 240 patients are shown in Table 2. Pneumonia and empyema were the most common causes of respiratory failure of those who needed prolonged mechanical ventilation, and 52 percent of these patients were discharged from the RCC without the need of a ventilator.

Among the successfully weaned group (133 patients; 55.4%), 37.6% (50 patients) were discharged to a chronic care hospital, 44.4% (59

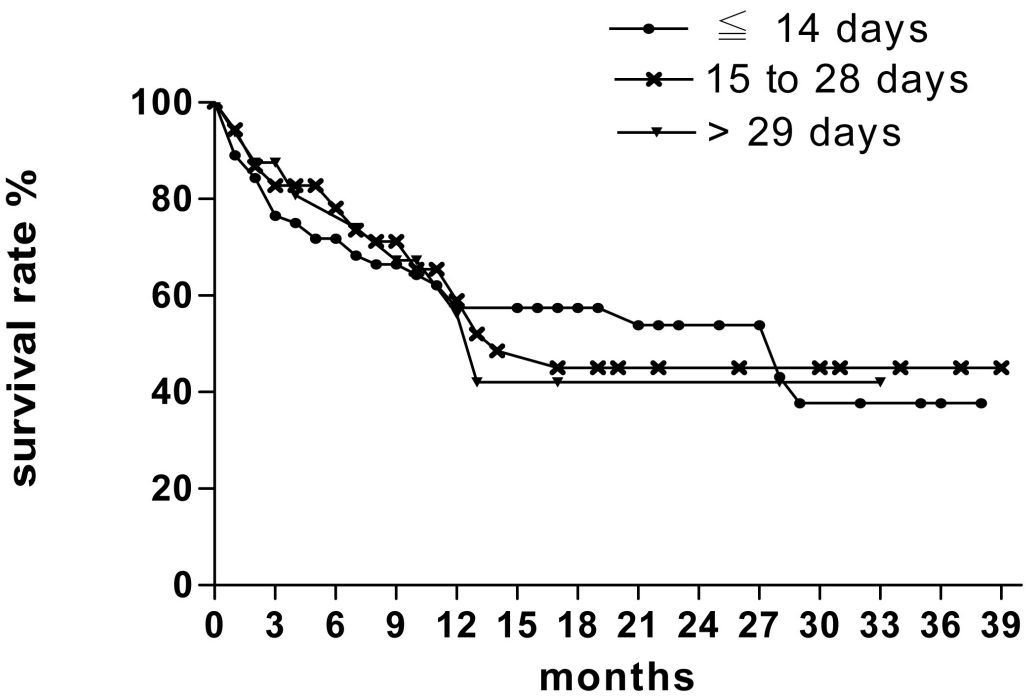


	1 m.	3 m.	6 m.	1 year	2 year
240 patients	70%	58%	54%	43%	35%
successful	91%	82%	75%	58%	49%
unsuccessful	69%	49%	46%	40%	30%

Fig. 1. KM survival curve estimates for all 240 patients, 133 patients with successful weaning and 68 patients with unsuccessful weaning, revealing a significant difference between the successfully and unsuccessfully weaned groups (*P* value <0.0001).

patients) were discharged to their home, 11.3% (15 patients) were discharged to a nursing home, and 6.8% (9 patients) died during hospital stay. Among the unsuccessfully weaned group (68 patients; 28.3%), 5 patients were transferred to ICU care: 3 patients later expired, and the other 2 were transferred to the RCW; 63 patients were discharged to a RCW for further weaning.

KM survival rate estimates for all 240 patients, 133 successfully weaned patients, and 68 unsuccessfully weaned patients, are shown in Figure 1. In comparision, the survival curve was significantly different between the successfully and unsuccessfully weaned groups ($p < 0.0001$). We further divided the 133 successfully weaned patients into 3 groups, based on weaning time in the RCC. The early weaning group was defined as those patients whose RCC stay was <14 days, the mid-term group had an RCC stay of 15 to 28 days, and the late weaning group was defined as those with an RCC stay >28 days; As shown in Figure 2, KM survival rate estimates for all 64 successfully weaned patients in the early weaning group was: 1 month, 89%; 3 months, 73%; 6 months, 72%; 1 year, 58%; 2 years, 54%; the overall weaning rate was 28.7% during this period. For the 53 successfully weaned patients in the mid-term group, KM survival rate estimates were: 1 month, 94%; 3 months, 83%; 6 months, 78%; 1 year, 59%; 2 years, 46%; the overall



	1 m.	3 m.	6 m.	1 year	2 year
≤ 14 days	89%	73%	72%	58%	54%
15 to 28 days	94%	83%	78%	59%	46%
> 29 days	94%	88%	76%	57%	42%

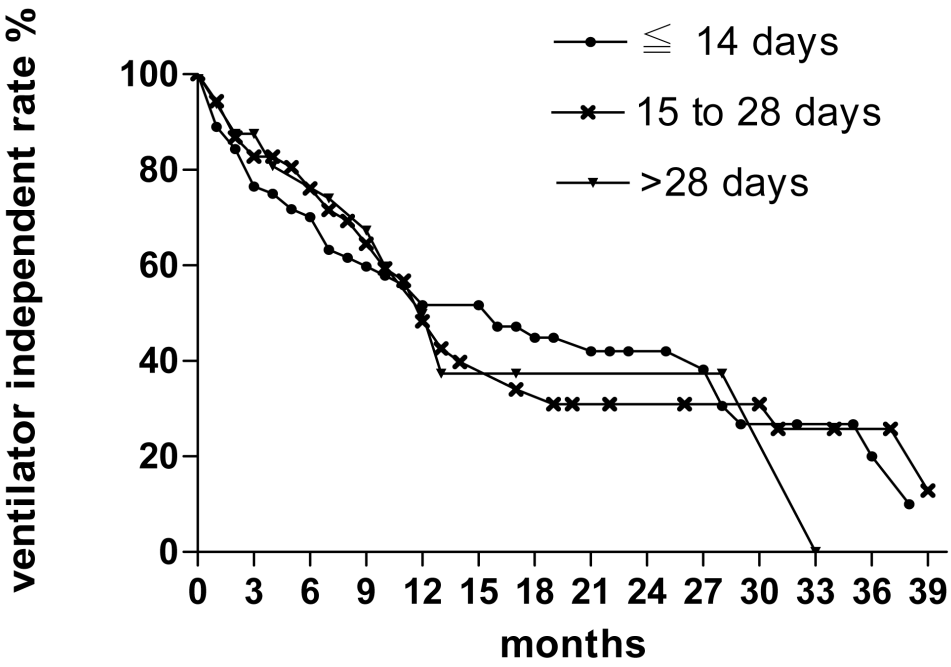
Fig. 2. KM survival curve estimates for the 3 subgroups of 133 successfully weaned patients based on weaning time in the RCC. There was no significant difference among these 3 groups.

weaning rate was 35.6%. For the 16 successfully weaned patients in the late weaning group, KM survival rate estimates were: 1 month, 94%; 3 months, 88%; 6 months, 76%; 1 year, 57%; 2 years, 42%. The overall weaning rate was 16%. Comparatively, the weaning rate of each of the 3 periods was significantly different ($p < 0.0001$). The weaning rate was lower in the late weaning period of RCC stay. There was no significant different among these 3 groups in terms of survival rate and ventilator-independence rate (Figure 3, Table 3).

Discussion

In this study of outcomes of patients discharged from the RCC, our main findings were as follows: 1. The 2-year survival rate among the prolonged mechanical-ventilator dependent patients admitted to our RCC was low. 2. The pattern of the post-discharge survival rate showed a steep decline within the first year, with a slower decline thereafter. 3. Long-term survival rates were lower for older patients, but there was no difference between genders. 4. The weaning rate in the late period of RCC stay was low. 5. Early or late successful weaning did not have an impact on long-term outcomes after discharge from the RCC.

This study extends the limited available



	1 m.	3 m.	6 m.	1 year	2 year
≤ 14 days	86%	76%	70%	36%	30%
15 to 28 days	94%	83%	76%	42%	42%
> 29 days	94%	87%	76%	42%	42%

Fig. 3. KM ventilator-independent curve estimates for 3 subgroups of 133 successfully weaned patients based on weaning time in the RCC. There was no significant difference among these 3 groups.

experience gleaned from the RCC. Specifically, we are aware that the survival rates at <1 year post-RCC discharge were low. In this study regarding the outcomes of patients weaned successfully in the RCC, only 58% of 133 patients were alive in the 1 year following hospital admission. An analysis of the risk factors for 2-year mortality identified a high-risk group consisting of patients who were >75 years old; the 2-year survival rate in this group was 39%, in contrast to 63% for the low-risk group (i.e., those between 65 and 75 years old).

The 2-year survival rates in the current study add to the data of the single available report of 5-year survival by Schonhofer *et al*. [5]. In that earlier study, the 5-year survival rate estimated for 21 at-risk patients was 33%; this rate showed a steep decline from 3 months post-hospital discharge (67%) to 3 years after discharge (38%). Similarly, our experience suggests that the steepest decline in survival occurred within the first year following RCC discharge, with a slower decline between 1 and 2 years. In an early series by Spicher and White [6] studying outcomes of 250 patients receiving mechanical ventilation for >10 days and discharged from conventional ICUs between 1979 and 1984, the rate of hospital survival was 39.2%. The 1-year and 2-year survi-

Table 3. The weaning rate during different periods of RCC stay, and the outcomes of 3 subgroups of successfully weaned patients after discharge from the RCC.

RCC stay	< 14 days	15 to 28 days	>28 days	*P*-value
Total patients	64	53	16	
Weaning rate	26.7%	33.3%	16.7%	<0.0001*
Survival rate 1 month	89%	94%	94%	NS**
3 month	73%	83%	88%	NS
6 month	72%	78%	76%	NS
1 year	58%	59%	57%	NS
2 year	54%	46%	42%	NS
Ventilator-independent rate				
1 month	86%	94%	94%	NS
3 month	76%	83%	87%	NS
6 month	70%	76%	76%	NS
1 year	36%	42%	42%	NS
2 year	30%	42%	42%	NS

*Significant difference between the >28 days group and the <14 days group, and between the >28 days group and the 15-28 days group.
**NS = not significant

val rates were 28.6% and 22.5%, respectively, which were considerably lower than the survival rates in our RCC (43% and 35%, respectively). Morganroth *et al*. [7] reported a 1-year survival rate of 30%, which again was lower than that observed in our RCC (Table 4).

The possible reasons for the poor short-term survival rate of our RCC patients may include the patients' overall poor physical condition, septic infection (current pneumonia), apnea with sputum impaction, and cardiac arrhythmia attack due to hypoxemia, but our results were better than those of the above studies. We hope that these results will prompt further inquiry and analysis of the factors that influence long-term survival in order to bring about better long-term outcomes.

In conclusion, patients discharged from the RCC had a poorer prognosis if they were ventilator-dependent. The weaning rate is lower in the late period of RCC stay (>28days), but early or late weaning from the ventilator in the RCC did not have an impact on long-term survival in those

Table 4. Summary of available reports regarding long-term outcomes of patients in weaning units

Study/year	Patients No.	Reported survival rates, %
Morganroth *et al*. 7/1984		30 (1 yr)
Spicher *et al*. 6/1987	250	28.6 (1 yr)
		22.5 (2 yr)
Gracey *et al*. 4/1995	132	76 (1 yr)
		72 (2 yr)
Scheinhorn *et al*. 9/1997	1,123	38 (1 yr)
Carson *et al*. 11/1999	133	23 (1 yr)
Nasraway *et al*. 12/2000	97	49.5 (1 yr)
		33 (2 yr)
Schonhofer *et al*. 5/2002	403	38 (3 yr)
		33 (5 yr)
James k *et al*. 8/2003	162	43 (1 yr)
		32 (2 yr)
		27 (3 yr)
		19 (5 yr)
Current series	240	43 (1 yr)
		35 (2 yr)

patients who were successfully weaned and discharged from the RCC.

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呼吸照護中心出院後患者之預後

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背景：因為在醫院的呼吸器脫離訓練單位中, 比較少注意到有關於病患的長期預後，我們試著評估在南台灣的一個大學醫學中心從呼吸照護中心出院的病患預後。

方法：前瞻性的數據收集從西元 2001 年 12 月到 2004 年 12 月，在 3 年的時間追蹤的那些呼吸照護中心出院的病患。這些數據包括年齡，性別，潛在疾病，呼吸器總使用天數，加護病房以及呼吸照護中心的停留天數和呼吸器使用天數，離院狀況及後續照顧單位 。以醫院的病歷記錄和直接詢問病患和 / 或家庭成員的電話訪談追蹤調查。

結果：全部總共 240 位長期呼吸器依靠(≥ 21 天)的病患進入呼吸照護中心，總住院死亡率是 16.3% (39 位病患)， 68 位病患(28.3%)由於呼吸器脫離不成功，因此轉移到慢性呼吸照護中心， 133 位病患(55.4%)成功脫離呼吸器而離開呼吸照護中心。早期呼吸器脫離(RCC 停留 14 天內)的呼吸器脫離成功率 26.7% ，中期呼吸器脫離(RCC 停留 15-28 天) 33.3% ，和晚期呼吸器脫離(RCC 停留>28 天) 16.7% ，據統計晚期呼吸器脫離者其成功呼吸器脫離的比率較低。 The Kaplan-Meier (KM) 存活曲線估計如下： 1 個月， 70% (95% 的信賴區間 [CI]， 65% 到 75%)； 3 個月， 58% (52% 到 66%)， 6 個月， 54% (46% 到 62%)；1 年， 43% (36% 到 50%)；2 年， 35% (28% 到 43%)。比較呼吸器脫離失敗者 KM 存活曲線估計，它們在這兩組之間的結果方面相當不同。

結論：大約一半的病患可以在我們的呼吸照護中心成功的呼吸器脫離。呼吸器無法脫離而離開呼吸照護中心之患者比起呼吸器脫離而離開呼吸照護中心之患者有明顯較低之存活率。在成功呼吸器脫離者，早期脫離和晚期脫離並無影響長期存活率及呼吸器不使用率，所以我們仍應積極嘗試讓患者脫離呼吸器。*(胸腔醫學* ***2006; 21: 16-24****)*

關鍵詞：預後；存活；呼吸器脫離；長期呼吸器依靠

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Diagnosis of *Strongyloides* Hyperinfection Syndrome in a COPD Patient with Routine Sputum Smear Study — A Case Report and Literature Review

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Strongyloidiasis is an infection caused by *Strongyloides* stercoralis. In contrast to other helminthic parasites, *S. stercoralis* can complete its life cycle entirely within the human host. It can cause a wide spectrum of diseases in humans, ranging from chronic asymptomatic infections to a hyperinfective and often fatal syndrome, particularly in immunocompromised patients. *Strongyloides* hyperinfection syndrome is 1 of several clinical manifestations of strongyloidiasis and has a mortality rate exceeding 80%. A diagnosis of strongyloidiasis is usually made by detecting larvae in concentrated stool or duodenal fluid specimens, and sometimes by duodenal biopsy or sputum smears. We present a case of *Strongyloides* hyperinfection syndrome with lung involvement in a patient with chronic obstructive pulmonary disease (COPD) and liver cirrhosis, who suffered from severe shortness of breath, productive cough and herpes zoster neuralgia of the cervical nerve, diagnosed by a routine sputum smear study. The simultaneous daily concentrated stool smears and endoscopic duodenal biopsy were negative for rhabditiform larvae, while the consecutive daily sputum smears were rich in larvae. The clinical symptoms greatly improved after antihelminthic therapy with 2 courses of 12 mg oral ivermectin daily for 2 days. The larval count significantly decreased after the introduction of ivermectin, with a negative conversion of larvae on the sputum smears from the 15th hospital day. He was discharged from our hospital on the 35th day after admission in a stable clinical condition. Through this case experience, we concluded that the sputum smear study cannot be overlooked in the diagnosis of Strongyloides hyperinfection, particularly for COPD patients. The relevant literature is reviewed, including the risk factors, clinical symptoms, diagnosis, and prognosis of strongyloidiasis. ***(Thorac Med 2006; 21: 25-32)***

Key words: strongyloidiasis; *Strongyloides* hyperinfection syndrome; autoinfection

Introduction

Strongyloides stercoralis is a common intestinal nematode that affects 30~100 million people worldwide; it is endemic in Africa, Asia, Southeast Asia, and Central and South America [1], while the prevalence in the southern United States is 0.4%~6% [2]. Pulmonary strongyloidiasis has

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not been common in Taiwan over the past few years, to the best of our knowledge.

Strongyloides stercoralis eggs, hatched into uninfectious rhabditiform larvae, usually pass in the stool, and then molt again in the soil to become infectious filariform larvae. The infection begins when human skin contacts the infectious filariform larvae of *S. stercoralis*. The filariform larvae penetrate the skin, enter the venous circulation, and then pass to the lungs where they penetrate the alveolar air sacs. The larvae then ascend the tracheobronchial tree and are swallowed. Humans who have been infected may also be reinfected through the mucosa of the lower gastrointestinal tract or in the perianal area from larvae that have transformed into the filariform infective form [2].

The unique "autoinfection" ability of *S. stercoralis* means that it can complete its life cycle within a single human host. Hosts may have long periods of asymptomatic disease, and this may lead to a hyperinfection syndrome, where the disease is disseminated amid impaired cellular immunity [1].

Case Report

A 78-year-old male patient had suffered from underlying COPD for more than 10 years and was under treatment with an inhaled long-acting β2 bronchodilator and inhaled corticosteroid therapy. He also had a peptic ulcer with a Billroth II subtotal gastrectomy more than 30 years ago, hepatitis B with liver cirrhosis recognized for 2 years, and Grave's disease 28 years ago, which was treated with I^{131} therapy. He was a farmer who retired in 1980, and had been a heavy smoker with a 5-pack/day habit for more than 30 years, until 2 years before this admission.

He had suffered from cervical herpetic neuralgia and shortness of breath for more than 1 month before his arrival. He visited a local medical doctor for symptom control and had received a daily injection with analgesics, a bronchodilator, and a corticosteroid since the onset of symptoms. The breathlessness became exacerbated, and was associated with a severe productive cough about 3 days before admission. On arrival, he was found to have a moon face and central obesity, suggestive of iatrogenic Cushing's syndrome. Oral thrush was found as well. There was no fever, but tachycardia (120 beats/min) and tachypnea (35 times/min) were both noted. A diffuse wheezing sound was heard in the bilateral lungs. The abdomen was soft without tenderness and was ovoid in shape. The perianal skin was intact and clear. No hepatosplenomegaly was noted. Laboratory data showed a white blood cell count of 19,290 cells/mm^3 with 87% segments, 5% bands, 4% lymphocytes, and 2% eosinophils. The hematocrit was 21.3% with hemoglobin of 7.1 g/dl. Chest plain film (Figure 1) showed a left hilum downward deviation and left hemidiaphragm upward displacement, suggestive of a volume reduction of the left lower lobe. There was no significant interval change when compared with an older chest film from 2001. The patient was treated for COPD with secondary infection and acute exacerbation. A routine sputum study was immediately carried out. Incidentally, several living *Strongyloides* larvae were found on the sputum smear (Figure 2), and consistently presented in the follow-up daily sputum studies. Meanwhile, we were unable to detect any larvae in the daily concentrated stool routine study throughout the entire course. We started him on 1 course of antihelminthic therapy with ivermectin (12 mg daily for 2 days) on the third and fourth hospital days, with a gradual tapering of the dosage of steroid. On the second

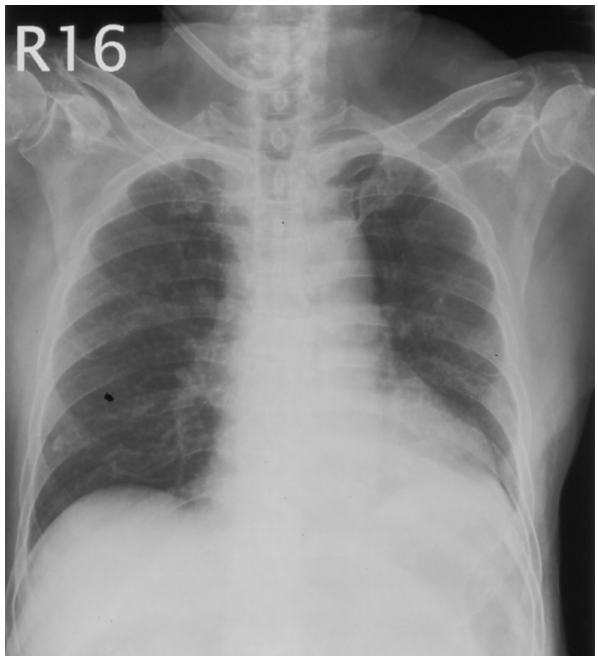
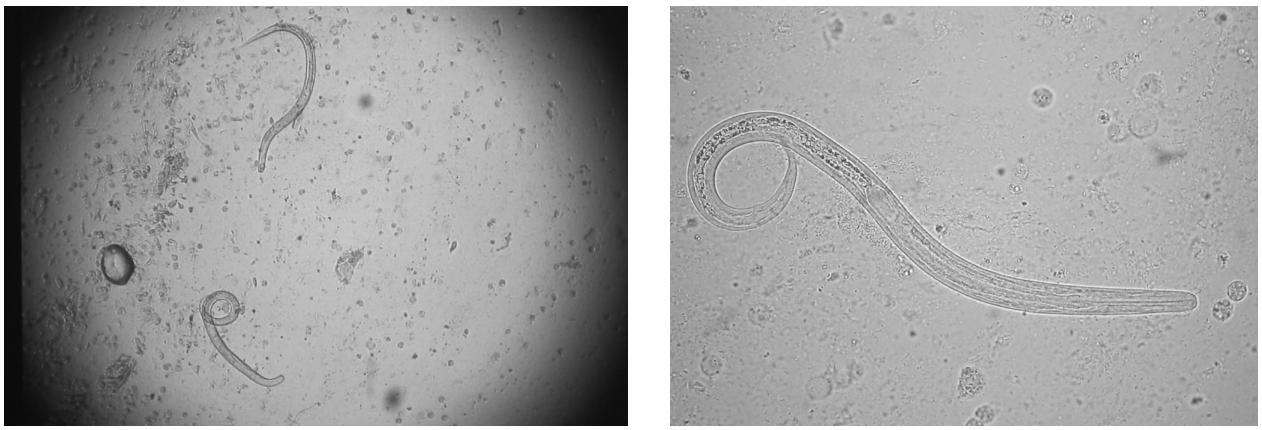


Fig. 1. Chest plain film showing a left hilum downward deviation and left hemidiaphragm upward displacement, suggestive of a volume reduction of the left lower lobe.

hospital day, the patient developed an episode of upper gastrointestinal bleeding and hepatic encephalopathy. His consciousness became drowsy, and he was in an agitated mood with elevated ammonia. A blood transfusion and laxative agents were given. His consciousness subsequently became alert. Chest high-resolution computed tomography (Figure 3) revealed a small area of ground-glass opacity in the right middle lobe and retrocardiac opacity in the left lower lobe with volume reduction. The liver had multiple hypodense lesions of various sizes, suggestive of multiple hepatic cysts. Human immunodeficiency virus (HIV) antibodies and human T lymphotropic virus I (HTLV-1) antibodies were both negative. The patient underwent panendoscopy on the 10th hospital day, which revealed a marginal ulcer. The result of an endoscopic jejunum biopsy, for the purpose of detecting *Strongyloides*, was negative for malignant cells, or parasite ova or larvae. Larvae were found on the daily sputum smears until the 6th day after therapy with ivermectin. During this period, larval numbers and their spontaneous movement decreased day by day. After that, larvae were not found again, except for 1 episode of a relatively small amount of larvae from the sputum smear on the 15th hospital day, without significant discomfort. The clinical symptoms, such as shortness of breath, productive cough, and wheezing sounds, greatly improved after therapy with ivermectin. Bronchoscopy was performed on the 26th hospital day, and the



(A) (B)

Fig. 2. A, B *Strongyloides stercoralis* larvae identified in sputum

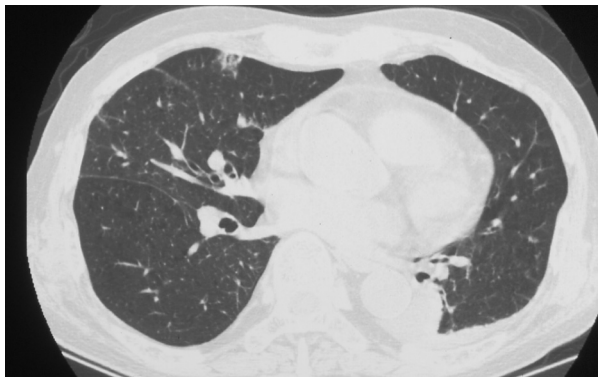


Fig. 3. Chest HRCT showing a small area of ground-glass opacity in the right middle lobe and a retrocardiac opacity in the left lower lobe with volume reduction.

bronchial washing fluid from the left lower lobe was negative for larvae. Unfortunately, he was found to have a spiking fever with shaking chills and consciousness disturbance that evening. The complete blood cell count showed significant peripheral eosinophilia with a white blood cell count of 8680 cells/mm^3 and 12.7% eosinophils. We gave him another course of ivermectin therapy (12 mg oral daily for 2 days) starting that night. The fever subsided by the following morning. The hemogram consistently showed an elevated eosinophil count (up to 2135 cells/mm^3 and 18.9% of the white blood cell count) after the episode of fever. The blood culture, performed during the spiking fever episode, yielded *Salmonella* group B. He was treated with a course of parenteral ciprofloxacin. His general condition greatly improved; he was discharged on the 35th day and has been followed at the OPD. No additional larvae were found on the sputum smears after the 15th day of hospitalization. We were unable to detect larvae in any of the concentrated stool smears throughout the entire admission course.

Discussion

Chronic infection with *S. stercoralis* is often asymptomatic, but it can cause gastrointestinal, cutaneous, or pulmonary symptoms [3]. Gastrointestinal symptoms are the most common, and the respiratory tract is the system most frequently affected outside the gastrointestinal tract [1]. The most common gastrointestinal problems are diarrhea, nausea, vomiting, and abdominal pain [3-4]. A cutaneous infection typically involves the perianal area with a migratory, serpiginous rash that can spread to the buttocks, groin, or trunk [3].

Pulmonary manifestations range from none to coughing, wheezing, a choking sensation, hoarseness, pleuritic chest pain [4], hyperacute pneumonitis [5], lung abscess [6], acute respiratory distress syndrome (ARDS) [7-8], respiratory failure [9], hemoptysis (massive in some cases), pneumothorax, respiratory alkalosis, palpitations, atrial fibrillation, dyspnea, and, rarely, respiratory collapse [10]. Lung tissues may show alveolar hemorrhage [10-11].

Gram-negative or polymicrobial bacteremia from the migration of larvae through the bowel wall is another common presentation of disseminated infection [1]. In the present case, the *Salmonella* bacteremia may have been caused via this pathogenesis.

The patient had wheezed for many years and was being treated for COPD with an inhaled long-acting β2 bronchodilator and inhaled corticosteroid. The cause of the bronchospasms could have been related to COPD or *Strongyloides*. However, the role of *Strongyloides* cannot be ignored, because of the dramatic improvement in the bronchospasms after ivermectin therapy with tapering of the systemic corticosteroid. Nevertheless, 1 report mentioned that successful

treatment of *Strongyloides* cannot improve bronchospasms with a wheezing sound [13].

Eosinophilia, which is usually present in strongyloidiasis without hyperinfection, is often suppressed or absent from disseminated disease [1, 10-12]. Patients who have increased peripheral eosinophilia during hyperinfection appear to have a better prognosis [10-12]. In the present case, the patient was found to have a normal eosinophil count on arrival. We suppose that this was related to the impaired immunity, evidenced by a Cushing's-like appearance and a coinfection with herpes zoster and oral candidiasis. The peripheral eosinophilia developed after treating the strongyloidiasis and tapering the systemic corticosteroid after the patient had achieved a relatively stable condition.

The diagnosis of hyperinfection syndrome implies the presence of signs and symptoms attributable to increased larval migration [10]. The association between impaired cellular immunity and a hyperinfective state was first reported in 1966 [1]. In the case of drug-induced or disease-associated defects in cellular immunity, such as with corticosteroid or cytotoxic chemotherapy, HTLV-1 infection, HIV infection, hematologic malignant disease, decreased gastric acidity, and malnutrition, the autoinfection may result in a massive increase in the parasite burden and dissemination to almost all organ systems, including the lungs, liver, and central nervous system [1]. It often manifests as hemorrhagic bronchopneumonia, hemorrhagic enteritis, Gram-negative sepsis, or meningitis [14]. One study estimated that disseminated strongyloidiasis occurs in 1.5%~2.5% of infected patients [1].

In the setting of compromised cellular immunity, *Strongyloides* hyperinfection is often diagnosed late, and mortality can reach 70%~86% [1, 4] [15-16]. Multiple stool samples collected on different days should be examined to ensure the complete eradication of larvae, given the high false-negative rate with a single sample [3]. In some reports, examination of a single stool sample may have missed 70% or more cases owing to the low parasite burden and intermittent larval excretion [17-19]. Diagnostic sensitivity increases up to 50% with examination of 3 stool samples, and can exceed 90% if 7 serial stool samples are examined. Sputum samples from infected immunocompetent individuals usually do not demonstrate these larvae, but they may be observed in respiratory specimens from immunocompromised patients, especially after development of a well-described hyperinfection syndrome [20]. In the present case, the stool specimens were always negative for larvae even while the specimen of the sputum was rich in living larvae.

Radiographic manifestations most frequently show bilateral or focal interstitial infiltrates [10-12]. Sometimes these infiltrates might be too minimal to be detected by routine chest X-ray. We suppose a high-resolution CT scan (HRCT) of the chest may be more sensitive for detecting interstitial lesions than a conventional roentgenogram. However, the cost of a chest HRCT is much higher than a conventional chest X-ray, particularly when HRCT is applied as a follow-up tool. Furthermore, with chest images, it is sometimes difficult to establish the pathognomonic diagnosis of pulmonary strongyloidiasis, due to the comorbidity of strongyloidiasis with other pulmonary disorders, such as COPD or bronchiectasis.

Serologic testing with an enzyme-linked immunosorbent assay is both sensitive and specific, with an estimated sensitivity of 82%~95% and specificity of 84%~92% [1]. However, to our knowledge, this testing is not common and is not currently available in Taiwan. Monitoring a fall in *Strongyloides* antibody titers after therapy may

be more helpful than a stool examination [1].

Thiabendazole has been the most commonly used antihelminthic for strongyloidiasis, but more recent studies have shown ivermectin to be better tolerated, with a higher cure rate [3, 10-11]. It has been used successfully with hyperinfections. Repeated courses of standard therapy may provide only temporary clearance of the organism in immunosuppressed patients. Since this disorder has a high relapse rate (15%), such patients should receive prolonged treatment [4, 21]. Parenteral ivermectin may also be useful in *Strongyloides* hyperinfection [22], particularly in patients who are unable to take oral medication.

Autoinfection is the leading cause of persistent *Strongyloides* infection in non-endemic areas. Fatal infections may occur in immunocompromised hosts secondary to hyperinfection and an overwhelming infestation. Early diagnosis of pulmonary strongyloidiasis is difficult, particularly when patients have associated COPD or bronchiectasis which may display similar symptoms, e.g., wheezing, shortness of breath, and a productive cough.

In conclusion, a delayed diagnosis usually results in an extremely high case-fatality rate, so clinicians have to maintain a suspicion of strongyloidiasis when these symptoms are refractory to treatment. In addition, sputum smears, as well as a stool study, may play important roles in detecting *Strongyloides* larvae, particularly in a hyperinfection status.

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經由痰液常規抹片檢查診斷慢性阻塞性肺疾合併糞小桿線蟲過度感染—一病例報告和文獻回顧

蕭建隆　徐志育　吳錦桐

糞小桿線蟲感染症是由 *Strongyloides stercoralis* 所引起的一種全身性的寄生蟲感染症。和其他寄生蟲不同的是，它可以在體內完成自體感染的整個過程。而它寄生在人體身上可以沒有症狀長達 50 年以上。但是在細胞免疫功能異常的人身上，它可能會造成致命性高達 80% 以上的 *Strongyloides* hyperinfection syndrome。診斷上通常是藉由濃縮的大便抹片及十二指腸的抽取液來直接觀察糞小桿線蟲的幼蟲蟲體。我們報告一位慢性阻塞性肺病及肝硬化的 78 歲老先生因氣促、喘鳴、咳痰和帶狀泡疹引發的左側頸神經痛而送來醫院治療。來院之前已在外院診所接受長達 1 個月以上的類固醇治療。在住院的當天，我們在常規的痰液抹片檢查意外發現了糞小桿線蟲幼蟲的存在。然而在此同時，反覆的糞便檢查卻一無所獲，甚至連消化道內視鏡小腸切片也無法找到此蟲體。我們開始使用每天一次 12 毫克 ivermectin 兩天，來治療糞小桿線蟲的過度感染症候群 (*Strongyloides* hyperinfection syndrome)。病人的症狀逐漸改善，蟲體的數目和活動力顯著的減少，並且在入院的第 15 天之後再也找不到蟲體了。病人因病情穩定而在住院的第 35 天出院繼續在門診追蹤治療。由此個案的經驗，我們發現不可忽略痰液的常規抹片檢查在診斷慢性阻塞性肺疾合併糞小桿線蟲過度感染的重要性。同時我們回顧一些文獻報告，並且討論糞小桿線蟲過度感染症候群之危險因子及臨床表現之症狀，此外也討論其診斷方法以及治療。*(胸腔醫學 **2006; 21: 25-32**)*

關鍵詞：糞小桿線蟲感染症，糞小桿線蟲過度感染症，自體感染

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Cryptococcal Laryngitis: A Case Report

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Infections caused by *Cryptococcus neoformans* range from those in an asymptomatic state to systemic disease, especially in immunocompromised hosts. Laryngeal cryptococcal infections are extremely rare - only 7 cases have been reported in the literature. We present a case of cryptococcal laryngitis in an 83-year-old male with chronic obstructive pulmonary disease (COPD) and long-term corticosteroid use. The patient was admitted with a 14-day history of dysphagia, hoarseness, respiratory distress, and upper airway obstruction that necessitated tracheostomy. After intensive respiratory care and fluconazole treatment, his symptoms improved. ***(Thorac Med 2006; 21: 33-39)***

Key words: cryptococcal laryngitis, cryptococcosis, laryngitis

Introduction

Cryptococcosis of the larynx was first described in 1975 by Reese [1]; 6 additional cases have been reported since then [2-7]. *Cryptococcus neoformans* is an encapsulated and well-documented pathogenic yeast [8-9]. The organism resides in soil and avian excrement, especially that of pigeons. Those who work with pigeons are at an increased risk of exposure, but most infected individuals do not have significant exposure to pigeons. Exposure generally causes a self-limiting subacute pulmonary infection in immunocompetent hosts, or spreads hematogenously, resulting in invasion of the central nervous system (CNS). Once it has invaded the CNS, the infection is fatal if not treated appropriately. One of the most important features of cryptococcal infections in patients with human immunodeficiency virus (HIV) infection, compared to those without, is that the former has a very high rate of relapse after treatment (30~50%) [10]. Cryptococcal infections occur predominantly in patients with T-cell-mediated immune defects, especially those with acquired immunodeficiency syndrome (AIDS) and those with transplant-related immunosuppression [11]. Acute epiglottitis is most common among children, and is a serious disease because of its potential for sudden fatal airway obstruction in previously healthy persons. Fatal airway obstruction can occur without warning, indicating a need for early protection of the airway in adults as well as in children [12]. However, cryptococcal infections rarely present as fungal laryngitis. Cryptococcus can infect the larynx in both immunocompromised and immu-

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nocompetent hosts.

Case Report

An 83-year-old man presented with hoarseness, sore throat, and dysphagia for 2 weeks. He had a 25-year history of pipe smoking, but had quit after being diagnosed with chronic obstructive pulmonary disease (COPD) in 1987. He had been receiving high doses of oral corticosteroids at another institution to control his symptoms during the past 10 years. We tried a high dose of Seretide (salmeterol/fluticasone propionate) combination therapy to taper his oral corticosteroids. Later, his COPD was brought under control with a lower dose of glucocorticosteroids (predisolone, 5 mg a day) and Seretide 2-puff inhalation twice a day (salmeterol 200 mcg/ fluticasone propionate 1000 mcg) for the following 2 years at our hospital. He had had no foreign travel history for more than 1 year and no exposure to pigeons in his neighborhood. Physical examination was unremarkable, although it revealed dyspnea and diffuse wheezing in both lung fields. The chest radiograph disclosed bilateral pulmonary emphysema without notable change compared to previous films. Laboratory studies showed LDH 527 IU/L, cholesterol 260 mg/dL, C-reactive protein 18.4 mg/dL (normal range, 0-0.8 mg/dL), and positive urine cryptococcal antigen. The patient refused a lumbar puncture for cerebrospinal fluid (CSF) studies after laryngeal biopsy proved cryptococcal infection. His arterial blood gas showed pH: 7.459, PCO_2: 45.3 mmHg, PO_2: 112.9 mmHg, HCO_3: 30.5 mmol/L, and O_2 saturation: 98.3% with nasal oxygen at 3 liters per minute.

The fibrobronchoscopic examination revealed a bilaterally edematous and erythematous epiglottis with nearly 85% obstruction of the airway. The false and true vocal cords were mobile. There were multiple, white, exudative papules

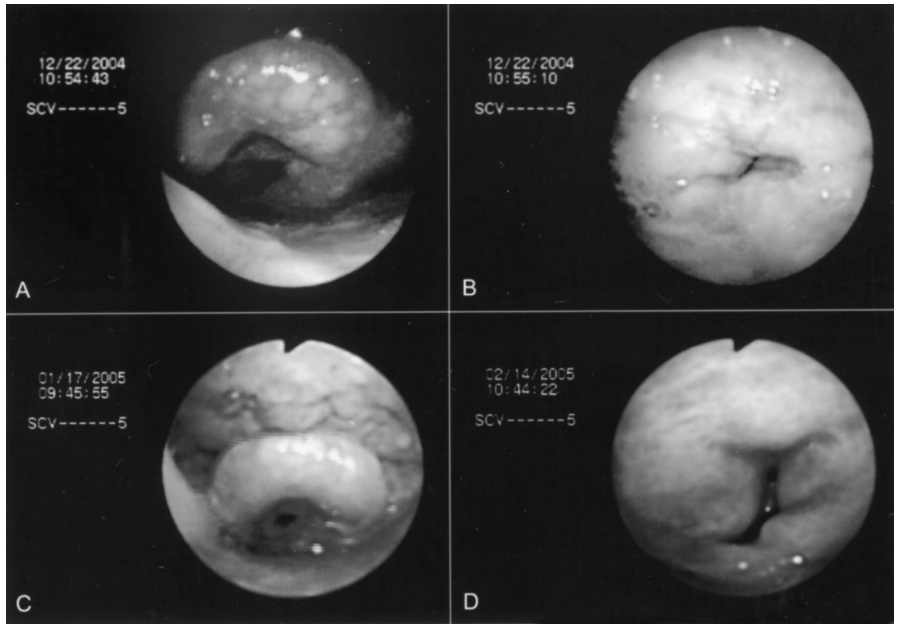

Fig. 1. (A, B) Bronchoscopy reveals bilaterally edematous and erythematous epiglottis with nearly 85% obstruction. There were multiple, white, exudative papules on the vocal cords and epiglottis mucosa. (C, D) Follow-up bronchoscopy demonstrates that the white exudative lesions on the vocal cords and epiglottis had disappeared.

over the vocal cords and epiglottis mucosa (Figures 1A & 1B). The patient had severe dyspnea after admission. The otorhinolaryngist was consulted for the upper airway obstruction, and tracheostomy was performed. Biopsy of the lesion gathered 4 tissue fragments up to 0.2 x 0.1 x 0.1 cm in size. The pathology showed chronic granulomatous inflammation-expressing inflammatory cells and a few giant cells. Gomori's methenamine silver (GMS) and mucicarmine stains demonstrated microorganisms that ranged in size from approximately 4~6 μm in diameter, and were consistent with *Cryptococcus* organisms (Figures 2 & 3). Fungus culture of the supraglottic post commissure biopsies was negative. The patient improved after tracheostomy and intravenous fluconazole 200 mg twice a day for 5 weeks. A fibrobronchoscopic follow-up was done and the white exudative lesions on the vocal cords and epiglottis had disappeared (Figures 1C & 1D).

Discussion

Acute epiglottitis is a serious disease because of its potential for sudden fatal airway obstruction in previously healthy persons. It may be caused by infective organisms including *Haemophilus parainfluenzae*, *Streptococcus pneumoniae*, and group A streptococci. The less common etiologies include *Staphylococcus aureus*, mycobacteria, *Herpes simplex virus*, Candida, thermal causes (including those associated with crack cocaine smoking), and caustic insults. Rapid swelling of the epiglottis results in airway obstruction and asphyxia [13]. The risk of death is high due to sudden airway obstruction and the difficulty in intubating patients with extensive swelling of the supraglottic structure. Tracheostomy may be necessary for any patient with epiglottitis. The patient may deteriorate precipitously, and airway equipment, including that for cricothyrotomy, should be available at bedside [12].

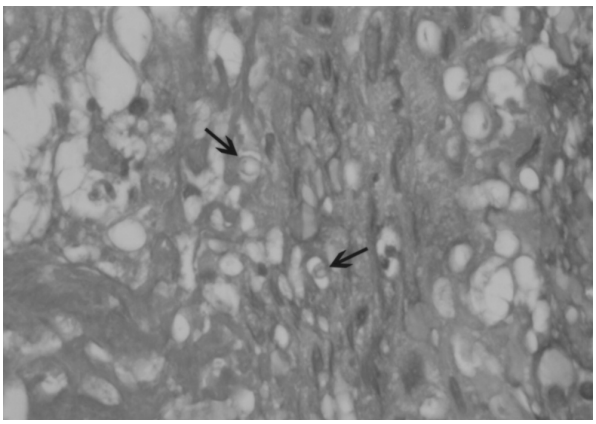

Fig. 2. Small, ovoid, and encapsulated yeast microorganisms (arrow) (H&E stain, x400).

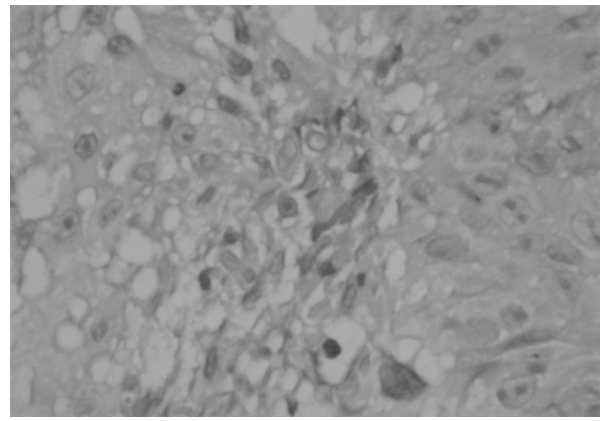

Fig. 3. Pathological exam reveals characteristic ovoid, thin-wall, yeast-like microorganisms (Mucicarmine stain, x400).

Cryptococcus neoformans is an encapsulated fungus, measuring 4~6 μm, and is surrounded by a polysaccharide capsule. It is globally distributed, and commonly found in soil, avian fecus, fruit, wood, and vegetables [14]. Airborne transmission is thought to occur, with subsequent respiratory infection and dissemination in HIV-infected patients in the absence of a cell-mediated response. About 5% of HIV-infected patients develop disseminated cryptococcosis, and most

cases are seen in patients with a CD4+ cell count lower than 50/mm^3 [11].

Cryptococcal infections occur predominantly in patients with T-cell-mediated immune defects, especially those with AIDS and transplant-related immunosuppression [11, 15]. Corticosteroid therapy and cancer chemotherapy are also predisposing factors for the development of cryptococcal infections. The incidence of cryptococcosis is increased in subjects with hematologic malignancies, sarcoidosis, and diabetes mellitus [15-16].

The most common presentation of cryptococcal infection is meningitis. Pneumonia is described in 10~30% of patients. Patients with lung involvement usually have disseminated infection. The demonstration of the organism in respiratory secretions is an indication for a thorough evaluation of cryptococcal meningitis [17]. The best option for disease diagnosis in terms of high sensitivity and quick results is the detection of cryptococcal polysaccharide antigens by latex particle agglutination in body fluids, such as CSF, serum and urine. The direct examination, the histological analysis, and the culture can have discordant results. The drugs of choice for cryptococcal infection are amphotericin B, 5-flucytocine, itraconazole and fluconazole [18].

A Medline search revealed only 7 cases of Cryptococcus infection of the larynx, reported from 1975 to 2004, and our patient would be the eighth (Table 1) [1-7]. All reported patients were adults between the ages of 31 and 87 years, and included 7 males and 1 female. Presenting symptoms included hoarseness (8/8), dyspnea (2/8), and cough (2/8). There were 2 cases, including ours, with severe respiratory distress and upper airway obstruction that necessitated tracheostomy. Their underlying diseases included AIDS, diabetes mellitus, COPD, asthma, cryptococcal pneumonia history, smoking, and alcohol abuse (Table 1). One patient had been exposed to soil rich in chicken manure [1]. Six patients were immunocompromised, including 1 with HIV infection [3] and 2 with diabetes mellitus [4-5]. Those patients with COPD or asthma had a history of long-term oral (2/8) or inhaled corticosteroid use (2/8). Our patient had COPD and used both oral and inhaled corticosteroids.

Serologic cryptococcal antigen tests of the CSF, blood, and urine are usually negative in cryptococcal laryngitis. Only in Kerschner's patient [5] was the serum cryptococcal antigen positive. In our patient, the cryptococcal antigen was positive in the urine. No diagnostic method has 100% sensitivity and specificity for cryptococcosis—a combination of several methods is recommended. A diagnosis based on combined culture and tissue results is the gold standard method, with greater specificity and almost 100% sensitivity for cryptococcosis diagnosis [19]. Both the bronchial washing in Reese's patient [1] and laryngeal biopsy specimen in Nadrous's patient [7] grew *Cryptococcus neoformans*. In other cases, the blood, CSF, and urine fungal cultures were all negative. All of these cases, including ours, had tissue biopsies and positive special fungal stains proving cryptococcal infection. Two cases [2, 4] received only endoscopic polypectomy without medical treatment. Six other cases, including ours, were treated with antifungal chemotherapy (amphotericin B, itraconazole and/or fluconazole). In all 8 cases, the symptoms improved or the disease was successfully cured during a period of 1 to 17 months. In our case, fibrobronchoscopic follow-up revealed resolution of the white exudative lesions on the vocal cords and epiglottis (Figures 1C & 1D), but residual mild swelling of the epiglottis. The patient's pulmonary function test was worse 1 year before

Table 1. Summary of 8 reported cases of cryptococcal laryngitis

Author	Patient (Age, sex)	Symptoms	Underlying disease	Steroid dependent	Diagnosis	Treatment
Reese [1] 1975	47, M	hoarseness, dyspnea	hypertension, CAD	no	biopsy, bronchial washing*	tracheostomy, amphotericin B
Smallma [2] 1989	31, F	hoarseness	unknown	no	biopsy	endoscopic polypectomy
Browning [3] 1992	46, M	hoarseness	AIDS, cryptococcal pneumonia	no	biopsy	amphotericin B fluconazole
Frisch [4] 1995	73, M	hoarseness	DM, smoking	no	biopsy	endoscopic polypectomy
Kerschne [5] 1995	61, M	hoarseness	COPD, DM, smoking, alcohol abuse	predisolone 60 mg/day	biopsy, blood antigen (+)	fluconazole
Isaacoson [6] 1996	87, M	hoarseness, dry cough	COPD, smoking	dependent before, without steroid for years	biopsy	fluconazole
Nadrous [7] 2004	55, M	hoarseness, cough	asthma	high dose inhaled steroid	biopsy, culture¡Þ	itraconazole, fluconazole
Current case	83, M	hoarseness, dyspnea	COPD, smoking	predisolone 5 mg/day inhaled steroid	biopsy, urine antigen(+)	tracheostomy, fluconazole

M: male, F: female, DM: diabetes mellitus, CAD: coronary artery disease

COPD: chronic obstructive pulmonary disease

AIDS: acquired immunodeficiency syndrome

*: Bronchial washing cultured *Cryptococcus neoformans*

+: Biopsy fungal cultures grew *Cryptococcus neoformans*

(FEV1: 1.07 L/min, FEV1/FVC: 54%). Because of concern due to his poor pulmonary function and episodic dyspneic symptoms, we decided not to remove his tracheostomy tube until his upper airway obstruction had reached complete remission. He has been undergoing oral fluconazole treatment and outpatient follow-up.

Conclusion

Cryptococcal laryngeal infection is rare, but it should be included in the differential diagnosis of laryngitis in immunocompromised patients, including patients who have inhaled and/or who are oral steroid-dependent.

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新型隱球菌性咽喉炎：一病例報告及文獻回顧

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新型隱球菌性咽喉炎，相當的罕見—目前僅有七例病例報告。新型隱球菌的感染程度，由沒有症狀至全身性感染皆可見，特別在免疫不全的病人身上。我們將報告一位 83 歲男性，長期使用類固醇控制慢性阻塞性肺疾病，他因為喉嚨痛及吞嚥困難約 14 天，至門診求助，住院後因呼吸窘迫及上呼吸道阻塞，需接受氣切來維持呼吸道暢通，在接受積極照護及 Fluconazole 治療後，症狀有明顯改善。*(胸腔醫學 **2006; 21: 33-39**)*

關鍵詞：新型隱球菌性咽喉炎，新型隱球菌症，咽喉炎

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Multiple Pulmonary Tumors as the Initial Manifestation of Cervix Uteri Malignant Melanoma — A Case Report

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We report a case of malignant melanoma of the cervix uteri with multiple lung metastasis diagnosed in a 39-year-old female patient. The patient presented persistent cough with scanty sputum as the first symptom, and no pigmented lesion of the anus, vulva, or skin. The chest film showed multiple varied nodules and masses at both lungs. Pathology of the bronchoscopic biopsy via LB6 showed malignant melanoma. Cytology of the uterine cervix smear revealed malignant melanoma. Colposcopy showed a 0.5x0.8x0.5-cm sized, pigmented lesion on the anterior lip of the cervix. Pathology of the biopsy showed malignant melanoma. Brain computed tomography showed multiple metastasis of the brain. We review the literature and discuss the clinical manifestation, radiographic evaluation, and adjuvant therapy of metastatic melanoma. ***(Thorac Med 2006; 21: 40-45)***

Key words: melanoma, cervix, lung metastasis

Introduction

Primary malignant melanoma of the uterine cervix is rare, and lung metastasis of melanoma of the cervix is even rarer. Primary malignant melanoma of the uterine cervix is usually diagnosed at an advanced stage and with a poor prognosis; vaginal bleeding is the most common complaint. Melanoma frequently metastasizes to the lung. Typical radiologic findings of a pulmonary metastasis include multiple peripherally located, round variable-sized nodules and diffuse thickening of the interstitium. We present a case with multiple pulmonary tumors as the initial presentation of malignant uteri cervix melanoma.

Case Report

This 39-year-old female patient had been in stable condition until 1 month before admission, when she had cough with scanty sputum. She had no fever, chills, or shortness of breath. She was in Mainland China at that time, and she was told she had upper airway infection. She developed progressive symptoms of cough in spite of medication prescribed in a regional hospital in China. In addition, shortness of breath and dyspnea on exertion developed. The chest film in July 2003 showed multiple mass lesions in the bilateral lungs, with the biggest lesion located in the left lower lung. She had gradual abdominal disten-

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tion, and ascites was noted. She had had body weight loss of 7 kg in the month before admission. After returning to Taiwan in July, she was admitted to our hospital. Her vital signs were: body temperature, 36.8°C; respiratory rate, 14 breaths/minutes; pulse rate, 80 beats/minutes; and blood pressure, 120/80 mmHg. Physical examination showed rale-like breathing sounds in bilateral lungs, and shifting dullness of the abdomen. She also had bilateral lower leg pitting edema. The chest film showed a mass lesion in the left lower lobe with multiple nodules in the bilateral lung fields. (Figure 1) Chest computed tomography showed a mass lesion, 3x5-cm in size, at the left hilum, and multiple nodular lesions. (Figure 2) Lung metastasis of an unknown origin was highly suspected. An abdominal sonogram showed massive ascites, and abdominal computed tomography also showed ascites and suspected peritoneal carcinomatosis. The brain CT on 20 July showed suspected multiple metastases. The fiberbronchoscopy on 21 July was grossly normal. Biopsy was done via the anteroposterior segment of the left upper lobe (LB1+2c), and the superior segment of the right lower lobe under fluoroscopy. Brushing cytology and bronchial lavage were negative. Pathology of the bronchoscopic biopsy revealed oval-to-spindle shaped neoplastic cells

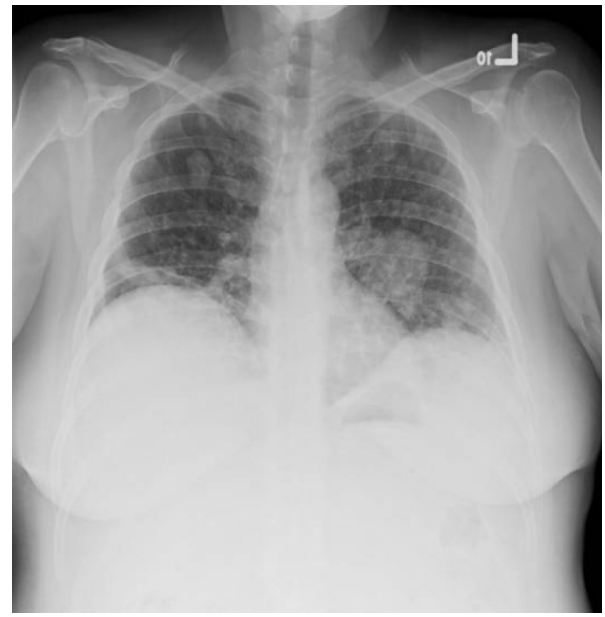

Fig. 1. Chest photography revealing a mass lesion in the RLL with multiple nodules in bilateral lungs

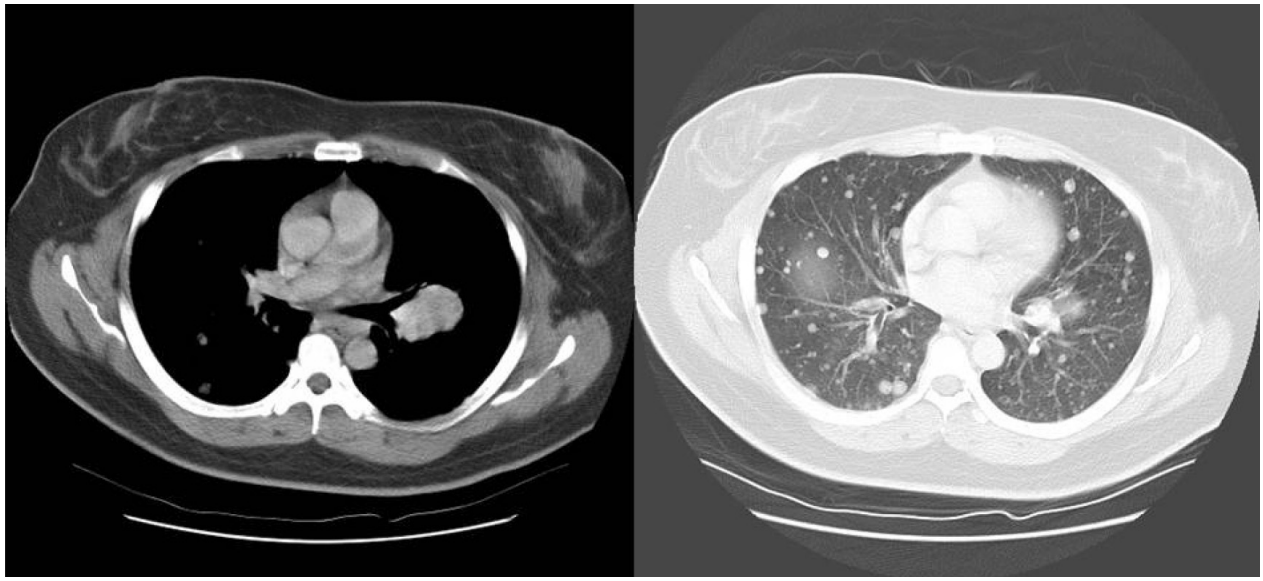

Fig. 2. CT scan of the chest showing a mass lesion in the RLL with multiple nodules in bilateral lungs. (left-mediastinum window, right-lung window).

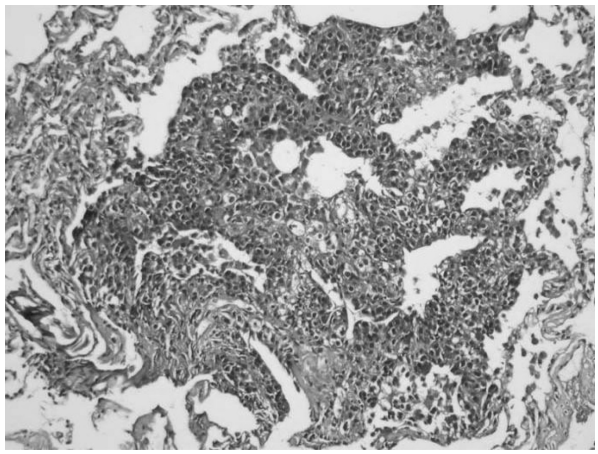

Fig. 3. The pathology of the fiberbronchoscopic biopsy of the lung. Sections show lung parenchyma with an aggregate of oval-to-spindle shaped neoplastic cells. (x200)

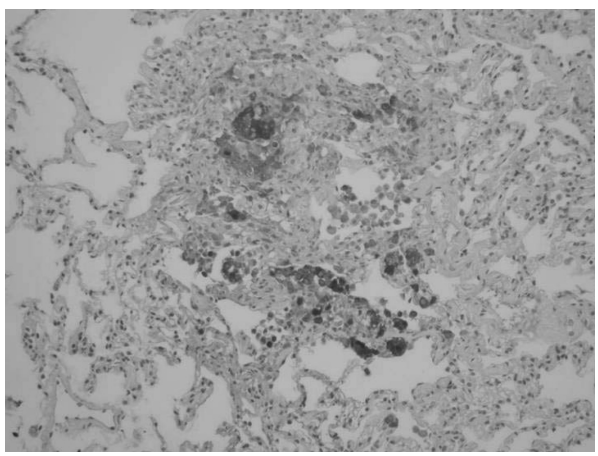

Fig. 4. The tumor cells in the lung are immunoreactive to S-100. (x200)

with a deposition of melanin pigments. (Figure 4). The patient had no skin lesion, and no gynecological complaint, such as vaginal bleeding; she had regular menstruation. A gynecological specialist was consulted, and the PAP smear cytology on 18 July was positive for malignant cells; melanoma was suspected. Colposcopy on 23 July showed a pigment lesion, 0.5x0.8x0.5 cm in size, on the anterior lip of the cervix. Pathology of the colposcopic biopsy of the cervix showed cervical tissue with sheets of oval-to-spindle-shaped neoplastic cells infiltrated into the submucosa (Figure 5). The overlying squamous epithelium was intact. Melanin pigment deposits were also encountered. During hospitalization, the patient had abdominal fullness and progressive shortness of breath. Abdominal computed tomography showed moderate ascites and peritoneal carcinomatosis. She was transferred to the Oncology Department on 27 July, and a pig-tail catheter was inserted for ascites drainage. Cytology of the ascites also showed melanoma. Chemotherapy with Temadol 380 mg per day and thalidomide 200 mg per day were prescribed for 5 days, beginning 29 July. Intraperitoneal chemotherapy was considered, but was not administered due to the patient's unstable condition. The patient expired on August 14 due to septic shock.

Discussion

Primary melanoma of the female genitalia is a rare disease. Five percent of all melanomas in females arise in the genital tract [1-2]. The vulva and vagina are the most common sites of the primary origin of mucosal melanoma of the female genital tract. The cervix is a rare site for primary malignant melanoma. More often, the cervix is involved secondarily as a result of local extension from vaginal/vulvae melanomas, and occasionally it may be a site of hematogenous metastasis from a primary melanoma elsewhere. The diagnosis may be missed on cervical smears unless a careful search is made for pigmented cells. Melanoma of the cervix occurs in women ranging from 20 to 75 years of age, the most common presenting complaints being vaginal bleeding or discharge, often of a short duration [3-4]. Weight loss and hematuria may be the other complaints.

It is very important to rule out a melanoma

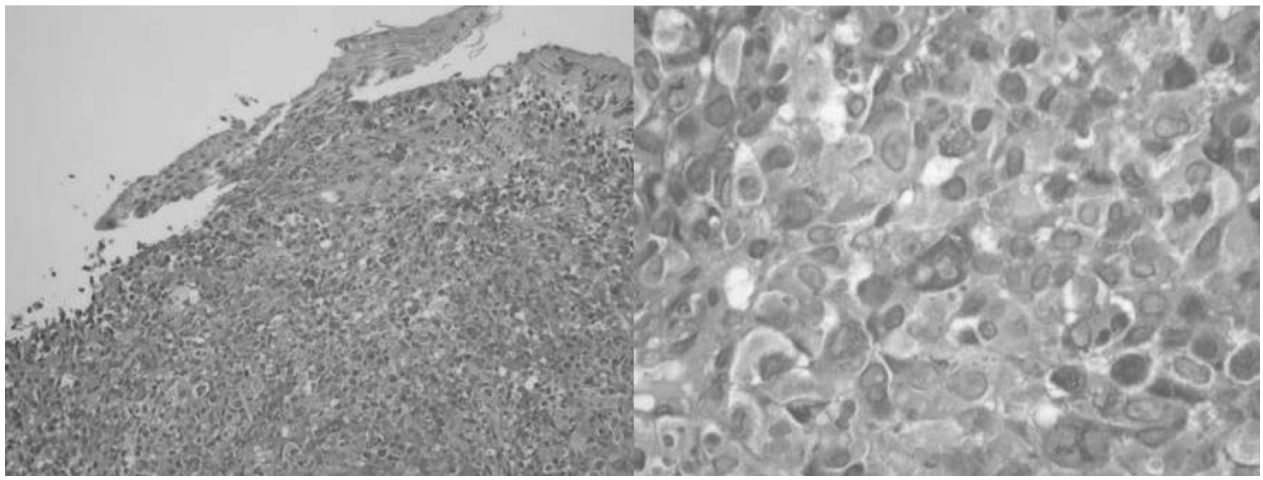

Fig. 5. The pathology of the cervix biopsy. Cervical tissue with sheets of oval-to-spindle shaped neoplastic cells infiltrated into the submucosa. (Left - x100; right - x400).

elsewhere in the body before a diagnosis of primary cervical melanoma is made. The cervix is not a common site for metastatic malignancies, because it has a limited blood supply and the cervical fibrous stroma provides a poor site for the growth of tumors. According to Morris and Taylor [5], the 4 criteria for diagnosis of primary melanoma include: (a) presence of melanin in the normal cervical epithelium; (b) absence of melanoma elsewhere in the body; (c) demonstration of junctional change in the cervix; and (d) metastases following the pattern of cervical carcinoma. The diagnosis of cervical melanoma is made usually on histopathology and can be confirmed by special stains for melanin, immunohistochemical staining, and by electron microscopy. There are very few case reports of the diagnosis of melanoma of the cervix based on cervical smear/scrape cytology.

The lung is an extremely common site for metastases. Large autopsy series of patients with extrathoracic malignancies reveal pulmonary metastases in 20%-54% of patients [6-7]. Among autopsy cases, the breast, colon, kidney, uterus, and head and neck are the most common primary sites with pulmonary metastasis [7-8]. Typical radiologic findings of pulmonary metastasis include multiple peripherally-located, round, variable-sized nodules (hematogenous metastasis) and diffuse thickening of the interstitium (lymphangitic carcinomatosis) [9-10]. Among cases of multiple nodules detected with CT, 73% were reported to be pulmonary metastases [11]. Pulmonary metastases in melanoma are common, but solitary metastases are rare, occurring in less than 1% of cases [12]. A solitary pulmonary melanoma could represent either a metastasis or a primary lung neoplasm.

Although most melanomas develop in sunlight-exposed areas on the back or legs, these tumors may also develop in anatomic areas usually not exposed to sunlight, such as the oral mucosa, genital and perianal areas, subungual areas, and plantar surfaces, as well as the scalp and palms. For this reason, a thorough examination of the skin and mucosal surfaces is essential for early diagnosis. In a patient with visible growth on the cervix, fine needle aspiration cytology may prove to be a useful diagnostic tool, especially when the cervical smear/scrape

cytology is non-diagnostic [13].

As is true for other melanomas, surgical excision remains the mainstay of therapy for primary genital lesions. The prognosis of uterine cervix melanoma is similar to melanoma elsewhere in the body. The disease can take a fulminate course with the development of distant metastasis or may remain quiescent for a few years, manifesting elsewhere in the body within 3 years of diagnosis. Recurrence usually manifests in the vagina or labia and along suture lines. The satisfactory treatment of melanoma still depends on early diagnosis. Regardless of the site of involvement of the melanoma, the prognosis is most closely associated with the depth of invasion of the lesion at the time of diagnosis. Prolonged survival of 2 years or longer for patients with disseminated melanoma was shown to depend on gender, site of primary metastasis, number of metastatic sites, and Karnofsky performance status [14].

Conclusion

Mucosal melanoma of the female genitalia is a rare disease that carries a dismal prognosis. The possibility of metastatic melanoma should be excluded before making a diagnosis of primary cervical melanoma, if the patient has multiple pulmonary tumors as the initial manifestation of cervix uteri malignant melanoma. This tumor is usually locally advanced at the time of initial presentation. The satisfactory treatment of melanoma depends on early diagnosis.

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肺部多發性腫瘤爲初始表現之原發子宮頸黑色素細胞癌—一病例報告

吳政哲　李毓芹*　彭瑞鵬*

原發於子宮頸的黑色素細胞癌相當罕見。合併肺部轉移的子宮頸黑色素細胞癌更是少見。子宮頸黑色素細胞癌在臨床上診斷不易而且被診斷出來時已通常相當晚期，預後也不好。常見於肺部轉移的原發腫瘤有乳癌、頭頸部腫瘤、大腸癌或胃癌。黑色素細胞癌常轉移侵犯至肺部。常見的影像學表現為多發性結節或腫塊。肺部多發性腫瘤若診斷為黑色素細胞癌轉移時，應仔細檢查病患的皮膚或黏膜是否有原發黑色素細胞癌。黑色素細胞癌主要治療方式為手術切除。病人的預後好壞通常決定於病人的術前診斷分期。*(胸腔醫學 2006; 21: 40-45)*

關鍵詞：黑色素細胞癌、子宮頸、肺部轉移

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Hughes-Stovin Syndrome in a Patient with Behçet's Disease — A Case Report

Ching-Yu Yeh, Chung-Hung Shih, Fong-Chieh Wang

Hughes-Stovin syndrome (HSS) is a very rare disorder with a combination of multiple pulmonary artery aneurysms and deep venous thrombosis or thrombophlebitis. Hughes-Stovin syndrome and Behçet's disease (BD) are the 2 known non-congenital, noninfectious diseases that produce pulmonary aneurysms. The relationship between them is still controversial. We report a very rare case of Hughes-Stovin syndrome in a patient with Behçet's disease. The patient initially presented with chest pain, hemoptysis, fever, chills, and engorged superficial veins on the trunk. Multiple pulmonary artery aneurysms and deep venous thrombosis were ascertained by thoracic magnetic resonance angiography (MRA), angiography, and chest and abdominal computed tomography (CT). BD was diagnosed with recurrent oral ulcers, genital ulcers, and skin lesions. The patient was treated with combinations of corticosteroid, colchicine, and cyclophosphamide. ***(Thorac Med 2006; 21: 46-52)***

Key words: Hughes-Stovin syndrome, Behçet's disease, pulmonary artery aneurysms

Introduction

Most pulmonary artery aneurysms are associated with congenital cardiovascular diseases, whereas less common causes include infection (tuberculosis, mycotic infection, or syphilis), trauma, and degenerative changes of the pulmonary arteries. Multiple pulmonary artery aneurysms are often observed in patients with Hughes-Stovin syndrome or Behçet's disease [1, 18-19]. Both HSS and BD with pulmonary involvement have a high mortality despite treatment [1-8, 10-19]. We report a very rare case of Hughes-Stovin syndrome coexisting with Behçet's disease.

Case Report

A 32-year-old man was admitted due to intermittent hemoptysis, chest pain, fever, chills, and edema in both legs. Physical examination revealed clear breathing sounds and superficial veins engorgement on the trunk. The hemogram showed leukocytosis with normocytic anemia (white blood cells 17,880/mm^3 with 76.7% neutrophils, hemoglobin 11.8 gm/dL, and a platelet count of 244,000/mm^3). Routine blood biochemistry, urinalysis, electrocardiogram, and arterial blood gas in room air were within normal range. Chest X-ray showed multiple round opaci-

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ties in the bilateral lungs (Figure 1). Chest and abdominal CT revealed multiple variable-sized pulmonary artery aneurysms in both lungs (Figure 2). Occlusion of the inferior vena cava with engorged abdominal subcutaneous vessels was also noted.

The coagulation studies were normal (prothrombin time 10.2 seconds, activated partial thromboplastin time 26 seconds). The venereal disease research laboratory, human immunodeficiency virus 1 and 2, hepatitis B surface antigen, antineurophilic cytoplasmic autoantibodies, anti-extractable nuclear antigen antibodies, C3, C4, and anti-cardiolipin antibodies were all negative. Antinuclear antibody showed positive (80x). Sputum and blood cultures revealed no growth.

Chest MRA (Figure 3) and angiography (Figures 4A and 4B) showed bilateral multiple pulmonary arterial aneurysms and a left pulmonary artery embolism. Even with the diagnosis

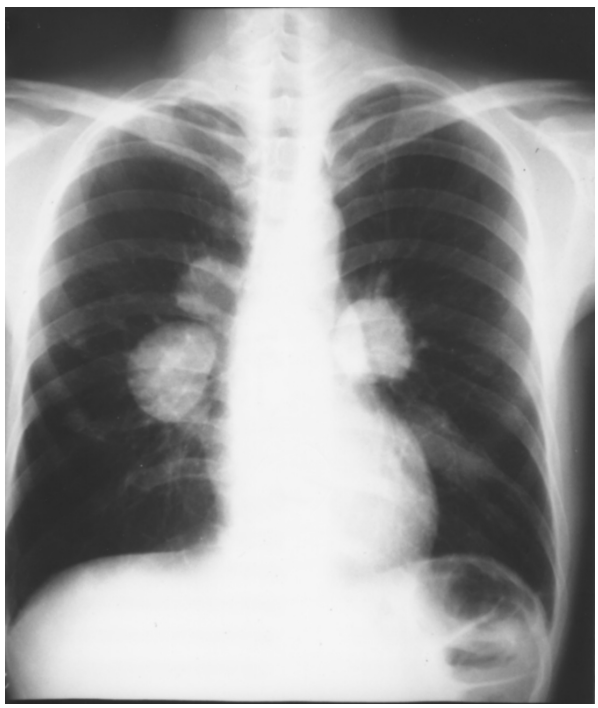


Fig. 1. Chest X-ray, PA view, shows multiple round opacities over bilateral lungs, mostly in the hilar area.

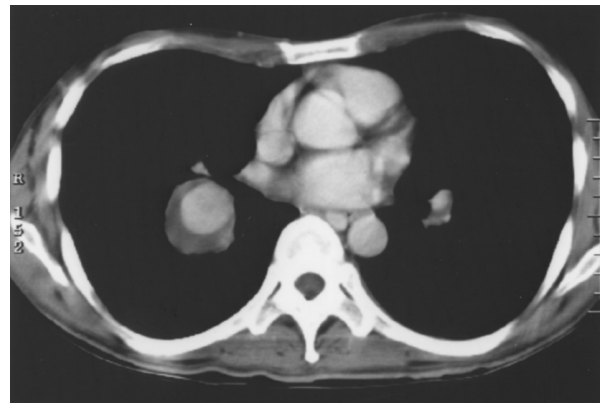


Fig. 2. Chest CT with contrast reveals crescent mural thrombus and vascular enhancement, compatible with pulmonary artery aneurysms, in the bilateral hilums.

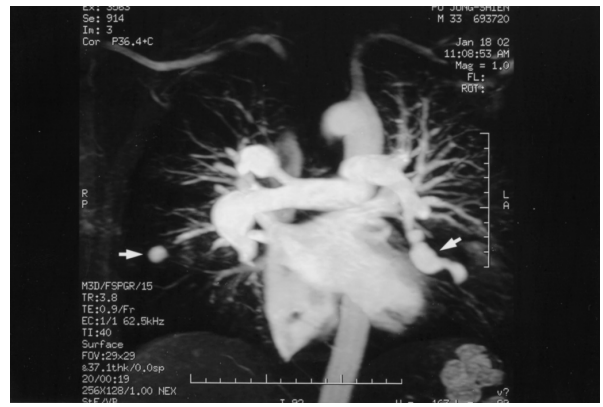
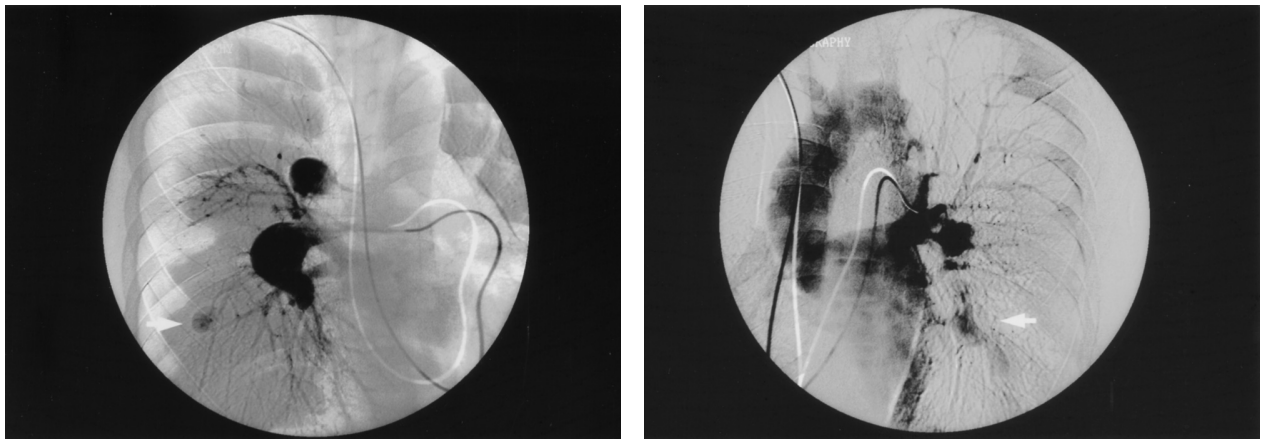


Fig. 3. Chest sagittal 3D reconstruction of MRA images: bilateral multiple pulmonary artery aneurysms are demonstrated. The arrows show the small-sized aneurysms which are not apparent on the CXR.

of Hughes-Stovin syndrome, the patient insisted on receiving supportive treatment. Initially, methylprednisolone 80 mg intravenously per 8 hours for 3 days was administrated; we then shifted to oral prednisolone 15 mg daily. After the diagnosis, he was admitted several times with the same problems in the following 10 months. During this period, Behçet's disease was diagnosed with recurrent oral ulcers, genital ulcers, and skin lesions (papulopustular lesions). We treated the patient with combinations of steroid, colchicine, and cyclophosphamide, but the result was



(A) (B)

Fig. 4A & 4B. Angiography demonstrates bilateral multiple variable-sized pulmonary artery aneurysms. The arrows show the small-sized aneurysms which are not apparent on the CXR.

disappointing.

Discussion

Behçet, a Turkish professor of dermatology, first described this disease in 1937 in a patient with a triad of recurrent oral ulcers, genital ulcers and relapsing ocular inflammation [2-4, 6-8]. Other features include dermatologic manifestations such as erythema nodosum, pseudofolliculitis, papulopustular lesions or acneiform nodules, subcutaneous or deep vein thrombophlebitis, epididymitis, arterial aneurysms or occlusions, central nervous system involvement, arthritis, gastrointestinal involvement, and a positive pathergy test - a hypersensitivity response to a sterile needle prick with an erythe-matous papule formation >2 mm in 24-48 h [3-7, 9]. BD is now recognized as a systemic disorder mainly affecting young adults between the ages of 20 and 40 in Mediterranean, Middle Eastern and Far Eastern countries. The male-to-female ratio differs from 1 area to another [2-7, 10]. The diagnostic criteria of BD are recurrent oral ulcerations plus 2 of the following conditions: recurrent genital ulcerations, eye lesions, skin lesions, and a positive pathergy test [3, 5-6, 11]. This case was compatible with the diagnostic criteria.

Pathologically, 4 types of vascular lesions of BD are recognized: arterial occlusion, arterial aneurysm, venous occlusion, and varices [3-4, 7, 9]. Histologically, aneurysm formation is characterized by rupture of internal and external elastic laminae with a thickening of the intima, degeneration of the media, and vasculitis of the vasa vasorum with a perivascular infiltration of lymphocytes [5-6, 8-9]. The vascular system is involved in up to 25% of BD patients, and the prevalence of involvement of the lung approaches 5% and, in some studies, up to 19% [3-6, 8, 12-13]. Pulmonary involvement and arterial aneurysm formation are thought to be a poor prognosis [3-6, 9, 13]. The rupture of pulmonary aneurysms is the leading cause of death [3-6, 13].

The combination of multiple pulmonary artery aneurysms and peripheral venous thromboses is rarely described. It was first reported by Beattie

and Hall in 1911 and later by Hughes and Stovin in 1959. This complex syndrome has been referred to as the Hughes-Stovin syndrome, and it occurs almost exclusively in young males [1, 7, 10, 14-17]. The angiographic and histopathological findings reported for HSS patients show similarities to those seen in BD patients [17-19]. Several investigators have suggested that HSS is actually a variant of BD rather than a discrete clinical entity [6-7, 13, 18]. However, typical symptoms of BD, such as oral or genital ulcerations, skin lesions, eye lesions, or arthritis/arthralgia are not present in most cases of HSS [1, 16, 20]. The link between Hughes-Stovin syndrome and Behçet's disease remains necessarily speculative because the etiologies of both disorders are still uncertain [7]. This patient had a very rare case of HSS coexisting with BD.

The typical symptoms of HSS include fever, chills, venous thrombosis, cough, and intermittent hemoptysis. The course is often progressive, causing massive hemoptysis and death after rupture of a pulmonary artery aneurysm. In some cases, pulmonary artery aneurysms were treated successfully, either medically, surgically, or with transcatheter embolization [1-2, 6-7, 9, 14, 16-18, 21-22]. Therefore, for the sake of survival, early diagnosis and management of the pulmonary aneurysm is necessary [1].

The imaging of subjects with an aneurismal form of BD has been a challenge. Conventional CT, venography, angiography, or MRA provides the modality of diagnosis. However, contrast studies of the arteries and veins carry certain high risks for complications in patients with BD. Venous puncture, intravenous infusion, rapid injection of a large quantity of contrast material, and insertion of a venous catheter may either initiate a thrombosis or aggravate an existing thrombosis within the peripheral veins, or an aneurysm may develop at the site of the arterial puncture. The frequency of these complications is not known, and there is no effective means of prevention [5, 9]. MRA has the potential to provide adequate diagnosis and preoperative planning in a noninvasive manner [7]. Multiplanar imaging without the need for contrast agent injection has an obvious advantage, compared with other modalities. Thrombosed aneurysms can be depicted as well as patent ones, and a better overall view of the surrounding parenchyma is obtained. Recently, spiral CT/CT angiography has been introduced as another tool for vascular imaging. However, the necessity of an intravenous contrast agent injection is a significant disadvantage over noncontrast magnetic resonance imaging (MRI) and MRA [6, 9]. In this patient, we performed CT, angiography and MRA without any complications.

The small number of cases identified has precluded controlled studies of the optimal management of pulmonary artery aneurysms in patients with either HSS or BD. The treatment of HSS is similar to that of BD therapy; steroid alone or in combination with immunosuppressants (cyclophosphamide or azathioprine) has been suggested. However, the effectiveness is in doubt because of the fatal course of most cases in spite of treatment [7, 10, 13, 16]. Colchicine was reported to be successful in a single HSS patient [19]. Treatment with anticoagulants is potentially dangerous in view of the frequency of hemoptysis as a cause of death in both pulmonary BD and HSS [7, 10, 16]. The resection of affected segments is a method of preventing aneurysm rupture. However, most of the aneurysms are located bilaterally, making resection extremely difficult [1, 7, 15, 22]. In BD patients, there is also a 25% risk of recurrent aneurysms, usually at the anastomosis site [9, 19]. Selective

transcatheter embolization of the pulmonary artery aneurysm is a viable therapeutic alternative method, since it allows complete occlusion of the aneurysm, but no long-term follow-up data exist [2, 7, 15-16, 22]. In this case, the pulmonary aneurysms were located bilaterally. We treated the patient with combinations of steroid, colchicine and cyclophosphamide, but the outcome was disappointing.

In conclusion, the early diagnosis and management of HSS or BD with pulmonary involvement is a necessity, due to the high mortality. MRA is a better choice for the diagnosis of HSS or BD with pulmonary involvement. The main treatment for both HSS and BD patients includes corticosteroid, immunosuppressants, surgical resection, or embolization. However, none of these alone or in combination provides a favorable outcome. The management of both HSS and BD patients should be individualized.

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貝賽特氏病病人合併 Hughes-Stovin 症候群—病例報告

葉靖宇　施崇鴻　王鋒杰

Hughes-Stovin 症候群為一非常罕見的疾病合併有多發性肺動脈瘤及深部靜脈栓塞或血栓靜脈炎。Hughes-Stovin 症候群和貝賽特氏病是兩種已知會發生肺動脈瘤的非先天性、非感染性疾病。兩者之間的關聯性仍有爭議。我們報告一個非常罕見的病例為貝賽特氏病合併 Hughes-Stovin 症候群。病人一開始的表現為胸痛、咳血、發燒、寒顫及軀幹出現表面靜脈充血。胸腔核磁共振血管攝影、血管攝影、胸腔及腹部電腦斷層診斷出多發性肺動脈瘤及深部靜脈栓塞。反覆性口腔潰瘍、生殖器潰瘍及皮膚病灶診斷出貝賽特氏病。病人接受合併使用皮質類固醇、秋水仙素及環磷醯胺的治療。*(胸腔醫學* ***2006; 21: 46-52)***

關鍵詞：Hughes-Stovin 症候群，貝賽特氏病，肺動脈瘤

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Precursor T-Lymphoblastic Leukemia/Lymphoma Presenting with a Huge Left Lung Mass — A Case Report

Ming-Hsien Huang, Wen-Chung Chen, Wei-Cheih Lin, Chang-Wen Chen, Han-Yu Chang, Tzuen-Ren Hsiue

Leukemia with a lung mass presentation has been rarely reported. We describe a 65-year-old man who developed a huge lung mass on the left side with compression of the mediastinum and respiratory failure. Precursor T-lymphoblastic leukemia/lymphoma was diagnosed after bone marrow biopsy and left lung mass biopsy. He received leukophoresis for a blastic crisis and chemotherapy for leukemia. Unfortunately, neutropenic fever developed later, and the patient died of septic shock. ***(Thorac Med 2006; 21: 53-58)***

Key words: leukemia; lymphoma; lung mass; precursor T-lymphoblastic leukemia/lymphoma

Introduction

Lymphoblastic neoplasms may present as leukemia and/or lymphoma; there are 2 separate disorders: precursor B-lymphoblastic leukemia/lymphoma and precursor T-lymphoblastic leukemia/lymphoma. These diseases are all uncommon, each constitutes less than 2% of all adult non-Hodgkin's lymphomas. Precursor T-lymphoblastic leukemia is more common in children and young adults, with males more frequently affected than females.

The patient described herein was an elderly man with an initial presentation of a huge lung mass on the left side, with compression of the mediastinum and respiratory failure.

Case Report

A 65-year-old man was told he had a left lung nodule by a practitioner 3 years before admission, but he paid no attention to it. He had a history of smoking 1 pack per year for 40 years. He complained of increasing shortness of breath, severe productive cough, and difficulty swallowing for 3 months before admission. In addition, body weight loss within weeks and shaking chills with mild fever lasting for several days were noted. Initially, he visited a local hospital, where the chest X-ray and computed tomography showed a huge mass occupying the entire left lung. After an episode of acute respiratory failure, he received emergency endotracheal intubation and

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mechanical ventilation. He was then transferred to our hospital and admitted to the intensive care unit for further management.

On admission, his consciousness was clear; his body temperature was 37.3°C, pulse rate 68 beats per minute, respiratory rate 18 per minute, and blood pressure 134/75 mmHg. Pink conjunctivae and anicteric sclerae were noted, the neck was supple, without cervical and axillary lymphadenopathy, the breathing sounds were decreased in the left lung field, a regular heart beat without murmur was found, the abdomen was soft without tenderness, the liver tip was palpable 2 cm below the right costal margin, and the extremities moved freely without pitting edema. The neurological examination revealed no abnormality. Urinalysis was normal. The hemoglobin (Hb) was 11.5g/dl, the white blood cells (WBC) 291,100/μl (blasts 89%, metamyelocytes 0.5%, band forms 1%, lymphocytes 2.5%), platelets 227,000/μl; lactate dehydrogenase (LDH) 2547 IU/L, albumin 2.7g/dl, and globulin 2.0g/dl. The cerebral spinal fluid (CSF) study was normal, and the human immunodeficiency virus (HIV) study was negative. The chest radiography (Figure 1) showed a huge mass occupying the entire left lung with displacement of the mediastinum to the right side. The computed tomography (CT) of the thorax revealed a huge left extrapulmonary mass with compression of the left lung posteriorly and displacement of the mediastinum. The huge heterogeneous soft tissue mass occupied the entire left lung with complete collapse and displacement of that portion of the lung. The tumor was at least 10x23 cm in size. Focal areas of calcification and multiple areas of low density, suggesting central necrosis, were noted. (Figures 2A & 2B). An ultrasonographic study of the abdomen revealed hepatomegaly and no biliary tract dilatation. Aspiration biopsy of the lung tumor under CT guidance and

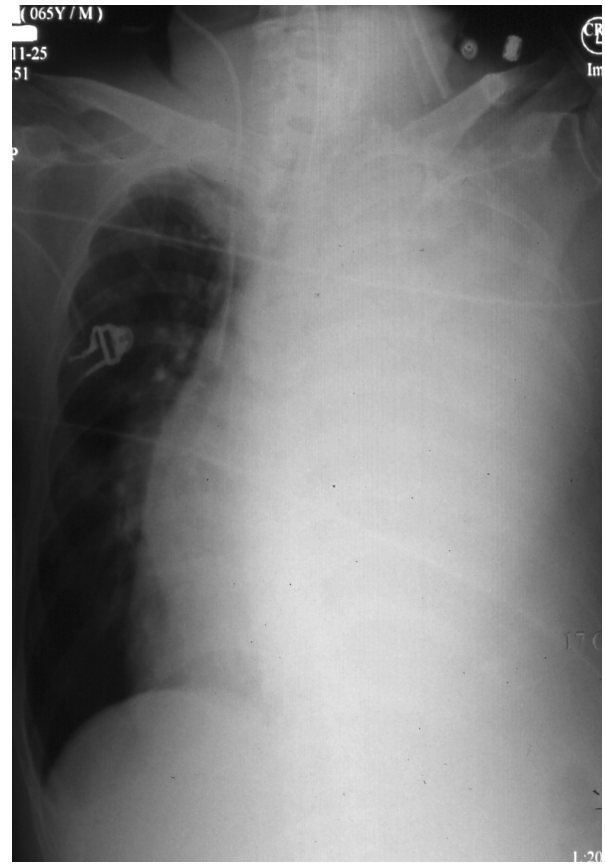
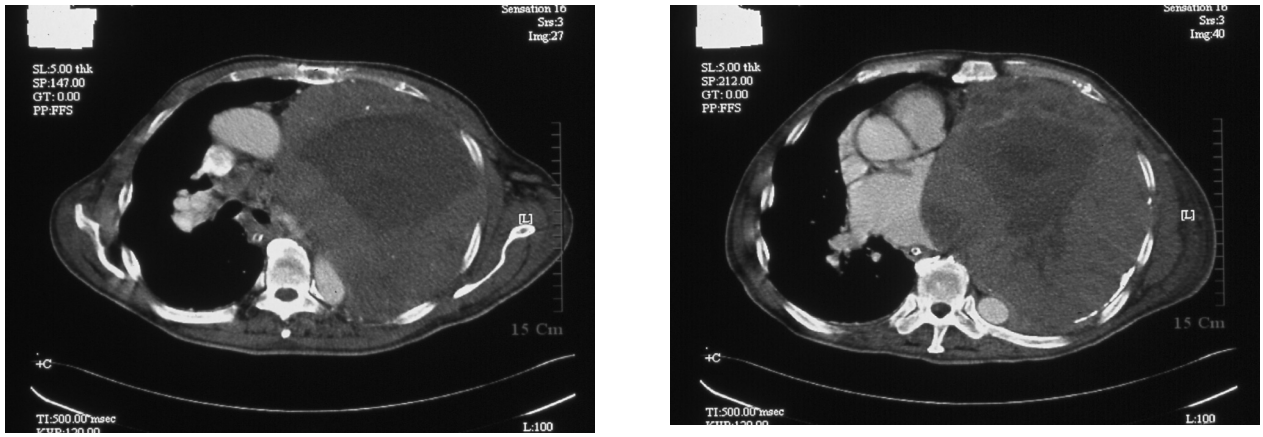


Fig. 1. Chest radiograph on admission shows a complete opacity on the left side of the lung with tracheal deviation to the right side.

bone marrow aspiration biopsy were both done. The bone marrow aspirate smear showed lymphoblastic infiltration, accounting for about 70-80% of mononuclear cells. The tumor cells had medium to large nuclei, fine chromatin, scant cytoplasm, and inconspicuous nucleoli. The bone marrow biopsy showed an interstitial infiltration of lymphoblasts, accounting for about 40-50% of the mononuclear cells. Immunostaining revealed that the tumor cells were positive for TdT. Flow cytometric analysis of the bone marrow cells revealed the T-cell lineage of the tumor cells. The lung biopsy disclosed nests of atypical lymphoid cell infiltration. The morphology and immunostaining of TdT revealed involvement of the lymphoblasts. The pathologic diagnosis was



(A) (B)

Fig. 2A & 2B. Chest CT scan shows a huge left lung mass with central necrosis. The mass was extrapulmonary in origin with compression of the left lung posteriorly and displacement of the mediastinum to the right side, without pleural effusion.

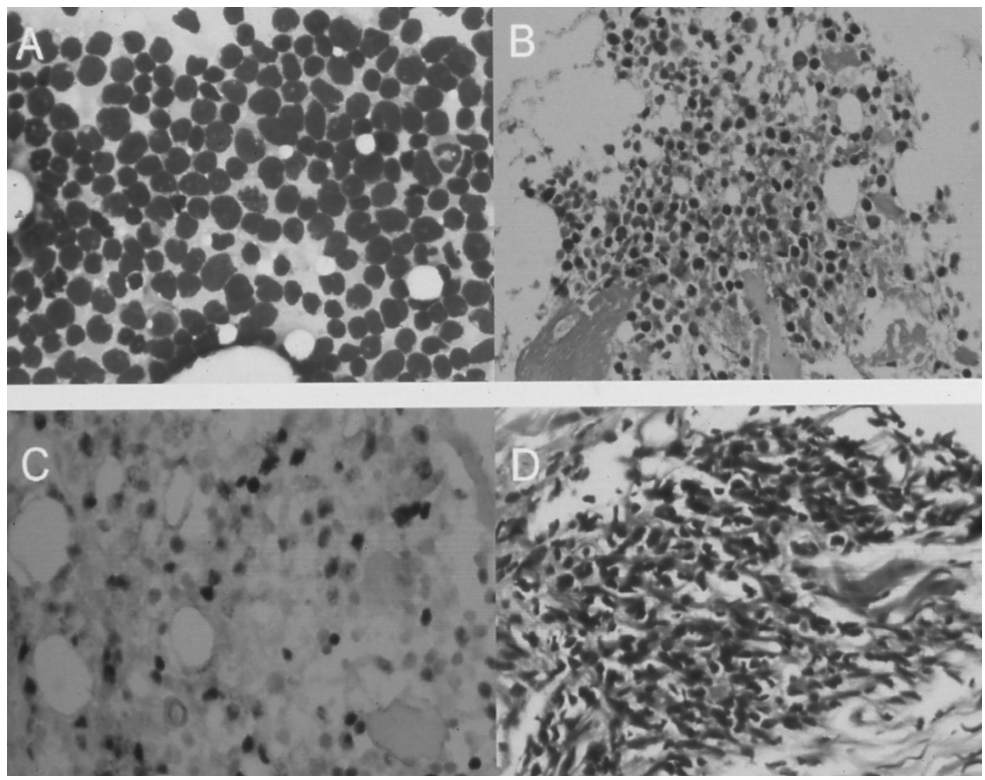


Fig. 3. Precusor T-lymphoblastic lymphoma/leukemia. A Lymphoblasts in the bone marrow aspiration smear. The tumor cells have irregular nuclei, a high nuclear/cytoplasmic ratio, fine chromatin, and inconspicuous nucleoli (H&E stain, 400x). B Lymphoblastic infiltration in the bone marrow biopsy (H&E stain, 400x). C Immunostaining for TdT in the bone marrow biopsy. Tumor cells are stained brown on their nuclei and account for about 40-50% of mononuclear cells (TdT immunostain, 400x). D Mediastinum involvement by tumor cells (H&E stain, 400x).

precursor T-lymphoblastic lymphoma/leukemia (Figure 3). The patient underwent leukophoresis 4 times for a blastic crisis, and 1 course of chemotherapy was performed. Unfortunately, the patient later developed neutropenic fever. Although empiric antibiotics with pipiracillin and gentamicin were administrated, the patient died of septic shock 15 days after admission.

Discussion

There are 2 separate lymphoblastic neoplasm disorders [1]: precursor B-lymphoblastic leukemia/lymphoma and precursor T-lymphoblastic leukemia/lymphoma. These diseases are all uncommon. Precursor T-lymphoblastic leukemia/lymphoma occurs most frequently in late childhood, adolescence, and young adulthood, with a male predominance. It comprises 15% of childhood ALL (acute lymphocytic leukemia) and 25% of adult ALL [2], as well as 2% of adult non-Hodgkin's lymphoma [3].

Precursor T-lymphoblastic leukemia/lymphoma can present either as an ALL or as an aggressive lymphoma. It can also present with bone marrow failure, although the severity of anemia, neutropenia, and thrombocytopenia is often less than that in precursor B-lymphoblastic leukemia/lymphoma. These patients sometimes have very high white cell counts, lymphadenopathy, and hepatosplenomegaly, and young men may present with a large mediastinal mass and pleural effusion. Both presentations have a propensity to metastasize to the CNS (central nervous system); this involvement is often present at diagnosis [4]. Patients with bone marrow involvement have a very high incidence of CNS infiltration. Precursor T-lymphoblastic leukemia/lymphoma is typically composed of small to medium-sized blast cells with scant cytoplasm, moderately condensed to dispersed chromatin and indistinct nucleoli, variably involving the bone marrow and the blood (precursor T-acute lymphoblastic leukemia), thymus and/or lymph nodes (precursor T-lymphoblastic lymphoma). The serum LDH concentration is also usually elevated. Approximately 60% of patients develop bone marrow infiltration and a subsequent leukemic phase indistinguishable from T-cell ALL [5].

Clinically, a case is defined as lymphoma (LBL) if there is a mediastinal or other mass lesion and <25% blasts in the bone marrow. It is classified as leukemia (ALL) if there are >25% bone marrow blasts, with or without a mass lesion. Patients are usually males in their 20s or 30s who present with lymphadenopathy in the cervical, supraclavicular, and axillary regions (50%), or with a mediastinal mass (50 to 75%) [6]. In most patients, the mediastinal mass is anterior and bulky, and is associated with pleural effusion. These masses can be associated with complications such as SVC (superior vena cava) syndrome, tracheal obstruction, and pericardial effusions with or without tamponade. Abdominal involvement is very unusual, and is found primarily in the liver and the spleen. Prior to the current aggressive therapy, this disease was rapidly fatal. The prognosis is usually worse than that of precursor B-cell neoplasms. Adults with precursor T-cell ALL who present with high LDH levels or bone marrow or CNS involvement often need bone marrow transplantation as part of their primary therapy.

Our patient was an elderly man who had very high white cell counts and a high serum LDH level, without anemia and thrombocytopenia. He had hepatosplenomegaly and a huge mediastinal mass with compression of the trachea, and developed respiratory failure. Though there was a huge mediastinal mass, there were none of the usual

complications of pleural effusion, pericardial effusion, or superior vena cava syndrome. No CNS involvement was noted after the brain CT and CSF (cerebrospinal fluid) studies. After chemotherapy, unfortunately, neutropenic fever developed and this patient died of septic shock 15 days after admission.

In conclusion, precursor T-lymphoblastic leukemia/lymphoma should be a part of the differential diagnosis when dealing with a huge lung mass shadow in the chest radiograph. The disease is rare and has a poor prognosis, especially in elderly patients.

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以巨型左肺腫瘤表現的先驅 T 細胞淋巴母細胞性白血病 / 淋巴瘤—病例報告

黃明憲　陳文宗　林偉傑　陳昌文　張漢煜　薛尊仁

白血病合併肺部腫瘤的病例是罕見的，文獻上很少被報告。在此我們報告一位 65 歲男性病例長出一個左側肺部巨大腫瘤並且壓迫到縱膈腔合併呼吸衰竭，經過骨髓切片和左肺腫瘤病理切片之後，被診斷為先驅 T 細胞淋巴母細胞性白血病 / 淋巴瘤(Precursor T- lymphoblastic leukemia/lymphoma)。因為 blastic crisis 所以他接受 leukophoresis 和化學療法。由於 neutropenic fever ，該病患死於隨後的敗血性休克。本例病人為 65 歲男性少見，而且無 CNS 侵犯，也無肋膜積液更是少見。報告此病例是當 CXR 影像出現肺部巨大腫瘤並且壓迫到縱膈腔合併呼吸衰竭時，也需要將 Precursor T- lymphoblastic leukemia/lymphoma 列為鑑別診斷之一，因為此疾病是少見的，尤其是在年老的患者其預後不佳。*(胸腔醫學* ***2006; 21: 53-58)***

關鍵詞：白血病、淋巴瘤、肺腫瘤、先驅 T 細胞淋巴母細胞性白血病 / 淋巴瘤

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Adenocarcinoma of the Lung with Ovarian Metastasis: A Case Report

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Ovarian adenocarcinoma can be either a primary ovarian neoplasm or metastasis from another primary site. Approximately 6% of ovarian cancers are metastatic, usually from the stomach, breast, pancreas, kidney, or colon. Reports of ovarian metastasis from lung cancer are relatively uncommon, even in autopsy series. Only approximately 5% of females with lung cancer have ovarian metastasis at autopsy. We report a 23-year-old woman who was diagnosed with adenocarcinoma of the lung, left upper lobe, with multiple brain metastasis, in December, 2001. She received cranial irradiation for brain metastasis and systemic chemotherapy, beginning in January, 2002. About 1 year later, she complained of lower abdominal tenderness, and a huge pelvic mass, about 20 centimeters in diameter, was disclosed by abdominal CT scan. Left salpingo-oophorectomy and pelvic lymph node dissection were performed in January, 2003. Pathology showed that the tumor cells were in a tubulopapillary pattern; their cytoplasm was clear and the nuclei were pleomorphic. Immunohistochemical staining with thyroid transcription factor-1 (TTF-1) showed nuclear staining in the tumor cells, compatible with lung cancer metastasis to the ovary. Even though ovarian metastasis is a rare presentation of lung cancer, the possibility should always be kept in mind when an ovarian tumor is found after lung cancer has been diagnosed. ***(Thorac Med 2006; 21: 59-64)***

Key words: ovarian metastasis, thyroid transcription factor-1

Introduction

Ovarian tumors can be a primary neoplasm or metastasis from other sources of malignancy such as the stomach, breast, pancreas, kidney, and colon. Ovarian metastasis is a rare presentation of lung cancer and the differential diagnosis between primary and metastatic ovarian cancer is important, because the treatment modality and prognosis for these 2 cancers are quite different. Since the clinical symptoms of primary or metastatic ovarian tumors are similar, it is difficult to distinguish these cancers by the clinical course alone. However, it is helpful to use specific immunochemistry stains to identify other primary cancers. The use of monoclonal antibody to thyroid transcription factor 1 has a high specificity for lung cancer and thyroid cancer, especially adenocarcinoma [1, 6-7]. CK-7 is another useful marker in discriminating metastasis from primary ova-

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rian cancer [1].

Case Report

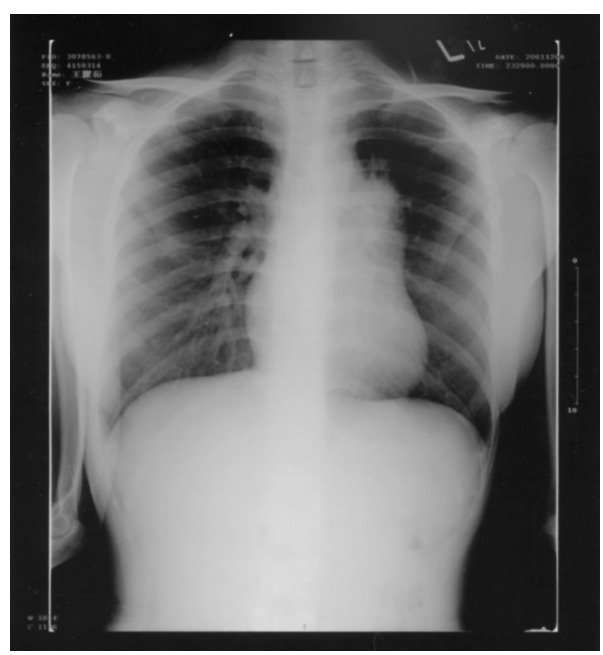
A 23-year-old woman was admitted to our hospital in December 2001 with the complaint of headache and blurred vision for days. She had been quite well in the past and had no history of smoking. A chest X-ray showed a mass lesion in the anterior mediastinum (Figure 1A). Computed tomography of the chest revealed a soft tissue density mass lesion in the left upper lobe with central necrosis and mediastinal lymphadenopathy (Figure 1B). Bronchoscopic brushing cytology revealed adenocarcinoma (Figure 2A). Due to the symptoms of headache and blurred vision, a computed tomography was done, and revealed multiple brain metastases. The patient underwent brain irradiation with 3000 cGy, beginning in December 2001; systemic chemotherapy with navelbine plus cisplatin was also administered, upon completion of the cranial irradiation. After 6 months of chemotherapy with navelbine plus cisplatin, the main lesion of the lung had shrunk. The patient was then in stable condition, and was followed up at our outpatient department.

One year later, she complained of lower abdominal tenderness, and a huge pelvic mass, about 20 cm in diameter, was found by abdominal computed tomography (Figure 1C). Under the impression of primary ovarian cancer, a left salpingo-oophorectomy and pelvic lymph node dissection were performed in January, 2003. Pathology revealed that the tumor cells were in a tubulopapillary pattern. The cytoplasm was clear and the nuclei were pleomorphic (Figure 2B). Indeed, thyroid transcription factor-1 (TTF-1) immonohistochemical staining showed nuclear staining in the tumor cells (Figure 2C); this result was highly suggestive that the ovarian tumor was a secondary tumor from the lung cancer. Based on the pathologic features and the clinical course, adenocarcinoma of the lung with ovarian metastasis was suspected.

She began receiving salvage chemotherapy with taxotere plus cisplatin in October 2002. Unfortunately, the brain lesion progressed, so she underwent additional cranial irradiation with 2500 cGy, beginning in July 2003. She became lost to follow-up in September 2003.

Discussion

Approximately 6% of ovarian cancers are metastasis from other organs [2], especially from the stomach, breast, pancreas, kidney, and colon. Ovarian metastasis is a rare manifestation of primary lung cancer [5]. A literature review indicates that only approximately 5% of women with lung cancer have ovarian metastasis at autopsy



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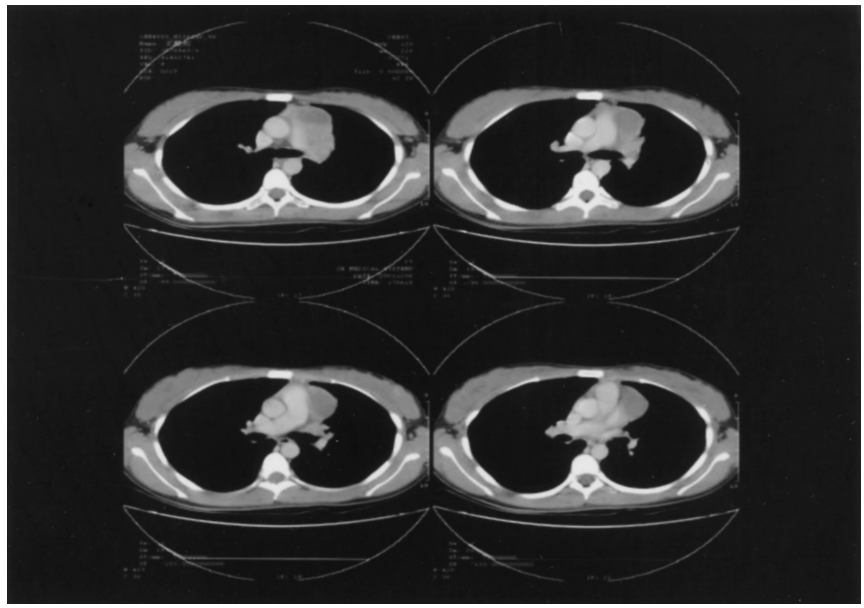

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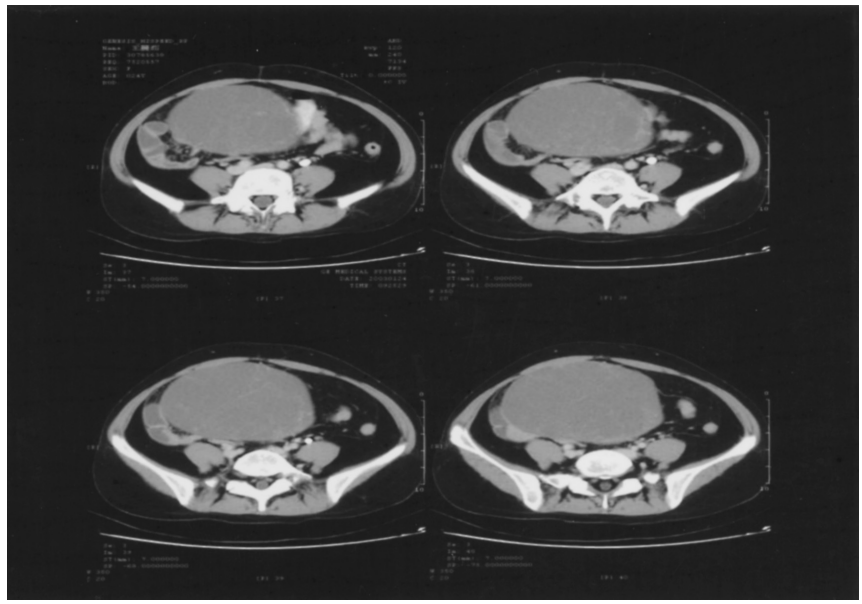
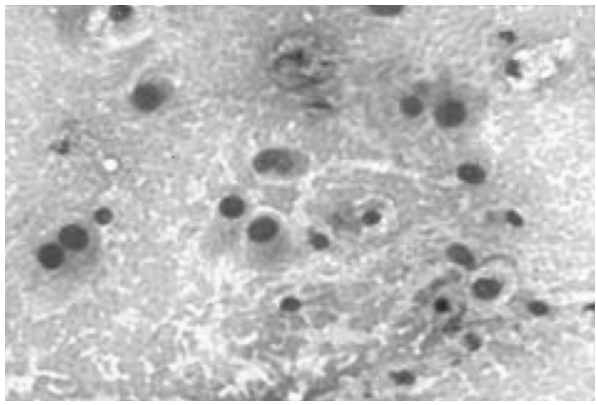


(C)

Fig. 1. (A) Chest X-ray showing a mass lesion in the anterior mediastinum. (B) Chest computed tomography showing a mass lesion in the left upper lobe with central necrosis and mediastinal lymphadenopathy. (C) A huge pelvic mass was found by abdominal computed tomography.

[2]. In the past 20 years, only a few cases of lung cancer with ovarian metastasis have been reported. Young *et al*. [3] reported 7 cases of lung cancer with ovarian metastasis, including 3 small cell carcinoma, 2 adenocarcinoma, 1 large cell carcinoma, and 1 carcinoid tumor. The ages of the 7 patients ranged from 26 to 66 years old. In addition, Yeh *et al*. [4] reported a case of bronchioal-



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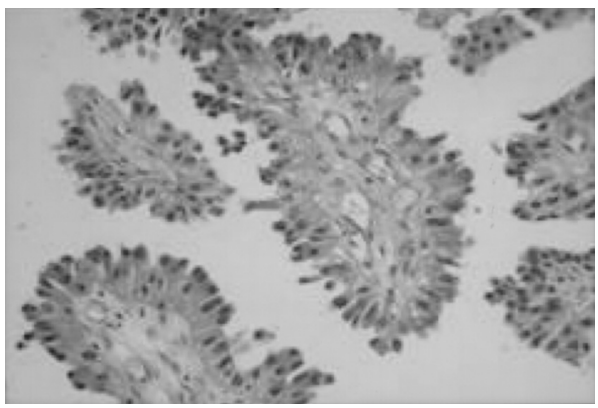

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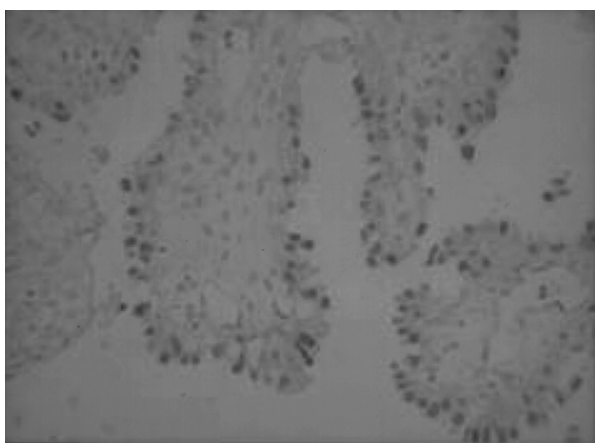

(C)

Fig. 2. (A) Bronchoscopic brushing from the left upper lobe mass lesion and cytology revealed adenocarcinoma. (B) Pathology showed adenocarcinoma from the specimen of the ovary. (C) A positive TTF-1 reaction was found in the specimen from the ovary.

veolar carcinoma of lung with ovarian metastasis in 2003.

Most primary ovarian cancer is adenocarcinoma in type. Our patient was a young woman with adenocarcinoma of the lung who subsequently developed ovarian metastasis 1 year later. The patient received chemotherapy with navelbine plus cisplatin, and shrinkage of the main pulmonary lesion was noted. However, the ovarian metastasis was found about 1 year later. The probable explanation for this is that tumor heterogeneity led to the different treatment outcome of the different metastatic sites. Lung cancer with progressive disease that developed ovarian metastasis was another consideration. It is important to distinguish primary ovarian cancer from metastatic adenocarcinoma to the ovary because of the different treatment modality, regimens, and prognosis. Chhieng *et al*. [1] reported that an adenocarcinoma is most likely to be a primary lung cancer when it has a positive TTF-1 and CK-7 reaction, and a negative CK-20 reaction. Ng WK *et al*. [6] found that thyroid transcription factor-1 is highly sensitive and specific in differentiating metastatic pulmonary from extrapulmonary adenocarcinoma in cytology specimens, with a sensitivity of 88.2% and a specificity of 100%. Mee Sook Roh *et al*. [7] also reported a similar result, with sensitivity at 69% and specificity at 95%. Our patient underwent a left salpingo-oopherectomy, and the specimen from the lesion showed TTF-1 reactivity. This result was highly suggestive that this ovarian tumor was a secondary tumor from the lung cancer. The possibility of primary ovarian cancer with brain and lung metastasis could not be totally excluded in this case. However, the tumor specimen from the ovary showed TTF-1 reactivity, which meant that the ovary was not likely the primary lesion.

In addition, this ovarian tumor was not found initially, but developed 1 year after diagnosis and treatment. Chest computed tomography showed that the pulmonary lesion was a solitary mass that was not likely to be a metastatic lesion. Based on the above findings, primary lung cancer with ovarian and brain metastasis was the most obvious diagnosis.

In conclusion, even though ovarian metastasis is a rare manifestation of lung cancer, the possibility should always be kept in mind when an ovarian tumor is found after lung cancer has been diagnosed. Use of the monoclonal antibody for TTF-1, Ck-7, and CK-20 as immunohistochemical staining is helpful in differentiating primary and metastatic pulmonary adenocarcinoma from primary ovarian cancer.

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肺腺癌合併卵巢轉移—病例報告

王蘭福* 陳育民*,** 彭瑞鵬*,**

卵巢腺癌可以是原發性病灶亦可以是轉移性病灶。大約百分之六的卵巢腫瘤是轉移性病灶，特別是由胃、乳房、胰臟、腎臟以及大腸轉移而來。在病理解剖報告中由肺癌轉移至卵巢的情況並不常見。大約百分之五的女性肺癌患者在接受病理解剖時會發現卵巢轉移病灶。我們提出一位二十三歲女性病患在二〇〇一年十二月診斷為左上肺葉肺腺癌合併腦轉移。病患在接受腦部放射線治療及全身性化學治療一年後出現腹部疼痛的情況。腹部電腦斷層檢查發現有一個二十公分大小的腫瘤。病患於二〇〇三年一月接受左側輸卵管及卵巢切除，病理報告顯示卵巢病灶為腺癌同時對甲狀腺轉錄因子-1(TTF-1)之免疫化學染色呈現陽性反應與原先推測之肺腺癌合併卵巢轉移之診斷吻合。儘管癌合併卵巢轉移的情形相當少見，在原先診斷為肺癌的病患之後出現卵巢腫瘤時仍應將卵巢轉移的可能性考慮在內。*(胸腔醫學* ***2006; 21: 59-64)***

關鍵詞：卵巢轉移，甲狀腺轉錄因子-1

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Non-small Cell Lung Cancer with Small Intestinal Metastasis — A Case Report and Review of the Literature

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A 47-year-old male was admitted to our hospital, and underwent an exploratory laparotomy with small intestinal resection due to suspected small intestine intussusception. The pathology of the intestine showed metastatic poorly differentiated carcinoma. CXR showed a mass in the left lower lobe of the lung, and adenocarcinoma was proved by bronchoscopic biopsy. After consulting with the pathologist, adenocarcinoma of the lung with small intestinal metastasis was diagnosed. Intestinal metastasis was found in 11% of lung cancers at autopsy, but it rarely produced symptoms. However, intestinal metastasis may produce gastrointestinal perforation, obstruction, bleeding and intussusception. Surgery may palliate the symptoms of some patients, however, the prognosis is poor. ***(Thorac Med 2006; 21: 65-69)***

Key words: intestinal metastasis, intussusception, adenocarcinoma

Introduction

Lung cancer with gastrointestinal tract metastasis is not rare in postmortem studies. However, the development of clinically apparent symptoms due to gastrointestinal metastasis is uncommon. As patients live longer now, due to the improvements in treatment and supportive care, small intestinal metastasis is found more frequently than before. In spite of this increment of small bowel metastasis, there are still very few lung cancer patients with intestinal obstruction as their first manifestation. Herein, we describe a patient with adenocarcinoma of the lung having multiple metastases to the small intestine and presenting with intestinal obstruction.

Case Report

A 47-year-old male was a victim of major depression under regular medication. Due to intermittent abdominal cramping pain and constipation lasting for 2-3 weeks, he called at our emergency room, and a KUB examination showed gas distension in the small intestine and colon. Ileus was suspected. A computerized tomography (CT) scan of the abdomen showed multiple jejunal tumors with jejunojejunal or jejunoileal intussusception and small bowel obstruction. In addition, a huge mass was incidentally found in the left lower lung field after chest X-ray examination. An emergency exploratory laparotomy was performed, with segmental rese-

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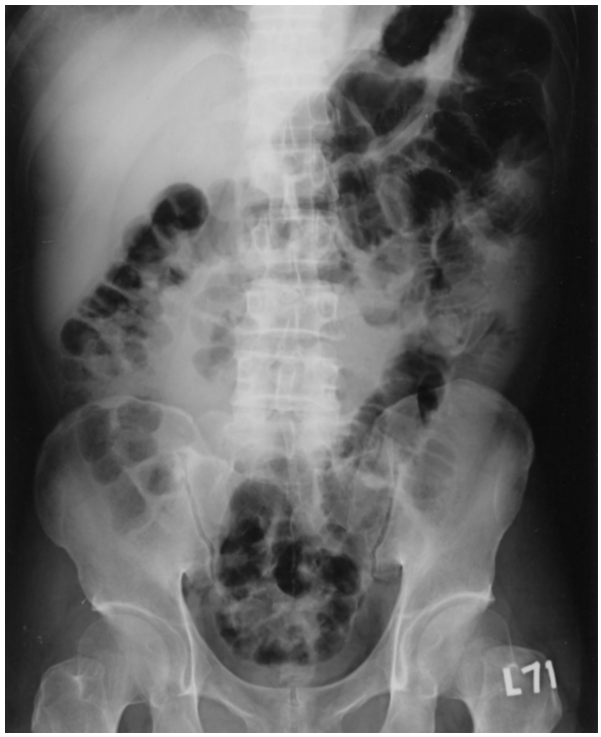

Fig. 1. KUB examination showing intestinal dilatation and ileus.

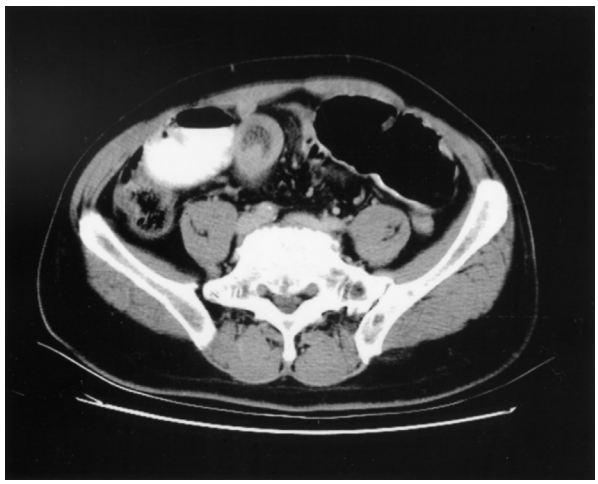

Fig. 2. Abdominal computerized tomography scan showing a "donut sign" at the transition zone in the right lower abdomen, in favor of intussusception with small bowel obstruction.

ction of 215 cm of the small intestine. The pathology of the small intestine revealed multiple intestinal tumors involving the whole intestine wall—metastatic, poorly-differentiated carci-

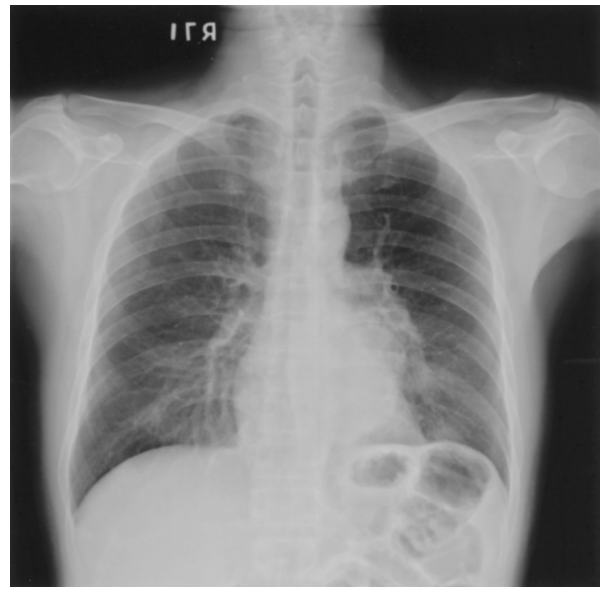

Fig. 3. Pathology of the intestine showing poorly differentiated carcinoma involving the whole intestinal wall. (X400, H&E stain)

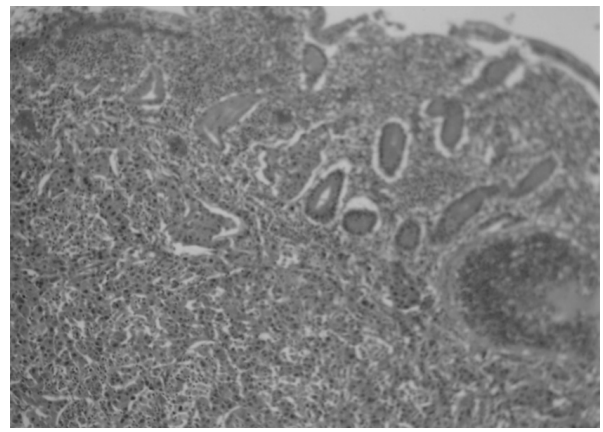

Fig. 4. Chest X-ray showing a mass in the left lower lobe.

noma was suspected. Lung cancer was considered the primary origin due to the huge mass in the left lower lung. A bronchoscopy was arranged, and showed total obstruction of the left common basal bronchus. Brushing was performed and the cytology was reported as adenocarcinoma. After consulting with the pathologist, adenocarcinoma of the lung with small intestinal metastasis was confirmed.

Discussion

Lung cancer has been the leading cause of cancer death in the world, mainly due to the use of tobacco. It was the second leading cause of cancer death in Taiwan with a mortality rate of 30.63 per 100,000 persons in 2003. The natural history of lung cancer is characterized by early dissemination, with at least 40% of patients having metastatic disease at the initial diagnosis. Lung cancer may metastasize to any organ. The commonest sites of metastatic disease are the liver, adrenal glands, brain, bone, kidney, and abdominal lymph nodes. Metastasis to the small bowel is rare, and may cause a diagnostic challenge. In a series of 431 autopsies from a cohort of 1650 NSCLC patients, 46 (11%) had a spread to the small intestine at autopsy; large cell carcinoma had the highest frequency, being the most frequent histological type [1]. In the same study, 12 out of 31 large cell carcinomas, 13 out of 108 adenocarcinomas, and 15 out of 199 squamous cell carcinomas, had small bowel metastases at autopsy. In another series of 218 consecutive autopies, 10 cases had small bowel involvement [2]. The frequency of small bowel involvement was 4.6%, and all were in patients with adenocarcinoma. All patients with small bowel metastasis at autopsy also had other concurrent metastatic sites, including the adrenals, mediastinal lymph nodes, liver, pleura, contralateral lungs, bones, and brain, with decreasing frequency [2].

Small bowel metastases of a primary carcinoma of the lung that produce clinical symptoms are extremely rare. An incidence of 0.5% was found in a study of 1544 patients [3]. In a report of 23 lung cancer patients with symptomatic intestinal metastasis, intestinal perforation and obstruction were the most frequent clinical manifestations. Other manifestations included gastrointestinal hemorrhage (occult or gross bleeding), ileus, and intussusceptions [4-11]. Most small intestinal metastases are found in the jejunum [11], but an explanation for this predominant localization is lacking.

Many variables have been tested for predicting the risk of small bowel metastasis, including age, gender, pretreatment lactate dehydrogenase, performance status, or stage, however, all were useless. Small intestinal metastasis from lung cancer could easily be overlooked during staging procedures, including abdominal ultrasound or an upper abdominal CT scan looking for liver or adrenal gland metastasis. It was not until lung cancer patients complained of acute abdominal pain, that we would consider the presentation of intestinal metastasis.

The median survival after diagnosis of intestinal metastasis from lung cancer is 4 weeks. (range: 1 to more than 20 weeks) [1]. Laparotomy and resection of the abdominal metastasis may be an effective treatment to palliate a gastrointestinal perforation or hemorrhage in selected patients.

In conclusion, small intestinal metastasis in non-small cell lung cancer patients has accounted for about 2-8% of cases, and this metastatic involvement has been significantly associated with systemic widespread metastasis. Symptomatic intestinal metastasis was most frequently presented as intestinal perforation or obstruction. This is kind of metastasis could be difficult to diagnose. Surgery can be useful to palliate selected patients, but the prognosis is poor.

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非小細胞肺癌合併小腸轉移—病例報告與文獻回顧

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一位四十七歲男性因腹痛至本院求診，KUB檢查及腹部電腦斷層檢查發現有腸套疊合併腸阻塞現象。經緊急小腸截除手術，其病理報告為轉移性分化不良型癌細胞。而術前胸部 X 光也意外發現左下肺葉有一腫塊，後經細胞學證實為肺腺癌。經會診病理科醫師後，確定為肺腺癌合併小腸轉移。在肺癌病患的死後解剖中，我們可發現 11% 的病人有小腸轉移，但他們極少造成症狀。小腸轉移的症狀包括腸穿孔、腸阻塞、腸出血和腸套疊。手術可改善部分人的症狀但長期預後是不好的。*(胸腔醫學* ***2006; 21: 65-69****)*

關鍵詞：小腸轉移，肺腺癌，腸套疊

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Traumatic Lacerations of the Right Middle Lobar Bronchus — A Case Report

Chun-An Lu, Yung-Heng Liu*, Chih-Hung Chen

Tracheobronchial injury is a rare, but serious complication of blunt thoracic trauma. The injury is always near the carina and the main bronchus, but is seldom in the right middle lobar bronchus. Surgical intervention of a deficiency is still the major treatment.

Herein, we described the case of a healthy 20-year-old woman with 2 traumatic lacerations of the right middle lobar bronchus (RMLB). She suffered blunt thoracic trauma in a traffic accident and clinically presented as chest pain and respiratory distress. The chest radiograph disclosed cervical and thoracic subcutaneous emphysema, pneumopericardium, rib fractures and left lung contusions and thoracic drainage in the right lung. The fiberoptic bronchoscopy found 2 longitudinal lacerations, 2 cm and 1 cm, respectively, on the posterior wall of the RMLB. The patient did not undergo surgical repair because the lesions were minor, and the clinical symptoms did not deteriorate. The lacerations healed well after 7 days of conservative treatment. She was discharged the next day. ***(Thorac Med 2006; 21: 70-74)***

Key words: blunt thoracic trauma, right middle lobar bronchus, laceration

Introduction

Motor vehicle accidents are the major cause of blunt thoracic trauma, which may damage the aorta and other organs in the mediaastinum, including the tracheobronchial tree, the heart, and the esophagus. Blunt tracheobronchial injury is rare (<2%), but may be lethal [1-2]. More than 80% of tracheobronchial injuries take place within 2.5 cm of the carina [3]. Only 1 case of lacerations of the right middle lobar bronchus (RMLB) was discovered in the literature [4]. We report herein a case of traumatic lacerations of the RMLB that healed well after conservative treatment.

Case Report

A 20-year-old female with no previous medical history was involved in a motor vehicle accident and sustained a blunt chest wall contusion. She complained of severe right chest pain and shortness of breath, and was sent to a local hospital by ambulance. Right thoracic drainage with a chest tube was performed there because of right pneumothorax, and the respiratory

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distress improved. She was transferred to our emergency room (ER) immediately.

Upon arrival at the ER, she was conscious, but acutely ill-looking. She had a body temperature 37.2°C, pulse rate of 121 beats per minute, respiratory rate of 20 breaths per minute, and blood pressure of 130/64 mm-Hg. Physical examination revealed a well-nourished individual. Crepitus was heard in the right neck and chest wall. Auscultation of the thorax revealed crackles in the left lung and a quick heartbeat. The remainder of the physical examination was unremarkable.

The chest radiograph taken at the ER displayed thoracic drainage in the right lung; right cervical,and thoracic subcutaneous emphysema; pneumopericardium; fractures of the posterior part of the left 4th and 5th ribs; and an ill-defined air space filling which hinted at lung contusions in the left lung (Figure 1). Fiberoptic bronchoscopy was performed to exclude tracheobronchial injury, and located a 2 cm and a 1 cm longitudinal laceration on the posterior wall of the RMLB (Figure 2). The chest surgeon was consulted and conservative treatment was favored because of the patient's relatively stable condition. The follow-up chest radiograph revealed residual subcutaneous emphysema of the right neck without pneumothorax, and the chest tube was removed. On the 7th day of admission, the 2nd fiberoptic bronchoscopy found that the lacerations were healing (Figure 3) and the lung contusions had also improved. She was discharged the next day.

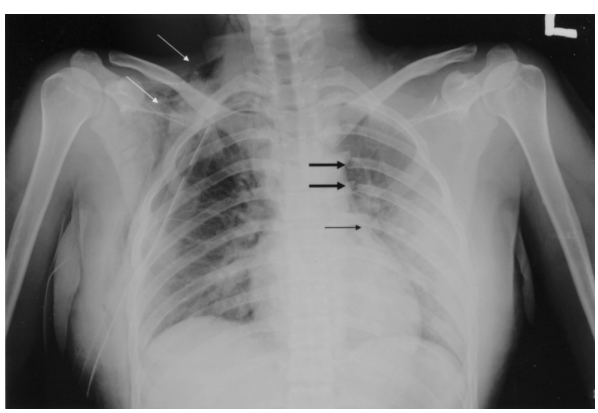

Fig. 1. Chest radiography reveals cervical and thoracic subcutaneous emphysema (white arrows), pneumopericardium (thin black arrow), fractures of the left 4th and 5th ribs (thick black arrows), thoracic drainage in the right lung, and diffuse ill-defined air space filling in the left lung.

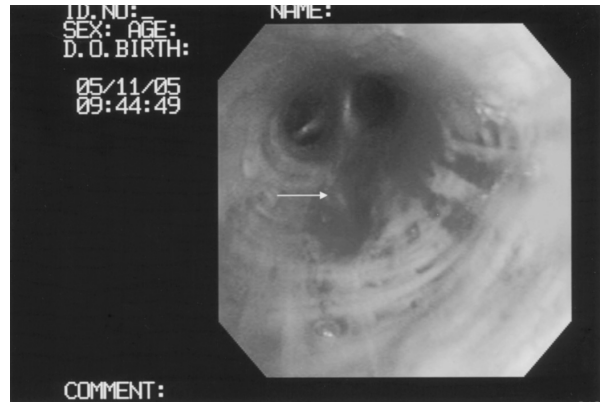

Fig. 2. The 1st fiberoptic bronchoscopy shows irregular, longitudinal lacerations with blood oozing (white arrow) on the posterior bronchial wall of the right middle lobar bronchus.

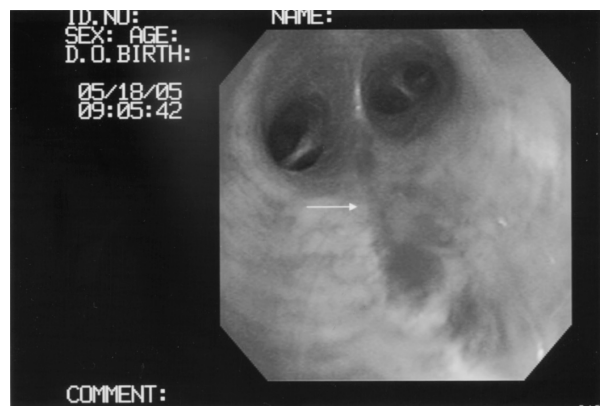

Fig. 3. The 2nd fiberoptic bronchoscopy demonstrates the healed bronchial lacerations (white arrow) on the 7th day of admission.

Discussion

Blunt tracheobronchial lacerations are rare, but fatal complications after thoracic traumatic injuries. Airway injuries may be missed in the presence of obvious damage to other major organs. It is associated with high morbidity and mortality, if the diagnosis is delayed. The clinical symptoms may be nonspecific. Dyspnea and respiratory distress are the most frequent symptoms. The chest radiograph and computed tomography are important sources of diagnostic information, but the findings are also nonspecific. The radiographic findings of airway injury are air leaks, including subcutaneous emphysema, pneumomediastinum, and pneumothorax. Subcutaneous emphysema is the most consistent radiographic finding [5]. When tracheobronchial injury is suspected, bronchoscopy should be performed to verify and locate any major airway injury [6-7]. As in our case, the clinical symptoms, signs, and chest radiograph showing an air leak in the subcutaneous lung and pericardium all pointed to an airway injury. The fiberoptic bronchoscopy also confirmed 2 linear lacerations of the RMLB.

Most blunt injuries of the tracheobronchial tree encompass the intrathoracic trachea and main stem bronchus, with only 4% of these injuries in the cervical trachea [8], which is predominantly involved in the penetrating injuries [9]. The exact mechanism of intrathoracic tracheobronchial injuries is unknown. Kirsh *et al*. [10] suggested 3 potential mechanisms as the cause of blunt tracheobronchial injuries. First, they noted that a sudden, forceful compression of the anteroposterior thoracic cage results in a widening of the transverse diameter. Airway disruption takes place if lateral force exceeds airway elasticity. The second mechanism is a consequence of high airway pressure due to the compression of the airway between the sternum and the vertebral column against a closed glottis. The third mechanism may be a rapid deceleration injury which makes a shearing force at the points of relative fixation, as the carina is tethered by the aortic arch. This patient was sitting in the front seat when she suffered a direct impact and bilateral thoracic contusions in the accident. We suspected that a widening of the transverse diameter and high airway pressure were the main mechanisms of these lacerations of the RMLB, because they were not fixed in the thorax. Kanai *et al*. [4] explained the causes of this phenomenon: First, the lower amount of cartilage in the RMLB results in lacerations under high airway pressure. Second, the long axis of the RMLB and trunk are parallel, and the RMLB is easily affected by direct impaction from the right lateral direction. However, the exact mechanisms are indeterminate because of the small number of cases. A large series is needed to define them.

Primary surgical repair of major tracheobronchial lacerations is always required, but patients with small uncomplicated bronchial tears may be treated successfully without surgical interventions [6-7]. These minor injuries may heal well without negative sequelae under conservative treatment. Non-surgical repair must be considered in small (<2 cm) tears caused by endotracheal intubation in stable patients [11], but the exact size required for surgery has not been recommended in blunt tracheobronchial injuries, because they are always associated with injuries to other organs. As in our case, the largest laceration was 2 cm, and the air leak did not continue. She was treated conservatively, and the lacerations healed well a week later. Because of the extent of a blunt trauma needed to produce airway injury, associated injury is also common, and may be a primary determinant of survival. This patient

was also associated with uncomplicated pulmonary contusions and simple rib fractures. She was observed without surgical intervention, and the follow-up chest radiograph revealed a resolution of the lung contusions. Later, she was discharged.

In conclusion, tracheobronchial lacerations are rare, especially to the right middle lobar bronchus, but are a serious complication of blunt thoracic trauma, so clinicians should consider it a probable complication of blunt thoracic trauma. The primary treatment of a large laceration is surgical repair, but minor tears may be treated successfully with conservative management.

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外傷導致的右中葉支氣管撕裂傷—病例報告

盧俊安　劉永恆*　陳志弘

在胸部鈍挫傷中，氣管支氣管撕裂傷是罕見但是是非常嚴重的併發症。它大部分發生氣管隆凸和主支氣管的位置。發生在右中葉支氣管更是罕見。開刀修復是對於氣管支氣管撕裂傷的主要治療方法。

本篇報告提出一位 20 歲健康女性因為外傷導致右中葉支氣管撕裂傷的病例報告。她在車禍中受到胸部的直接鈍挫傷，臨床的表現主要以胸痛及呼吸窘迫為主。在胸部 X 光發現頸部及胸部的皮下氣腫、心包膜氣胸、肋骨骨折 、左邊肺葉挫傷和右胸放置了一根胸管。在軟式的支氣管鏡的檢查下發現在右中葉支氣管的後壁分別各有一個 2cm 及 1cm 長的撕裂傷。由於撕裂傷口不大及臨床症候並未持續惡化，她並未接受開刀的治療。在 7 天後的支氣管檢查發現這些撕裂傷已經癒合相當的良好，她並在隔天出院。*(胸腔醫學* ***2006; 21: 70-74)***

關鍵詞：胸部鈍挫傷，右中葉支氣管，撕裂傷

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Spontaneous Closure of Tracheal Fistula caused by Descending Necrotizing Mediastinitis in a Diabetic Patient — A Case Report and Review of the Literature

Min-Li Chang, Horng-Chyuan Lin

We report our experience of the treatment of a 68-year-old female with a tracheal fistula which was associated with deep neck infection and descending necrotizing mediastintis.She received long-term care with endotracheal intubation and mechanical ventilator support after cervicomyotomy and transcervical mediastinal drainage. The fistula was healed. Thus, long-term controlled ventilation and mediastinal drainage were beneficial for the treatment of central airway injury. ***(Thorac Med 2006; 21: 75-81)***

Key word: tracheal fistula, descending necrotizing mediastinitis

Introduction

Descending necrotizing mediastinitis (DNM) is a lethal disorder that results from oropharyngeal or cervical infections spread along fascial planes into the mediastinum [1]. DNM originating from a cervicofacial infection such as a retropharyngeal abscess (RPA), deep cervical phlegmon (DCP), or deep cervical abscess (DCA), is quite rare [2]. The criteria for descending necrotizing mediastinitis include the clinical manifestation of severe cervical infection, radiologic features of mediastinitis, and the relationship between the oropharyngeal infection and the mediastinal process [3]. The mortality rate remains high (40%), although with aggressive mediastinal drainage and antibiotic treatment [4].

Widespread cellulitis, necrosis, abscess formation, and sepsis may occur in DNM [5]. Tracheal fistula is an infrequent complication in DNM. Moreover, it is also rare for a patient with a tracheal fistula caused by DNM to survive. Herein, we report a case of 68-year-old female who had diabetes and chronic asthma under oral steroid treatment. She experienced a tracheal fistula caused by DNM and survived after aggressive treatment with ventilator support and surgical drainage.

Case Report

The 68-year-old female is a case of chronic asthma that was under inhaled and oral steroid therapy. She also had congestive heart failure due

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to ischemic cardiomyopathy and diabetes mellitus. This time,she was admitted to the medical ICU on 2004-8-23 due to hypercapnic respiratory failure, and needed mechanical ventilator support. After management, she was weaned from the ventilator and transferred to the ward. Unfortunately, repeated hypercapnic respiratory failure occurred and re-intubation was performed on 2004-9-2. On the second day of re-intubation (hospital day 12), she suffered from fever and left neck swelling. The computed tomographic (CT) scan demonstrated fluid and air collections over left parapharyngeal , posterior cervical space, retropharyngeal space, and upper mediastinum (Figure 1). Under the diagnosis of deep neck infection with upper mediastinitis, transcervical debridement and drainage of the neck and upper mediastinum were performed by a surgeon. Many commonly-found germs and associated aerobic and anaerobic bacteria were detected. Culture of the obtained pus revealed *β-streptococcus Gr-non ABD, Viridans Streptococcus, Prevotella intermedia, Fusobacterium nucleatum, Peptostreptococcus anaerobius,* and *Peptostreptococcus sp*. Broad-spectrum antibiotics with teicoplanin, imipenem and metronidazole were administered. On hospital day 19, the second CT scan revealed an improvement of the deep neck infection and mediastinitis (Figure 2). On hospital day 29, the third CT scan revealed residual abscess in the left supraclavicular and left paraspinal space (Figure 3). However,much pus was drained from the endotracheal tube in the next 24 hours. Therefore, bronchoscopy was arranged on hospital day 30. A defect was noted on the membranous portion of the trachea, approximately 7 cm above the main carina (Figure 5). Surgical repair of the tracheal fistula was suggested, but was refused by the families because of

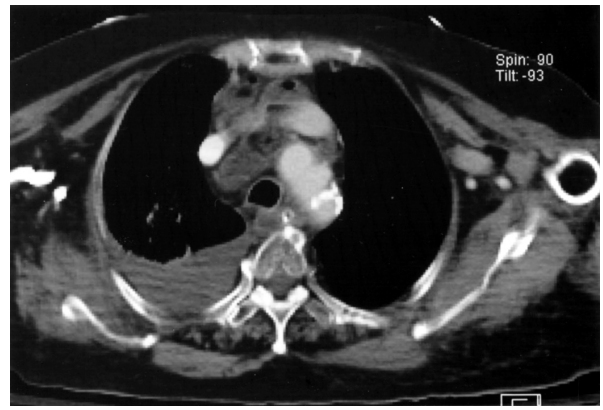

Fig. 2. 2nd Chest CT scan demonstrated improvement in the deep neck infection and mediastinitis (hospital day 19).

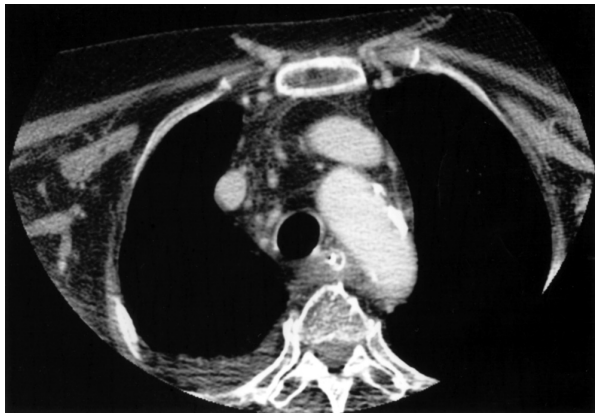

Fig. 1. Chest CT scan demonstrated left parapharyngeal space, posterior cervical,retropharyngeal space, and upper mediastinum with gas and fluid accumulation (hospital day 12)

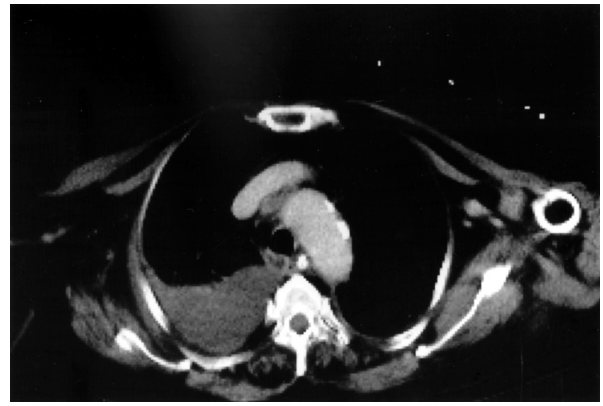

Fig. 3. 3rd Chest CT scan showed only minimal residual abscess in the left supraclavicular fossa and left paraspinal region (hospital day 29).

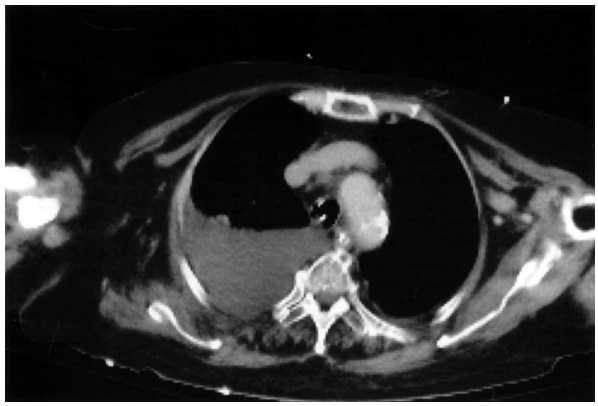

Fig. 4. 4th CT scan demonstrated that the deep neck infection and mediastinitis resolved without residual abscess (hospital day 50).

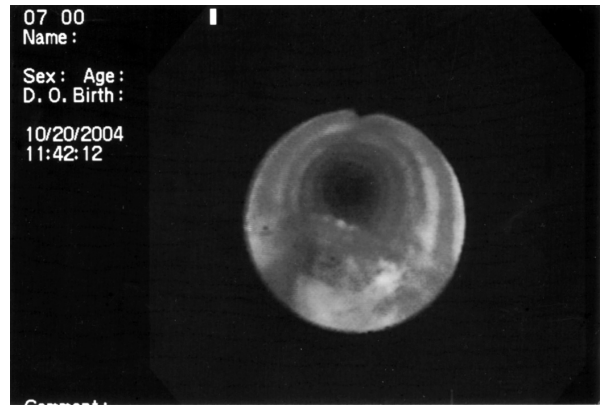

Fig. 6. Follow-up bronchoscopy demonstrated the tracheal fistula healed (hospital day 59).

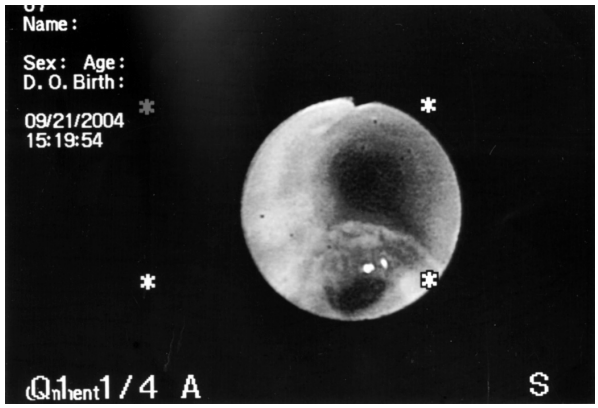

Fig. 5. Bronchoscopy showed a tracheal fistula in the membranous portion of the trachea, approximately 7 cm above the main carina (hospital day 30).

the high risk of surgery. The patient was continuously supported by pressure-limited ventilation with positive end-expiratory pressure. On hospital day 38, a third surgery with left neck debridement and irrigation was performed. On hospital day 44, follow-up bronchoscopy was performed. In order to check the tracheal fistula, we withdrew the endotracheal tube during the procedure. In the meanwhile, massive tracheal bleeding occurred with an unstable hemodynamic status and oxygenation. The bleeding stopped after re-intubation, cuff balloon inflation and transamine were administered. On hospital day 50, the fourth CT scan showed that there was no residual abscess (Figure 4). The amount of pus from the endotracheal tube also reduced gradually. On hospital day 59, bronchoscopy revealed closure of the tracheal fistula (Figure 6). Finally, the deep neck infection and necrotizing mediastinitis resolved after broad-spectrum antibiotic treatment with teicoplanin, imipenem and metronidazole for 6 weeks, as well as three times of surgical debridements of the deep neck infection, and transcervical drainage of the upper mediastinitis. The patient,she was then transferred to a long-term respiratory care center because of difficulty weaning. On hospital day 118, she received the elective tracheostomy. She was weaned off from ventilator support on hospital day 124. The patient was discharged on hospital day 177.

Discussion

Descending necrotizing mediastinitis (DNM) is a highly lethal disease originating from odontogenic, pharyngeal, or cervical infectious sources that descend along fascial planes into the mediastinum [1]. The Criteria for descending necrotizing mediastinitis are described by Estrera [4] include

the clinical manifestations of severe cervical infection, the radiologic features of mediastinitis, and the relationship between oropharyngeal infection and the mediastinal process. Estrera and associates reported a 40% mortality rate in the antibiotic era [4]. Necrotizing mediastinitis secondary to oropharyngeal infections is a recognized specific entity with a highly lethal evolution.

Local and general body defense mechanisms are usually sufficient to contain the proliferation of germs until repair of the mucous breach, except in certain cases, depending on the virulence of the germ and the degree of patient susceptibility. In a series reported by Makeieff *et al*. [6], two patients were diabetic, one was infected by the AIDS virus, and one presented with severe respiratory insufficiency. However, 13 others had no particular medical history. It is thus difficult to relate the disease to the poor general health status of the patient. Anti-inflammatory drugs may boost the diagnostic delay by decreasing the functional symptoms. The infection was clinically silent for a long period, and in almost all cases, the clinical signs were surprisingly weak considering the severity of the lesions discovered during surgery. In our case, diabetes mellitus and respiratory failure may have been the risk factors for the development of DNM, and long-term oral steroid use for asthma control may have delayed the diagnosis of DNM. Therefore, while an asthmatic and diabetic patient has persistent symptoms after the oropharyngeal infection being treated, DNM should be considered, and must be detected as soon as possible.

Marty-Ane *et al*. [7] reported that the aggressive surgical policy could maintain a low mortality rate (16.5%) in a series of 12 patients with this highly lethal disease. They used a stepwise approach, from transcervical mediastinal drainage to upper mediastinal drainage, according to the disease severity. Extensive mediastinitis cannot be adequately treated without mediastinal drainage. Ongoing mediastinal sepsis requires drainage through a major thoracic approach, without delay. Hasegawa *et al*. [8] proposed the simple classification of the degree of diffusion of DNM based on computed tomography. Lesion localized in the upper mediastinum above the tracheal bifurcation is defined as Type I, and may not always require aggressive mediastinal drainage. Type IIA DNM extends to the lower anterior mediastinum. The subxiphoidal mediastinal drainage or a thoracoscopic operation without sternotomy may provide adequate drainage in type IIA. Type IIB DNM extends to the anterior and lower-posterior mediastinum, and demands complete mediastinal drainage with debridement by thoracotomy [8].

The predominant aerobes cultured are α-hemolytic *Streptococcus, Staphylococcus aureus,* and *Klebsiella pneumoniae*. The predominant anaerobes cultured are *Prevotella* and *Porphyromonas* species, *Peptostreptococcus* species, and *Bacteroides fragilis* [9]. The anatomic characteristics of the neck and mediastinum, symbiosis between aerobic and anaerobic bacteria and alteration of the redox potential, and microenvironment-facilitating anaerobes growth can all contribute to the fulminant course of DNM. Broad-spectrum antibiotic coverage, such as cefoxitin, clindamycin, imipenem–cilastatin, a penicillin plus a β-lactamase inhibitor, and gentamicin are necessary.

Tracheal or bronchial fistula following DNM is a life-threatening complication. It is rare for a patient with a tracheal fistula caused by DNM to survive. In the report from Marty-Ane *et al*., one of 12 patients with DNM died on postoperative day 18 due to a tracheal fistula and respiratory failure [7]. Ruptures of the tracheobronchial tree

often present a dramatic, life-threatening situation, and would associate with tension pneumothorax and mediastinal emphysema, as well as prolapse of the esophageal wall into the tracheal lumen. In the later course of the injury, mediastinitis and sepsis can occur. The indications for surgical repair are based upon a synopsis of clinical, radiological, and endoscopical findings. Gabor *et al*. [10] suggested that tears involving the full thickness of the organ, lesions longer than 2 cm, and transmural ruptures involving the paracarinal region and/or prolapse of the oesophageal wall into the tracheal lumen are strong indicators of surgery. "Non-operative" treatment is reserved for patients in whom the laceration is either small (less than approximately 2 cm, predominantly in those localized in the upper two thirds of the trachea) and/or not involving the whole thickness of the tracheobronchial wall, as well as for patients in a poor general condition with a very high operative risk. "Non-operative" management includes intubation with the cuff distal to the tear and adequate antibiotic management [10]. In our case, bronchoscopy demonstrated the existence of a tracheal fistula, and much pus drainage from the endotracheal tube was noted. Therefore, we supposed that the tracheal fistula may have provid a drainage of mediastinitis related exudates and necrotic tissue. The continue suction from the endotracheal tube may have been helpful for the drainage. That may be one of the reasons why the patient can be survive from severe DNM. Of course, the spontaneous closure of the tracheal fistula is also the result of sufficient drainage of the DNM.

High ventilatory pressure should be avoided in patients with a tracheal fistula. Kato and associates [11] presented a 77 year-old male who had a 3 cm long tracheal fistula associated with DNM. The patient received pressure-limited ventilation with positive end expiratory pressure of 6 cm H_2O and end-inspiratory pressure of 23 cm H_2O. The fistula was recovered by spontaneous tracheoplasty with the esophageal anterior wall [11]. In our case, the respiration was supported by pressure-limited ventilation with positive end-expiratory pressure less than 8 cm H_2O, in order to prevent further injury to the tracheal fistula.

Kato and associates [11] also suggested that the cuff balloon of the endotracheal tube could be placed to cover the tracheal fistula and the cuff pressure maintain approximately 20 cm H_2O. The capillary perfusion pressure at the tracheal mucosa ranges from 25 to 30 mmHg. A cuff pressure higher than 32 mmHg may block capillary circulation within the mucosa [12]. Therefore, overinflation of the cuff stretches the membranous portion of the trachea and the trachea laceration develops [13], suggesting that the cuff pressure of the endotracheal tube should be continuously monitored in patients with a tracheal fistula.

Chest radiography usually demonstrates a widening of the superior mediastinum associated with ectopic gas bubbles and pleural effusion. An increase in cardiac size with decreasing vascular markings could be a sign of pericarditis with erosion of the major vessels. Contrast-enhanced neck and chest CT study is an extremely useful and reliable method for the early diagnosis of DNM and its complications. Mediastinal gas presence strongly correlates with mediastinal infection [14]. It is thought to be crucial to recognize the route of extension of the infection in order to select the optimal approach for efficient surgical drainage in each phase of this disease. CT scanning can provide accurate information for the optimal thoracic approach for efficient surgical drainage.

The re-intubation of this patient occurred on hospital day 44, due to massive tracheal bleeding

during withdrawal of the endotracheal tube. The massive bleeding from the tracheal fistula was life-threatening. The bleeding was stopped by placing and inflating the cuff of the endotracheal tube below the fistula. Therefore, it should be kept in mind that massive bleeding is a lethal complication of tracheal fistula caused by DNM.

In conclusion, tracheal fistula caused by DNM is a rare complication. Although surgical repair is regarded as the primary treatment of tracheal fistula, non-operative treatment may be successful in selected patients.

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下行性壞死縱膈腔炎引發氣管瘻管之自發性癒合

張敏麗　林鴻銓

氣管瘻管是下行性壞死縱膈腔炎的一個少見且嚴重的併發症，外科修補是氣管瘻管的主要處理方式。我們報告的病例是一個 68 歲女性因慢性氣喘及反覆呼吸衰竭而接受氣管內插管和呼吸器支持後出現深部頸部感染及下行性壞死縱膈腔炎，在抗生素及外科清瘡治療深部頸部感染及縱膈腔炎療程中，大量濃液出現在氣管插管，緊急軟式支氣管鏡檢查發現在氣管中段後方一個氣管瘻管，由於高度手術風險及家屬不同意手術， 因此嘗試保守治療，在 29 天後，氣管鏡追蹤發現氣管瘻管已自然癒合。病人因慢性氣喘、心臟衰竭及肌肉無力。因深部頸部感染併發縱膈腔炎而出現氣管瘻管自然癒合在文獻回顧上是罕見的。我們報告這個治療成功的案例，並且回顧的相關文獻。*(胸腔醫學 **2006; 21: 75-81**)*

關鍵詞：氣管瘻管，下行性壞死縱膈腔炎

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Dramatic Improvement of Severe Bronchorrhea after Gefitnib Treatment in a Patient with Possible Bronchioloalveolar Carcinoma

Shih-Chang Lin, Chao-Chi Ho*, Chong-Jen Yu, Pan-Chyr Yang

Bronchorrhea is not uncommon in patients with bronchioloalveolar carcinoma (BAC). Confirmation of the diagnosis of BAC often requires thoracotomy, because the diagnostic sensitivity of fiberoptic bronchoscopy and needle aspiration varies very widely (14% to 80%). Elevation of carcinoembryonic antigen (CEA) and cancer-associated antigen 19-9 (CA19-9) in the sputum is another way to suggest the possibility of BAC. Herein, we report an unusual case with profuse watery sputum and multilobar consolidation on the chest radiography. Severe hypoxic respiratory failure, which was refractory to conventional treatment for acute respiratory distress syndrome (ARDS), developed after admission. The sputum contained very high levels of CEA and CA19-9 (146.1 ng/ml and 77,873.0 U/ml, respectively), in spite of a nearly normal serum level. After treatment with gefitinib, the daily volume of sputum dramatically decreased, from 640 ml to 200 ml. The reduction in the sputum volume was associated with alleviation of the hypoxia and partial resolution of the consolidation. This case suggests the value of gefitinib in the treatment of severe bronchorrhea caused by malignancy. ***(Thorac Med 2006; 21: 82-88)***

Key words: bronchioloalveolar carcinoma; bronchorrhea; gefitinib; carcinoembryonic antigen (CEA), cancer-associated antigen 19-9 (CA19-9)

Introduction

The voluminous production of clear frothy sputum is 1 of the characteristic clinical features of bronchioloalveolar carcinoma (BAC) [1-3]. Bronchorrhea, defined as a profuse production of sputum of more than 100 mL per day [4], has been observed in patients with acute or chronic bronchitis, diffuse panbronchiolitis, bronchiectasis [5], and bronchioloalveolar carcinoma, but a large volume of watery sputum is presented only in patients with BAC. The pathophysiologic mechanisms underlying an excessive production of sputum, in which a variety of inflammatory mediators may be involved, are only partially understood. Several therapeutic interventions have been reported for bronchorrhea in patients with BAC, including parasympathetic blocking drugs, antihistamines, ACTH, corticoids, infiltration of the stellate ganglion, chemotherapy,

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and radiation therapy, but all failed to provide lasting and promising results [6]. The more recent therapeutic trials with erythromycin [7], clarithromycin and inhaled beclomethasone [8], inhaled indomethacin [9], and gefitinib [10-11] have reported success in controlling refractory bronchorrhea.

Herein, we report the case of a patient with massive watery sputum (up to 640 ml per day), and tumor markers in the sputum that were extremely high, compared with the serum level. Several therapeutic interventions had been used to control the bronchorrhea in this patient, including steroid, azithromycin, inhaled indomethacin, and gefitinib. We believe that the gefitinib may have played the most important role in the response. Invasive diagnositic procedures, including bronchoscopy and needle aspiration, were not performed because of his critical condition. Although this patient had some response to treatment, his family decided to take him home 2 weeks after admission.

Case Report

This 97-year-old man with hypertension and hypothyroidism under medical control had had dyspnea and productive cough with whitish, foamy sputum since August, 2004. The chest radiograph in Canada several months before the onset of symptoms revealed consolidation in the left lower lobe. Observation was suggested by the doctor because of his advanced age. He presented himself to our emergency department on January 26, 2005, due to severe dyspnea. There were no other symptoms of infection. On physical examination, the body temperature was 36.1°C, the pulse rate 88 beats per minute, and the respiratory rate 26 breaths per minute. The pulse oximetry was 63% in room air. The breathing sound revealed diffuse crackles. The white cell count was 8,750/μL without a left shift. The chest radiograph showed multilobar consolidation at the right upper and left lower lung (Figure 1). Initially, atypical pneumonia with ARDS was suspected, and he was treated with moxifloxacin empirically. He had no fever or hypothermia during hospitalization. Hypoxic respiratory failure developed in spite of oxygen therapy with a non-rebreathing mask. He was intubated and transferred to the intensive care unit for further therapy. Hypoxemia persisted even under 100% FiO_2, high positive end expiratory pressure (PEEP, 14-16), lying a prone position, and nitric oxide inhalation. Anti-pseudomonas penicillin was added for any possible nosocomial infection. Steroid was also tried empirically, but failed to improve oxygenation. Profuse watery sputum persistently flowed out through the endotrachial tube, with amounts up to 640 ml per day. Although BAC was highly suspected, the repeated

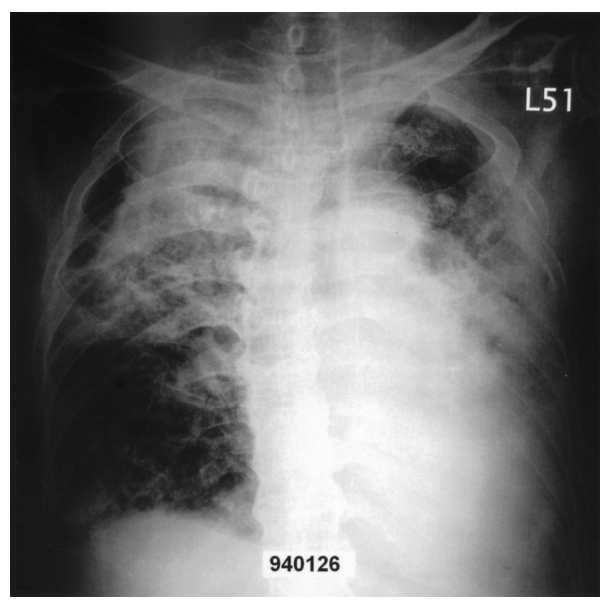

Fig. 1. Chest radiography revealing multilobar consolidation when the patient presented at our emergency department on January 26, 2005.

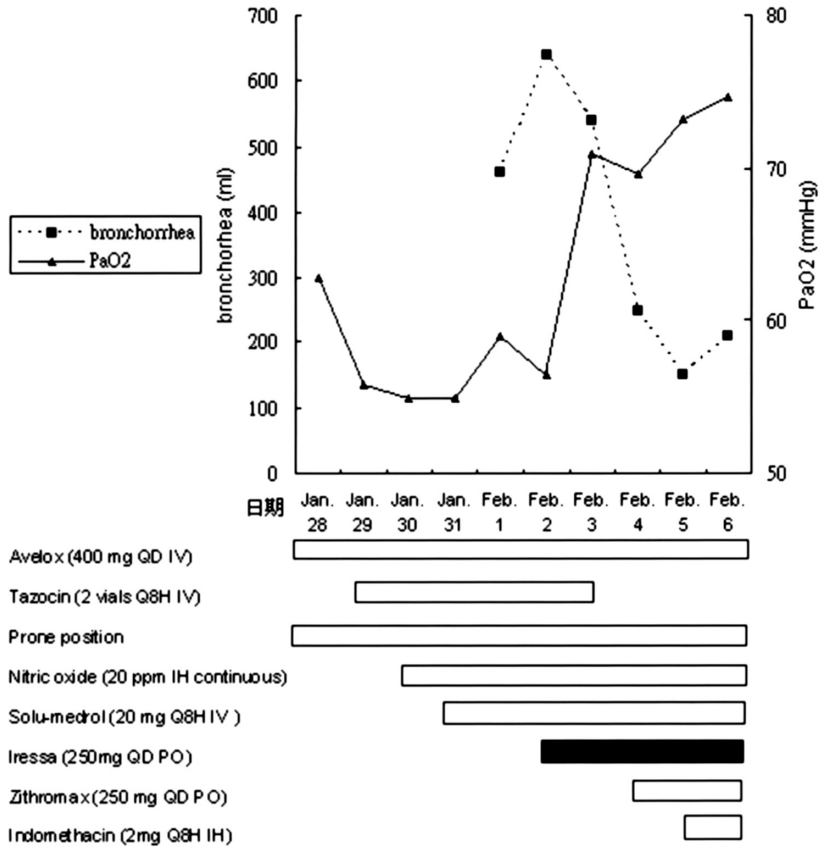

Fig. 2. The summary of the clinical course, showing the dramatic response (bronchorrhea and hypoxemia) to gefitinib.

sputum cytology examinations were all negative. However, invasive procedures were not possible due to his critical condition. Treatment for BAC-related bronchorrhea was initiated after high levels of CEA and CA19-9 in the sputum had been found (146.1 ng/ml and 77,873.0 U/ml respectively), in spite of the relatively normal serum level (CEA 3.85 ng/ml and CA19-9 100 U/ml). Gefitinib was started on February 2, followed by azithromycin (February 4) and inhalation of indomethacin (February 5). In addition, the intensive work-ups of infection foci, including blood cultures, sputum cultures, urinary legionella antigen, and serological tests of atypical pathogens and viruses were all negative. The amount of bronchorrhea declined dramatically after gefitinib, and the oxygenation also improved (summarized as Figure 2). Serial chest films also revealed partial resolution of the consolidation (Figure 3). However, his family requested a Do-Not-Resuscitate order, and finally took him home against medical advice on February 7, 2005.

Discussion

Tissue proof is usually mandatory to confirm the diagnosis in malignancy. Common methods such as transbronchial biopsy, needle aspiration biopsy, or bronchoalveolar lavage (BAL) are relatively insensitive in cases of BAC, because

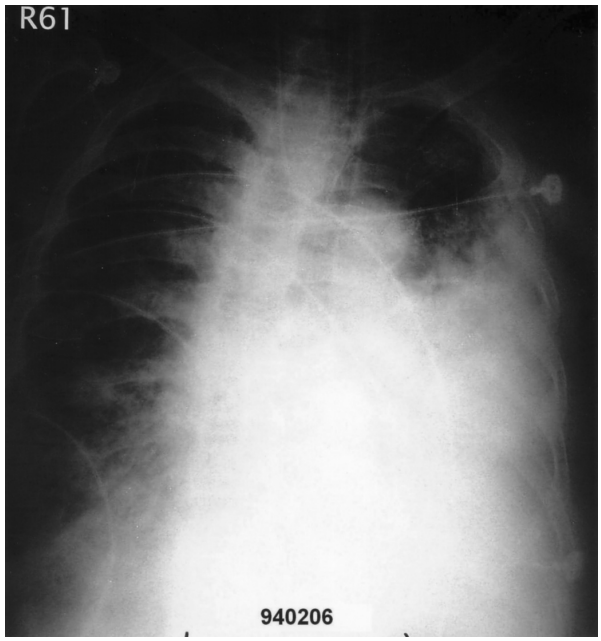

Fig. 3. Chest radiography revealing improved consolidation after gefitinib.

the tumor cells are often well differentiated. The diagnostic sensitivity of fiberoptic bronchoscopy has been reported to vary from 14% to 80% [12-13], and sensitivity by needle aspiration has been reported to be as low as 60%. About 60% to 77% of lesions have required thoracotomy to establish a definite diagnosis [12]. Another study, which focused on the accuracy of different diagnostic tools in pneumonic-type lung adenocarcinoma, reported the sensitivity of bronchial biopsy, transbronchial biopsy, bronchial aspiration, and BAL to be 21%, 80%, 44%, and 66%, respectively [13]. It is interesting that BAC in certain cases has a tendency to produce CEA and CA19-9, which secretes into the sputum. Therefore, examining the level of CEA and CA19-9 in the sputum may suggest the possibility of BAC [14].

In this case, not all invasive diagnostic procedures could be performed because of the patient's critical condition. The suspicion of BAC was based on extremely high levels of CEA and CA19-9 in the sputum, the clinical picture, and the dramatic response to gefitinib. In fact, this case had the highest CA 19-9 level in the sputum (77,873.0 U/ml) reported in the literature. The discrepancy in the tumor markers of the serum and sputum is not well understood, and may be due to the fact that BAC is relatively noninvasive, and usually grows and spreads along the bronchioalveolar space. Furthermore, we found a case report that showed the same discrepancy in a patient with a definite diagnosis of lung cancer [14]. In that case, the diagnosis of BAC was made by transbronchial lung biopsy. The serum levels of CEA and CA 19-9 were 0.5 ng/ml and 91.5 U/ml, and the sputum levels of CEA and CA 19-9 were 612.7 ng/ml and 33,057 U/ml, respectively. The researchers also checked the levels of electrolytes in the sputum, which were closer to those in the serum, except for the higher potassium level [14]. Another case report in 1975 described a case with severe BAC-related bronchorrhea (up to 9L/day) that caused fluid and electrolyte depletion [15]. We also found several earlier studies that evaluated the CEA and CA 19-9 in BAL fluid [16-18]. According to these studies, the level of CEA in BAL fluid is much higher in patients with lung cancer than nonmalignant lung diseases, and the level of CEA correlated well with the results of cytology [16]. One study even suggested the simultaneous determination of 2 markers in the serum, and that BAL fluid appears to be a useful adjunctive test in the diagnosis of lung cancer [18]. Although the value of tissue proof can never be overemphasized, it is not uncommon that invasive procedures, including bronchoscopy, are not allowed in certain situations, such as that of our patient. If the serum tumor markers and sputum cytology cannot help to make the diagnosis, tumor markers in the sputum or BAL fluid may be considered for the diagnosis or evidence of lung

cancer [16-18].

The management of BAC-related severe bronchorrhea seems not to be so disappointing now, with the development of gefitinib [10-11]. Traditional pharmacological approaches to airway clearance may be classified into several types, according to their different mechanisms: expectorants (hypertonic saline), 3 types of mucolytics (classical, peptide, and non-destructive), mucoregulatory agents (anti-cholinergic, glucocorticoids, indomethacin, macrolide), and cough clearance promoters (bronchodilators, surfactants) [19]. In cases with BAC-related bronchorrhea, the mucoregulatory agents and gefitinib may play a central role. In this case, the response (amount of bronchorrhea and oxygenation) to gefitinib was dramatic, so we believe that early therapeutic interventions for BAC-related bronchorrhea may provide many more benefits in oxygenation than conventional treatment for ARDS. The course might have been completely different if the gefitinib had been administered as soon as severe hypoxemia that was refractory to conventional treatment developed.

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Gefitinib 顯著改善大量支氣管漏於疑似肺泡細胞癌病人

林世章　何肇基*　余忠仁　楊泮池

支氣管漏 (bronchorrhea) 的表現在肺泡細胞癌 (bronchioalveolar carcinoma) 病患身上並不算少見，然而肺泡細胞癌的確定診斷常常需要開胸手術。因為不論是經支氣管鏡或經皮超音波指引切片其敏感度依不同研究差異甚大 (14% 到 80%)。事實上，藉由痰液中上升之腫瘤指標，如胚胎癌抗原 (carcinoembryonic antigen, CEA) 及癌抗原 19-9 (cancer-associated antigen 19-9, CA19-9) 也可以提供診斷之參考。我們在這個報告中提出一個罕見的病例是以大量水狀的支氣管漏及胸部 X 光多肺葉實質病變來表現並快速進展成嚴重的缺氧性呼吸衰竭。對病人投以急性呼吸窘迫症 (acute respiratory distress syndrome, ARDS) 的標準治療對於改善低血氧並無明顯幫助。我們稍後在痰液中偵測到非常高濃度的胚胎癌抗原及癌抗原。而在給予口服抗癌藥物 gefitinib 之後，每日的痰量迅速降低 (由六百四十降至兩百毫升)。除此之外，病人的血氧濃度和 X 光的實質病變也都得到明顯的改善。因此我們認為在治療肺泡細胞癌造成的嚴重支氣管漏時，可以考慮使用 gefitinib 。*(胸腔醫學* ***2006; 21: 82-88****)*

關鍵詞：支氣管漏，肺泡細胞癌， gefitinib ，胚胎癌抗原，癌抗原 19-9

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Pulmonary Sequestration with Rib Notching — A Case Report

Chen-Yu Wang, Gwan-Han Shen, Guan Chou*

Bronchopulmonary sequestration is a rare congenital pulmonary malformation. It is usually manifested as hemoptysis or recurrent pneumonia. On chest radiography, sequestration typically appears as a solid mass, a cystic lesion, or an air-fluid level, depending on the communication to the airway or the infection condition. However, pulmonary sequestration with rib notching on the chest radiograph has never been reported in the literature. Herein, we report a case of pulmonary sequestration with unilateral rib notching. ***(Thorac Med 2006; 21: 89-93)***

Key words: pulmonary sequestration, rib notching

Introduction

A bronchopulmonary sequestration is a region in the lung parenchyma that has an incomplete or no connection with the airway, and is supplied by an aberrant artery arising from the aorta or 1 of its branches, including the subclavian artery, splenic artery, gastric artery, intercostal artery, and coronary artery [1-2]. In 1964, Pryce first introduced the term, which is derived from the Latin verb sequestare, meaning "to separate" [3]. Sequestrations are anatomically classified as intralobar and extralobar. Both types consist of normal lung tissue. On chest radiography, intralobar sequestration can manifest as a mass, or a cystic lesion with or without an air fluid level. The left lower lobe is the most commonly involved site. Extralobar sequestration sometimes occurs in a subdiaphragmatic location and almost always involves the left hemithorax. A case report of pulmonary sequestration with unilateral rib notching on chest radiography and a literature review are presented herein.

Case Report

A 42-year-old man was admitted to this hospital because of hemoptysis and productive cough for 1 year. The patient had a history of pulmonary tuberculosis, and had been treated with complete anti-TB medication 22 years ago. However, he has suffered from hemoptysis 1-2 times per year and productive cough since the last pulmonary TB episode 22 years ago. He did not pay much attention to these attacks and visited local clinics each time. Unfortunately, the frequency and amount of hemoptysis had increased during the year before this admission. He first

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visited a local hospital for help, and was diagnosed with pneumonia. Even though antibiotics were prescribed, the symptoms were not alleviated. Finally, he was referred to our chest medicine outpatient clinic.

On examination, fine crackles and rhonchi were heard in the right lower lung field. The body temperature was 36.7ºC. Chest radiography showed patchy opacification with an air-bronchogram in the right middle lung field, and rib notching in the inferior aspect of the right 6th to 8th ribs (Figure 1). The white cell count was 8170 per cubic millimeter, with 69.9 percent neutrophils. Hemoglobulin was 15.2 mg/dl. The serum creatinine level was 1.1 mg per deciliter. Amoxicillin-clavulanate was prescribed in the beginning, under the impression of pneumonia. However, the right lung patch persisted. A computed tomographic aortography was performed, and revealed a sequestration of the superior segment of the right lower lobe (RB6). One small feeding artery arising from the medial posterior side of the thoracic aorta and focal dilated intercostal artery was found. The drainage vein returned to the right pulmonary vein (Figure 2).

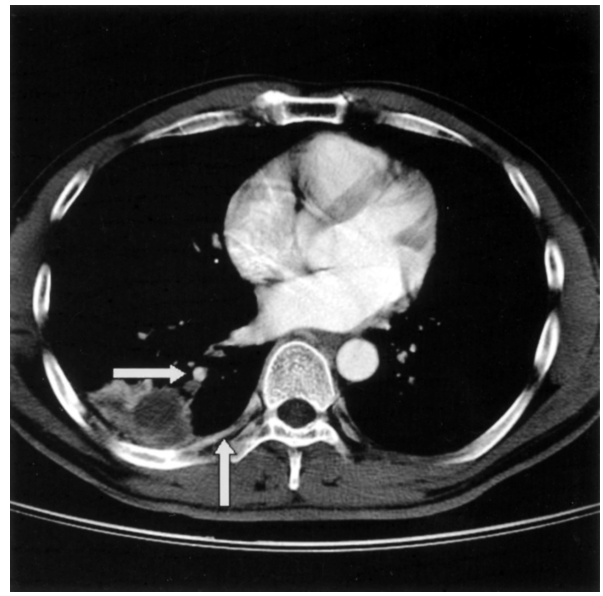

Fig. 2. Computed tomographic aortography showing superior segment of the right lower lobe (RB6) sequestration, and a small artery (upper white arrow) arising from the medial posterior side of the thoracic aorta. The dilated intercostal artery is marked by the lower white arrow.

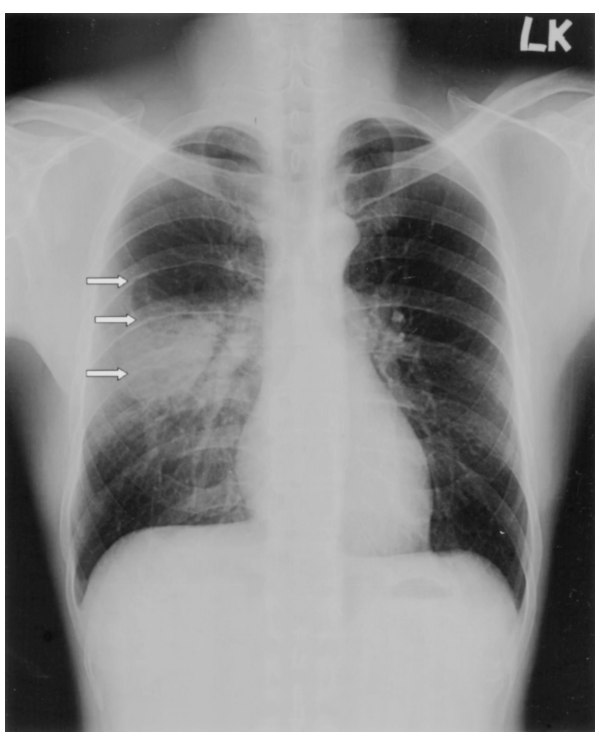

Fig. 1. Chest radiography showing increased patchy infiltration in the right middle lung field, with 6th to 8th rib notching (white arrow).

Under the impression of pulmonary sequestration, the chest surgeon was consulted. The patient underwent a right lower lobe lobectomy. Surgical pathology reported some purulent sticky material in the dilated cystic space. The finding was consistent with sequestration with secondary inflammation and bronchiectasis (Figure 3). The patient recovered well and was discharged on the 6th day after operation.

Discussion

Pulmonary sequestration is a rare congenital pulmonary malformation that comprises about

Fig. 3. Pathological examination showing a respiratory bronchiole with a feeding artery. (H&E stain; x40).

0.15-6.4% of all congenital pulmonary malformations [4]. Intralobar sequestration is more common than extralobar sequestration. Intralobar sequestration usually manifests as recurrent or chronic pneumonia. In contrast to extralobar sequestration, no sexual predominance has been recorded. Intralobar sequestration always affects the medial and posterior basal segments of the lower lobes. The left lower lobe was the most commonly (60%) involved site [5], but our case revealed a right lower lung lesion.

On chest radiography, sequestration typically appears as a solid mass, a cystic lesion, or air-fluid level, depending on the communication to the airway or the infection condition. Hang JD *et al.* reported 24 patients, 14 of whom presented with a solid mass, while the other 10 had a cystic mass [6]. Air-fluid levels due to bronchial communication were seen in 26% of intralobar sequestrations in another report [7]. In intralobar sequestration, blood usually is supplied from the lower thoracic artery or upper abdominal artery. Venous blood flow is mostly returned to the pulmonary venous system.

The computed tomographic appearance of sequestration is varies [7]. Characteristic features are a mass containing a solid or fluid components with an emphysematous lung or a lesion supplied by a systemic artery [8]. Our case demonstrated fluid containing a mass with a small feeding artery arising from the thoracic aorta. Seventy-three percent of the blood supply in intralobar sequestration comes from the thoracic artery [2].

Rib notching as a manifestation of intralobar sequestration has never been reported in the literature. It most frequently occurs on the inferior aspect and the etiology is variable (Table 1) [9]. The notches result from erosion of the dilated

Table 1. Differential diagnosis of inferior rib notching

ARTERIAL
Aortic obstruction
Coarctation of the aortic arch
Thrombosis of the abdominal aorta
Subclavian artery obstruction
Blalock-Taussig operation
Widened arterial pulse pressure
Decreased pulmonary blood flow
Tetralogy of Fallot
Pulmonary atresia (pseudotruncus)
Ebstein's malformation
Pulmonary valve stenosis
Unilateral absence of the pulmonary artery
Pulmonary emphysema
VENOUS
Superior vena cava obstruction
ARTERIOVENOUS
Pulmonary arteriovenous fistula
Intercostal arteriovenous fistula
NEUROGENIC
Intercostal neurogenic tumor
OSSEOUS
Hyperparathyroidism
IDIOPATHIC
*Sequestration

*Sequestration should be considered in the differential diagnosis of inferior rib notching

intercostal arteries. Notching or erosion of the inferior aspect was more common than involvement of the superior aspect [10]. The blood supply in our case came from a small branch originating from the thoracic aorta and drainage into the right pulmonary vein. No vessel obstruction, abnormal fistula, visible mass or congenital heart disease was found on the chest tomographic angiography. Researchers have supposed that recurrent infections increase focal blood flow and collateral circulation. Dilated intercostal arteries mean increased collateral circulation and an eroded inferior aspect of the rib. The notches are unilaterally distributed. Coarctation of the aorta with the coarctation site is distal to the left subclavian artery manifesting bilateral rib notching. If the coarctation is proximal to the left subclavian, only the right ribs are notched. Other etiologies of unilateral rib notching are Takayasu's arteritis, the Blalock-Taussig procedure, and unilateral absence of the pulmonary artery [11].

In conclusion, pulmonary sequestration should be suspected in cases of recurrent pulmonary infection and left lower lung distribution. A pneumonic patch with unilateral notching ribs implies the possibility of long-term infectious processes and recurrent episodes. Pulmonary sequestration should be added to the differential diagnosis of unilateral rib notching.

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游離肺合併肋骨下緣缺口—一病例報告

王振宇　沈光漢　周　冠*

游離肺是一個罕見的先天性肺部畸型，臨床上常以咳血及反覆性肺炎來表現。在胸部 X 光片上，常表現出實體病灶或囊狀病變。視與呼吸道交通的情況和感染程度，有時還會表現出空氣液體邊界。然而游離肺合併肋骨下緣缺口的影像學特徵尚未在文獻上被報告過。在此，我們報告一個游離肺合併肋骨下緣缺口的病例。*(胸腔醫學 **2006; 21: 89-93**)*

關鍵詞：游離肺，肋骨缺口

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Diffuse Panbronchiolitis Associated with Adult T-cell Leukemia — A Case Report

Wen-Chia Chuang, Chen-Chun Lin, Jia-Mo Lin, Diana Yu-Wung Yeh, Jiunn-Song Jiang, Shang Jyh Kao

Diffuse panbronchiolitis (DPB) is a disease characterized by chronic inflammation exclusively located in the respiratory bronchioles. It has been previously reported to occur exclusively in East Asians, primarily in Japanese, Korean, and Chinese populations. The definite causative agent remains unclear; neither environmental factors nor infectious agents have been demonstrated. A significantly high frequency of anti-HTLV-I antibody in patients with DPB, higher than in those with other diseases and healthy controls, has been reported. Adult T-cell leukemia/lymphoma (ATL) is a category of lymphoid malignancy characterized histologically by malignant lymphocytes with flower-shaped nuclei, and HTLV-1 has been recognized as a causative agent of ATL. We present a case of DPB complicated by ATL and review the relationship between them. ***(Thorac Med 2006; 21: 94-100)***

Key words: diffuse panbronchiolitis (DPB), adult T-cell leukemia (ATL), human T-cell lymphotropic virus type I (HTLV-I)

Introduction

Diffuse panbronchiolitis (DPB), first described by Yamanaka *et al*. in 1969, is a disease characterized by chronic inflammation exclusively located in the respiratory bronchioles [1]. Histologically, chronic inflammation mainly affects the respiratory bronchioles, with distinctive interstitial accumulations of foamy cells in the wall of the bronchioles, adjacent alveolar ducts, and alveoli [2]. Diffusely disseminated bronchiolitis and peribronchiolitis cause obstructive respiratory disorders and early hypoxemia. The prognosis of patients with this disease has been poor, with a 10-year survival rate of 33.2% in 1983, but long-term treatment with erythromycin has increased the 10-year survival rate to > 90% [3]. DPB was previously reported exclusively in East Asians, primarily in Japanese, Korean, and Chinese populations. A few cases have been reported in Europe and North America [4]. The definitive causative agent remains unclear; neither environmental factors nor infectious agents have been demonstrated to be the cause. Genetic influence may play an important role in the development of DPB. A strong association

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with B54 human leukocyte antigen has been shown [5]. In addition, a significantly high frequency of anti-HTLV-I antibody in patients with DPB, higher than in those with other diseases and healthy controls, was reported by Kimura in 1992 [6].

Adult T-cell leukemia/lymphoma (ATL), identified by Takatuki in 1977, is a category of lymphoid malignancy characterized histologically by malignant lymphocytes with flower-shaped nuclei [7]. In 1980, HTLV-1 viral particles were found in the cells of a patient who had ATL, and these viral particles have been recognized as a causative agent of ATL ever since [8]. There are 4 subtypes of ATL: acute, chronic, smoldering, and lymphoma. Regardless of the subtype, ATL is refractory to therapy. The major cause of death in any subtype is respiratory complications [9]. DPB is 1 of the possible pulmonary complications [10]. We herein present a case of DPB complicated by ATL and review the relationship between them.

Case Presentation

A 53-year-old female complained of dyspnea on exertion and productive cough for several years. She was a non-smoker and denied having any allergy history. She had been diagnosed with chronic sinusitis and bronchiectasis 2 years prior to visiting our chest clinic. The first chest X-ray we obtained revealed diffuse micronodular infiltrative shadows and tram lines in both lung fields (Figure 1). Physical examinations revealed bilateral fine crackles on auscultation of the chest. Spirometry revealed an obstructive disturbance (FVC, 45%; FEV1, 30%; FEV1/FVC, 56%). Blood gas analysis showed mild hypoxemia. (pH 7.447, PO_2 89, PCO_2 33 mmHg under a nasal prong for 2 l/min). High-resolution computed tomography of the lung showed centrilobular nodules with distal branching bronchovascular structures, and dilated airways with thickened walls (Figure2). *Pseudomonas aeruginosa* and *Haemophilus influenzae* were cultured from the

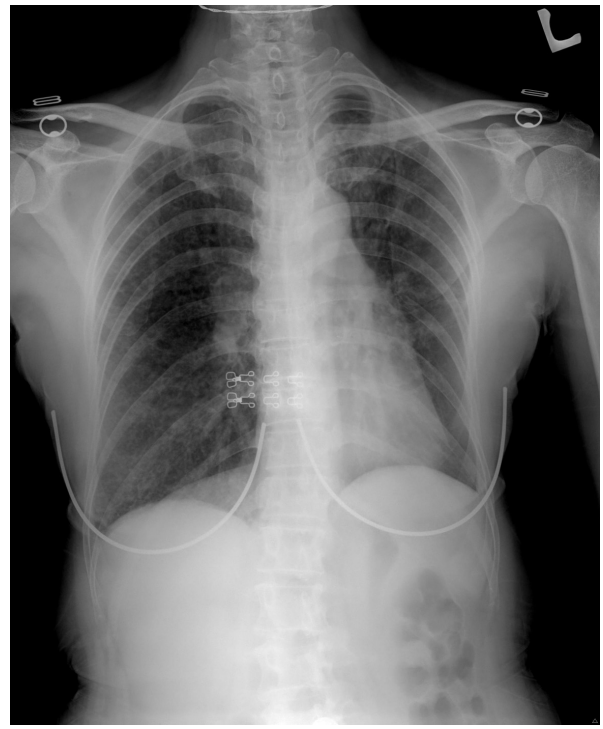

Fig. 1. Chest X-ray revealing diffuse micronodular infiltrative shadows and tram lines in both lung fields.

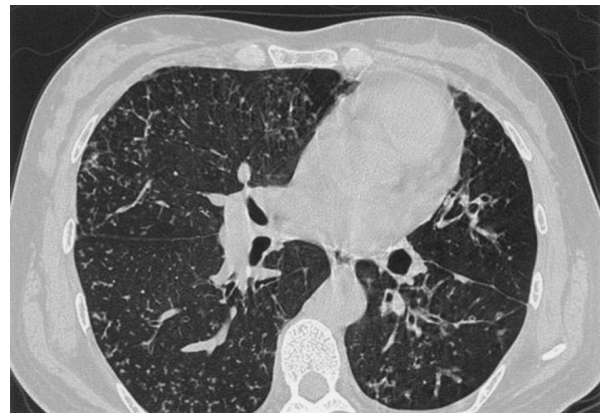

Fig. 2. High-resolution computed tomography of the lung showing centrilobular nodules with distal branching bronchovascular structures.

sputum. The leukocyte count was 8400/ul. Serum IgA was 108 mg/dl (normal range: 85-453 mg/dl). Cold hemagglutinin (CHA), rheumatoid factor and antinuclear antibody were both negative. On the basis of these data, a diagnosis of diffuse panbronchiolitis (DPB) was made, according to the clinical criteria established by Homma [1] in 1983.

The patient was then treated with low-dose erythromycin (500 mg/day) and followed up regularly at our clinic. Six months later, she was admitted to our hospital because of increasing dyspnea and fever for 8 days. The leukocyte count was 37,500/ul with 70.5% lymphocytes. A high C-reactive protein level (2.29 mg/dl, normal range, < 0.5 mg/dl) was noted. Chest X-ray showed diffuse micronodular shadows, patchy opacities and a wide mediastinum (Figure 3). Auscultation of the lungs revealed coarse crackles in the right lower lung and diffuse wheezing. An initial diagnosis of DPB and right lower lung pneumonia was made. At the beginning, empiric antibiotics with amoxicillin/clavulanic acid and gentamicin were administered. Mycoplasma Ab and urine legionella Ag were negative. *Pseudomonas aeruginosa* was cultured from the sputum 3 days later. Accordingly, the antibiotics were changed to piperacillin and gentamicin. The patient gradually became afebrile, however, persistent leukocytosis and a progressive change in the appearance of the lung infiltrates on the chest X-ray were noted. Antibiotics were then changed to piperacillin/tazobactam and erythromycin.

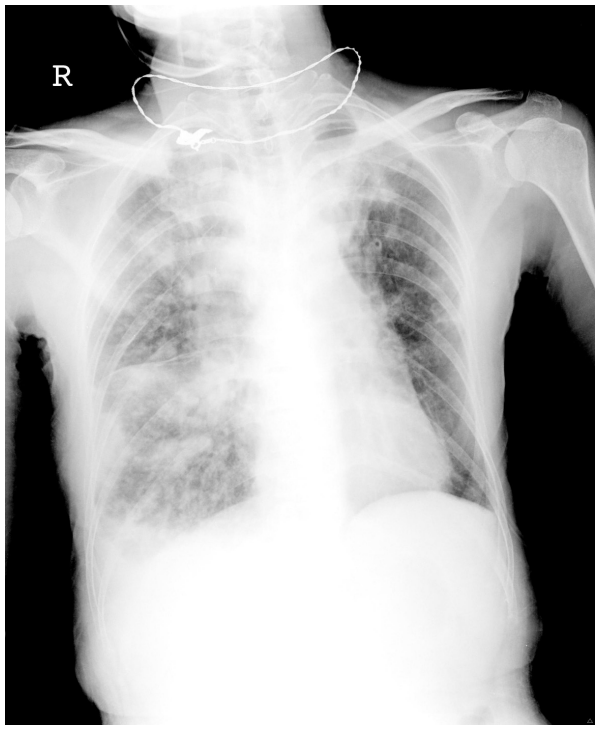

Fig. 3. Chest X ray showing diffuse micronodular shadows, patchy opacities, and a wide mediastinum.

Computed tomography of the chest was arranged, which revealed marked lymphoadenopathy in the bilateral axilla, hila, and the mediastinum; right-side pleural effusion was also noted. Several enlarged lymph nodes were palpable in the bilateral inguinal areas. Serum LDH was 425 mg/dl (normal range: 135-225 mg/dl). A chest echo was done, and a moderate amount of pleural effusion was found on the right side. The pleural effusion study revealed lymphocyte-predominant exudates with a WBC count of 12960/ul and LDH of 277 mg/dl. Pleural effusion cytology revealed abundant mature lymphoid cells. Lymphoma was highly suspected. A left inguinal lymph node excisional biopsy was done, and the result of the pathology report showed malignant T-cell lymphoma. The peripheral blood smear and bone marrow study showed lymphocytes with cloverleaf-shaped nuclear lobation. (Figure 4). Serologic examination also revealed that anti-HTLV-I antibody was positive by 128-fold. She was a carrier of human T-cell lymphotropic virus type I (HTLV-I). The diagnosis of adult T-cell leukemia (acute type) was finally made.

The patient began receiving chemotherapy with cyclophosamide, doxorubicin, vincristine,

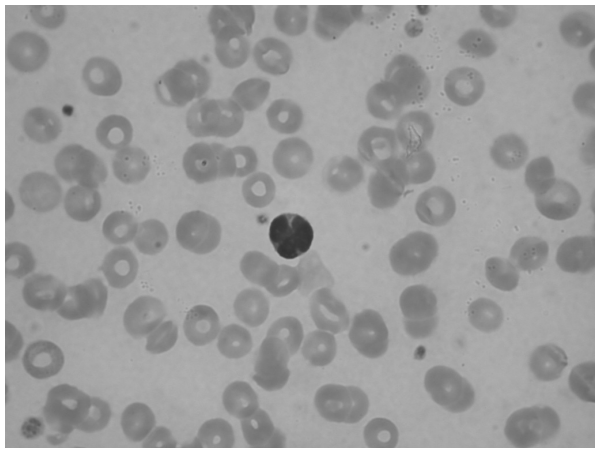

Fig. 4. Peripheral blood smear showing lymphocytes with clover-leaf-shaped nuclear lobation.

and prednisolone (the "CHOP" regimen). The patient's clinical symptoms, as well as the findings on chest-X rays, improved gradually. The patient was discharged 9 days later.

Discussion

The patient presented herein was a carrier of human T-cell lymphotropic virus type I (HTLV-I). She was diagnosed as having diffuse panbronchiolitis (DPB), based on the clinical criteria established by Homma [1] in 1983. These criteria included: (1) symptoms of chronic cough, sputum, and dyspnea on exertion; (2) physical signs consisting of coarse crackles, rhonchi, or wheezes on auscultation of the chest; (3) radiographic findings showing bilateral diffuse fine nodular shadows or chest CT scans revealing centrilobular micronodules; (4) pulmonary function studies showing at least 3 of the following 4 abnormalities: FEV1/FVC < 70%, VC < 80% of the predicted value, RV > 150% of the predicted value, PaO_2 < 80 mmHg; (5) additional clinical findings of chronic parasinusitis, increased cold hamagglutinin titers (x64 or higher), or increased immunoglobulin A. The clinical findings of our patient fulfilled most of the criteria, thus bronchoscopic biopsy or open lung biopsy was not arranged. However, the patient was also diagnosed as having the acute type of adult T-cell leukemia (ATL) 6 months later. Is there any relationship between DPB and ATL? HTLV-I retrovirus may be the key to the connection.

HTLV-I is the first human oncogenic retrovirus to be discovered, and is described as the causative agent of ATL [7]. Both HTLV-I and ATL have been shown to be endemic in some regions of the world, especially in southwest Japan [11], the Caribbean islands, and parts of Central Africa [12, 21]. Antibodies against HTLV-I have been found in over 1 million individuals [22], and more than 700 cases of ATL are diagnosed each year in Japan alone. The cumulative (life span of 70 years) incidence of ATL among HTLV-I carriers in Japan is estimated at 2.5% (3-5% in males and 1-2% in females), if competing risks for other diseases are disregarded [23].

The assertion that the clinical entity, TSP/HAM (tropical spastic paraparesis/HTLV-I associated myelopathy), is a non-neoplastic inflammatory process related to the HTLV-I infection, leads to the notion that HTLV-I may likely be the causative agent of some inflammatory disorders, such as arthritis, uveitis, and inflammatory pulmonary diseases [13-15]. DPB is 1 of the possibly-related inflammatory pulmonary diseases reported by Kikuchi *et al*. in 1996 [15]. Pulmonary complications in HTLV-I carriers have been reported to range from subclinical lymphocytic alveolitis and DPB, to lymphocytic interstitial pneumonia. [15, 19].

A nationwide histopathologic study in Japan to characterize pulmonary involvement in 32 HTLV-1 carriers with symptomatic chronic

pulmonary diseases demonstrated that 72% of the patients had bronchiolar involvement, rather than interstitial involvement, including DPB in 9 patients and chronic bronchiolitis in 14 patients [16]. Chronic bronchiolitis is pathologically characterized by the lymphocytic inflammation of small bronchi and membranous bronchioles without foamy cells, which are frequently characteristic of patients with DPB. Even so, could we say that HTLV-I-associated bronchiolitis (with a histological study revealing no foamy cells) is different from DPB? It is well-known that the diagnosis of DPB is based on clinical, functional, radiological, and histological findings. None of these is sufficient evidence by itself, since an isolated finding is nonspecific and could lead to a misdiagnosis. The current and popularly used diagnostic criteria are the clinical criteria described by Homma [1] in 1983.

The Ministry of Health and Welfare of Japan modified these criteria in 1995, yet histological proof is still deemed not necessary. In fact, Mukae *et al*. reported cases of HTLV-I carriers diagnosed with DPB using clinical criteria, yet whose histological findings showed no typical foamy cells [17]. This indicated that HTLV-I-associated bronchiolitis and DPB might overlap, under current diagnostic criteria. To assess whether these 2 conditions can be differentiated, Kadota *et al*., in 2004, reported on a study of 58 Japanese patients they had examined: 15 had HTLV-1-associated bronchiolitis and 43 had DPB (HTLV-1 was negative) [18]. Both conditions were compared using clinical symptoms, laboratory findings, radiological findings, histological findings, BAL fluid testing, and the treatment effect of macrolides. The study demonstrated that the clinical, laboratory, radiological, and bacterial features were strikingly similar in both patients with HTLV-1-associated bronchiolitis and those with DPB. Histological examinations also indicated an overlap between these 2 groups. However, long-term treatment with macrolides significantly improved mean PaO_2 in the DPB patients, more than in the HTLV-1-associated bronchiolitis patients. Therefore, HTLV-1-associated bronchiolitis might still be linked with conditions that are distinct from those of DPB, based on the different response to macrolides.

DPB complicated by ATL has been rarely reported. Ono *et al*. first reported a higher prevalence of DPB among patients with ATL, if compared with the general population [10]. He reported that 3 of their 43 patients with ATL were complicated by DPB in a follow-up study. In contrast, they encountered no DPB complication during the same period among the 129 cases of leukemia and non-HTLV-I-associated lymphoma. They posited 3 possible explanations for this relationship. First, slow viral infection via HTLV-I may induce the host's immune defense mechanism, resulting in chronic inflammation of the bronchioles. Second, HTLV-I may have an effect not only on lymphocytes but on bronchioles, as well as on the nervous system. Third, lymphocytes that are infected with HTLV-I may infiltrate the bronchioles. DPB may therefore increase the frequency of pulmonary infections, and subsequently interfere with the treatment of adult T-cell leukemia (ATL) and worsen the prognosis. As the prevalence of HTLV-I carriers in Taiwan is approximately 0.5% [20], the possibility of DPB co-existing with ATL should always be kept in mind.

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瀰漫性泛細支氣管炎併發成人 T 細胞白血病—病例報告

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瀰漫性泛細支氣管炎(Diffuse panbronchiolitis)是一呼吸性小支氣管慢性發炎之疾病。之前的報告病例多集中在東亞地區，主要在日本、韓國、中國。此病的致病因仍然不清楚，並未有確定的環境或感染因素被證實。曾有報告提出瀰漫性泛細支氣管炎的病人比一般健康人或有其他疾病的人有較高的機會發現人類嗜 T 淋巴球第一型病毒之抗體。成人 T 細胞白血病 / 淋巴瘤(Adult T-cell leukemia/lymphoma)是一個淋巴性惡性腫瘤，其組織特徵為具有花瓣狀細胞核的惡性淋巴球。而人類嗜 T 淋巴球第一型病毒被認為是成人 T 細胞白血病 / 淋巴瘤的致病因素。我們在此提出一個瀰漫性泛細支氣管炎合併成人 T 細胞白血病之病例報告，並且回顧此兩者之間相關的文獻。一位 53 歲的女性因活動性喘?及咳嗽有痰到胸腔科門診求診，經過檢查後她被診斷有瀰漫性泛細支氣管炎。然而 6 個月之後這個病人因發燒，白血球增多及身上多處淋巴結腫大入院，最後診斷患有成人 T 細胞白血病。 Ono *et al.*在 1989 年最先報告成人 T 細胞白血病的病人比一般人有更高的瀰漫性泛細支氣管炎盛行率。瀰漫性泛細支氣管炎會使成人 T 細胞白血病的病人更容易併發肺部感染，影響成人 T 細胞白血病的治療使愈後更差。在台灣，人類嗜 T 淋巴球第一型病毒的帶原者比非流行區高，因此也需留意瀰漫性泛細支氣管炎合併成人 T 細胞白血病的可能性。***(胸腔醫學 2006; 21: 94-100)***

關鍵詞：瀰漫性泛細支氣管炎，成人 T 細胞白血病，人類嗜 T 淋巴球第一型病毒

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Lymphangioleiomyomatosis with Chylothorax — A Case Report

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Pulmonary lymphangioleiomyomatosis (LAM) is an uncommon disorder of unknown etiology affecting women of childbearing age. It is characterized by the nonneoplastic proliferation of atypical smooth muscle cells within the lung parenchyma and elsewhere, leading to progressive loss of lung function. Clinical features include exertional dyspnea, cough, chest pain, recurrent pneumothorax, chylous pleural effusion, hemoptysis, eventual respiratory failure and, ultimately, death. We report a case of pulmonary LAM with chylothorax that developed in a 46-year-old woman. This patient suffered from cough and exertional dyspnea, and the chest X-ray showed left pleural effusion. Thoracocentesis demonstrated chylous effusion. The chest computed tomography (CT) scan revealed multiple cystic lesions. The clinical diagnosis, based on histological examinations with biopsy specimens, was pulmonary LAM. The chylothorax resolved after pleurodesis. ***(Thorac Med 2006; 21: 101-107)***

Key word: lymphangioleiomyomatosis, chylothorax, pleurodesis

Introduction

Chylothorax refers to the presence of lymphatic fluid in the pleural space secondary to leakage from the thoracic duct or 1 of its main tributaries. The fluid is milky and the triglyceride level is usually >110 mg/dl. Causes of chylothorax include: lymphoma, trauma, and post-surgical, idiopathic, congenital, and miscellaneous complications [1].

Pulmonary lymphangioleiomyomatosis (LAM) is characterized by a peribronchial, perivascular, and perilymphatic proliferation of abnormal smooth muscle cells. Occlusion of the lymphatic system results in chylous effusions or ascites. LAM accounts for < 10% of all cases of chylothorax.

Herein, we describe a patient with pulmonary LAM with chylothorax who was successfully treated by pleurodesis, and discuss the various aspects of pulmonary LAM.

Case Report

This 46-year-old woman was a non-smoker. She had a history of uterine myoma, and had undergone a hysterectomy 15 years before. No menstruation had been noted after surgery. Two

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months before presentation, she was admitted to a city hospital with a 1-week history of intermittent cough and exertional dyspnea. Her shortness of breath was attributed to a significant left pleural effusion. The fluid was drained and reported to be chylous. After repeated thoracenteses, her symptoms subsided. Unfortunately, cough and dyspnea developed again, shortly after discharge. She visited our chest outpatient department (OPD) because of the worsening symptoms. The patient denied fever, productive cough, hemoptysis, chest pain, general edema, or flank pain.

On admission, her temperature was 37°C, pulse rate 84/min, respiratory rate 20/min, and blood pressure 152/94 mmHg. Physical examination revealed diminished breathing sounds in the left hemithorax. Otherwise, she had no skin lesion, palpable lymphadenopathy or palpable abdominal mass. Routine laboratory examinations, including complete blood count, blood urea nitrogen and creatinine, and liver biochemical tests were all within normal limits. Electrocardiography showed normal sinus rhythm without evidence of ischemia or premature beat. The chest X-ray revealed a large amount of effusion in the left hemithorax, which pushed the mediastinum to the right (Figure 1). Chest ultrasonography detected a large amount of pleural effusion. The characteristics of the effusion were as follows: WBC, 317/μl (L:N 95:1); protein, 4.7g/dl; cholesterol, 90 mg/dl; and triglyceride, 2364 mg/dl. Since the thoracocentesis demonstrated chylous effusion, she had been on a low-fat diet to reduce the lymph accumulation. Her dyspnea subsided after chest tube drainage. Computed tomography (CT) of the chest demonstrated multiple thin-wall air cysts, ranging from 5 mm to 20 mm in diameter, scattered throughout both lungs, predominantly in the upper parts. Minimal residual left pneumothorax was seen, and there was no evidence of architecture distortion (Figure 2). The ultrasonography of the abdomen and kidney remained normal.

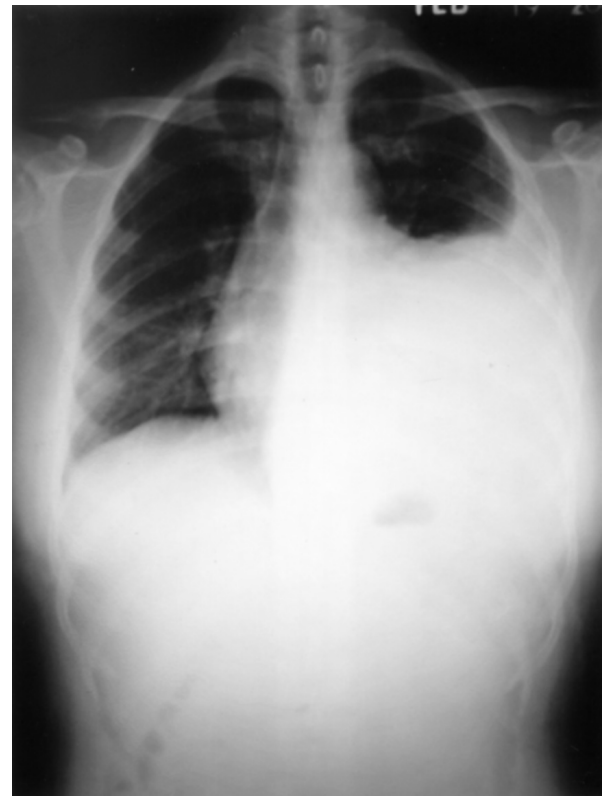


Fig. 1. Chest PA showing a large amount of effusion which pushed the mediastinum to the right.

A chest surgeon was consulted for surgical pleurodesis and lung biopsy. Two specimens were obtained, 1 from the left upper lobe and the other from the left lower lobe, by video-assisted thoracoscopic surgery (VATS). In the microscopic examination, these tissues demonstrated multiple foci of smooth muscle proliferation associated with focal cystic change. The muscle was intimately related to the blood vessels and distal airways and seemed to spin off these structures. The smooth muscle cells showed immunoreactivity to HMB 45, desmin, and smooth muscle actin. Hemosiderin-laden macrophages and focal emphysematous change were present (Figure 3).

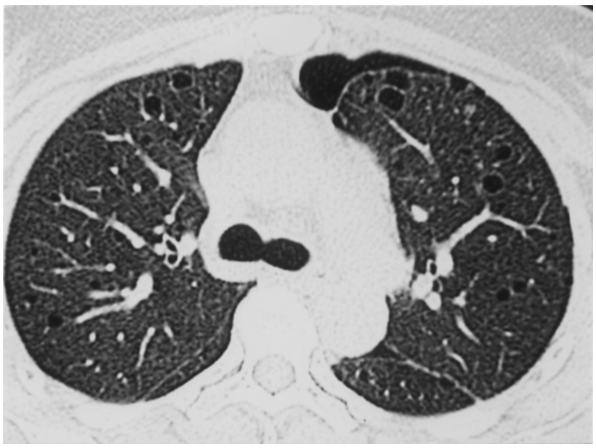
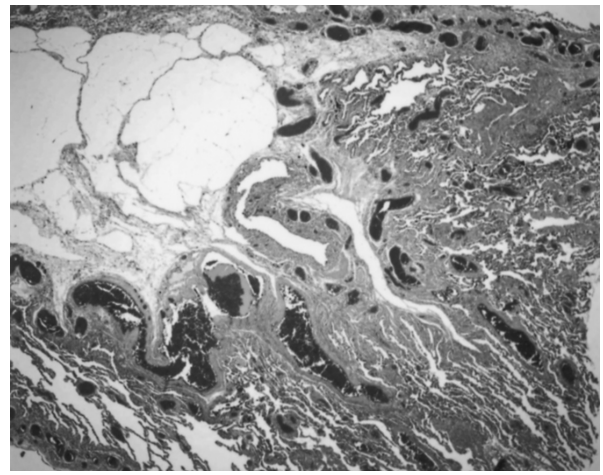
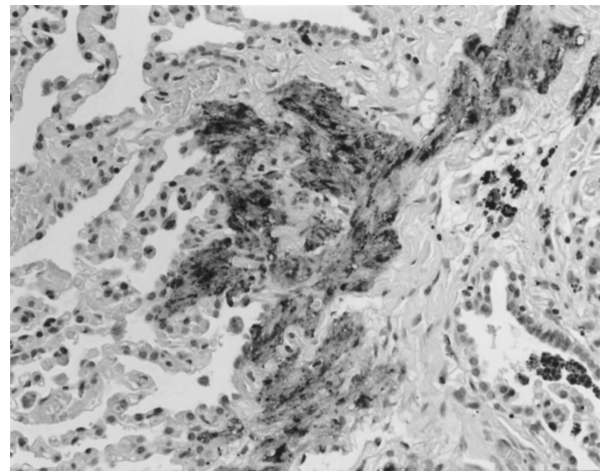


Fig. 2. Computed tomography of the chest demonstrating multiple thin-wall air cysts scattered throughout both lungs, and predominantly in the upper parts. Minimal residual left pneumothorax is seen. No evidence of architecture distortion



(A)



(B)

Fig. 3. (A) Haphazard proliferation of smooth muscles with focal cystic and emphysematous change. (H&E stain, x20). (B) The smooth muscles also show positive immunoreactivity with the melanoma antigen HMB45.

These findings demonstrated the features of LAM, therefore, the pathologic diagnosis was therefore pulmonary LAM.

The surgical pleurodesis failed to resolve the chylous effusion, therefore minocycline instillation was performed. Her chylothorax was successfully treated by chemical pleurodesis. Medroxyprogesterone acetate 100 mg/week was used to control the pulmonary LAM and chylothorax. A pulmonary function test (PFT) was performed at the OPD follow-up, and disclosed a mild degree of restrictive functional impairment [FEV1 = 1.64 (64) %, FEV1/FVC = (87) %; TLC = 2.78 (60) %; DLCO/VA = 5.86 (140) %]. She has been well since discharge.

Discussion

Lymphangioleiomyomatosis (LAM), as its name suggests, mainly involves the lungs where lymphatics (lymph), blood vessels (angio), and airways are surrounded by smooth muscle (leiomyo) proliferation. Although von Stossel [2] first described pulmonary LAM in 1937, the natural history of LAM remains poorly understood. LAM can occur as a rare sporadic disease or as a complication of tuberous sclerosis complex (TSC).

Pulmonary LAM most often affects women of reproductive age, and the average age at presentation is 34 years [3-6]. The proliferation of smooth muscle cells is thought to be related to hormonal secretion because the disease occurs

primarily in woman in their reproductive years. Exacerbations have been documented during pregnancy, during menses, with the use of birth control pills, and after exogenous estrogen administration. Presentation after menopause is unusual, but it may be seen in woman taking estrogen replacement therapy [5-9]. Since estrogen plays an important role in LAM, it is crucial to identify whether the patient has a normal menstrual cycle or not. The lack of menstruation does not equal menopause, especially in patients who have undergone hysterectomy. We can check the serum levels of follicle stimulating hormone (FSH), luteinizing (LH) and estradiol (E2) to decide whether menopause has occurred or not. A low E2, and high FSH and LH levels indicate menopause.

The commonest presenting pulmonary symptoms were dyspnea, cough, hemoptysis, and less frequently, chyloptysis. Extrapulmonary features of LAM include chylous ascites, renal angiomyolipomas, lymphangiomyomas and uterine leiomyomas [10-14]. Pneumothorax and chylothorax are 2 major complications of LAM. Pneumothorax is more common than chylothorax. Chylothorax has been described in up to 14% of patients with LAM at presentation, and in 22% to 39% during the course of the disease [3, 16]. The three main mechanisms of chylothorax formation in LAM include the following: (1) a chyle leak (secondary to proximal lymphatic obstruction or direct involvement) from the thoracic duct or its tributaries, (2) general oozing from pleural lymphatics or collateral vessels, and (3) a transdiaphragmatic flow of chylous ascites [13]. The thoracic duct turns to the left at the level of the aorta, so the chyle tends to appear on the left side [1]. This anatomy explains why our patient had left-sided chylothorax.

Ryu *et al.* [17] reported that the occurrence of chylothorax did not appear to correlate with the severity of lung involvement, history of pregnancies, degree of renal involvement with angiomyolipomas, or the presence of lymph node involvement detectable by CT. Repeated thoracenteses have been used to control the reaccumulation of chylothorax in some patients with LAM, although the drainage of chylous pleural fluid led to protein and lymphocyte loss. A low-fat diet or medium-chain-triglyceride diet may reduce lymph accumulation [18].

Pleurodesis, pleurectomy, or thoracic duct ligation should be considered for any symptomatic chylothorax that continues to reaccumulate after therapeutic thoracentesis [4, 7]. However, recurrent chylothorax has been reported after pleurodesis, and bleeding is the most serious complication in lung transplantation following pleurodesis [19].

The gross appearance of the lungs in LAM is that of diffuse cystic change evenly distributed throughout all zones. Histologically, the affected organs are infiltrated with an unusual form of smooth muscle cells, termed LAM cells. LAM cells react with human melanoma black (HMB)-45, an antibody generated against an extract of melanoma. HMB-45 staining is sensitive and specific for the presence of LAM cells and may help in confirming LAM.

The chest radiograph may be normal initially but, as the disease progresses, bilateral reticular shadowing and cystic change develop whilst lung volumes are either preserved or increased. The characteristic HRCT finding consists of multiple air-filled cysts distributed evenly throughout the lung field, with normal lung parenchyma. Cysts generally measure from 0.2 cm to 2 cm in diameter, and have discernible walls of approximately 0.1 cm. As the disease progresses, the cysts become more numerous, and occasionally

amalgamate to form bizarre shapes [20].

Because the CT findings in LAM are so distinctive, many physicians do not necessarily resort to open lung biopsy to make the diagnosis [6]. For our case, we consulted a chest surgeon to perform an operation, despite the fact that the CT demonstrated the unique findings of LAM. The chest surgeon can not only do a wedge biopsy, but can also perform pleurodesis at the same time.

Although surgical pleurodesis can be achieved by VATS, it failed to resolve the chylous effusion in our case. Perhaps there is a place in the pleural cavity that the scope cannot reach, thereby reducing the success rate of pleurodesis.

A reduction in the diffusion capacity of carbon monoxide is the most common initial abnormality in LAM. An obstructive physiology is more common than a restrictive one, but findings may be mixed [5]. The patient was afraid of interference by the chylothorax and tube thoracostomy, so she didn't have a PFT until discharge. The PFT findings showed a restrictive impairment without obstructive or diffusion capacity defect. There was no hyperinflation change on the CXR and a mild degree of cystic change on the chest CT. These findings perhaps explain why neither obstructive nor diffusion capacity defects were found during the PFT. The restrictive functional impairment was probably related to the pleurodesis effect.

Evidence of the benefits of the hormonal manipulation of LAM is still limited, and treatment results in a number of study series have been mostly inconclusive, although the evidence is probably best for progesterone [3, 6]. Medroxyprogesterone acetate was prescribed for our patient, because Taylor *et al.* [8] reported that a patient treated with progesterone for chylous effusion appeared to show more improvement than other patients. Progesterone can be given by intramuscular injection monthly, at a dose of 400-800 mg. Medroxyprogesterone may also be taken orally, 10-20 mg/day. However, progesterone therapy does not slow the decline in lung function in LAM [21].

Previous estimates of 10-year survival have ranged from 40% to 79%. Recent retrospective series reported a survival probability of approximately 90% after 5 years, 80% after 10 years, and 70% after 15 years of disease duration [3, 5]. Improved diagnosis and treatment, including lung transplantation, may have contributed to longer survival [22].

In conclusion, the picture of dyspnea and chylothorax, with or without pneumothorax, in a woman of childbearing age, likely suggests the diagnosis of LAM.

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淋巴血管平滑肌瘤併發乳糜胸之病例報告及文獻回顧

龔昱中　陳培然　陳碧芳*　劉洪彰**

肺淋巴血管平滑肌瘤是一個原因不明且罕見的疾病，侵犯對象以生育年齡女性為主。以肺實質及其他部位的異常平滑肌細胞增生為其特徵，並導致肺功能逐漸喪失。臨床表現有呼吸困難、胸痛、咳嗽、咳血、反覆性氣胸、乳糜胸，甚至呼吸衰竭，進而死亡。我們報告一位46歲女性罹患淋巴血管平滑肌瘤合併乳糜胸，出現咳嗽、呼吸困難，胸部x光片呈現左側肋膜腔積液，經胸腔穿刺術檢查確定是乳糜胸。而電腦斷層上則見到許多囊狀空泡的病變。經胸腔鏡手術與病理組織檢查後確定診斷為淋巴血管平滑肌瘤。乳糜胸則在肋膜沾黏術治療後，獲得改善並消失。*(胸腔醫學 **2006; 21: 101-107**)*

關鍵詞：淋巴血管平滑肌瘤，乳糜胸，肋膜沾黏術

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Pulmonary Function and Exercise Capacity of A Physician Who Recovered From Severe Acute Respiratory Syndrome

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Severe acute respiratory syndrome (SARS) is a new infectious disease with its initial worldwide outbreak in 2003. At that time (29 April to 26 May), there were 44 identified SARS patients, including 16 healthy hospital workers, in a nosocomial outbreak in a 2,500-bed medical center (Kaohsiung Chang Gung Memorial Hospital) in southern Taiwan Two medical workers developed acute respiratory distress syndrome (ARDS) and required intubation. Only 1 survived and later recovered. We followed up this patient with pulmonary function tests (PFTs), including spirometry and diffusing capacity, and high resolution computed tomography (HRCT) at 1 and 14 months after hospital discharge. A cardiopulmonary exercise test was performed at 14 months. Diffusing lung capacity for carbon monoxide (DLCO) was mildly impaired at the 1-month follow-up (77. 33%), but returned normal at the 12-month follow-up (82.60%). FEV1 and FEV1/FVC were within normal range, although minimal fibrosis was detected on the HRCT. Exercise capacity was normal, including the patient's recovery of physical fitness. ***(Thorac Med 2006; 21: 108-112)***

Key words: severe acute respiratory syndrome (SARS), pulmonary function, exercise capacity, cardiopulmonary exercise testing (CPET)

Introduction

A novel coronavirus infectious disease, known as severe acute respiratory syndrome (SARS), created global concern in 2003 [1]. The worldwide fatality rate was 11% (ranging from 7 to 27%) [2]. Many of the patients were healthcare providers with a history of close contact with SARS patients. Symptoms varied from mild fever to acute respiratory distress syndrome (ARDS), and even death. Patients who survived SARS acquired sequelae in lung functioning, such as a reduced diffusing capacity and restrictive ventilatory defects [4]. A cluster outbreak occurred at Kaohsiung Chang Gung Memorial Hospital (CGMH) in southern Taiwan in May 2003. Among 44 identified SARS patients at Kaohsiung CGMH, 16 were hospital workers [5]. Two

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patients, both medical doctors, developed ARDS and received ventilator support. One died during hospitalization, and another attained recovery. To determine if this infectious disease has a long-term influence on physical status, serial functional tests and image studies were carried out with this medical doctor who survived SARS.

Case Report

A 41-year-old married Asian male worked as a chest physician at Kaohsiung CGMH during the SARS outbreak period. He intubated a critically-ill patient who was later identified as a SARS patient. Fever developed 3 days later and concomitant myalgia, fatigue, and headache were also noted.

Chest X-ray showed bilateral patchy consolidation after 9 days of exposure (Figure 1), which rapidly progressed to markedly diffuse infiltrates compatible with ARDS (Figure 2). Intravenous immunoglobulin (IVIG) was infused, but the high fever persisted. On day 6, respiratory failure developed and intubation was implemented. Steroid pulse therapy was carried out later. His condition improved gradually and extubation was performed on day 26 (20 days after intubation). He was discharged after 49 days of hospitalization.

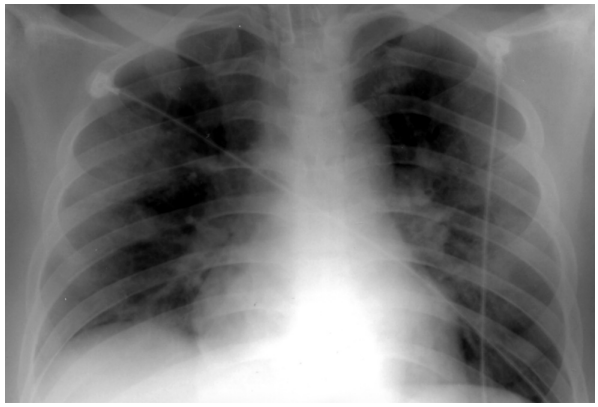

Fig. 1. CXR taken on day 9 after exposure

1-month follow-up

The patient exercised regularly at home and received frequent oximetry monitoring, which showed no oxygen desaturation. He underwent pulmonary function testing and high-resolution computed tomography (HRCT) at 1 month after discharge. Borderline low diffusing lung capacity (DLCO) was detected. The follow-up CXR revealed a normal appearance and HRCT revealed focal fibrotic scars in the left upper lung, lingula, and bilateral lower lungs (Figure 3). The data

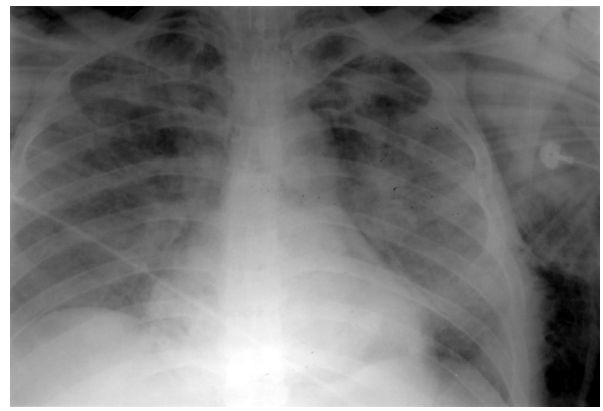

Fig. 2. CXR taken on day 11 after exposure was compatible with ARDS

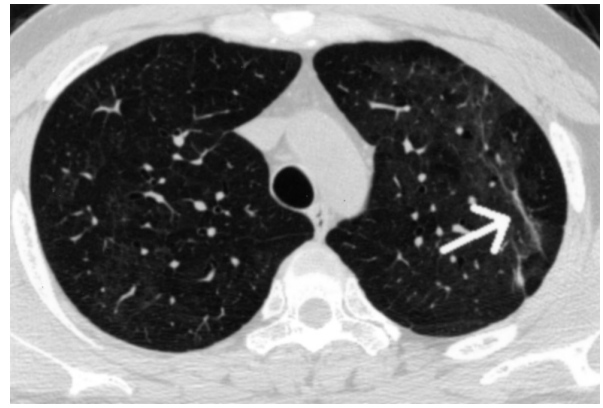

Fig. 3. HRCT was done at 1 month after discharge. Focal fibrotic scars can be seen. (arrow)

measured by spirometry were within normal range (Table 1).

12-month follow-up

The patient received follow-up exams comprising PFTs, cardiopulmonary exercise testing (CPET) and HRCT at 12 months after hospital discharge. PFTs attained normal value (Table 1), while CPET measurement was also normal (Table 2). No obvious change was noted on subsequent HRCT exams.

Discussion

In a review of the literature concerning the sequelae of SARS, restricted pulmonary function tests and reduced diffused lung capacity were reported [4]. Similar results were identified by Chiang and colleagues at Taipei Veterans General Hospital after following up 14 SARS patients for 8 months [6]. DLCO was less reduced among patients who had SARS without ARDS than among SARS patients with ARDS [7-8].

This physician had been healthy prior to this illness. Carbon monoxide diffusing capacity was slightly decreased (77.33%) at 1 month after hospital discharge, and was normal at 12 months. However, the spirometry, including FVC and FEV1, were within normal range at both the 1- and 12-month follow-ups, although minimal fibrotic change was detected by HRCT. CPET performed at 12 months demonstrated normal values, including maximal oxygen uptake (VO_2, max), breathing reserve (BR), heart rate reserve (HRR), and maximal voluntary ventilation (MVV). Ng *et al*. found that a reduced exercise capacity was common in patients who survived SARS [3]. Although this patient experienced muscle wasting during hospitalization and impaired diffusing capacity 1 month after discharge, no reduced exercise capacity was detected at the 12-month follow-up. However, occult cardiovascular impairment was suspected, since there was mild resting tachycardia and a mildly decreased anaerobic threshold (38.11% pred. VO_2, max). This was not revealed in the subsequent 2-dimensional echocardiography.

Whether or not therapies, (e.g., IVIG, steroid, ribavirin, diprivan, and muscle relaxants), have a disadvantageous impact on lung function or exercise capacity remains unclear. Physical deconditioning was considered the key element impairing exercise capacity. Exercise training programs increased maximal oxygen uptake and

Table 1. Pulmonary function tests of the patient at 1 and 14 months after hospital discharge.

	DLCO	VA	KCO	FEV1	FVC	FEV1/FVC	MMEF
1 month	77.33%	88.25%	89.62%	95.50%	97.70%	83.03%	81.00%
14 month	82.60%	91.90%	91.90%	104.30%	109.90%	80.29%	77.70%

DLCO: diffusion lung capacity of carbon monoxide; VA: alveolar volume; KCO: carbon monoxide transfer coefficient; FEV: forced expiratory volume in 1 second; FVC: forced vital capacity; MMEF: the maximal mid-expiratory flow

Table 2. Cardiopulmonary exercise testing of the patient at 14 months after hospital discharge.

	VO2, max%	O2/HR	AT	BR	HRR	MVV
14 months	88.00	15.50	38.11%	43%	23	122.50%

VO2, max: maximal oxygen uptake; HR: heart rate; AT: anaerobic threshold; BR: breathing reserve; HRR: heart rate reserve; MVV: maximal voluntary ventilation

ventilation [9]. This physician had regular exercise (Chinese shadow boxing) after SARS recovery, which might explain the normalization of the pulmonary function test and exercise capacity.

In conclusion, this previously healthy physician recovered from SARS and ARDS, and exhibited normal pulmonary function and exercise capacity 12 months after hospital discharge. Regular exercise probably plays an important role in restoring physical fitness.

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一個感染嚴重急性呼吸道症候群但存活的醫師的心肺功能變化

謝毓棠　蘇茂昌　王逸熙　林安伸　王瑞隆　林孟志

嚴重急性呼吸道症候群為一個在西元2003年發生的全球性新興傳染病。於4月29日至5月26日，總病床數達2500床的高雄長庚醫院爆發了群聚感染，總計有44位病患證實遭到感染，其中包含16位健康的醫護人員。有兩位醫師因急性呼吸窘迫症候群接受氣管內管插管及呼吸器治療，只有一位醫師存活並復原。我們在此病人出院後一個月及第十二個月進行肺功能以及高解析度電腦斷層檢查的追蹤，並於第十二個月進行了心肺運動功能的檢測。剛出院時，一氧化碳擴散能力 (DLCO) 顯示輕微受損 (77.33%)，在十二個月會回復到正常範圍 (82.60%)。HRCT顯示左上肺葉輕微纖維化，而肺功能維持在正常範圍 (FEV1及FEV1/FVC)。第十二個月時，運動心肺功能檢測報告正常。*(胸腔醫學* ***2006; 21: 108-112)***

關鍵詞：嚴重急性呼吸症候群，肺功能，心肺運動功能

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Multiple Nodular Pulmonary Lesions in a Human Immunodeficiency Virus-Infected Patient: an Unusual Manifestation of Invasive *Penicillium marneffei* Infection

Yu-Lin Tsai, Mao-Wang Ho*, Chih-Yen Tu, Hung-Jen Chen, Lai-Fong Kok**, Chuen-Ming Shih, Wu-Huei Hsu

Penicillium marneffei is endemic in southeastern Asian countries. In northern Thailand, it is the third most common opportunistic infection following tuberculosis and cryptococcosis in human immunodeficiency virus (HIV)-infected patients with acquired immunodeficiency syndrome (AIDS). The chest roentgenograms in such cases usually show mixed alveolar and interstitial infiltrates. We report a 60-year-old male HIV-infected patient with *P. marneffei* infection whose chest film initially presented with multiple nodular lesions. Generally, HIV patients with multiple pulmonary nodules should be considered as having pulmonary tuberculosis, *Pneumocystis carinii* pneumonia (PCP), cryptococcal pneumonia, Kaposi's sarcoma, or metastatic carcinoma. This case presented an unusual manifestation of invasive *P. marneffei* infection with multiple nodular pulmonary lesions. Thus, when HIV-infected patients present with multiple pulmonary nodules, *P. marneffei* infection should be considered. ***(Thorac Med 2006; 21: 113-118)***

Key words: *Penicillium marneffei*, acquired immunodeficiency syndrome, human immunodeficiency virus

Introduction

Penicilliosis is a disease caused by *Penicillium marneffei*, a dimorphic, soil-dwelling fungus [1-2]. It is endemic in Southeast Asia, Guangxi province in China, Hong Kong, and Taiwan. In northern Thailand, it is the third most common opportunistic infection following tuberculosis and cryptococcosis in human immunodeficiency virus (HIV)-infected patients, accounting for 15% to 20% of all AIDS-related illnesses [1]. The most common symptoms include fever, weight loss, cough, and generalized papular skin lesions, usually with central umbilication. The chest roentgenograms in such cases usually present mixed alveolar and interstitial infiltrates. We report a patient with invasive *P. marneffei* infection whose chest radiograph initially revealed multiple nodular densities in both lungs.

Case Report

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A 60-year-old HIV-infected Taiwanese man was admitted to China Medical University Hospital (CMUH) due to general weakness. The chest radiograph showed multiple nodular densities in both lungs (Figure 1). He was a single bussinessman, and was diagnosed with HIV infection in April 1998. He received highly active antiretroviral therapy irregularly at our Infectious Diseases outpatient clinic and had had pulmonary tuberculosis and *Pneumocystis carinii* pneumonia (PCP) previously, with successful medical treatment. He had suffered from general weakness, poor appetite, dyspnea on exertion, and chills for weeks. There was no recent travel history. On admission, physical examination revealed a chronically ill patient, with a body temperature of 35.7°C, pale conjunctiva, and bilateral crackles on auscultation. Otherwise, there was no remarkable finding. The laboratory data revealed WBC 1,370/ul with neutrophilic segments 37.3% and lymphocytes 47.4%, Hb 6.9 g/dL, Hct 22.4%, platelets 293,000/μl, AST 34 IU/L, ALT 16 IU/L, sodium 132 mmol/L, and potassium 4.0 mmol/L. Urine and stool routines were normal. Microbiological studies, including sputum for aerobic culture, acid -fast stain and mycobacterial culture, urine culture, and stool culture all had negative findings, but 2 sets of blood cultures grew *P. marneffei*. The CD4+ T lymphocyte count was 5 cells/μl, and the HIV-1 RNA viral load was 26, 500 copies/ml. Trimethoprim-sulfamethoxazole (TMP-SMZ) was initially used to cover possible PCP. On hospital day 2, spiking fever developed.

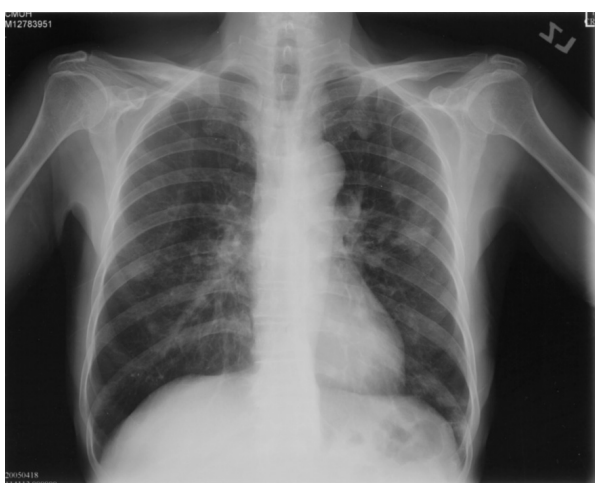

Fig. 1. Chest radiograph showing multiple nodular lesions in the bilateral lung fields.

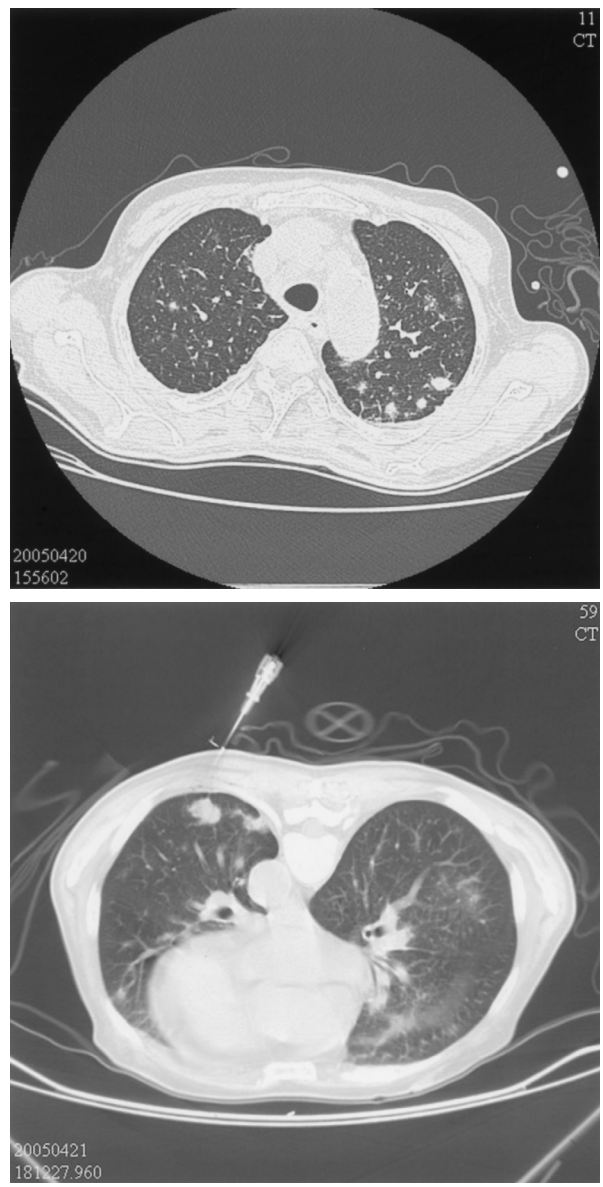

Fig. 2. HRCT showing multiple nodular lesions in the bilateral lung fields.

Ceftriaxone was added for possible bacterial infection. High-resolution computed tomography (HRCT) of the chest showed diffuse lymphadenopathy with multiple lung nodules (Figure 2). Due to a lack of no clinical response to medical treatment, CT-guided aspiration and biopsy of the lung nodules for culture and pathology was arranged. We also used empirical anti-TB agents. The pathology showed 2-3 μm yeast-like microorganisms with a septum. Both the blood culture and lung biopsy specimen culture grew mold. After subculture in sabouraud dextrose agar (SDA), a rapidly growing fluffy mold with red pigment was found, grossly. Microscopy revealed typical *P. marneffei* (Figure 3), and invasive *P. marneffei* infection was diagosed. After 14 days of amphotericin B treatment (0.6 mg/kg/day), the spiking fever subsided, and itraconazole (200 mg/day) was prescribed as the subsequent oral therapy. The cryptococcal antigen test, stool for parasites, and serum amebiasis Ab test were all negative. At the follow-up visit, the patient's chest radiographic presentation showed improvement, and he continued to receive itraconazole (200mg/day) therapy at our Infectious Diseases outpatient clinic.

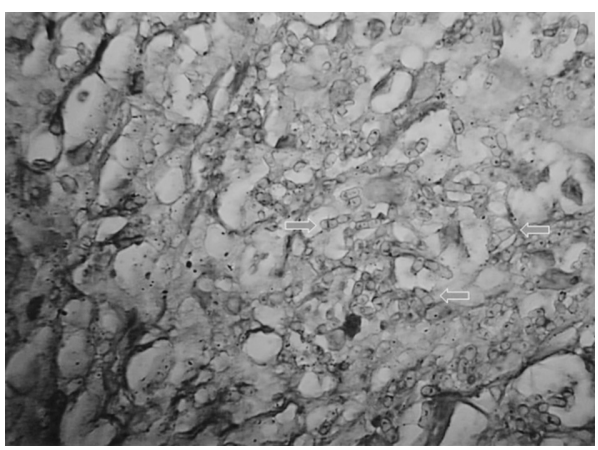

Fig. 3. Microscopic appearance from CT-guided aspiration. There were numerous typical penicillial forms of *Penicillium marneffei* with short, hyaline, and septated hyphae (arrow) (periodic-acid-Schiff stain. x100).

Discussion

P. marneffei is a dimorphic fungal pathogen which can cause disease in both immunocompetent and immunocompromised hosts. The fungus was first isolated from a bamboo rat in Vietnam in 1956 [3]. The first naturally infected case, reported in 1973, was an American missionary with Hodgkin's disease who had been living in Southeast Asia [4]. In northern Thailand, it is the third most common opportunistic infection following tuberculosis and cryptococcosis in HIV-infected patients [1], accounting for 15% to 20% of all AIDS-related illnesses. The disease is related to soil exposure, especially during the rainy season (May to October). The fungus grows as mold at 25°C on an SDA medium and produces a characteristic soluble red pigment that diffuses into the agar. Microscopically it has typical penicillial features with short, hyaline, septate, and branched hyphae, and laterally and terminally located conidiophores [5].

The clinical presentation of *P. marneffei* is often mistaken for tuberculosis, cryptococcosis, or histoplasmosis. The most common symptoms include fever, weight loss, cough, and generalized papular skin lesions, usually with central umbilication or necrosis. The most common sites of skin lesion include the upper trunk and head. Anemia is a prominent laboratory finding. Respiratory symptoms (e.g., cough and shortness of breath) occur in about one-third of patients. Leukopenia, thrombocytopenia, pericarditis, or gastroenteritis may occur [2]. The chest roentgenograms in such cases usually show mixed alveolar and interstitial infiltrates. Localized or patchy infiltrates with or without abscess, or empyema have been seen on

chest radiographs. The average number of CD4+ T lymphocytes in these patients was 63.8 cells/ mm^3.

The definitive diagnosis of this disease can only be made by direct visualization of the fungus using different staining techniques, such as Grocott-Gomori methenamine-silver nitrate stain, periodic acid-Schiff stain, or Wright's stain [1], or by getting a positive culture from infected material obtained from different sites [6], including the blood, bone marrow, lymph nodes aspirates [5], skin biopsies, and less frequently, bronchoalveolar lavage fluid.

Penicilliosis due to *P. marneffei* is a potentially fatal systemic fungal infection. The mortality rate of patients with Penicilliosis had been high [2], mostly because of a lack of timely diagnosis. Amphotericin B, followed by itraconazole, is the standard treatment for *P. marneffei* infection [7]. The duration of amphotericin B treatment (0.6 mg/kg/day) is 2 weeks, followed by an additional 10 weeks of itraconazole. This regimen is reported to have a greater than 97% response rate for disseminated *P. marneffei* infection [7]. Without secondary prophylaxis, however, most patients will suffer from a relapse within 6 to 12 months. Itraconazole (200 mg daily) is an effective secondary prophylaxis against *P. marneffei* [8]. Given the strong association with soil exposure, especially during the rainy season, HIV-infected patients living in or traveling to endemic areas should avoid activities that will potentially increase their exposure.

The chest radiographic presentation of *P. marneffei* infection has been discussed, and includes single or multiple cavitary lesions with a smooth or irregular thin wall [9], non-excavated round opacities [10], bilateral diffuse reticulonodular infiltrates [11], and solitary pulmonary nodules [12]. In the unusual case presented herein, the initial chest film presented with multiple nodular densities, not the usual pattern of mixed alveolar and interstitial infiltrates. In Taiwan, the number of AIDS cases has increased rapidly in recent years, and the case number of *P. marneffei* infections might increase among these AIDS patients. Since *P. marneffei* infections cause morbidity and death among AIDS patients, doctors in Taiwan should be more familiar with the clinical manifestations and radiographic presentation of this disease. Awareness of its existence by clinicians and microbiologists will reduce the mortality rate through early diagnosis and treatment.

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多發性肺結節在愛滋病患感染馬氏青黴菌（*Penicillium marneffei*）：少見的肺部X光片表現

蔡育霖　何茂旺*　涂智彥　陳鴻仁　郭麗芳**　施純明　徐武輝

馬氏青黴菌具有二形性，即是於37℃時呈酵母細胞狀，在25℃時見則呈黴菌狀。馬氏青黴菌感染具有地域性，好發於東南亞、中國南及西南方、香港、台灣、泰國、越南、菲律賓等一帶。而在某些國家，馬氏青黴菌病更是愛滋病人中常見的感染。例如在泰國北部，馬氏青黴菌病僅次於結核病及隱球菌感染，成為第三種最常見的伺機性感染。大部份馬氏青黴菌感染在胸部X光片上的表現大多呈現混合肺泡和間質性浸潤。

我們提出這個病例：一位60歲男性愛滋病患，一開始胸部X光片以多發性結節表現，懷疑是結核菌感染、隱球菌感染、卡波西氏肉瘤、或轉移性癌症。後來血液培養、經電腦斷層指引抽取組織培養、以及病理報告均是馬氏青黴菌感染。我們提出這個病例就是讓臨床醫師在看到愛滋病患胸部X光片以多發性結節表現時，能把馬氏青黴菌感染列入其中之一鑑別診斷，亦能儘早給予治療。*(胸腔醫學* ***2006; 21: 113-118)***

關鍵詞：馬氏青黴菌，後天免疫缺乏症候群，愛滋病

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Pulmonary Alveolar Proteinosis Treated With Whole Lung Lavage: A Case Report and Literature Review

Kuang-Hua Cheng, Ming-Jen Peng, Chien-Chuan Chen*

Pulmonary alveolar proteinosis is a rare disease which was described first in 1958 as an "accumulation of periodic acid-Schiff (PAS)-positive material in the alveolar space". A 55-year-old male smoker was admitted due to slowly progressive exertional dyspnea with mild productive cough for 9 months. Chest radiography revealed bilateral diffuse lung infiltrates. Arterial blood gas showed hypoxemia with impaired diffusion capacity. Chest tomography showed patchy areas of ground glass opacities with a crazy-paving pattern. Alveolar proteinosis was proved by open-lung biopsy. Therapeutic whole lung lavage was performed 3 times monthly. His symptoms and arterial oxygen tension improved thereafter. ***(Thorac Med 2006; 21: 119-125)***

Key words: pulmonary alveolar proteinosis, crazy paving, whole lung lavage

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease which was described first in 1958 as an "accumulation of periodic acid-Schiff (PAS)-positive material in the alveolar space" [1]. Its estimated annual incidence is 0.36-3.7 cases per million population. The male-to-female ratio in several series has ranged from 2:1 to 4:1 [2]. The most common symptoms are exertional dyspnea and nonproductive cough [3-4]. Coughing with "chunky" sputum has sometimes been described [5]. The typical age at presentation is 30 to 50 years. A few cases have been reported in infants and children [6]. The described biochemical abnormalities may include elevated serum levels of lactate dehydrogenase (LDH), other protein products of the pulmonary epithelial cells, including carcinoembryonic antigen, cytokeratin 19, and the mucin KL-6, and the levels of the surfactant proteins A, B, and D, although none of these findings are specific for PAP [7]. Certain features on high-resolution CT scanning of the chest have strongly suggested PAP. Open-lung biopsy has been the gold standard for reaching the definitive diagnosis. Whole-lung lavage remains the most effective treatment.

The disease has no racial predilection, and some cases have been reported in Taiwan. Therapeutic experience with wholelung lavage or bronchofiberscopic lobar lavage [17] has also been reported. Herein, we described our experience in treating a PAP patient with therapeutic whole lung lavage.

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Case Report

This 55-year-old man worked in a glass-grinding factory for 7-8 years about 20 years ago, and smoked 1 pack of cigarettes per day for 40 years. He had been quite well until 9 months prior to admission, when he noted dyspnea on exertion. Occasional cough with white-yellowish sputum was noted. There was no orthopnea, fever, weight loss, hemoptysis, or arthralgia.

Three months before admission, he underwent a hemorrhoidectomy. The chest radiograph showed diffuse pulmonary infiltrates, especially in the lower lung field (Figure 1). A chest consultation was recommended, but the patient did not pay attention to it. Gradually, his dyspnea worsened.

On admission, his body temperature was 36.9 degrees Celsius, with a respiratory rate of 22/minute. Blood pressure was 117/88 mmHg. Chest auscultation showed clear breathing sounds without crackles or wheezing. There was no cyanosis, clubbing fingers, or lower leg edema. His hemogram disclosed hemoglobin at 16.5 g/dL. Biochemistry data were all within normal limits, except for an elevated LDH level (LDH = 373 mg/dL). Blood gas analysis showed hypoxemia (PO_2 = 56.9 cmH_2O) (Table. 1). Chest radiography demonstrated diffuse pulmonary infiltrates which showed essentially the same pattern as the radiography taken 3 months ago.

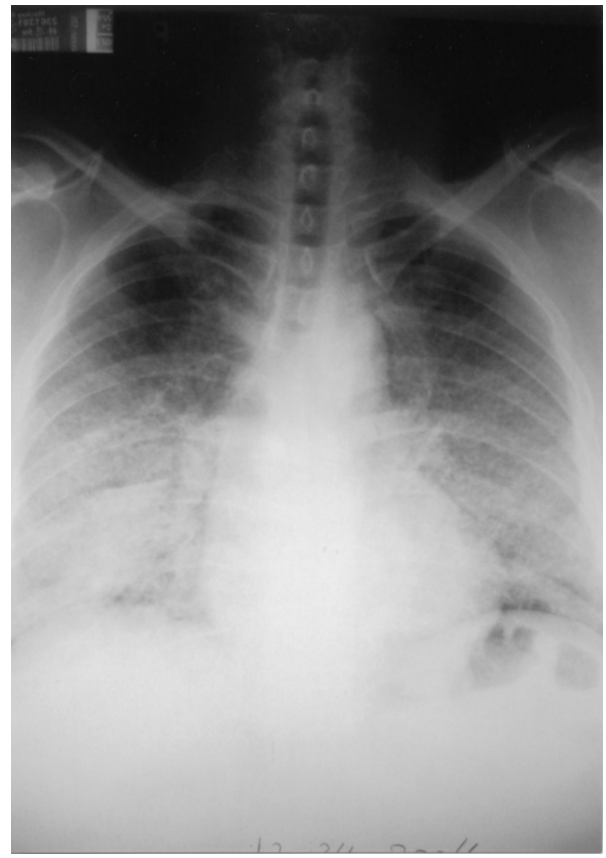

Fig. 1. Initial chest radiography showing air-space consolidations in bilateral lower lungs.

Chest HRCT (high-resolution computerized tomography) revealed patchy areas of ground glass opacities and interlobular septal thickening

Table 1. Blood gas analysis (in room air)

	pH	PCO_2	PO_2	HCO_3	O_2 Sat	Comment
11/4/2004	7.389	32.5	56.9	19.2	89.7%	On first admission
12/9/2004	7.438	32.8	52.6	21.7	88.7%	Before 1st WLL
12/17/2004	7.420	32.3	61.8	20.5	92.4%	After 1st WLL
1/05/2005	7.445	31.2	44.8	20.9	83.3%	Before 2nd WLL
1/17/2005	7.444	34.8	56.8	23.4	90.0%	After 2nd WLL
2/15/2005	7.420	36.7	51.5	23.3	87.4%	Before 3rd WLL
2/23/2005	7.437	35.7	72.1	23.6	95.1%	After 3rd WLL

*WLL: whole lung lavage

in a crazy-paving pattern throughout both lungs (Figure 2). Bronchoscopy with bronchoalveolar lavage (BAL) yielded milky fluid. His pulmonary function test revealed a mild restrictive lung defect and mild impairment of diffusing capacity (FEV1/FVC 85%; TLC 3.27L, 68 %; DLCO 57% of predicted value). The exercise pulmonary function test showed rapid desaturation after 3 minutes of exercise. (the oximeter decreased from 87% to 77% , while the workload increased from 0 to 45 watts). An open-lung biopsy by means of VATS was performed. The biopsy demonstrated a diffuse intra-alveolar accumulation of amorphous eosinophilic granular material (Figure 3). Within the eosinophilic material, scattered empty round spaces, cholesterol clefts, macrophages, and red blood cells were found. The eosinophilic material was positive for PAS (periodic acid-Schiff) stain. These findings were compatible with PAP. The BAL fluid under electron microscopy showed concentrically laminated myelin figures (Figure 4).

Therapeutic whole lung lavage was performed under general anesthesia 1 month after diagnosis. Eight liters of warm normal saline were infused sequentially via a double-lumen endotracheal tube into the left lung. Whitish milky fluid was obtained first, and then the lavage fluid became clearer and clearer. Follow-up CXR showed decreased infiltrates in the left lung field. The patient's dyspnea and blood oxygen concentration improved slightly after the first lavage, and bilateral wholelung lavage was performed 20 days later. His PaO_2 level showed mild improvement (Table. 1). He still worked in the construction yard, where he risked silica exposure. But he quit the job under our advice, and another bilateral whole lung lavage was performed again 1

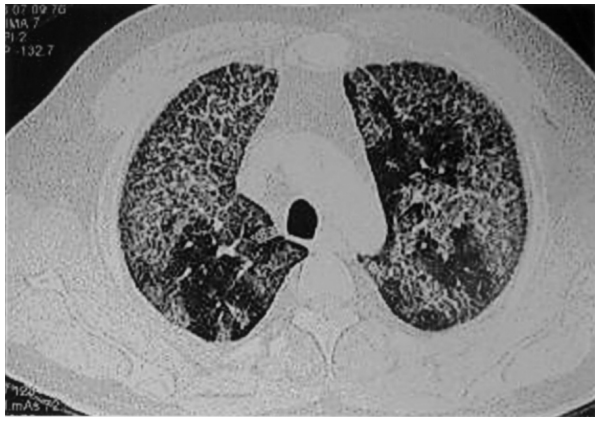

Fig. 2. Chest CT revealing patchy areas of ground glass opacities and interlobular thickening in crazy-paving pattern.

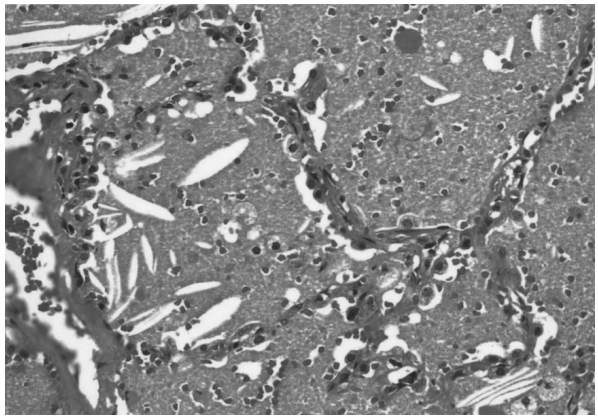

Fig. 3. Light microscopy, it revealing eosinophilic materials in the alveolar space with scattered empty round spaces, cholesterol clefts, macrophage and red blood cells. (H&E 200X)

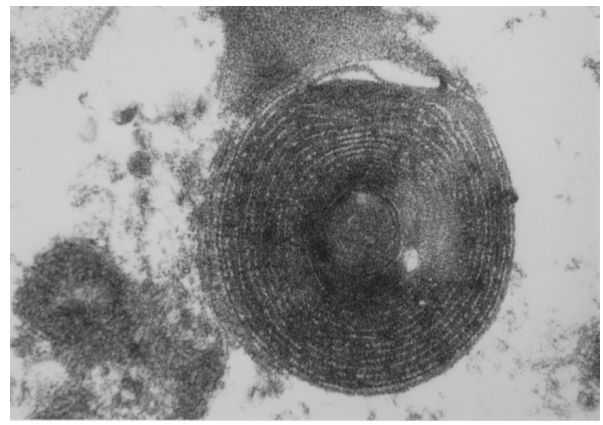

Fig. 4. Concentrically laminated phospholipid structures (lamellar bodies) were found under electron microscopy (12000X)

month later. Both his dyspnea on exertion and blood gas data improved.

Discussion

Pulmonary alveolar proteinosis (PAP) occurs in 3 clinically distinct forms: congenital, secondary, and acquired. The congenital form was due to mutations in the genes encoding surfactant protein B or C, or the β_C -chain of the receptor for granulocyte-macrophage colony-stimulating factor (GM-CSF) [8-10]. Secondary PAP develops in association with conditions involving functional impairment or reduced numbers of alveolar macrophages. Such conditions include some hematologic cancers, pharmacologic immunosuppression, inhalation of inorganic dust (e.g., silica) or toxic fumes, and certain infections. There are some recognized causes of adult PAP, including lysiuric protein intolerance, acute silicosis and other inhalation syndromes, immunodeficiency disorders, malignancy and hematological disorders [7]. However, more than 90% of all cases of PAP occur as a primary acquired disorder of unknown etiology. The understanding of the possible pathogenesis came unexpectedly in 1994, with a study of gene-knockout mice lacking hematopoietic growth factor GM-CSF [11]. A pulmonary abnormality develops that resembles alveolar proteinosis.

Acute-onset silicosis was recognized in the 1930s, and was called "acute silico-proteinosis" because its histological appearance resembled to PAP [12]. It was associated with heavy short-term exposure to high concentrations of inhaled free silica. With the improved occupational health and safety standards put in place since the 1980s, this condition has been rarely reported. Our patient had a multi-year exposure to silica in the glass-grinding factory and construction yard. The duration and amount of the dust inhaled could not be documented clearly. His PAP might have been associated with silica particles. Although his dyspnea seemed to improve faster after he left the construction yard, the response could be the result of repeated whole lung lavage. We would like to assume his PAP was due to the secondary PAP. However, since we did not check the GM-CSF auto-antibody, we could not completely rule out the possibility of the acquired form of PAP.

Diagnosis of PAP requires open-lung biopsy in most cases, and this remains the gold standard, although false negatives are possible because of sampling error. Another diagnostic modality is bronchoalveolar lavage. The characteristic findings for PAP are a milky appearance with large amounts of granular acellular eosinophilic proteinaceous material and morphologically abnormal "foamy" macrophages engorged with diastase-resistant PAS-positive intracellular inclusions. The presence of concentrically laminated phospholipid structures, called lamellar bodies, on the electron microscopic examination of BAL fluid can be confirmatory [13].

Elevation of serum lactatedehydrogenase (LDH) is the most common laboratory abnormality in PAP patients. The elevation is usually mild, approximately 25% above normal. The serum LDH isoenzyme distribution is normal. Serial measurements of the LDH level in individual cases have suggested that the level of the enzyme may be useful as an indicator of disease severity. The LDH level is not predictive of survival.

A retrospective analysis of 303 cases found clinically significant spontaneous improvement in 24 patients (8 percent) [7]. The standard treatment is still therapeutic whole lung lavage, which was first applied by Dr. Jose Ramires-Rivera in 1964. The procedure provided a survi-

val benefit. The patients who underwent lavage at any time during the course of their disease had a superior survival, with a 5-year actuarial survival rate from diagnosis of 94 ± 2%, compared with 85 ± 5% for those not receiving such treatment ($p = 0.04$) [7]. Paired pre-lavage and post-lavage data for PaO_2, [A-a] D_{O2}, FEV_1, vital capacity or DL_{CO} were available in 47 patients, and a favorable response was claimed for 85% of the patients.

Patients often feel dramatic improvement after the lung lavage: 30% to 40% of patients require only 1 lavage. The mean increase of arterial PO_2 is 20.1 mmHg within 3 months following the lavage. However, the median total number of procedures performed was 2 (range, 1 to 22) [7].

Fiberoptic bronchoscopy lobar lavage is an alternative treatment. It does not require endotracheal intubation, double-lumen tubes, general anesthesia, or a postoperative care facility. However, the volume of the lavage fluid thus was limited to about 2 liters [17], roughly one- tenth of the volume that would be used in a whole-lung lavage. Therefore, fiberoptic bronchoscopy lobar lavage is not effective for patients with advanced cases of PAP.

Studies in mouse models of pulmonary alveolar proteinosis revealed the critical roles of GM-CSF in surfactant homeostasis. The levels of GM-CSF in bronchoalveolar lavage fluid and plasma are actually elevated in the acquired form, thus ruling out the possibility that the disease is due to the absence of GM-CSF itself [14]. Bronchoalveolar lavage fluid from patients with acquired PAP inhibited the ability of GM-CSF to stimulate the proliferation of normal monocytes and a GM-CSF-dependent cell line, and competitively inhibited the binding of GM-CSF to cells bearing GM-CSF receptors [15]. The inhibitory activity was due to a neutralizing IgG antibody against GM-CSF [16]. Several prospective phase 2 trials of subcutaneous GM-CSF therapy for acquired pulmonary alveolar proteinosis have been undertaken. The results are encouraging (with a response rate of 9/14 patients in 1 series).

In conclusion, our patient had secondary PAP associated with silicate inhalation. His clinical manifestations, images, and pathologic pictures were typical. However, his PaO_2 improvement was less than expected. Further management included repeated therapeutic whole lung lavage sessions, and an investigation of the autoantibody to GM-CSF.

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肺蛋白質沉積症—病例報告與文獻回顧

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肺蛋白質沉積症是少見之疾病。它於1958年被提出，特色是在肺泡中有periodic acid-Schiff特殊染色陽性物質的沉積。一個55歲男性於住院前九個月開始有呼吸困難以及輕微咳嗽。胸腔x光片顯示瀰漫性間質浸潤。動脈血氧分析顯示低血氧濃度以及擴散能力降低。胸部電腦斷層發現區域毛玻璃樣病變與碎石路模式（crazy-paving pattern）。肺部病理切片確認肺蛋白沉積症診斷。病人後續接受多次全肺灌洗術治療。其臨床症狀以及動脈血氧濃度逐漸改善。*(胸腔醫學* ***2006; 21: 119-125)***

關鍵詞：肺蛋白沉積症，碎石路模式，全肺灌洗術

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Congenital Pulmonary Venolobar Syndrome in Adults — Two Case Reports

Hsu-Liang Chang, Inn-Wen Chong*, Jhi-Jhu Hwang, Tung-Heng Wang, Chih-Jen Yang, Ming-Shyan Huang

The congenital pulmonary venolobar syndrome (CPVS) is a rare congenital abnormality of the thorax that may appear singly or in combination. The common components of CPVS include hypogenetic lung, partial anomalous pulmonary venous return, absence of a pulmonary artery, pulmonary sequestration, systemic arterialization of the lung, absence of the inferior vena cava, and an accessory diaphragm. The rare components of CPVS include tracheal trifurcation, eventration of the diaphragm, partial absence of the diaphragm, horseshoe lung, esophageal and gastric lung, anomalous superior vena cava, and absence of the left pericardium.

Herein, we present 2 young adult patients with CPVS. The first had a case of classic scimitar syndrome with right pulmonary venous drainage into the inferior vena cava. The other presented with partial anomalous drainage of the left pulmonary vein into the left branchiocephalic vein. A literature review is also included. ***(Thorac Med 2006; 21: 126-132)***

Key words: congenital pulmonary venolobar syndrome, scimitar syndrome, partial anomalous pulmonary venous return, PAPVR

Introduction

The first case report of pulmonary venous drainage into the vena cava was published in 1836 by Cooper [1]. Felson later coined the term "congenital pulmonary venolobar syndrome" (CPVS) in an attempt to encapsulate the congenital abnormalities of the thorax that may appear singly or in combination [2]. CPVS is a rare congenital disease of the thorax. The common components of CPVS are hypogenetic lung with or without dextrocardia (including lobar agenesis, aplasia, hypoplasia), partial anomalous pulmonary venous return (PAPVR), absence of a pulmonary artery, pulmonary sequestration, systemic arterialization of the lung, absence of the inferior vena cava, and an accessory diaphragm [1-2]. The rare components of CPVS include tracheal trifurcation, eventration of the diaphragm, partial absence of the diaphragm, horseshoe lung, esophageal and gastric lung, anomalous superior vena cava, and absence of the left pericardium [3-10]. The scimitar syndrome is a form of CPVS consisting of a partial anomalous pulmonary

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venous return from the right lung to the inferior vena cava (IVC). The roentgenographic appearance of the anomalous right pulmonary vein resembles a scimitar (a curved Turkish sword)—hence the name. Herein, we present 2 young adult cases of CPVS.

Case Presentation

Case 1

A 26-year-old female presented with slight shortness of breath and a nausea sensation. She denied cough or fever. She also denied asthma or a history of smoking. Physical examination revealed no significant heart murmur, but diminished breathing sounds in the right lower lung. An electrocardiogram demonstrated normal sinus rhythm without any abnormalities. The chest X-ray showed a small right hemithorax, elevation of the right hemidiaphragm, an engorged tubular shadow at the medial aspect of the right lower lung, and dextroposition of the heart (Figure 1A). Contrast-enhanced chest computed tomography (CT) revealed a shift of the mediastinum and heart to the right, partial anomalous right pulmonary venous drainage into the inferior vena cava, and

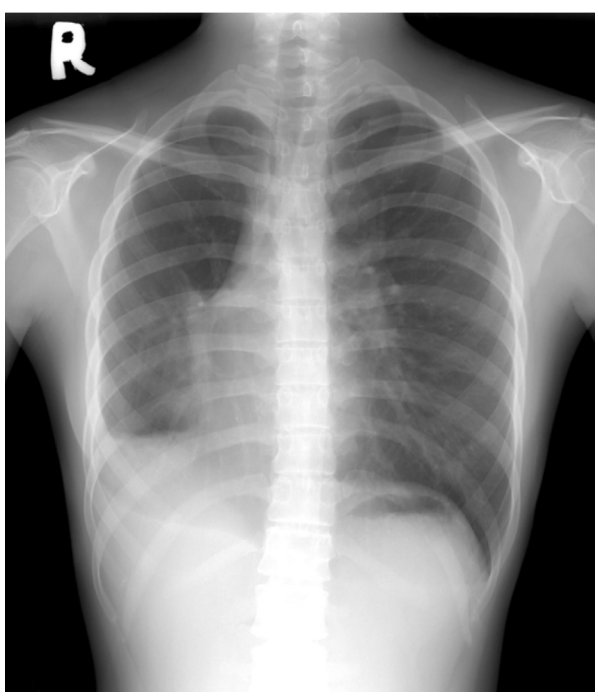

Fig. 1A. (Case 1) Chest X-ray shows a small right lung, elevation of the right hemidiaphragm, an engorged tubular shadow at the medial aspect of the right lower lung, and dextroposition of the heart.

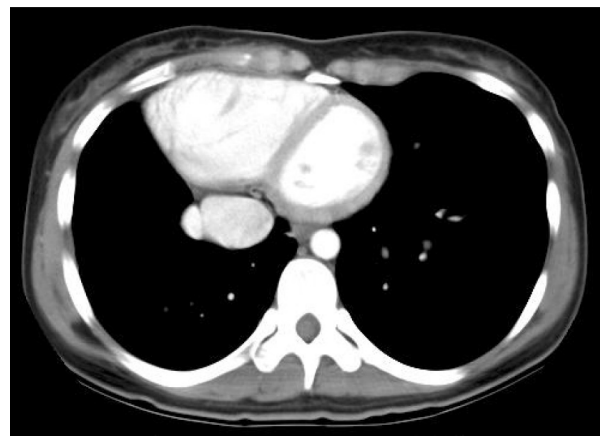

Fig. 1B. (Case 1) Enhanced chest CT shows a shift of the mediastinum to the right and right pulmonary vein drainage into the inferior vena cava.

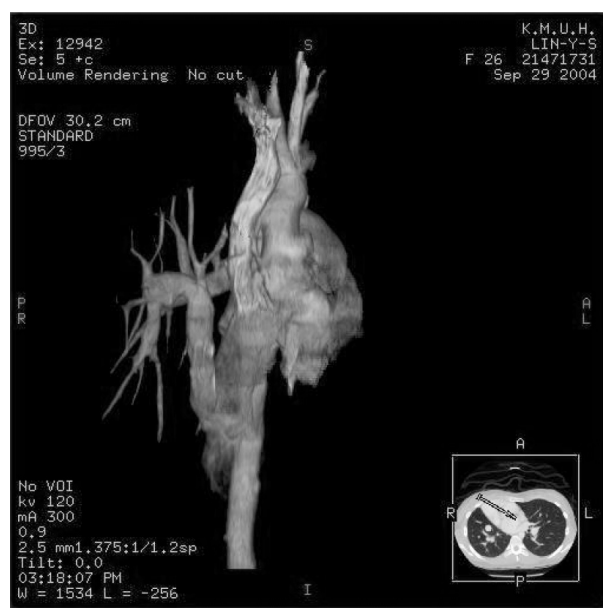

Fig. 1C. (Case 1) Reconstructed chest CT reveals right pulmonary venous drainage into the inferior vena cava.

agenesis of the right middle lobe (Figure 1B, 1C), which was consistent with the diagnosis of scimitar syndrome. The echocardiography revealed no intracardiac shunting.

Case 2

This 36-year-old male was asymptomatic. He denied cough, fever, shortness of breath, or hemoptysis. Physical examination revealed no significant heart murmur, and normal breathing sounds. An electrocardiogram demonstrated normal sinus rhythm with no abnormalities. The chest X-ray revealed left hilar enlargement (Figure 2A). Contrast-enhanced chest CT revealed the pulmonary vein of the left upper lobe draining into the left branchiocephalic vein, and a patent trachea and brachial trees (Figure 2B), which were consistent with the diagnosis of congenital pulmonary venolobar syndrome. The echocardiography revealed no intracardiac shunting.

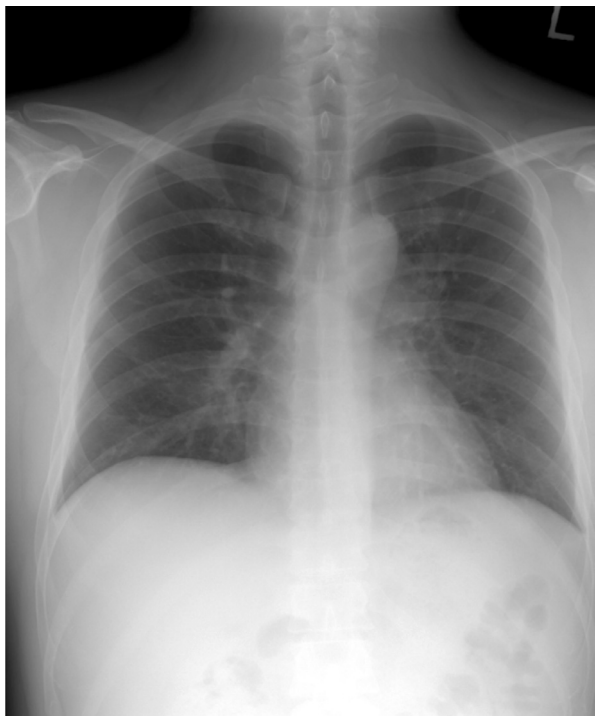

Fig. 2A. (Case 2) Chest X-ray shows left hilar enlargement.

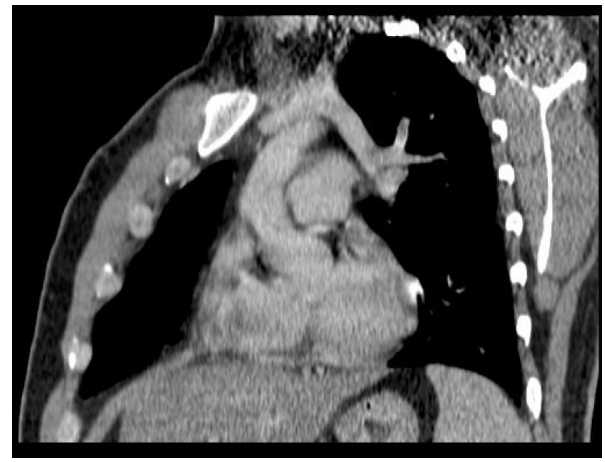

Fig. 2B. (Case 2) Enhanced chest CT reveals left upper lobe drainage of the pulmonary vein into the left branchiocephalic vein.

Discussion

The incidence of CPVS is probably 1-3 per 100,000 live births, and is associated variably with other congenital cardiopulmonary abnormalities [4]. This syndrome is more common in females. The most constant components of the syndrome are hypogenetic lung and partial anomalous pulmonary venous return (PAPVR) [1]. The clinical symptoms depend on the degree of shunting, the number of anomalous veins and the concomitant cardiac or pulmonary disease. Most patients are asymptomatic, but the symptoms of heart failure or pulmonary hypertension may occur in some infantile forms of CPVS [11-12]. Other symptoms reported are fatigue, dyspnea on exertion, paroxysmal tachycardia, chest discomfort, hemoptysis, and pulmonary infection [4, 11-12]. In the presentation, 1 of our patients was slightly short of breath, and the other was asymptomatic.

The involved lung is usually hypoplastic, with underdevelopment of both the bronchial trees and the vascular structures. The malformation is more common in the right lung than the left, and 1 or

more lobes may be absent [4-5, 11]. The right upper and middle lobes are most commonly affected in patients with hypogenetic lung [10]. In our case 1, right middle lobe agenesis was noted. The other associated thoracic abnormalities include PAPVR, pulmonary sequestration, systemic arterialization of the lung, absence of the inferior vena cava, and accessory diaphragm, tracheal trifurcation, eventration of the diaphragm, partial absence of the diaphragm, horseshoe lung, esophageal and gastric lung, anomalous superior vena cava, and absence of the left pericardium [1-10]. Scimitar syndrome is a form of CPVS consisting of partial anomalous pulmonary venous return from the right lung to the inferior vena cava (IVC), with or without hypoplasia of the right lung, with dextroposition of the heart, and an anomalous systemic arterial supply to a portion of the right lung (usually the lower lobe). Case 1 is a classic case of scimitar syndrome. Bronchiectasis is also found in a few patients with CPVS.

In CPVS, the anomalous vein usually drains into the IVC below the right hemidiaphragm, but drainage into the right atrium, SVC, azygos vein, hepatic vein, or portal vein has been reported [4, 6-7, 10, 12-13]. In case 1, the anomalous right pulmonary vein drained into the IVC, as in classic scimitar syndrome. In case 2, the patient presented with partial anomalous drainage of the left pulmonary vein into the left branchiocephalic vein. CPVS involving the left lung has been rarely reported. To our knowledge, this is the first case of left pulmonary venous drainage into the left branchiocephalic vein in CPVS. Pulmonary sequestration is defined as a segment of the lung tissue that is separate from the tracheobronchial tree and is supplied by a systemic artery, rather than a pulmonary artery. Intralobar sequestration is more common than extralobar sequestration in patients with CPVS [10]. Rare variants of sequestration, such as bilateral sequestration and gastric or esophageal lung, have been reported in patients with CPVS [9, 14]. Horseshoe lung is a rare abnormality in association with CPVS, and is an isthmus of pulmonary parenchyma extending from the right lung base across the midline, behind the pericardium, and joining the posterior basal segment of the lungs [3-4].

Concomitant heart disease is present in up to 25% of patients, most commonly atrial septal defect (ASD) of the sinus venous type [12]. Such cases are usually noted in infancy or childhood, and the prognosis depends on the severity of the cardiac abnormality [12]. Other cardiac abnormalities, such as ventricular septal defect, patent ductus arteriosus, coarctation of the aorta, hypoplastic left heart, tetralogy of Fallot, and pulmonary arterial hypertension have been reported [12, 15]. There were no cardiac abnormalities in our 2 cases.

The chest X-ray shows an anomalous curvilinear vascular structure toward the right atrium or the IVC (scimitar sign), and may reveal a small right hemithorax with a shift of the heart and mediastinum to the right, an elevated right hemidiaphragm, and a small or absent right pulmonary artery in scimitar syndrome (such as in the roentgenographic finding of case 3-dimensional) and magnetic resonance imaging are helpful in identifying PAPVR drainage, an absence of the pulmonary artery, diaphragmatic defects, pulmonary sequestration, and other associated lesions [16]. In addition, computed tomography and magnetic resonance angiography can be used as a non-invasive procedure to detect the pulmonary vascular anatomy in this syndrome. Two-dimensional echocardiogram and color-flow Doppler mapping are helpful in delineating the anatomy of the venous drainage, the septal defect, and the shunting volume [17]. Cardiac catheterization can

be useful in detecting the pulmonary venous drainage of each lung, the cardiac anomalies, and the degree of left-to-right shunt that might warrant surgical correction [13].

The management of patients with CPVS depends on the patient's age and severity of symptoms. In asymptomatic patients, conservative treatment is recommended [18]. There are 2 indications for surgical intervention: (1) a large left-to-right shunt exceeding 50%, resulting in pulmonary hypertension and heart failure (2), pulmonary sequestration, and/or recurrent pulmonary infections [13, 19]. The goal of surgery is the reduction of left-to-right shunting, redirection of the pulmonary venous return, and correction of congenital cardiac disorders [18]. Partial lobectomy or pneumonectomy is used for recurrent pulmonary infections or pulmonary sequestration [13].

In conclusion, congenital pulmonary venolobar syndrome is a rare congenital abnormality of the thorax that may appear singly or in combination with other disease. Concomitant heart disease, most commonly atrial septal defect, is present in up to 25% of cases. Most patients are asymptomatic, and conservative treatment is suggested. Few patients with a large left-to right shunt or other complications are suggested for surgery.

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先天性肺靜脈葉症候群—兩個病例報告

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先天性肺靜脈葉症候群(congenital pulmonary venolobar syndrome, CPVS)是一種罕見的胸腔先天性的異常，可能單獨出現或合併其他異常疾病。先天性肺靜脈葉症候群中常見的要素包括肺部發育不全、部分肺靜脈回流異常、肺動脈缺乏、肺隔離、肺部的系統性動脈化、下腔大靜脈缺乏及副橫膈膜的發生；少數的要素包含氣管三分支化、橫膈膜膨出、部分橫膈膜缺乏、馬蹄形肺臟、食道和胃部的隔離肺、上腔大靜脈異常及左心包膜的缺乏。在此我們提出兩個先天性肺靜脈葉症候群的病例，一個是典型的scimitar症候群，表現出右側肺動脈灌流至下腔大靜脈；而另一位病例則是左側部分肺動脈灌流至左側臂頭靜脈。在此並回顧歷年來與此種病例相關的文獻報告。*(胸腔醫學* ***2006; 21: 126-132)***

關鍵詞：先天性肺靜脈葉症候群， scimitar 症候群，部分肺靜脈回流異常

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