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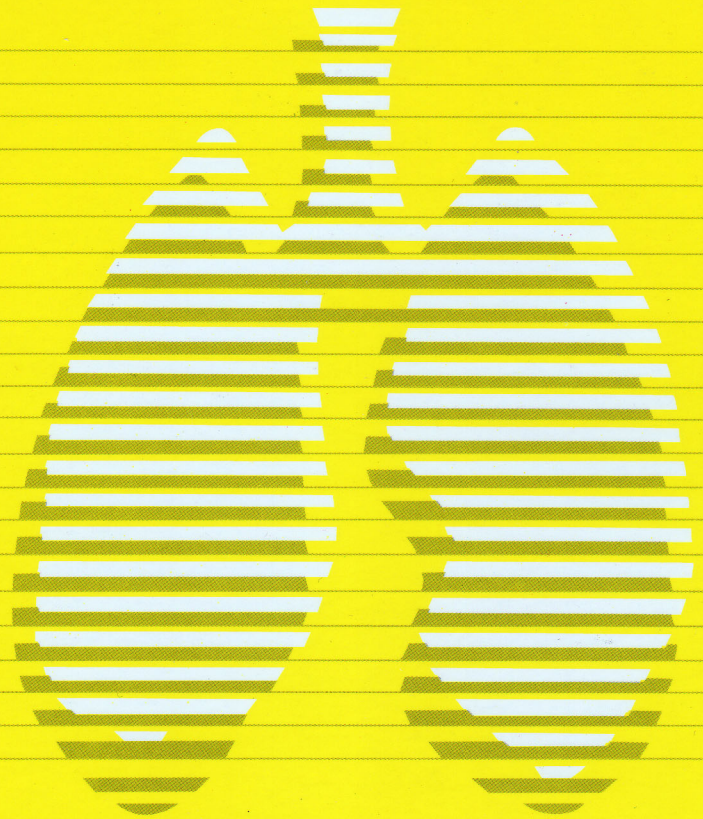

台灣胸腔暨重症加護醫學會

11217 台北市北投區石牌路二段201號

5.No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan 11217, R.O.C.

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Thoracic Medicine

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Orginial Articles

Case Reports

Diagnostic Yield of Endobronchial Ultrasound-Guided Transbronchial Biopsy in Peripheral Pulmonary Lesions

Jiun-Ting Wu, Chao-En Huang, Yu-Feng Wei, Chien-Tung Chiu, Yung-Fa Lai

Objective: Endobronchial ultrasound (EBUS) has emerged as a new diagnostic tool that allows bronchoscopists to see beyond the airway. The radial-type miniature probe can localize peripheral pulmonary lesions (PPLs) prior to transbronchial biopsy (TBB). The purpose of this retrospective study was to evaluate the factors affecting the diagnostic yield of lung lesions using EBUS-guided bronchoscopic examinations performed by highly experienced bronchoscopists.

Methods: From 2009 to 2010, 144 patients with pulmonary lesions that were beyond the segmental bronchus received EBUS examinations at E-DA Hospital. Their medical records were reviewed and analyzed retrospectively.

Results: Pulmonary lesions were found in 120 patients (83.3%) using EBUS. Lesion size was a determining factor for the visibility of the PPLs. A definitive diagnosis was established in 114 of the 120 patients. The diagnostic rate of EBUS-TBB in EBUS-visible lesions was 82.4% (94/114). The overall diagnostic yield of EBUS-guided bronchial examinations was 65.3% (94/144). Binary logistic regression analysis revealed that a lesion size larger than 3 cm, the probe within the lesion, and the lesion located in the left upper lobe relative to the right lower lobe were independent predictors of diagnostic yield (p=0.029, 0.029 and 0.036, respectively).

Conclusions: Lesion size is a significant factor influencing the visibility of PLLs. The lesion size, the probe position and the lesion location (left upper lobe relative to the right lower lobe) were independent predictors of diagnostic yield by EBUS-guided bronchoscopic examination. ***(Thorac Med 2012; 27: 318-326)***

Key words: endobronchial ultrasound (EBUS), transbronchial biopsy (TBB), peripheral pulmonary lesions (PPLs)

Introduction

The diagnostic approach with regard to peripheral pulmonary lesions (PPLs) is technically challenging using conventional bronchoscopy. Endobronchial ultrasound (EBUS) is a

Division of Pulmonary Medicine, Department of Internal Medicine, E-DA Hospital / I-Shou University, Kaohsiung, Taiwan

Address reprint requests to: Dr. Yung-Fa Lai, Division of Pulmonary Medicine, Department of Internal Medicine, E-DA Hospital / I-Shou University, Kaohsiung, Taiwan, No. 1, Yida Road, Jiao-Su Village, Yan-Chao District, Kaohsiung City 824, Taiwan

valuable tool to help visualize PPLs. EBUS, first introduced in 1990 by Hurter and Hanrath, has been evaluated in several clinical studies and has been shown to provide information about the location of PPLs [1-2]. The EBUS guidance procedure also reduces discomfort and improves the accuracy of diagnosis in PPLs compared to conventional bronchoscopy [3-4]. The diagnostic yield of EBUS using a radial-type miniature probe has been reported to be 61-80% [5-6]. To increase the diagnostic yield of EBUS-guided procedures, measuring and applying the distance between the orifice of the bronchus and the lesion has been reported as an alternative to a guide sheath (GS) and fluoroscopy [7].

Although previous studies have shown that the location, size and CT appearance of PPLs and the position of the probe are statistically significant predictors of diagnostic sensitivity [8-9], these factors have always been influenced by the technique and experience of those performing the examinations [10]. EBUS has been available at E-DA Hospital since June 2009. The present study was undertaken to analyze the factors affecting the visibility of PPLs and the diagnostic yield of EBUS-guided examinations performed by well-trained bronchoscopists in daily practice.

Methods

Patients

From June 2009 to July 2010, 632 patients received bronchoscopy examinations for various indications at E-DA Hospital. Of these 632 patients, 144 with PLLs that were not visualized under flexible video bronchoscopy were eligible for EBUS examinations. The medical records of these patients were retrospectively reviewed. Both chest roentgenogram (CXR) and chest computerized tomography (CT) were used to determine the size and location of these lesions. Lesions were divided into solid nodule/mass-like or alveolar/consolidative patterns, based on the imaging findings.

Bronchoscopic procedure and EBUS-transbronchial biopsies

A flexible video bronchoscope (BF-260, Olympus, Tokyo, Japan) was used for all procedures in this study. Bronchoscopy was performed under local anesthesia with 2% lidocaine. A 20-MHz radial-type miniprobe EBUS (UM-S20-20R, Olympus, Tokyo, Japan) equipped with an endoscopic ultrasound system (EU-M30S, Olympus, Tokyo, Japan) was used in all procedures. Once the lesion had been identified with an EBUS image, the distance between the bronchial orifice and the lesion was measured. The location of the probe was defined as within the lesion or adjacent to the lesion. After locating the PLL, the EBUS probe was then withdrawn and transbronchial biopsy (TBB) and bronchial washing were performed. Biopsy specimens were taken and submitted for histological examinations by a pathologist. EBUS and bronchoscopic procedures were performed by 3 well-trained bronchoscopists, all of whom had more than 3 years of experience. If the bronchoscopy examinations could not offer the definite diagnosis, the patients underwent a percutaneous CT-guided biopsy, pleural effusion study, pleural biopsy, operation (video-assisted thoracoscopy, lobectomy, wedge resection) or clinical/radiological follow-up for a final diagnosis.

Statistical analysis

Two-sided Fisher's exact tests and chi-

square tests were used for categorical variables. Continuous variables were analyzed using independent-samples Student's *t*-tests. Binary logistic regression was used to assess the contribution of significant predictors influencing diagnostic yield by EBUS-guided TBB. The Statistical Package for the Social Sciences software package version 16.0 was used (SPSS Inc., Chicago, IL, USA). A p value less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 144 patients (98 males and 45 females) with an average age of 63.40 ± 13.72 years (range 20-88 years) received EBUS for advanced localization of PLLs. The pulmonary lesions were mass or nodule-like in 117 patients (81.3%), and alveolar or consolidative in 27 patients (18.8%). The mean diameter of the pulmonary lesions was 4.25 ± 2.11 cm (range 0.4-13.0 cm). Of the 144 patients in this study, 120 had lesions which could be visualized on EBUS images, and 131 had a final diagnosis (Figure 1).

EBUS-TBB

Factors related to the visualization of lesions

The lesions of 120 patients were visible on EBUS images, with a visualization rate of 83.3% (120/144). The features associated with the visualization on EBUS are summarized in Table 1. The significant independent factors in the visualization yield were lesion size (mean size (p<0.001), lesion > 3 cm vs. ≤ 3 cm (p=0.001), and lesion > 2 cm vs. ≤ 2 cm (p=0.043)). There were no significant differences related to the location and appearance in CT findings.

Factors influencing the diagnostic yield by EBUS-TBB

One hundred thirty-one patients with a final diagnosis were analyzed in this study, and the final diagnosis was made by EBUS-TBB in 94 patients. The overall diagnostic yield of EBUS-

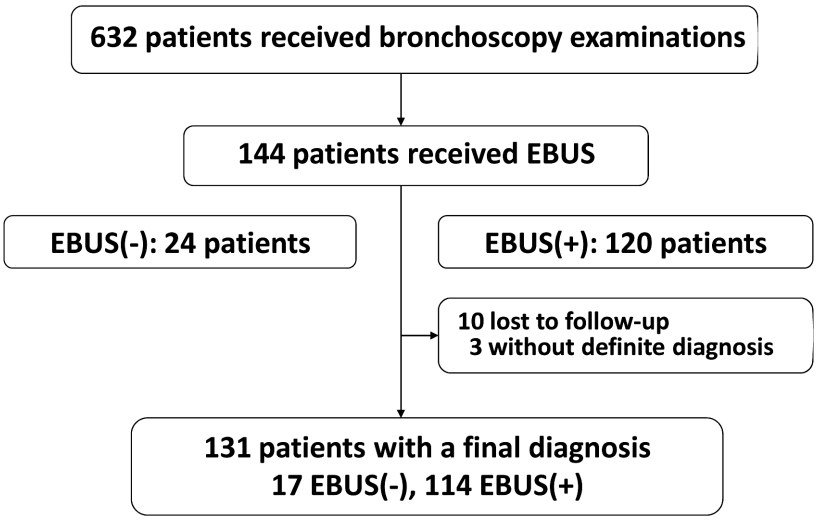

Fig. 1. Patient profile.
*EBUS = Endobronchial ultrasound, EBUS(+) = Lesions visible on EBUS, EBUS(-) = Lesions invisible on EBUS

Table 1. Characteristics of the patients undergoing EBUS

	EBUS(+) N=120 (83%)	EBUS(-) N=24 (17%)	*p*-value
Age (yrs)	64.1 ± 12.7	59.9 ± 17.9	0.169
Male gender (%)	85 (71%)	13 (54%)	0.110
Lesion size (cm)	4.6 ± 2.1	2.7 ± 1.3	<0.001
Distribution of lesion size			
> 3 cm	88 (91%)	9 (9%)	0.001
≤ 3 cm	32 (68%)	15 (32%)	
> 2 cm	112 (85%)	19 (15%)	0.043
≤ 2 cm	8 (62%)	5 (38%)	
Location of lesion			0.481
LUL	38 (83%)	8 (17%)	
LLL	24 (86%)	4 (14%)	
RUL	30 (88%)	4 (12%)	
RML	14 (70%)	6 (30%)	
RLL	14 (88%)	2 (12%)	
Lesion on CT findings			1.0
Nodule/mass	97 (81%)	20 (83%)	
Alveolar/consolidative	23 (19%)	4 (17%)	

*EBUS = Endobronchial ultrasound, EBUS(+) = Lesions visible on EBUS, EBUS(-) = Lesions invisible on EBUS, LUL = left upper lobe, LLL = left lower lobe, RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe

TBB was 65.3% (94/144). The final diagnosis of all lesions is shown in Table 2. Sixty-five patients were diagnosed with malignant disease and 66 were diagnosed with benign lesions. Thirty-seven patients (34.7%) had a non-diagnostic bronchoscopy, with the diagnosis being established by other methods such as surgical biopsy or resection (15 patients), cytology or bronchial washing culture (7 patients), CT-guided biopsy (6 patients), pleural biopsy (3 patients), and pleural effusion cytology (1 patient). Five patients were diagnosed as having benign lesions based on the clinical course and imaging follow-up.

In 20 of the 37 patients without a definite diagnosis, PLLs were visualized by EBUS. Of the lesions revealed by EBUS, the overall diagnostic yield was 82.5% (94/114). The factors influencing the diagnostic yield of EBUS-TBB are listed in Table 3. The size of the lesions (mean and > 3 cm or ≤ 3 cm) (p<0.001 and p=0.005, respectively) and the probe position on EBUS images (within or adjacent to the lesions) (p=0.011) were statistically significant factors influencing the diagnostic yield of EBUS-TBB. The age of the patients, gender, distance of probe insertion, location of the lesion, and appearance of the lesion did not affect the diagnostic yield by EBUS-TBB.

Using binary logistic regression analysis, the diagnostic yields of EBUS-TBB for lesions > 3 cm were significantly higher when the probe was within the lesion and the lesion was located in the left upper lobe than for lesions ≤ 3 cm when the probe was adjacent to the lesion, and the lesion was located in the right lower

Table 2. Final diagnosis of 131 patients

Final Diagnosis	EBUS(+)	EBUS(-)
Malignant lesions (n=65)		
Adenocarcinoma	40	1
Squamous cell carcinoma	7	
Small cell carcinoma	6	1
Non-small cell lung cancer	5	1
Metastatic cancer[+]	6[+]	
Other (MALT lymphoma)	1	
Benign lesions (n=66)		
Tuberculosis	24	6
Pneumonia	23	2
Chronic fibrosis (granuloma)	9	3
Cryptococcus	3	
Aspergillus	2	
Organizing pneumonia	1	1
Hamartoma	1	1
Pulmonary sequestration	1	1
Actinomycosis	1	
Sclerosing hemangioma	1	
Total	131	17

*EBUS = Endobronchial ultrasound, EBUS(-) = Lesions invisible on EBUS

+2 nasopharyngeal cancer, 1 breast cancer, 1 endometrioid cancer, 1 malignant melanoma, 1 colon cancer

lobe (p=0.029, p=0.029 and p=0.036, respectively) (Table 4).

No major complications such as severe hypoxemia, significant post-procedure bleeding or pneumothorax were observed in this study.

Discussion

The utility of EBUS as an adjunct for the diagnosis of PPLs has been well investigated [3,6]. However, the diagnostic yield of EBUS-guided TBB can be influenced by the experience and proficiency of the bronchoscopists. In this study, the EBUS procedures were performed by 3 well-trained bronchoscopists (each performing at least 30 procedures per year). The visualization yield of EBUS for PPLs was 87% and the overall diagnostic yield was 65.3%, which are comparable to other studies without fluoroscopy-guided or sheath-guided TBB [7,11].

The lesion size was a statistically independent factor in determining the visibility of PLLs in this study (p<0.001). No statistical difference in visualization was noted with regard to the locations and image findings of the lesions. When the lesion size was > 3 cm, the visibility of the lesion was 91%, and when the lesion size was ≤ 2 cm, the visualization yield was 62%. Our visualization yield results for small-sized PLLs

Table 3. Characteristics and results of EBUS-TBB

	Identified EBUS-TBB N (%)	Unidentified EBUS-TBB N (%)	*p*-value
Patients numbers	94 (65.3)	20 (34.7)	
Age (years)	64.4 ± 12.3	62.3 ± 11.7	0.475
Male gender (%)	65 (69%)	15 (75%)	0.603
Lesion size (cm)	4.9 ± 2.1	3.5 ± 1.7	0.009
Distribution of lesion size			
> 3 cm	75 (88%)	10 (12%)	0.005
≤ 3 cm	19 (66%)	10 (34%)	
> 2 cm	90 (84%)	17 (16%)	0.102
≤ 2 cm	4 (57%)	3 (43%)	
Position of the probe			0.011
Within the lesion	81 (87%)	12 (13%)	
Adjacent to the lesion	13 (62%)	8 (38%)	
Depth of probe insertion (cm) (from bronchial orifice)	4.2 ± 1.5	4.8 ± 1.1	0.147
Location of lesion			0.203
LUL	35 (92%)	3 (8%)	
LLL	19 (79%)	5 (21%)	
RUL	22 (85%)	4 (15%)	
RML	10 (71%)	4 (29%)	
RLL	8 (67%)	4 (33%)	
Lesion on CT finding			0.246
Nodule or mass	74 (80%)	18 (20%)	
Final diagnosis			0.187
Malignant	49 (79%)	13 (21%)	
Benign	45 (86%)	7 (14%)	

*EBUS = Endobronchial ultrasound, TBB = Transbronchial biopsy, LUL = left upper lobe, LLL = left lower lobe, RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe

were slightly higher than in a previous study (49%) [8]. This discrepancy may have been due to the different levels of experience of the bronchoscopists. To achieve a better visualization yield of PLLs, new technologies such as electromagnetic navigation bronchoscopy and bronchoscope insertion guidance systems have been developed in recent years [12-13].

In our study, the overall diagnostic yield when the EBUS probe was located within the lesion was significantly higher (87%) than when the probe was located adjacent to the lesion (62%, p=0.011). The position of the probe was undoubtedly a significant factor influencing the diagnostic yield, which is consistent with the results of previous studies [7-8]. The diagnostic yield of PLLs > 3 cm in mean diameter was significantly higher than that of PLLs ≤ 3 cm in mean diameter (p=0.009). Although small PLLs ≤ 2 cm in mean diameter had an obviously

Table 4. Binary logistic regression of factors influencing the diagnostic yield of EBUS-TBB

	Univariate *p*-value	Multivariate *p*-value	Odds ratio (95%CI)
Lesion size > 3 cm	0.005	0.029	3.463 (1.133-10.580)
Probe within the lesion	0.011	0.029	4.023 (1.156-14.001)
Location of lesion	0.203		6.828 (1.133-41.141)
LUL vs. RLL		0.036	
LLL vs. RLL		0.270	
RUL vs. RLL		0.072	
RML vs. RLL		0.648	

*LUL = left upper lobe, LLL = left lower lobe, RUL = right upper lob, RML = right middle lobe, RLL = right lower lobe, 95%CI = 95% confidence interval

lower diagnostic yield (57%) than those > 2 cm (84%), there was no statistically significant difference. The yield rate was similar to that in the report by Yang *et al*. [3], but mildly inferior to other previous studies [7-8]. The reason for this may be the small number of patients with small PLLs in our study (6%, 7/114). A diagnostic yield of less than 70% is usually observed with small PPLs, and no significant differences between PLLs > 2 cm and ≤ 2 cm in mean diameter have been reported in previous studies without the use of fluoroscopy and GS [7-8]. The application of EBUS-GS for small PLLs (lesion ≤ 2 cm) may be the ideal choice, since it has been proven to have a better diagnostic yield, and also provides access to bronchial lesions for repeated biopsy and protects against bleeding post-biopsy [13-14].

A previous study showed that the diagnostic yield of EBUS-TBB was affected by the distribution distance from the hilum, and that peripheral PLLs had a significantly lower yield than central PLLs [8]. In our study, we found that a shorter probe insertion distance achieved a better identification and diagnosis of PLLs, but without statistical significance (p=0.147). Our study results are comparable to those of Chung *et al*., who reported that the mean measured probe insertion distances were not significantly different between patients whose lesions were diagnosed or not [7]. This may be because the position of the probe within or adjacent to the lesion could overcome the effect of the biopsy forceps being dislocated from the target bronchus of peripheral PLLs after EBUS withdrawal.

Binary logistic regression analysis in our study revealed that the diagnostic yields of lesions located in the left upper lobe were significantly higher than the yields of lesions located in the right lower lobe. This result is consistent with those of Yang et al. [3], and may be explained by the fact that TBB under EBUS guidance may overcome the anatomically sharp angle of the left upper lobe, and thus achieve a better diagnostic yield than the complex airway of the right lower lobe. In addition, the bronchoscope was usually handled by the left hand of the operator, and a video monitor was positioned at the left side of the operator, which may have also led to a better diagnostic yield of the left upper lobe lesions than the right lower lobe lesions.

There are some limitations to our study.

First, the study was a retrospective and consecutive analysis, and the study population was substantially different in terms of general characteristics. Although it was difficult to determine the distribution of lesion sizes, locations, imaging characteristics and final diagnoses (benign or malignant), the patients included in the analyses were typical of those in daily clinical practice. Second, nearly 10% of the patients (10 lost to follow-up and 3 without a definite diagnosis) with lesions visible on EBUS were excluded from the analysis in our study, and this bias may have influenced the analysis of the diagnostic yield of PLLs using TBB. Third, the limited number of patients analyzed in this study may have influenced the power of our findings, and therefore a larger prospective study should be conducted to confirm the findings of our study.

In conclusion, lesion size was a significant factor influencing the visibility of PLLs. Lesion size, the probe position and the lesion's relative location (left upper lobe relative to the right lower lobe) were independent predictors of diagnostic yield by EBUS-guided bronchoscopic examinations performed by well-trained bronchoscopists.

References

1. Hurter T, Hanrath P. Endobronchial sonography: feasibility and preliminary results. Thorax 1992; 47: 565-7.
2. Kurimoto N, Murayama M, Morita K, *et al*. Clinical applications of endobronchial ultrasonography in lung disease. Endoscopy 1998; 30 (suppl 1): A8-12.
3. Yang MC, Liu WT, Wang CH, *et al*. Diagnostic value of endobronchial ultrasound-guided transbronchial lung biopsy peripheral lung cancers. J Formos Med Assoc 2004; 103: 124-9.
4. Shirakawa T, Imamura F, Hamamoto J, *et al*. Usefulness of endobronchial ultrasonography for transbronchial lung biopsies of peripheral lung lesions. Respiration 2004; 71: 260-8.
5. Herth FJ, Ernst A, Becker HD. Endobronchial ultrasound-guided transbronchial lung biopsy in solitary pulmonary nodules and peripheral lesions. Eur Respir J 2002; 20: 972-4.
6. Paone G, Nicastri E, Lucantoni G, *et al*. Endobronchial ultrasound-driven biopsy in the diagnosis of peripheral lung lesions. Chest 2005; 128: 3551-7.
7. Chung YH, Lie CH, Chao TY, *et al*. Endobronchial ultrasonography with distance for peripheral pulmonary lesions. Respir Med 2007; 101: 738-45.
8. Huang CT, Ho CC, Tsai YJ, *et al*. Factors influencing visibility and diagnostic yield of transbronchial biopsy using endobronchial ultrasound in peripheral pulmonary lesions. Respirology 2009; 14: 859-64.
9. Yoshikawa M, Sukoh N, Yamazaki K, *et al*. Diagnostic value of endobronchial ultrasonography with a guide sheath for peripheral pulmonary lesions without X-ray fluoroscopy. Chest 2007; 131: 1788-93.
10. Roth K, Eagan TM, Andressen AH, *et al*. A randomised trial of endobronchial ultrasound-guided sampling in peripheral lung lesions. Lung Cancer 2011; 74: 219-25.
11. Chao TY, Lie CH, Chung YH, *et al*. Differentiating peripheral pulmonary lesions based on images of endobronchial ultrasonography. Chest 2006; 130: 1191-7.
12. Eberhardt R, Anantham D, Herth F, *et al*. Electromagnetic navigation diagnostic bronchoscopy in peripheral lung lesions. Chest 2007; 131: 1800-5.
13. Asano F, Matsuno Y, Tsuzuku A, *et al*. Diagnosis of peripheral pulmonary lesions using a bronchoscope insertion guidance system combined with endobronchial ultrasonography with a guide sheath. Lung Cancer 2008; 60: 366-73.
14. Kurimoto N, Miyazawa T, Okimasa S, *et al*. Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest 2004; 126: 659-65.

支氣管內超音波導引經支氣管切片診斷肺部周邊病灶

吳俊廷　黃照恩　魏裕峰　邱建通　賴永發

前言：支氣管內超音波（Endobronchial ultrasound, EBUS）的臨床應用，讓支氣管鏡檢查產生新的進展。藉由幅射型微小探頭（radial-type mininature probe）定位肺部周邊病灶，有助於導引經支氣管切片，但診斷率會因為操作者經驗而影響。本研究的目的是分析 EBUS 在具有豐富經驗者的操作下，導引經支氣管切片診斷肺部周邊病灶的影響因子。

方法：將 2009 年至 2010 年間，所有於本院因肺部周邊病灶接受 EBUS 檢查的病患，進行回溯性病歷及影像資料分析。

結果：研究期間共 144 位病患因肺部周邊病灶接受 EBUS 檢查，120 位（83.3%）可得著 EBUS 影像，病灶大小是主要決定因子。在所有得到最後診斷的 131 位病患中，則有 114 位可得 EBUS 影像，94 位藉由 EBUS 導引經支氣管切片，直接得確切診斷。因此，當 EBUS 可見病灶時，診斷率為 82.4%（94/114）。就所有接受 EBUS 檢查的病患而言，整體診斷率為 65.3%（94/144)。二項式邏輯迴歸分析（Binary logistic regression analysis）顯示，病灶大於 3 公分相較小於等於 3 公分、EBUS 探頭置於病灶內相較於鄰接病灶、及病灶位於左上葉相較於右下葉，是影響 EBUS 導引經支氣管切片診斷率的獨立影響因子（p=0.029, 0.029 and 0.036）。

結論：就肺部周邊病灶而言，病灶大小是影響可否得著 EBUS 影像的決定因子。病灶大小、EBUS 探頭位置、及病灶位於左上葉相較於右下葉，則是影響 EBUS 導引經支氣管切片診斷率的獨立影響因子。
(胸腔醫學 ***2012; 27: 318-326)***

關鍵詞：支氣管內超音波，經支氣管切片，肺部周邊病灶

義大醫療財團法人義大醫院 / 義守大學　內科部　胸腔內科

索取抽印本請聯絡：賴永發醫師，義大醫療財團法人義大醫院 / 義守大學　內科部　胸腔內科，824 高雄市燕巢區角宿里義大路 1 號

Evaluating the Validity of Serum Neopterin in the Diagnosis of Pulmonary Tuberculosis Infection with Different Severities

Wen-Cheng Chao*,**, Ying-Hsun Wu***, Ruay-Ming Huang****, Shun-Tien Chien***

Background: Neopterin, produced by macrophages in tuberculosis (TB) infection, is still rarely used in clinical practice because of the poor validity. No study has been conducted to evaluate its efficacy under different clinical conditions. In this study, we aimed to investigate the role of serum neopterin in pulmonary TB infection of different severities.

Materials and Methods: We prospectively enrolled culture-proved pulmonary TB patients attending a TB referral hospital in southern Taiwan, and collected their serum for analysis.

Results: In all, 78 TB patients and 20 healthy controls were enrolled; 42 (54%) patients had severe TB, defined as sputum acid-fast stain (AFS) above 1+ and 36 (46%) had mild TB with AFS below or equal to 1+. In the severe TB patients, serum neopterin ($p<0.005$) and interferon-γ ($p<0.05$) were higher than in the controls, but tumor necrosis-α, monocyte chemotactic protein-1, and interleukine-6 were similar to the controls. The 5 tested biomarker levels were similar between the mild TB cases and the controls, so the poor validity in this patient population was not surprising. We found that serum neopterin has better accuracy in diagnosing severe TB than the other biomarkers.

Conclusion: Serum neopterin is an accurate diagnostic biomarker in severe pulmonary TB cases, but not in mild TB cases. ***(Thorac Med 2012; 27: 327-337)***

Key words: neopterin, tuberculosis, biomarker, severity

Introduction

Mycobacterium tuberculosis (TB) infection is still an important public health problem, not only in Taiwan but also throughout the world. Approximately 13,000 people in Taiwan and 9 million in the world develop active disease each year [1-2].

Biomarkers, however, have been rarely used during clinical practice in TB because of their relatively poor validities in diagnosis, severity classification, or prognosis prediction [3-4]. One

*Department of Internal Medicine, Taichung Veteran General Hospital, Chiayi Branch, Chiayi, Taiwan; **Institute of Clinical Medicine, National Cheng Kung University Medical College, Tainan, Taiwan; ***Division of Internal Medicine, Chest Hospital, Department of Health, Executive Yuan, Taiwan; ****Division of Internal Medicine, Hualien General Hospital, Department of Health, Executive Yuan, Taiwan

Address reprint requests to: Dr. Shun-Tien Chien, Chest Hospital, Department of Health, 864, Zhongshan Rd., Rende Dist., Tainan City 71742, Taiwan

of the causes of poor validity is that TB infection actually has a broad clinical disease spectrum resulting from complex host and pathogen interactions [5]. Hence, each biomarker has its specific clinical condition in which it is applied. For example, the T cell immunity-based marker should not be used in a TB-endemic country such as Taiwan, because of the tremendous confounding effect of latent TB infection [6]. But, macrophage activation markers, less influenced by latent TB infection, are promising TB biomarkers since macrophages play the pivotal role in TB pathogenesis [7].

Neopterin is produced by macrophages after stimulation by interferon-γ (IFN-γ) [8], and has been used as a marker of immunological activity in several diseases such as sarcoidosis, atherosclerosis, malignancies, sepsis, and TB infection [9-12]. Several studies have found an elevation of neopterin levels in serum, bronchoalveolar lavage fluid, and even urine of TB patients. However, neopterin is still rarely used in clinical practice because of its relatively poor validity to diagnose TB, and its known overall area under the curve (AUC) of approximately 60% using receiver operating characteristics (ROC) analysis [13-15]. But those studies did not elucidate the effect of disease severity on the clinical use of neopterin to diagnose TB, because few patients with severe TB infection have been enrolled in most studies. This study was conducted at the Chest Hospital, a TB referral center with 51 isolation beds; most of the advanced TB cases in southern Taiwan are referred to this hospital.

In this study, we aimed to investigate the role of serum neopterin in pulmonary TB infection with different severities. We first demonstrated that neopterin is an accurate diagnostic biomarker in severe pulmonary TB infection, but not in mild cases. Then, we showed that neopterin not only had an independent role beyond the downstream cytokines of IFN-γ in TB infection, but its dynamic change cannot be used as a prognostic biomarker to identify non-viable bacilli phenomena in severe TB patients with persistently positive AFS after anti-TB treatment for 8 weeks.

Materials and Methods

Patients

In this study, we used the Center for Disease Control (CDC) reporting system to prospectively enroll, from January 2010 to December 2010, TB patients at the Chest Hospital, a TB referral center in southern Taiwan with 51 negative-pressured isolation beds. The TB diagnosis was based on adequate microbiological evidence, which can be positive microscopy showing acid-fast rods, or positive PCR or culture. Around 10 cc of venous blood was taken for analysis, and the clinical data, including chest X-ray (CXR), sputum acid-fast stain (AFS) grades, culture results and other important clinical data, were recorded. Patients receiving health examinations at the Chest Hospital were enrolled as healthy controls.

Cytokines determination

The blood samples were centrifuged at 6^{o}C for 15 minutes and the serum samples were stored at -80^{o}C in a refrigerator for later analysis. In this study, we used ELISA to analyze neopterin (Human Neopterin ELISA kit, IBL Inc.) and IFN-γ (Human IFN-γ ELISA kit, R&D systems). We used luminex to measure the concentration of tumor necrosis factor-α (TNF-α), monocyte chemotactic protein-1 (MCP-1), and interleukine-6 (IL-6) (Luminex xMAP, Milli-

pore).

Statistical analysis

All data were first tested for normality using the Kolmogorov-Smirnov test. Data were presented as frequencies (n) or percentages (%) for categorical factors and as means ± standard deviation for continuous factors. Differences between patient subgroups were tested by Student's *t* test for comparison between 2 distinct groups and the one-way ANOVA test, followed by Tukey's *post hoc* test for more than 2 groups. The Mann-Whitney U test was used for comparison of non-normally distributed data between 2 distinct groups. Different biomarkers were tested for their association using Pearson correlation analysis, and their diagnostic performance in discriminating severe cases from mild TB cases and healthy controls was derived by receiver-operating characteristics (ROC) analysis. Statistical significance was set at $p < 0.05$, 2-sided. Data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Subject characteristics

In all, 78 TB patients and 20 healthy controls were enrolled. Of the 78 patients, 42 (54%) were severe cases, defined as sputum AFS above 1+, and 36 (46%) were mild cases with AFS below or equal to 1+. We found that the severe cases had a higher probability of fever (10/42; 24%), body weight loss (23/42; 55%), and higher white cell counts, but the percentages of neutrophils or lymphocytes, serum albumin levels, and serum electrolyte levels were similar to the mild cases. In comparing the classification system based on AFS grades used here to the other frequently used classification system based on CXR findings, we found that the moderately advanced TB cases (28 cases) as defined by CXR findings were actually mixed mild (12/28; 43%) and severe (16/28; 57%) cases using the classification system based on AFS grades (Table 1).

Serum biomarkers in TB patients with different severities and healthy controls

In this study, we measured the macrophage-activating biomarkers, including serum neopterin and IFN-γ, chemokine (MCP-1) and innate immunity-related cytokines, including TNF-α and IL-6. To minimize the differential error, we stored all serum samples in a -80°C refrigerator, and measured the 5 immunogenic biomarker levels of all enrolled patients at the same time. We first found that the immunogenic biomarker levels in the mild TB patients were all similar to those of the healthy controls. Next, we found that only macrophage-activating biomarkers, including serum neopterin and IFN-γ, were elevated in severe TB patients, compared to the mild TB cases or healthy controls, while MCP-1, TNF-α, and IL-6 were not elevated at all (Table 2). We further evaluated the serum neopterin levels in healthy controls and TB cases using the 2 severity classification systems based on AFS grades or CXR findings, and discovered that the serum neopterin levels were elevated in severe TB cases using the AFS grades classification system and in moderately advanced and far-advanced TB cases using the CXR finding classification system (Figure 1A and 1B).

Correlations between different biomarkers and their ability to diagnose TB

The trend of the level of serum neopterin and IFN-γ was found to be quite similar between the mild and severe TB patients. Hence, we examined their association and diagnostic

Table 1. Characteristics and laboratory data of patients and healthy subjects (controls)a

Characteristic	Tuberculosis patients		Controls (n=20)	*p* value
	Severe tuberculosisb (n=42)	Mild tuberculosisc (n=36)		
Gender (male : female)	36 : 6	24 : 12	11 : 9	NS
Age (years)	58 ± 19	61 ± 23	58 ± 17	NS
Clinical findings				
Actual body weight (kg)	53.5 ± 12.7	56.8 ± 10.6	62.4 ± 10.1	NS
BMI	19.9 ± 3.9	21.5 ± 2.8	23.5 ± 3.3	$p<0.05$
Fever	10 (24)	0 (0)	NA	$p<0.05$
Cough	36 (86)	24 (67)	NA	NS
Body weight loss	23 (55)	8 (22)	NA	$p<0.05$
Laboratory data				
White blood cell count (10^3/μl)	8777 ± 3081	7642 ± 3103	6800 ± 1678	$p<0.05$
Hemoglobin (g/dl)	12.1 ± 2.9	13.1 ± 1.7	14.3 ± 1.2	NS
Neutrophils (%)	68.3 ± 11.7	69.7 ± 11.9	66.7 ± 26.3	NS
Lymphocytes (%)	21.3 ± 10.1	20.7 ± 10.2	24.1 ± 21.4	NS
Albumin (mg/dl)	3.6 ± 0.6	3.7 ± 0.7	4.3 ± 0.3	NS
Sodium (mmol/L)	134.1 ± 24	133.1 ± 32.7	145 ± 10	NS
Calcium (mg/dl)	8.0 ± 1.0	7.9 ±	8.1 ± 0.9	NS
Sputum smear				
Negative	0	24	NA	NA
Positive, 1+	0	12	NA	NA
2+	9	0	NA	NA
3+	14	0	NA	NA
4+	19	0	NA	NA
Chest X-ray severity				
Minimal	0	18	NA	NA
Moderately advanced	12	16	NA	NA
Far-advanced	30	2	NA	NA

[a] Data represent number (percentage), median (range), or mean ± SD. BMI, body mass index; NA, not applicable.

[b] Positive tuberculosis culture with acid-fast stain 2+, 3+ or 4+

[c] Positive tuberculosis culture with acid-fast stain negative or 1+

performance to discriminate severe TB cases from mild TB cases and healthy controls (Table 3). We discovered that serum neopterin and IFN-γ were only weakly correlated (r=0.324; p: 0.005). In the ROC curves, the area under the curve (AUC) values of serum neopterin and IFN-γ to predict severe TB cases were 0.89 and 0.81, respectively (Figure 2). We then speculated that neopterin had a role independent from the downstream cytokines of IFN-γ in TB infection, and that serum neopterin was a better diagnostic biomarker than IFN-γ.

Table 2. Serum levels of neopterin and other biomarkers

	Tuberculosis patients		Controls
	Severe tuberculosis	Mild tuberculosis	
Neopterin (nmol/L)	46.1 ± 53.2*	16.0 ± 9.2	10.3 ± 3.1
IFN-γ (ng/dl)	98.9 ± 124**	36.5 ± 17.5	22.2 ± 8.5
MCP-1 (ng/dl)	381.5 ± 196	373.8 ± 185.7	452.0 ± 144.1
TNF-α (ng/dl)	11.8 ± 15.9	5.2 ± 3.7	5.4 ± 3.2
IL-6 (ng/dl)	62.4 ± 66.2	61 ± 77.8	111.5 ± 258.6

*$p < 0.005$ versus controls and mild tuberculosis

**$p < 0.05$ versus controls and mild tuberculosis

The use of neopterin as a diagnostic biomarker in severe TB patients

At last, we explored the use of dynamic serum neopterin change as a prognostic biomarker in severe TB patients. Our previous study found that in advanced TB patients, even those that received standard anti-TB treatment for 8 weeks, the sputum AFS was still positive in around 60% of patients. (unpublished data) However, the final culture results became negative in half of these patients, and we thought that the non-viable bacilli were the major cause of this smear-positive but culture-negative phenomenon. Therefore, we identified 16 patients with positive AFS after standard anti-TB treatment for 8 weeks; 8 of them were culture-negative and were defined as fast responders, and the other 8 were still in a culture-positive status and were defined as slow responders. We found no significant change in serum neopterin levels before and after treatment in both the fast and slow responders (Figure 3). Serum neopterin was an accurate diagnostic biomarker in severe TB patients collectively, but not in mild TB cases or when used as a prognostic biomarker in severe TB cases.

Discussion

Herein, we first reported that systemic inflammatory responses, including fever, body weight loss, leucocytosis and the elevation of macrophage-specific cytokines were stronger in severe TB patients than in mild TB patients or healthy controls. We next demonstrated that neopterin levels can be used as a diagnostic marker with high validity in severe TB cases.

AFS grades were used for severity classification in this study. In fact, a "gold standard" for TB severity classification does not exist. CXR been used to classify patients into minimal, moderately advanced, and far-advanced groups since 1969 [16]. However, not only do blurred definitions exist, but also subjective CXR interpretations essentially bring differential errors [17]. As a consequence, more studies have used AFS titers for classification -- they have clear criteria and the interpreters are unaware of the clinical conditions, which in turn can minimize differential errors [18]. But, sputum sampling quality may be an important bias when using AFS grades as severity classification. Since the Chest Hospital is a TB referral center, we have a standard protocol and well-trained staff to en-

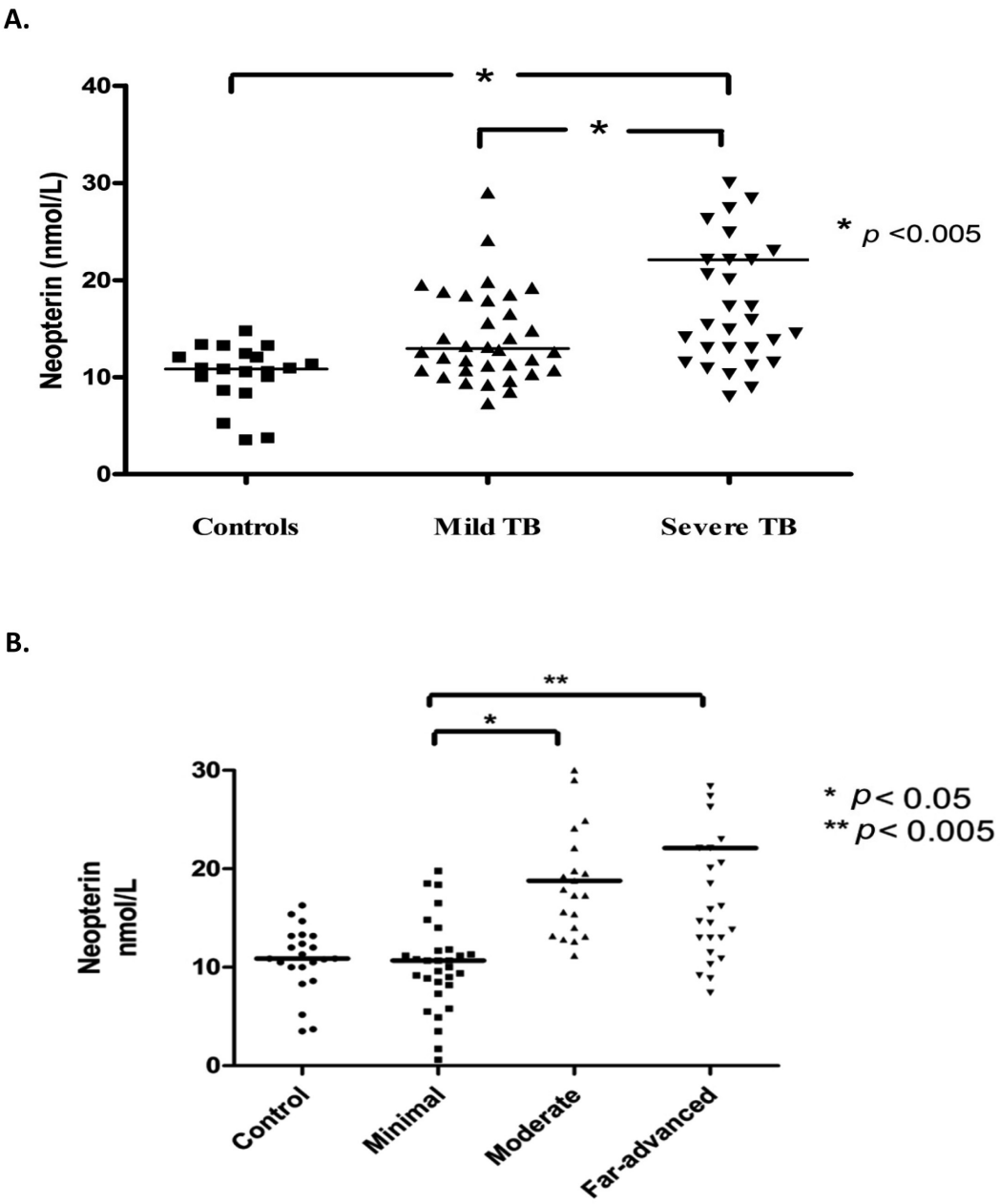

Fig. 1. Serum neopterin in TB patients with different severities classified by AFS grades (A) or CXR findings (B).
A. Mild TB cases were defined as AFS ≤ 1+, and severe TB cases were defined as AFS > 1+. B. CXR findings were classified into minimal, moderately advanced, and far-advanced, based on criteria proposed by the American Thoracic Society in 1969.

sure adequate sputum samples. Hence, we used sputum AFS grades rather than CXR findings for severity classification in this study.

We demonstrated that the tested inflammatory biomarker levels in mild TB patients were all similar to those of healthy controls; this matched with the clinical observation that most mild TB patients experienced only minimal clinical symptoms without a significant systemic inflammatory response. This may explain at

Table 3. Correlations between different biomarkers

		Neopterin	IFN-γ	TNF-α	MCP-1	IL-6
Neopterin	Pearson Correlation	1	0.324**	0.117	-0.187	-0.073
	Sig. (2-tailed)		0.005	0.371	0.149	0.574
IFN-γ	Pearson Correlation	0.324**	1	0.055	-0.254	-0.033
	Sig. (2-tailed)	0.005		0.716	0.089	0.827
TNF-α	Pearson Correlation	0.117	0.055	1	0.137	0.193
	Sig. (2-tailed)	0.371	0.716		0.292	0.136
MCP-1	Pearson Correlation	-0.187	-0.254	0.137	1	0.062
	Sig. (2-tailed)	0.149	0.089	0.292		0.634
IL-6	Pearson Correlation	-0.073	-0.033	0.193	0.062	1
	Sig. (2-tailed)	0.574	0.827	0.136	0.634	

** Correlation is significant at the 0.01 level (2-tailed).

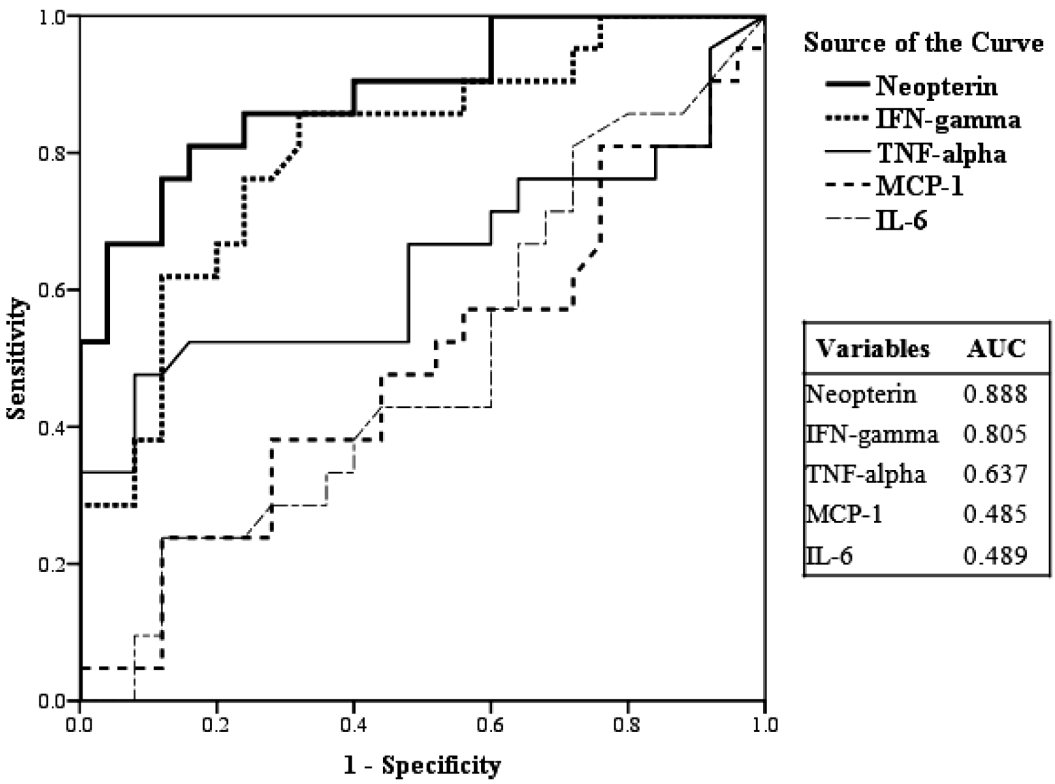

Fig. 2. ROC curves of different biomarkers
ROC curves of each biomarker to predict severe TB cases.

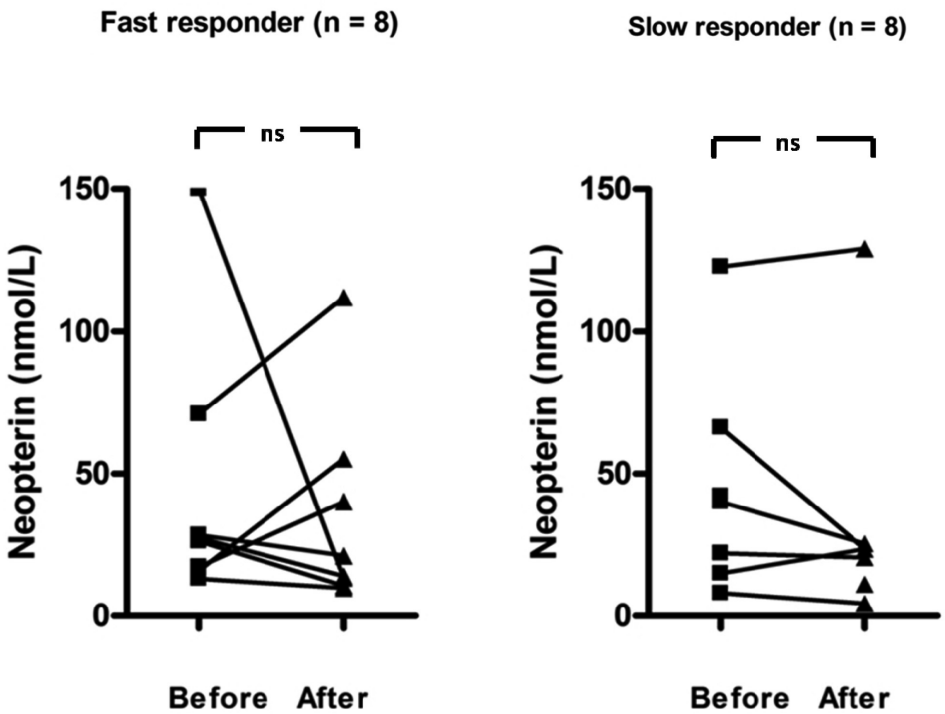

Fig. 3. Dynamic changes in neopterin in patients with persistent sputum smear-positive after anti-TB treatment for 8 weeks

The sputum AFS were still positive in 16 severe TB patients after standard anti-TB treatment for 8 weeks. The final culture results were negative for 8 patients who were defined as fast responders and still positive for the other 8 patients who were defined as slow responders. (The data were analyzed by paired t-test, ns: non-significant)

least partially the poor validity of inflammatory biomarkers that are applied in TB, since most TB cases are mild cases as a result of the current global public health awareness and surveillance for TB. We further found that only macrophage-activating biomarkers, including serum neopterin and IFN-γ, were elevated in severe TB patients, while chemokine or innate immunity-related cytokines were not elevated. Thus, we postulated that the elevation of neopterin and IFN-γ were specific to TB infection, rather than a non-specific inflammatory response.

Previous studies showed that neopterin was secreted by macrophages after stimulation by IFN-γ, but recent studies reported that neopterin may be independent from IFN-γ, since IFN-γ-deficient individuals still have neopterin secretion [19]. By investigating correlations between neopterin and other inflammatory biomarkers, we found that neopterin did correlate with IFN-γ, rather than other inflammatory biomarkers, but the correlation strength was weak (r=0.324). So, we speculated that neopterin had a unique role during TB infection, rather than just acting as a downstream cytokine of IFN-γ.

Taking these investigations 1 step further, we explored whether neopterin could be used as a prognostic biomarker to predict treatment response in severe TB cases. Our previous unpublished study found that AFS-positive but culture-negative sputum was frequently seen in advanced TB patients, and that non-viable

bacilli may be the major cause of this phenomenon. So, it is crucial to search for a biomarker that can predict early on whether there will be culture conversion, because 2 months are needed to obtain the final culture results. Our study showed that the dynamic change in neopterin failed to predict final culture results in these persistently AFS-positive patients. We postulated that if the neopterin was secreted by macrophages after exposure to TB cell wall-related antigen, then it was unsurprising that the antigen stimulation effect was similar in both viable and non-viable bacilli. It may be possible in the future to search for a TB secreting protein-related biomarker to distinguish viable from non-viable bacilli.

The immunological basis of TB, such as the beneficial role of macrophages and granuloma during TB infection in a mice model, has been studied in recent years [19]. However, scant human studies can be found because of the minimal systemic inflammatory responses in most TB patients. Hence, in this study, we focused on the clinical presentation and inflammatory response of 42 severe TB patients. We first determined that sputum smear-positive but culture-negative TB was frequently seen in severe TB patients after treatment for 8 weeks, and that this may alert the clinician that the sputum smear alone should not be used to judge the clinical response after treatment in severe TB cases. Our recent study of 182 severe TB cases in 5 TB centers in Taiwan also confirmed this finding (unpublished data). In addition, we explored the role of neopterin in TB of different severities, its relationship with IFN-γ and other macrophage-associated biomarkers, and the dynamic change in severe TB cases. We thought these findings would provide at least some practical evidence of clinical and immunological responses in severe TB patients.

The major limitation of this study is that we collected serum after treatment from some severe TB cases only, rather than all TB patients. The current isolation policy suggests that all active TB patients are admitted for 2 weeks, after which they can be discharged and treated with Directly Observed Therapy (DOT). Therefore, only those patients with a persistently positive smear were kept in the hospital after treatment for 8 weeks.

In conclusion, this study demonstrated that neopterin is an accurate diagnostic biomarker in severe pulmonary TB cases, but not in mild TB cases. We also showed that neopterin may have an independent role different from the downstream cytokines of IFN-γ in TB infection, but its dynamic change failed to identify the non-viable bacilli phenomena in persistent AFS-positive severe TB cases. Further studies of macrophage responses to TB-secreting protein may find a solution to this problem in the future.

Acknowledgment

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References

1. Global tuberculosis control: epidemiology, strategy, financing: WHO report 2009. World Health Organization., 2009.
2. Center for Disease Control Annual Report 2009. Taiwan: Centers for Disease Control, Department of Health, R.O.C.(Taiwan), 2009: 1-116.
3. Martin A, Barrera L, Palomino JC. Biomarkers and diagnostics for tuberculosis. Lancet 2010; 376: 1539-40; author reply 40.

4. Perrin FM, Lipman MC, McHugh TD, *et al*. Biomarkers of treatment response in clinical trials of novel antituberculosis agents. The Lancet Infectious Diseases 2007; 7: 481-90.
5. Wallis RS, Pai M, Menzies D, *et al*. Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice. Lancet 2010; 375: 1920-37.
6. Wanchu A, Dong Y, Sethi S, *et al*. Biomarkers for clinical and incipient tuberculosis: performance in a TB-endemic country. PloS ONE 2008; 3: e2071.
7. Parida SK, Kaufmann SH. The quest for biomarkers in tuberculosis. Drug Discovery Today 2010; 15: 148-57.
8. Niederwieser D, Huber C, Wachter H. [Neopterin, a new biochemical marker for the detection of activated T lymphocytes]. Wien Klin Wochenschr 1983; 95: 161-4.
9. Lacronique J, Auzeby A, Valeyre D, *et al*. Urinary neopterin in pulmonary sarcoidosis. Relationship to clinical and biologic assessment of the disease. The American review of respiratory disease 1989; 139: 1474-8.
10. Baydar T, Yuksel O, Sahin TT, *et al*. Neopterin as a prognostic biomarker in intensive care unit patients. Journal of critical care 2009; 24: 318-21.
11. Sucher R, Schroecksnadel K, Weiss G, *et al*. Neopterin, a prognostic marker in human malignancies. Cancer letters 2010; 287: 13-22.
12. Sugioka K, Naruko T, Matsumura Y, *et al*. Neopterin and atherosclerotic plaque instability in coronary and carotid arteries. Journal of atherosclerosis and thrombosis 2010; 17: 1115-21.
13. Mohamed KH, Mobasher AA, Yousef AR, *et al*. BAL neopterin: a novel marker for cell-mediated immunity in patients with pulmonary tuberculosis and lung cancer. Chest 2001; 119: 776-80.
14. Immanuel C, Swamy R, Kannapiran M, *et al*. Neopterin as a marker for cell-mediated immunity in patients with pulmonary tuberculosis. Int J Tuberc Lung Dis 1997; 1: 175-80.
15. Yuksekol I, Ozkan M, Akgul O, *et al*. Urinary neopterin measurement as a non-invasive diagnostic method in pulmonary tuberculosis. Int J Tuberc Lung Dis 2003; 7: 771-6.
16. Falk A, O'Connor JB, Pratt PC, *et al*. Diagnostic standards and classification of tuberculosis. National Tuberculosis and Respiratory Disease Association 1969; 12: 68-76.
17. Zellweger JP, Heinzer R, Touray M, *et al*. Intra-observer and overall agreement in the radiological assessment of tuberculosis. Int J Tuberc Lung Dis 2006; 10: 1123-6.
18. Murray PR, Elmore C, Krogstad DJ. The acid-fast stain: a specific and predictive test for mycobacterial disease. Annals of internal medicine 1980; 92: 512-3.
19. Sghiri R, Feinberg J, Thabet F, *et al*. Gamma interferon is dispensable for neopterin production in vivo. Clinical and diagnostic laboratory immunology 2005; 12: 1437-41.
20. Rubin EJ. The granuloma in tuberculosis--friend or foe? N Engl J Med 2009; 360: 2471-3.

評估以血清 Neopterin 在不同嚴重度肺結核患者之診斷效度

趙文震 *,** 吳盈勳 *** 黃瑞明 **** 簡順添 ***

背景：Neopterin 是巨噬細胞所分泌之生物標誌，研究已證實在結核感染會上升但因整體診斷效度不佳鮮少有研究討論其在不同臨床狀況時的應用，本研究旨在探討血清中 Neopterin 在不同嚴重度肺結核患者之診斷效度。

方法：我們前瞻性收案 2010 年 1 月至 2010 年 12 月間因痰液培養確診結核而入住胸腔病院之肺結核患者，我們收集患者血液並分析血清中 Neopterin 及相關細胞激素和臨床狀況之間的相關性。

結果：我們共收集 78 位不同嚴重度肺結核患者及 20 位健康對照組血清並檢測其生物標誌，我們以痰液抗酸染色價數區分患者嚴重度，42 位（54%）一價以上定義為嚴重結核；36 位（46%）抹片陰性或是一價的患者定義為輕度結核。我們發現相對於健康人，血清中巨噬細胞相關之細胞激素如 Neopterin（p<0.005）及 Interferon-γ（p<0.05）在嚴重結核個案會明顯升高，相對地非巨噬細胞相關細胞激素如 TNF-α、IL-6 及局部作用的單核細胞趨化蛋白 -1（MCP-1）則無明顯差異。另外輕度結核患者上述生物標誌之血清濃度皆無明顯上升這應該也是生物標誌應用一般肺結核時診斷效度不佳的原因。於變化並不能早期區分測抹片陽性患者培養陰轉與否。最後我們證實 Neopterin 和 IFN-γ 之間的相關強度並不強（r=0.324, p=0.005）所以應有其獨立於 IFN-γ 的意義，最後我們分析上述五種生物標誌後發現 Neopterin 在嚴重結核個案有最好的診斷效度。

結論：血清中 Neopterin 濃度在嚴重肺結核個案具良好的診斷效度，在輕度肺結核個案其診斷效度不佳。*(胸腔醫學 **2012; 27: 327-337**)*

關鍵詞：Neopterin，結核，生物標誌，嚴重度

* 台中榮總嘉義分院 內科，** 成大醫學院臨床醫學研究所，*** 行政院衛生署胸腔病院 內科
**** 行政院衛生署花蓮醫院 內科
索取抽印本請聯絡：簡順添醫師，行政院衛生署胸腔病院 內科，71742 台南市仁德區中山路 864 號

Chronic Obstructive Pulmonary Disease Assessment Test (CAT) Correlated Well with Modified Medical Research Council (mMRC) Dyspnea Scale

Ming-Ju Tsai*,***, Hsiu-Ping Huang**, Cheng-Yuan Wang*, Chih-Jen Yang*,***,****, Chau-Chyun Sheu*,*****, Jen-Yu Hung*,****, Tung-Heng Wang*,**,*****, Ming-Shyan Huang*,***,****

Background: Chronic obstructive pulmonary disease (COPD) is among the leading causes of disability. The COPD Assessment Test (CAT) has been advocated recently as a good health status measurement tool for COPD patients in daily practice. Both the CAT and the Modified Medical Research Council (mMRC) Dyspnea Scale were recommended for the assessment of COPD symptoms in the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report. However, little evidence to date has shown a correlation between these 2 measurements.

Methods: Patients more than 40 years of age, with a diagnosis of COPD and a smoking history of more than 10 pack years were prospectively enrolled from the chest clinic of a medical center in Taiwan. The CAT score and mMRC grades were recorded on the first visit and then every 8 weeks for 6 months. Spearman's correlation coefficients (ρ) between the CAT scores and mMRC grades recorded on the same visit were calculated.

Results: In total, 36 patients with COPD were enrolled in this study. Five patients were excluded due to early withdrawal, and the data of the remaining 31 patients were analyzed. The CAT score trended toward a weak correlation with the mMRC grade on the first visit, but was highly correlated with the mMRC grade on the next 3 visits (weeks 8, 16, and 24) ($\rho>0.7$; $p<0.05$). The correlation was better in patients with a more severe airflow limitation (GOLD class 3 and 4). In most cases (83%), the CAT score and mMRC grade indicated the same level of symptoms, as defined in the 2011 GOLD report.

Conclusions: Although the small sample size may have impacted the results, we found that the CAT score had a good correlation with the mMRC grade, especially in patients with a more severe airflow limitation and on follow-up visits. Therefore, as a simple tool, the mMRC scale may be used as a substitute for the CAT in busy clinics in Taiwan. This pilot study may provide preliminary evidence to support the clinical application of the CAT or mMRC scale per

*Division of Pulmonary and Critical Care Medicine; **Respiratory Therapy Team, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital; ***Graduate Institute of Medicine, College of Medicine; ****Department of Internal Medicine, School of Medicine, College of Medicine; *****Department of Respiratory Therapy, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Address reprint requests to: Dr. Cheng-Yuan Wang, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, No. 100, Tzyou 1st Road, Kaohsiung 807, Taiwan

the 2011 GOLD report in Taiwan. Further studies are needed to clarify the application of the CAT in a clinical setting in Taiwan. ***(Thorac Med 2012; 27: 338-348)***

Key words: chronic obstructive pulmonary disease, Chronic Obstructive Pulmonary Disease Assessment Test, Medical Research Council grade

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the airway that is "characterized by a persistent airflow limitation that is usually progressive," and is among the leading causes of disability [1]. With a high and increasing prevalence, COPD has become a major public health problem that leads to disability and mortality [1-4]. Previous approaches to assess COPD severity have focused on changes in lung function; however, this assessment measurement alone does not capture the full impact of the disease [2].

For patients with COPD, a variety of health status measurements have been developed to provide information complementary to that obtained from spirometry, for the purpose of optimizing everyday care [2,5]. Many of these measurements, such as St George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire (CRQ), and the COPD Clinical Questionnaire (CCQ), are well validated as measurements of disability related to COPD, but are too lengthy and complex to be used in daily clinical practice [2,6-10].

Dyspnea, or breathlessness, is the major symptom of COPD. As dyspnea is a complex subjective sensation, it is difficult, yet necessary to develop a simple tool to quantify this symptom in medical research [11]. Fletcher *et al*. devised the Medical Research Council (MRC) Dyspnea Scale in the 1950s, and since that time, this short questionnaire has been in widespread use, allowing patients to indicate the extent to which their dyspnea affects their disability [2,11-13]. The MRC Dyspnea Scale is a scale used to grade the degree of breathlessness related to activities, and has grades ranging from 1 to 5 (a higher grade represents more dyspnea on activity) [11-13]. The MRC has been advocated for use as a tool complementary to measuring the degree of airway obstruction (usually evaluated with forced expiratory volume in 1 second) in COPD patients [4,9], and has been further shown to be a prognostic predictor of survival [11,14]. However, some experts have offered the criticism that the MRC scale measures only a single aspect of the health effect of COPD and is poorly responsive to change [2]. Modified MRC (mMRC) grades are calculated as MRC grades minus 1 (Table 1) [1,11].

As there is a need for a validated, short and simple tool to fully quantify the impact of COPD in daily clinical practice, the COPD Assessment Test (CAT) (Table 1), a new 8-item questionnaire, was developed in recent years to assess and monitor COPD [15]. When using the test, the patient scores each question from 0 to 5, based on severity, with a score of 5 representing the most severe. The CAT has a total scoring range of 0 to 40 (a higher score represents a poorer health status) [15]. In addition to the degree of dyspnea, the test covers many other

Table 1. Chronic Obstructive Pulmonary Disease Assessment Test (CAT) and Modified Medical Research Council (mMRC) Dyspnea Scale

Chronic Obstructive Pulmonary Disease Assessment Test (CAT)*			
Number	Better	Score range	Worse
Q1	I never cough	0 – 5	I cough all the time
Q2	I have no phlegm (mucus) in my chest at all	0 – 5	My chest is full of phlegm (mucus)
Q3	My chest does not feel tight at all	0 – 5	My chest feels very tight
Q4	When I walk up a hill or one flight of stairs I am not breathless	0 – 5	When I walk up a hill or one flight of stairs I am very breathless
Q5	I am not limited doing any activities at home	0 – 5	I am very limited doing activities at home
Q6	I am confident leaving my home despite my lung condition	0 – 5	I am not at all confident leaving my home because of my lung condition
Q7	I sleep soundly	0 – 5	I don't sleep soundly because of my lung condition
Q8	I have lots of energy	0 – 5	I have no energy at all

Modified Medical Research Council (mMRC) Dyspnea Scale†	
Grade	Degree of breathlessness related to activities
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on the level or walking up a slight hill.
2	I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level.
3	I stop for breath after walking about 100 meters or after a few minutes on the level.
4	I am too breathless to leave the house or I am breathless when dressing.

* Adapted from http://www.catestonline.org/ and [15-16,18].

† Adapted from [11-13].

aspects, including cough, phlegm, chest tightness, limitation of activity, confidence when leaving home, sleep, and energy [15]. The CAT has been shown to be well-correlated with the SGRQ and CCQ, and corresponding clinical scenarios, along with a "ladder of severity" have been described [5,15-17]. CAT scores vary little between countries, genders, and age groups (patients more than 65 years old versus younger patients) [15-16,18]. Furthermore, the CAT is sensitive to changes in health status following exacerbations, and is responsive to pulmonary rehabilitation [16,18-20]. In addition to its adoption in COPD patients, the CAT has also been validated as a good measurement for assessing the health status of patients with interstitial lung disease (ILD) [21].

In December, 2011, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Scientific Committee published a revision of their consensus report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD* (2011 GOLD report). In this revision, both the CAT and the mMRC scale were recommended for the assessment of COPD symptoms, and were put on the same axis for use in classifying patients into groups (A, B, C, or D) [1]. However, there was no evidence showing

whether mMRC grades correlated well with CAT scores when the report was published. The aim of this study, therefore, was to investigate the correlation between these 2 measurement tools. In addition, we also tested whether the CAT and mMRC scale concordantly classified patients, as suggested in the 2011 GOLD report.

Material and Methods

Patients more than 40 years of age, with a diagnosis of COPD (based on the presence of a post-bronchodilator forced expiratory volume in 1 second [FEV_1] to forced vital capacity [FVC] ratio of less than 70%) and a smoking history of more than 10 pack years were prospectively enrolled from the chest clinic of a medical center in southern Taiwan. The answers to questions in the CAT and MRC Dyspnea questionnaire were recorded on the first visit and then every 8 weeks for 6 months. Modified MRC (mMRC) grades were calculated as MRC grades minus 1. Spirometry was performed, and the severity of airflow limitation was classified according to the 2011 GOLD report (GOLD class 1, 2, 3, or 4).

The protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-990213). Informed consent was obtained from all participants.

Statistical analysis

Data were entered and analyzed using JMP statistical software (version 8.0, SAS Institute Inc., Cary, NC, USA). All baseline characteristics of the study population were presented as mean values with standard deviations (means ± SD) or numbers and percentages, unless otherwise indicated. The scores and grades were presented as median and interquartile range. Spearman's correlation coefficient was used to show the correlation between the CAT scores and the mMRC grade at each visit (week 0, week 8, week 16, and week 24) and in the overall pooled data. In addition, the correlations between the score of each question on the CAT and the mMRC grade at each visit were also analyzed. The patients were further classified into 2 subgroups: GOLD class 1 and 2 and GOLD class 3 and 4. The correlations between the CAT score and the mMRC grade in the pooled data of the 4 visits were examined for each subgroup. A p-value less than 0.05 was considered significant.

According to the recommendations of the 2011 GOLD report, a CAT score higher than or equal to 10 or a mMRC grade higher than or equal to 2 was considered to indicate a high level of symptoms, while a CAT score lower than 10 or a mMRC grade lower than 2 was considered to indicate a low level of symptoms. If the CAT score and mMRC grade obtained on the same visit indicated the same level of symptoms, they were considered concordant. Otherwise, the results were classified as "worse in CAT" (CAT score indicating a high level of symptoms, but mMRC grade indicating a low level of symptoms), or "worse in mMRC" (mMRC grade indicating a high level of symptoms, but CAT score indicating a low level of symptoms). The number and percentage of the concordant events, "worse in CAT" or "worse in mMRC" were calculated.

Results

Thirty-six patients with COPD were enrolled in this study, but 5 were excluded due to early withdrawal. Of the remaining 31 patients

Table 2. Baseline characteristics of the study population*

Characteristic	Value
Patients – no.	31
Male sex – no. (%)	31 (100%)
Smoking history (pack-year) – no. (%)	
≤ 30	14 (45%)
31-60	9 (29%)
> 60	8 (26%)
Current smoker – no. (%)	9 (29%)
Age (year) – mean ± SD	76.1 ± 10.2
FEV_1 / FVC (%) – mean ± SD†	47.9 ± 12.3
FEV_1 (% of the predicted value) – mean ± SD†	43.4 ± 17.7
Severity of airflow limitation – no. (%)†	
GOLD 1	1 (3%)
GOLD 2	10 (32%)
GOLD 3	15 (48%)
GOLD 4	5 (16%)

* FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.
† Data from post-bronchodilator spirometry.

Table 3. Correlations of mMRC grade with CAT score*

Item	Week 0 (n=31)		Week 8 (n=31)		Week 16 (n=30)		Week 24 (n=29)	
	ρ	*p*-value	ρ	*p*-value	ρ	*p*-value	ρ	*p*-value
CAT-Q1	0.0622	0.7397	0.4694	0.0077	0.6145	0.0003	0.5317	0.0030
CAT-Q2	0.2018	0.2763	0.4795	0.0063	0.4152	0.0225	0.7414	<0.0001
CAT-Q3	-0.1736	0.3504	0.2586	0.1601	0.4087	0.0249	0.7079	<0.0001
CAT-Q4	0.4877	0.0054	0.8141	<0.0001	0.7090	<0.0001	0.4593	0.0122
CAT-Q5	0.4831	0.0059	0.5304	0.0021	0.5850	0.0007	0.5149	0.0043
CAT-Q6	0.5165	0.0029	0.4186	0.0191	0.5923	0.0006	0.3341	0.0765
CAT-Q7	0.0101	0.9569	0.3653	0.0433	0.3076	0.0982	0.3248	0.0856
CAT-Q8	0.2438	0.1863	0.4790	0.0064	0.4085	0.0250	0.3713	0.0473
CAT-total	0.3434	0.0586	0.7624	<0.0001	0.7159	<0.0001	0.7000	<0.0001

* The correlations are presented as Spearman's ρ and the *p*-values between the CAT score items and the mMRC grade recorded on the same visit. CAT denotes Chronic Obstructive Pulmonary Disease Assessment Test; mMRC, Modified Medical Research Council. Q1 to Q8 represent the questions on the CAT questionnaire (Table 1), in order.

analyzed, all were male, with a mean age (± standard deviation) of 76.1 ± 10.2 years. Twenty patients (65%) had severe airflow limitation (FEV_1 less than 50% of the predicted value, i.e. GOLD class 3 and 4). Two patients were lost to follow-up, 1 in week 16 and the other in week

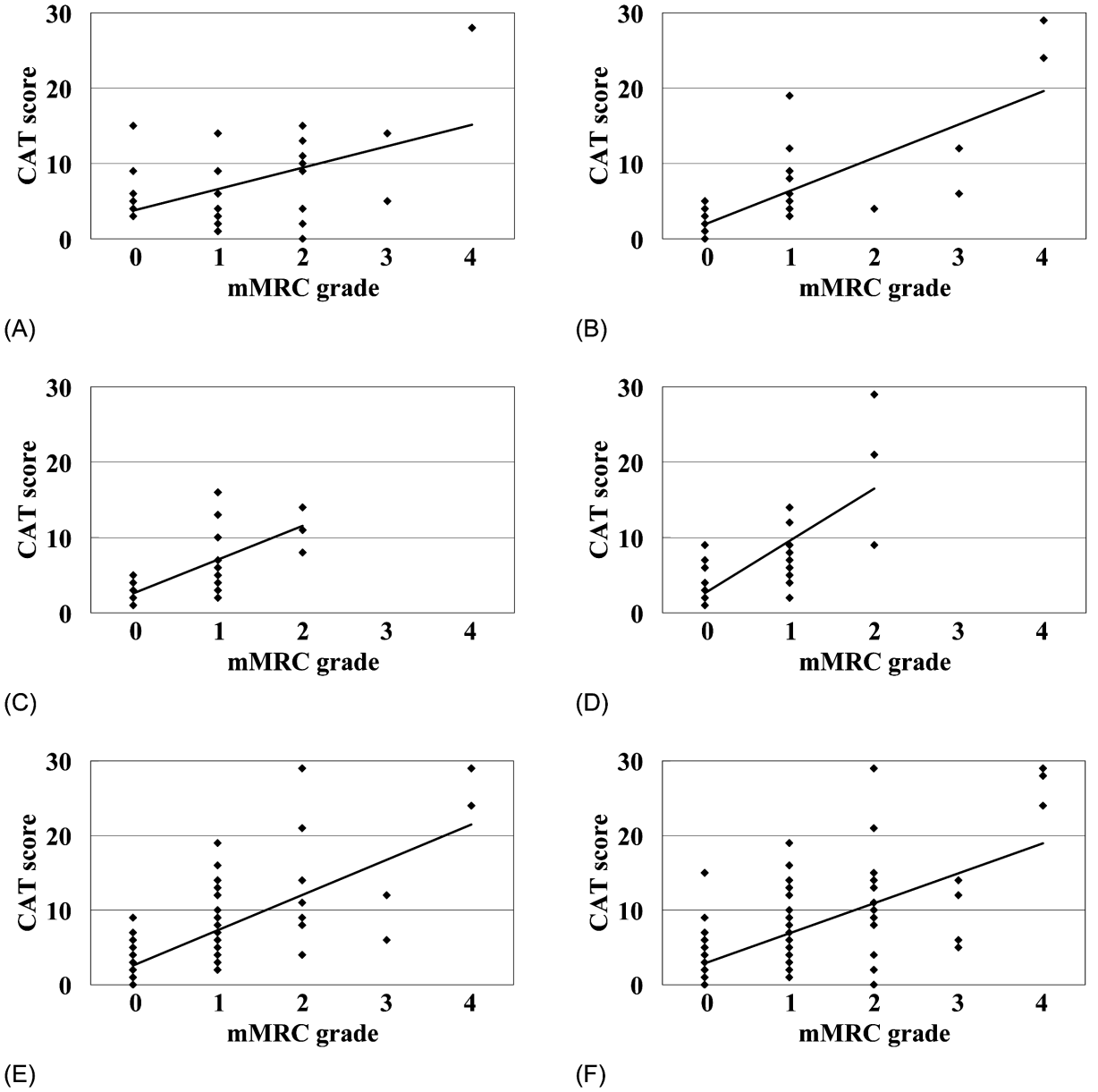

Fig. 1. Correlations between mMRC grade and CAT score on each visit. (A) Week 0 (ρ=0.3434, p=0.0586); (B) Week 8 (ρ=0.7624, p<0.0001); (C) Week 16 (ρ=0.7159, p<0.0001); (D) Week 24 (ρ=0.7000, p<0.0001); (E) Week 8-24 (n=90, ρ=0.7227, p<0.0001); (F) Overall (n=121, ρ=0.6135, p<0.0001).

24 (Table 2).

The median (interquartile range) of the CAT score was 5 (3 – 11) at the first visit, and 4 (2 – 8), 3 (2 – 8.5), and 4 (2 – 8.5) at weeks 8, 16, and 24, respectively. The CAT score trended toward a weak correlation with the mMRC grade on the first visit (ρ=0.3434; p=0.0586) and was highly correlated with the mMRC grade on the 3 follow-up visits (weeks 8, 16, and 24) (ρ≥0.7; p<0.0001) (Table 3) (Figure 1A-D). The overall pooled data showed a moderate correlation between the CAT score and the mMRC grade

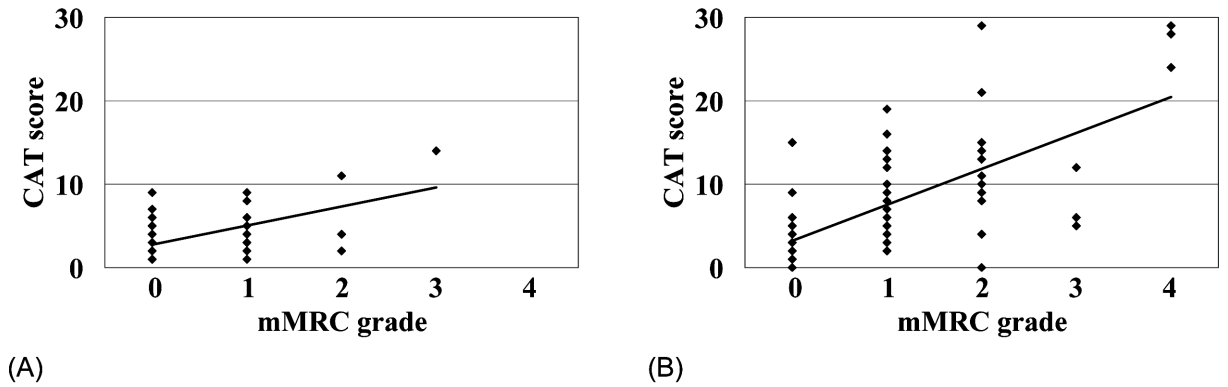

Fig. 2. Correlations between mMRC grade and CAT score in patients with different degrees of airflow limitation. (A) GOLD class 1 and 2 (n=42, ρ=0.4439, p=0.0032); (B) GOLD class 3 and 4 (n=79, ρ=0.6493, p<0.0001).

Table 4. Concordances of mMRC grade with CAT score in assessments of symptoms according to the 2011 GOLD report*

Week	n	Concordant	Worse in CAT	Worse in mMRC
Week 0	31	24 (77%)	2 (6%)	5 (16%)
Week 8	31	26 (84%)	2 (6%)	3 (10%)
Week 16	30	24 (80%)	5 (17%)	1 (3%)
Week 24	29	26 (90%)	2 (7%)	1 (3%)
Overall	121	100 (83%)	11 (9%)	10 (8%)

*According to the recommendations of the 2011 GOLD (Global Initiative for Chronic Obstructive Lung Disease) report, a CAT score higher than or equal to 10 or a mMRC grade higher than or equal to 2 is considered to indicate a high level of symptoms, while a CAT score lower than 10 or a mMRC grade lower than 2 is considered to indicate a low level of symptoms. If the CAT score and mMRC grade obtained on the same visit indicated the same level of symptoms, they were considered concordant. Otherwise, the results were classified into "worse in CAT" (CAT score indicating a high level of symptoms, but mMRC grade indicating a low level of symptoms), or "worse in mMRC" (mMRC grade indicating a high level of symptoms, but CAT score indicating a low level of symptoms). Data are presented as number (percentage). CAT denotes Chronic Obstructive Pulmonary Disease Assessment Test; mMRC, Modified Medical Research Council.

(ρ=0.6135, p<0.0001) (Figure 1F); when excluding the data of the first visit, a high correlation was found (ρ=0.7227, p<0.0001) (Figure 1E). This correlation was better in patients with GOLD class 3 and 4 (ρ=0.6493, p<0.0001) than in those with GOLD class 1 and 2 (ρ=0.4439, p=0.0032) (Figure 2). The fourth and fifth questions on the CAT significantly correlated with the mMRC grade throughout the study period (ρ>0.48; p<0.05) (Table 3). Overall, the seventh question of the CAT showed the least correlation with the mMRC grade (ρ<0.37; p>0.04) (Table 3). In most cases (83%), the CAT score and the mMRC grade indicated the same level of symptoms as defined in the 2011 GOLD report (Table 4).

Discussion

In the 2011 GOLD report, both the CAT and the mMRC scale were recommended for the assessment of COPD symptoms, and were

put on the same axis to classify patients into groups (A, B, C, or D), although no supporting rationale was provided [1]. Clear differences have been shown between CAT scores and MRC dyspnea scale grades [16], but there has been little evidence to date showing whether CAT scores correlate with MRC grades [20-21]. In the present study, the CAT score trended toward only a weak correlation with the mMRC grade at the first visit. In contrast, the CAT score showed a significantly high correlation with the mMRC grade on the following 3 visits (weeks 8, 16, and 24). This may be explained by the older age of the enrolled patients, who may have had difficulty in properly understanding the new questionnaire the first time they saw it. The true correlation between the CAT score and the mMRC grade may therefore have been masked by interference due to unfamiliarity with this patient-completed questionnaire -- once the patients became familiar with it, the true correlation was revealed.

Although there was a significantly high correlation between the CAT score and the mMRC grade, the correlation coefficient remained less than 0.8, suggesting that differences existed between these 2 questionnaires. The mMRC scale evaluated only the degree of breathlessness related to activities, whereas the CAT included additional information, such as cough, sputum, chest tightness, sleep quality, and energy. In the present study, the fourth and the fifth questions of the CAT significantly correlated with the mMRC grade throughout the study period. These 2 questions evaluated the degree of dyspnea related to activities and the limitation of activities related to dyspnea. The similarity of the content between these 2 questions and the mMRC scale may explain our findings. In contrast, sleep quality related to the lung condition, evaluated by the seventh question of the CAT, was not addressed in the mMRC scale. Therefore, the seventh question of the CAT showed the least correlation with the mMRC grade in the present study.

The application of the CAT or mMRC scale in clinical practice, as suggested in the 2011 GOLD report, has not been evaluated. According to the 2011 GOLD report, a CAT score lower than 10 or mMRC grade lower than 2 indicates a low level of symptoms. Patients with a low level of symptoms are classified into group A or C, and the others are classified into group B or D. In our study, we found that the CAT score and mMRC grade indicated the same level of symptoms, thus concordantly classifying the patients, in most cases.

Compared to other redundant evaluation tools, and in particular the SGRQ, the CAT is a comprehensive and objective, but not time-consuming, tool for evaluating the symptoms and disease status of COPD, and is easily used in daily clinical practice. The CAT also provides a much more thorough evaluation of the symptoms and disease status than the mMRC scale, and this is why the CAT has been advocated recently as a routine assessment tool in caring for COPD patients recently. In contrast, it has been proposed that the mMRC scale is too simple to provide a complete evaluation of the disease status of patients with COPD. As demonstrated in the present study, the mMRC grade correlated well with the CAT score. Therefore, we believe that it may serve as a good alternative tool for evaluating symptoms, especially in a busy clinic in Taiwan. Furthermore, as this study demonstrated that the correlation between the CAT score and the mMRC grade was even better in patients with more severe airflow limitation (GOLD class 3 and 4) and on follow-up

visits, using the mMRC scale as a substitute for the CAT may be even more reasonable. In addition, the original design of the CAT requires the patients to answer the questions. However, since many COPD patients are too old to finish the questionnaire by themselves, the mMRC scale may be more applicable for older COPD patients. Further studies on the application of the CAT with older patients are warranted.

The small sample size and the male predominance of the study population were the major limitations of this study. However, since no study has assessed the application of the CAT in Taiwan to date, and as little evidence has shown that the CAT score correlates well with the MRC grade, this pilot study may provide preliminary evidence to support the clinical application of the CAT or mMRC scale per the 2011 GOLD report in Taiwan. Further studies are needed to clarify the application of the CAT in a clinical setting in Taiwan.

In conclusion, we found that the CAT and mMRC scale correlated well with each other, and in most cases, concordantly classified the patients as suggested by the 2011 GOLD report. With the increasing adoption of the CAT worldwide, we are looking forward to further data supporting its role in clinical practice, especially in specific populations.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available at: http://www.goldcopd.org/. [date accessed: February 22, 2012]
2. Jones PW, Price D, van der Molen T. Role of clinical questionnaires in optimizing everyday care of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2011; 6: 289-96.
3. Jones PW, Brusselle G, Dal Negro RW, *et al*. Health-related quality of life in patients by COPD severity within primary care in Europe. Respir Med 2011; 105: 57-66.
4. O'Donnell DE, Aaron S, Bourbeau J, *et al*. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. Can Respir J 2007; 14 Suppl B: 5B-32B.
5. Jones PW, Tabberer M, Chen WH. Creating scenarios of the impact of COPD and their relationship to COPD assessment test (CAT) scores. BMC Pulm Med 2011; 11: 42.
6. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med 1991; 85 Suppl B: 25-31; discussion 3-7.
7. Jones PW, Quirk FH, Baveystock CM, *et al*. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992; 145: 1321-7.
8. van der Molen T, Willemse BW, Schokker S, *et al*. Development, validity and responsiveness of the Clinical COPD Questionnaire. Health Qual Life Outcomes 2003; 1: 13.
9. Bestall JC, Paul EA, Garrod R, *et al*. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999; 54: 581-6.
10. Jones P, Harding G, Wiklund I, *et al*. Improving the process and outcome of care in COPD: development of a standardised assessment tool. Prim Care Respir J 2009; 18: 208-15.
11. Stenton C. The MRC breathlessness scale. Occup Med (Lond) 2008; 58: 226-7.
12. Fletcher CM, Elmes PC, Fairbairn AS, *et al*. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. Br Med J 1959; 2: 257-66.
13. Fletcher CM. The clinical diagnosis of pulmonary emphysema; an experimental study. Proc R Soc Med 1952; 45: 577-84.
14. Nishimura K, Izumi T, Tsukino M, *et al*. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002; 121: 1434-40.
15. Jones PW, Harding G, Berry P, *et al*. Development and first validation of the COPD Assessment Test. Eur Respir J 2009; 34: 648-54.

16. Jones PW, Brusselle G, Dal Negro RW, *et al*. Properties of the COPD assessment test in a cross-sectional European study. Eur Respir J 2011; 38: 29-35.
17. Ringbaek T, Martinez G, Lange P. A comparison of the assessment of quality of life with CAT, CCQ, and SGRQ in COPD patients participating in pulmonary rehabilitation. COPD 2012; 9: 12-5.
18. Mackay AJ, Donaldson GC, Patel AR, *et al*. Utility of the COPD Assessment Test (CAT) to evaluate severity of COPD exacerbations. Am J Respir Crit Care Med 2012.
19. Dodd JW, Hogg L, Nolan J, *et al*. The COPD assessment test (CAT): response to pulmonary rehabilitation. A multicentre, prospective study. Thorax 2011; 66: 425-9.
20. Jones PW, Harding G, Wiklund I, *et al*. Tests of the responsiveness of the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test TM (CAT) following acute exacerbation and pulmonary rehabilitation. Chest 2012.
21. Nagata K, Tomii K, Otsuka K, *et al*. Evaluation of the COPD assessment test (CAT) for measurement of health-related quality of life in patients with interstitial lung disease. Respirology 2012; 17: 506-12.

慢性阻塞性肺病評估問卷（CAT）與修改版醫學研究委員會（mMRC）呼吸困難程度計分有良好相關性

蔡明儒 *,*** 黃脩評 ** 王程遠 * 楊志仁 *,***,**** 許超群 *,*****
洪仁宇 *,**** 王東衡 *,**,***** 黃明賢 *,***,****

前言：慢性阻塞性肺疾病是造成失能的主要疾病之一。近來，慢性阻塞性肺病評估問卷（CAT）被推廣在日常診療中用於評估病人的健康狀況。2011 年版 GOLD 指引建議使用 CAT 及修改版醫學研究委員會呼吸困難程度計分（mMRC）來評估慢性阻塞性肺疾病的症狀。不過，至今鮮有證據顯示這兩個評估工具的結果有良好的相關性。

方法：本研究於台灣南部的一家醫學中心胸腔內科門診招募四十歲以上且有抽菸史（大於十包 - 年）的慢性阻塞性肺疾病病患。在初次收案時及之後每八週回診（三次回診）時，紀錄 CAT 各項問題之分數及 mMRC 之分數。計算同次門診之 CAT 各項分數及總分與 mMRC 分數的斯皮爾曼氏相關係數。

結果：本研究共收錄 36 名病患，有 5 名中途退出。分析剩下的 31 人之資料顯示 CAT 總分與 mMRC 分數在初次收案門診時有一個弱相關的趨勢，而於之後的三次追蹤時達到顯著的高度相關（$\rho>0.7$; $p<0.05$）。在有較嚴重氣道阻塞（GOLD 第 3 及第 4 類）的病人，這相關性會比較好。依據 2011 年版 GOLD 指引，在大多數（83%）的狀況下，CAT 分數與 mMRC 分數會將病人分到相同的症狀等級中。

結論：雖然這個研究的樣本數很少，不過仍然顯現 CAT 總分與 mMRC 分數有很好的相關性，尤其在有較嚴重氣道阻塞的病人以及用在追蹤的時候。因此，在台灣地區繁忙的門診作業中可以使用 mMRC 這種簡單的量表來取代 CAT。這項試驗性的研究可以提供在台灣地區依照 2011 年版 GOLD 指引於臨床上使用 CAT 及 mMRC 的初步證據支持。期待有更進一步的研究來探討在台灣地區使用 CAT 於臨床照護的相關議題。*(胸腔醫學 **2012; 27: 338-348**)*

關鍵詞：慢性阻塞性肺病，慢性阻塞性肺病評估問卷，醫學研究委員會呼吸困難程度計分

高雄醫學大學附設中和紀念醫院 內科部 胸腔內科 * 胸腔內科呼吸治療小組 **
醫學院 醫學研究所 *** 醫學系 **** 呼吸治療學系 *****
索取抽印本請聯絡：王程遠醫師，高雄醫學大學附設中和紀念醫院 內科部 胸腔內科，高雄市 807 自由一路 100 號

Chronic Obstructive Pulmonary Disease with Acute Respiratory Failure and an Incidental Finding of Tracheobronchomalacia: A Case Report

Li-Chung Chiu*, I-Hao Su**, Kuo-Chin Kao*, Chien-Ying Liu*, Cheng-Ta Yang*, Chien-Da Huang*

Tracheobronchomalacia (TBM), characterized by more than 50% expiratory reduction of the cross-sectional area of the trachea and bronchus, may cause respiratory failure. Its etiology may be congenital or acquired. Acquired TBM is reportedly associated with endotracheal tubes and tracheostomy, closed chest trauma, lung resection, radical neck dissection, radiation therapy, chronic obstructive pulmonary disease (COPD), relapsing polychondritis, paratracheal vascular abnormality, and chronic or recurrent infection. Herein, we report a 50-year-old male COPD patient with TBM resulting in hypercapnic respiratory failure. Flow-volume loop, bronchoscopy and 4-dimensional dynamic volume computed tomography (4D CT) of the lung confirmed the diagnosis of TBM. This case report broadens the understanding of the contribution of expiratory central airway collapse to COPD morbidity. Clinicians should be alert to the possibility of TBM when acute respiratory failure is noted in COPD patients. ***(Thorac Med 2012; 27: 349-356)***

Key words: tracheobronchomalacia, chronic obstructive pulmonary disease, acute respiratory failure, four-dimensional dynamic volume computed tomography

Introduction

Tracheobronchomalacia (TBM) is the weakening of airway walls or supporting cartilage, with more than 50% expiratory reduction in the tracheal and bronchial diameter [1-2]. Its etiology may be congenital or acquired [1]. TBM may be asymptomatic, cause non-specific symptoms like cough, dyspnea, sputum production and hemoptysis, or even progress to acute respiratory failure. TBM is usually confused with chronic obstructive pulmonary disease (COPD), and their relationship is attracting the interest of physicians.

This case report describes a 50-year-old male with COPD who presented with fever, productive cough, and dyspnea. He had hypercapnic respiratory failure on admission. Flow-volume loop, bronchoscopy and 4-dimensional dynamic volume computed tomography (4D

*Department of Thoracic Medicine, and **Department of Medical Imaging and Intervention, Chang Gung Memorial Hospital, and School of Medicine, Chang Gung University, Taipei, Taiwan
Address reprint requests to: Dr. Chien-Da Huang, Department of Thoracic Medicine, Chang Gung Memorial Hospital, 5 Fushing Street, Gueishan Shiang, Taoyuan 333, Taiwan

CT) of the lung revealed the presence of TBM. Aside from clarifying the relationship between COPD and TBM, this report provides a better understanding of how expiratory central airway collapse contributes to COPD.

Case Report

A 50-year-old male, a former smoker for more than 30 years, had a history of COPD with an obstructive pattern on a post-bronchodilator pulmonary function test (PFT) using spirometry, and presented with a forced expiratory volume in 1 second (FEV_1) of 18%, forced vital capacity (FVC) of 52%, and FEV_1/FVC ratio of 28%. He suspected tracheal and bilateral main bronchi narrowing and presented to the emergency room (ER) with fever, productive cough, and dyspnea of several days' duration. Chest x-rays (Figure 1) showed emphysematous change with increased lung markings. Empirical moxifloxacin, aerosol therapy, and systemic steroids were initially prescribed for COPD with acute exacerbation. The patient was subsequently admitted to the chest ward and the clinical symptoms improved after treatment.

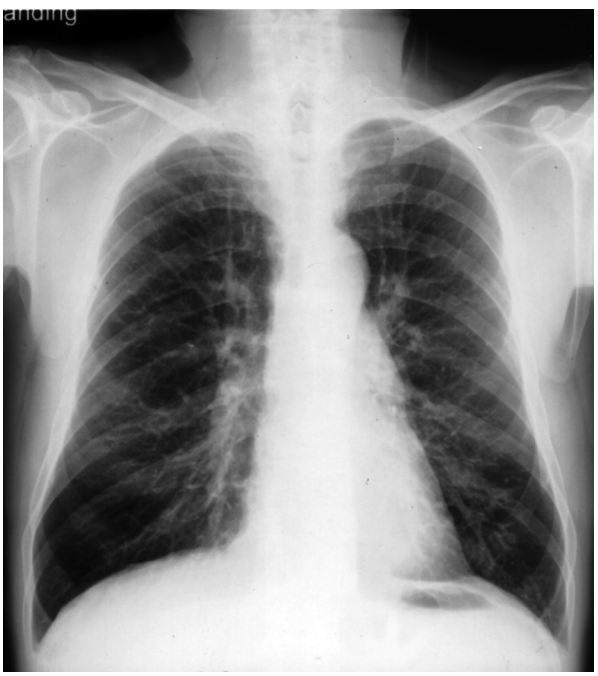

Fig. 1. Chest x-rays showed emphysema with increased lung markings on both lungs.

Six days later, there was a sudden onset of shortness of breath with stridor. Nebulized bronchodilator therapy for symptomatic relief failed. There was also consciousness change, and arterial blood gas (ABG) showed CO_2 retention ($PaCO_2$ = 134 mmHg). Emergency endotracheal tube intubation was performed due to hypercapnic respiratory failure, and he was subsequently admitted to the intensive care unit (ICU). After the application of mechanical ventilatory support, consciousness was restored and CO_2 retention resolved.

Because of the history of airway narrowing with stridor, and suspected endobronchial lesions, dynamic airway collapse or upper airway obstruction, chest CT and bronchoscopy were arranged during the ICU admission under mechanical ventilatory support. Chest CT revealed tracheo-bronchial stenosis and diffused centrilobular emphysema (Figure 2); bronchoscopy showed no cartilaginous rings along the entire tracheal wall, intact but diffusely swollen and slightly injected tracheal mucosa, and markedly narrowed tracheal and bronchial lumens, especially during expiration (Figure 3). A thoracic surgeon was consulted during the patient's ICU stay, but considered that stenting was not indicated. Extubation was performed successfully under stable conditions and the patient tolerated the Venturi mask 50% well. He was transferred to the general ward after 3 days of extubation.

A 4D CT (Toshiba AquilionONE^{TM} 320-slice CT system) scan arranged to survey dynamic changes in the large airways revealed TBM with extreme luminal narrowing during

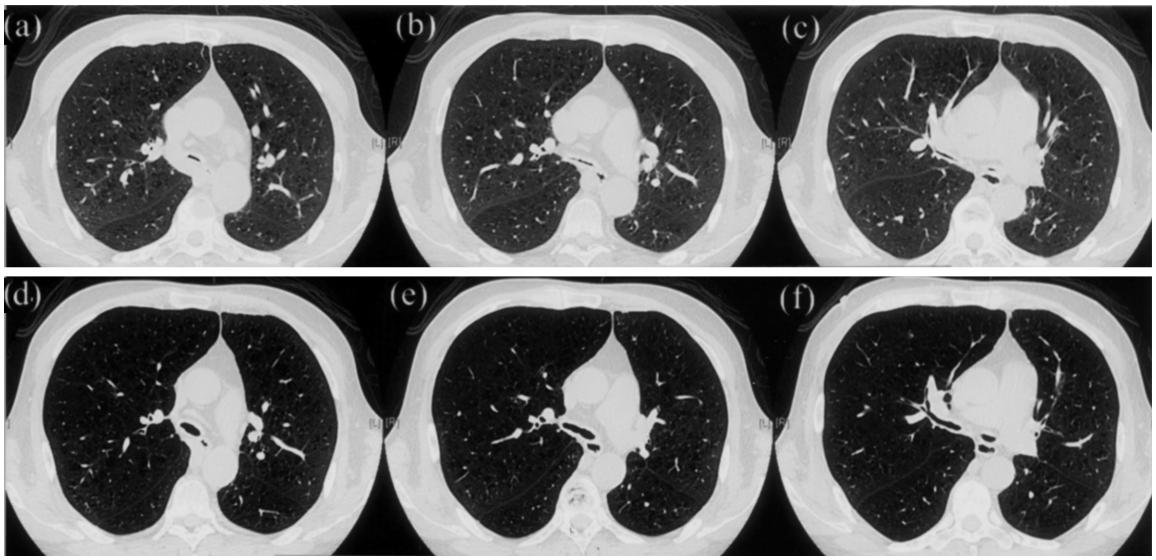

Fig. 2. High-resolution CT showed extreme tracheal luminal narrowing during the expiratory phase, especially at the (a) distal trachea, (b) carina, and (c) bilateral main bronchi, compared to the inspiratory phase at the (d) distal trachea, (e) carina, and (f) bilateral main bronchi.

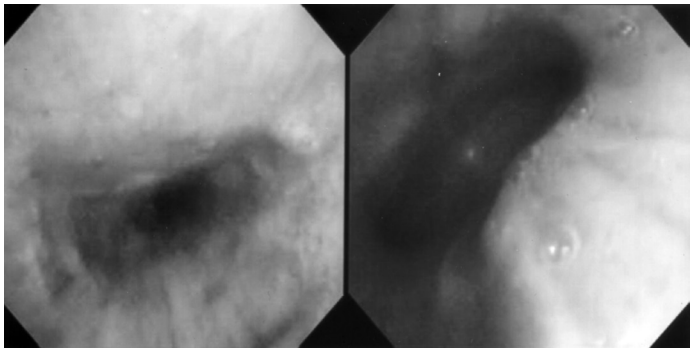

Fig. 3. Bronchoscopy showed no cartilaginous ring and narrowed tracheal and bronchial lumens, especially during expiration.

the expiratory phase, especially in the distal trachea and bilateral main bronchi (Figure 4). Autoimmune diseases, such as relapsing polychondritis, were excluded by the rheumatologist. Flow-volume loop showed rapid maximum expiratory flow reduction after an initial peak and flow oscillations in the expiratory curve (Figure 5).

The thoracic surgeon was consulted again for implantation of a Y-stent during the general ward course. However, no indication for stent implantation was suggested. Nasal bi-level positive airway pressure (BiPAP) was prescribed nocturnally for airway patency. The patient was discharged without symptoms after a 1-month ward admission and had regular outpatient follow-up.

Discussion

TBM is an uncommon condition that presents with nonspecific symptoms and is often

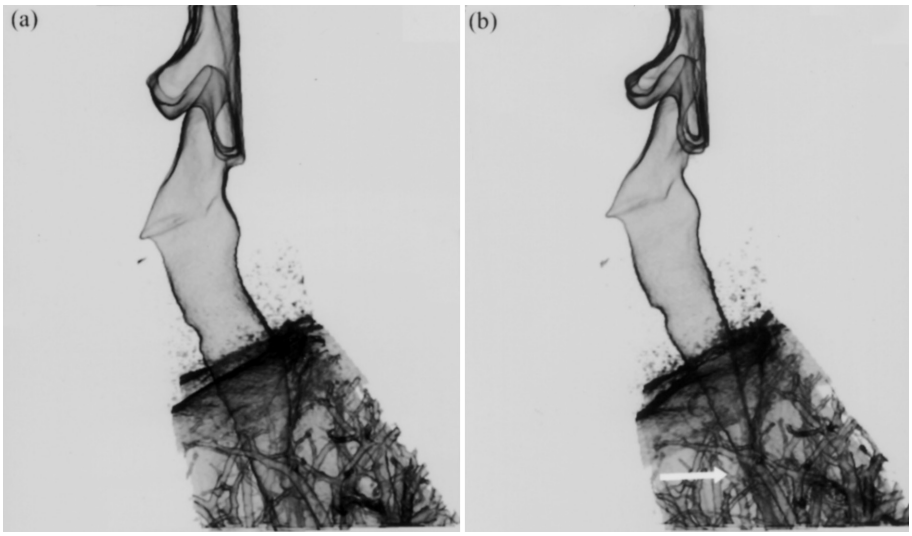

Fig. 4. 4D dynamic volume CT of inspiration (a) and expiration (b) showed extreme luminal narrowing at the distal trachea during expiration (b. white arrow).

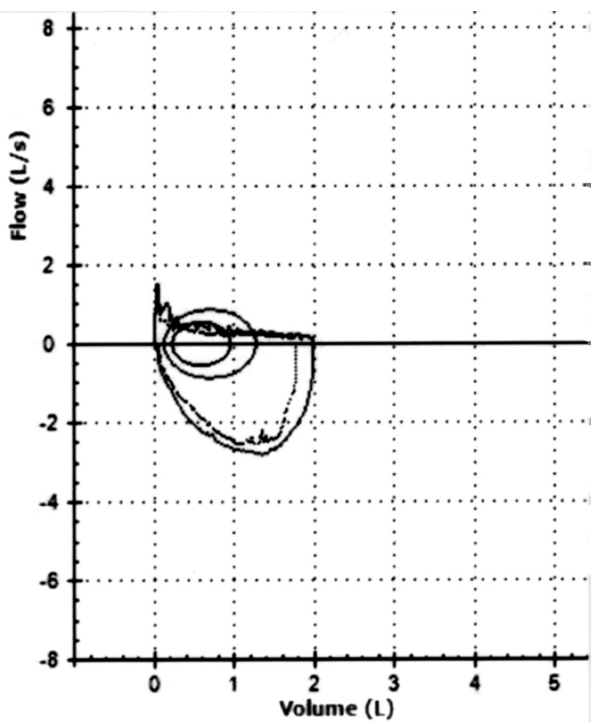

Fig. 5. Flow-volume loop showed rapid maximum expiratory flow reduction after the initial peak and flow oscillations in the expiratory curve.

misdiagnosed as asthma or COPD [3]. The etiology can be congenital or acquired. Congenital causes include tracheobronchomegaly or Mounier-Kuhn syndrome and diffuse airway dilatation [3]; endotracheal intubation and tracheostomy are the most common causes of adult-acquired TBM [4]. Other causes of acquired TBM include closed chest trauma, lung resection, radical neck dissection, radiation therapy, COPD, relapsing polychondritis, paratracheal vascular abnormality, extrinsic compression of the trachea and chronic or recurrent infection [3,5].

TBM is more common in middle-aged and elderly male smokers [6-7]. It may exhibit upper airway collapse during forced expiration, a form of dynamic airway obstruction, and might cause hyperinflation and air trapping [2]. TBM can cause variable intrathoracic airway obstruction and increasing airway resistance and exertion in breathing, and the respiratory muscles may no longer be able to maintain adequate minute volume, which may lead to hypercapnic respiratory failure. TBM is a progressive disease that can cause considerable morbidity and even mortality. Unexplained extubation failure should raise the possibility of TBM [6]. This

report of a 50-year-old male COPD patient with TBM resulting in acute hypercapnic respiratory failure is a reminder for clinicians to be alert to the possibility of TBM when acute respiratory failure is noted in younger COPD patients with expiratory stridor due to upper airway collapse.

Bronchoscopic visualization of dynamic airway collapse is the "gold standard" for the diagnosis of TBM [1]. Dynamic inspiratory-expiratory multi-detector CT (MDCT) can create 3-dimensional (3D) images of the airways at a higher speed and at a high resolution, and may offer a feasible alternative to bronchoscopy for suspected TBM [8]. Dynamic magnetic resonance imaging of the airways during forced expiration and cough can also be used to evaluate TBM [9]. A recent study reported that dynamic volume CT provides distinct images of the larynx, distinguishes the function of the vocal cords during respiration, and can recognize possible vocal cord dysfunction. This technique can potentially provide a simple, non-invasive evaluation to identify laryngeal dysfunction and improve the management of asthma [10].

Another study revealed that 4D dynamic isotropic, isophasic and isovolumetric imaging of the central airway using 320-raw MDCT is a viable technique that provides a more precise assessment of central airway dynamics than conventional MDCT for diagnosing TBM, despite respiratory motion. Peak airway collapse does not occur synchronously throughout the airway in the 4D CT evaluation. The proximal trachea exhibits peak collapse at a later phase of expiration than the distal trachea [11]. Nonetheless, further study is needed to reduce the effective radiation dose and the partial volume artifacts from excess airway movement, and to survey the benefits of diagnosing dynamic tracheal disorder using 4D CT [11]. In this case report, bronchoscopy and 4D CT confirmed the diagnosis of TBM, thereby providing a better understanding of the contribution of dynamic expiratory central airway collapse to the morbidity of COPD.

The ability to diagnose TBM by PFT is limited, but some characteristics suspicious of TBM are made evident in the PFT, including (1) biphasic morphology, or a rapid reduction in maximum expiratory flow after the initial peak, related to central airway collapse; (2) a break or notch in the expiratory phase of the flow-volume loop, a sudden flow decrease at the beginning of expiration when the airway collapses; (3) flow oscillations in the expiratory curve, reproducible sequence of alternating flow decelerations and accelerations; and (4) reduction in maximum voluntary ventilation [1,3]. However, the above PFT findings, suspicious of TBM, cannot be distinguished from other conditions, such as increased dynamic airway collapse, obstructive sleep apnea, and neuromuscular disorders of the larynx [12]. Furthermore, central airway collapse is unrelated to the degree of obstruction as expressed by FEV_1 [13].

The relationship between TBM and COPD is still not well understood. The incidence of TBM may be as high as 23% in COPD patients, 44% in chronic bronchitis patients [14], and 1% of all patients undergoing bronchoscopy [15-16]. TBM may be an extension of peripheral airway obstruction and related to smoking, due to the chronic inflammatory response [2]. TBM can also accelerate the progression of COPD [17]. About half of COPD patients have airway weakness on dynamic expiratory CT in all the Global Initiative for Chronic Obstructive Lung Disease stages, and half of TBM patients have a "frown-like" shape of the airway lumen [18]. Therefore, TBM should be considered in COPD

patients with unexplained dyspnea or acute respiratory failure.

Distinguishing between COPD and TBM clinically is not easy, because symptoms and signs are often nonspecific and overlapping [1]. Expiratory stridor and dyspnea due to acute respiratory failure might be considered as important signs related to TBM in COPD patients. Expiratory stridor may worsen in the supine position, with respiratory infection, or during times of increased airflow, such as during coughing. Inspiratory stridor may be found if there is malacia of the extrathoracic trachea. TBM may produce a characteristic cough, a barking cough, because of expiratory collapse and vibration of the floppy membranous wall against the anterior airway wall [3]. Besides this, TBM patients may present episodic choking, recurrent pulmonary infection, and even syncope associated with forced expiration or cough. In TBM patients with respiratory failure under mechanical ventilation, positive airway pressure may splint airway collapse. Therefore, removal of positive pressure may unmask airway collapse and patients may experience respiratory distress requiring reintubation [2].

There are no definite treatment guidelines for TBM. Asymptomatic patients do not need any treatment. On the other hand, initial treatment may include cessation of smoking and control of respiratory tract infections and symptoms of underlying diseases [1]. Stents can restore airway structure and improve symptoms and ventilatory function, but can also lead to possible complications like granulation and mucous plugs. There are 3 types of stents: metal, silicon and hybrids. However, there is no ideal indication for stenting at present and it is only considered in severely symptomatic patients [1,19]. Tracheobronchoplasty is a recommended surgical procedure with posterior tracheobronchial splinting using a polypropylene mesh to prevent expiratory protrusion into the airway lumen and to improve dyspnea, health-related quality of life, functional status, and exercise capacity [20].

Continuous positive airway pressure (CPAP), as a pneumatic stent, can lower pulmonary resistance, maintain patent airways, improve expiratory flow, and decrease breathing effort [1]. Nocturnal and intermittent daytime nasal CPAP is helpful to TBM patients when used as adjunctive therapy [21]. Nasal BiPAP was prescribed nocturnally for airway patency in the current case since there was co-existent COPD. The patient was discharged without symptoms and was regularly followed up as an outpatient. No further acute respiratory failure episodes were noted.

In conclusion, symptoms of TBM mimic COPD and are usually under-diagnosed. Clinicians should be alert to the possibility of TBM when acute respiratory failure is noted in COPD patients.

Acknowledgements

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References

1. Majid A, Fernandez L, Fernandez-Bussy S, *et al*. [Tracheobronchomalacia]. Arch Bronconeumol 2010 Apr; 46(4): 196-202.
2. Kandaswamy C, Balasubramanian V. Review of adult tracheomalacia and its relationship with chronic obstructive pulmonary disease. Curr Opin Pulm Med 2009 Mar;

15(2): 113-9.
3. Carden KA, Boiselle PM, Waltz DA, *et al*. Tracheomalacia and tracheobronchomalacia in children and adults: an in-depth review. Chest 2005 Mar; 127(3): 984-1005.
4. Feist JH, Johnson TH, Wilson RJ. Acquired tracheomalacia: etiology and differential diagnosis. Chest 1975 Sep; 68(3): 340-5.
5. Hasegawa I, Boiselle PM, Raptopoulos V, *et al*. Tracheomalacia incidentally detected on CT pulmonary angiography of patients with suspected pulmonary embolism. AJR Am J Roentgenol 2003 Dec; 181(6): 1505-9.
6. Collard P, Freitag L, Reynaert MS, *et al*. Respiratory failure due to tracheobronchomalacia. Thorax 1996 Feb; 51(2): 224-6.
7. Murgu SD, Colt HG. Treatment of adult tracheobronchomalacia and excessive dynamic airway collapse: an update. Treat Respir Med 2006; 5(2): 103-15.
8. Lee EY, Litmanovich D, Boiselle PM. Multidetector CT evaluation of tracheobronchomalacia. Radiol Clin North Am 2009 Mar; 47(2): 261-9.
9. Suto Y, Tanabe Y. Evaluation of tracheal collapsibility in patients with tracheomalacia using dynamic MR imaging during coughing. AJR Am J Roentgenol 1998 Aug; 171(2): 393-4.
10. Holmes PW, Lau KK, Crossett M, *et al*. Diagnosis of vocal cord dysfunction in asthma with high resolution dynamic volume computerized tomography of the larynx. Respirology 2009 Nov; 14(8): 1106-13.
11. Wagnetz U, Roberts HC, Chung T, *et al*. Dynamic airway evaluation with volume CT: initial experience. Can Assoc Radiol J 2010 Apr; 61(2): 90-7.
12. Boiselle PM, Ernst A. Tracheal morphology in patients with tracheomalacia: prevalence of inspiratory lunate and expiratory "frown" shapes. J Thorac Imaging 2006 Aug; 21(3): 190-6.
13. Loring SH, O'Donnell C R, Feller-Kopman DJ, *et al*. Central airway mechanics and flow limitation in acquired tracheobronchomalacia. Chest 2007 Apr; 131(4): 1118-24.
14. Jokinen K, Palva T, Nuutinen J. Chronic bronchitis. A bronchologic evaluation. ORL J Otorhinolaryngol Relat Spec 1976; 38(3): 178-86.
15. Herzog H. [Expiratory stenosis of the trachea and great bronchi by loosening of the membraneous portion; plastic chip repair]. Thoraxchirurgie 1958 Jan; 5(4): 281-319.
16. Jokinen K, Palva T, Sutinen S, *et al*. Acquired tracheobronchomalacia. Ann Clin Res 1977 Apr; 9(2): 52-7.
17. Johnson TH, Mikita JJ, Wilson RJ, *et al*. Acquired tracheomalacia. Radiology 1973 Dec; 109(3): 576-80.
18. Sverzellati N, Rastelli A, Chetta A, *et al*. Airway malacia in chronic obstructive pulmonary disease: prevalence, morphology and relationship with emphysema, bronchiectasis and bronchial wall thickening. Eur Radiol 2009 Jul; 19(7): 1669-78.
19. Ernst A, Majid A, Feller-Kopman D, *et al*. Airway stabilization with silicone stents for treating adult tracheobronchomalacia: a prospective observational study. Chest 2007 Aug; 132(2): 609-16.
20. Majid A, Guerrero J, Gangadharan S, *et al*. Tracheobronchoplasty for severe tracheobronchomalacia: a prospective outcome analysis. Chest 2008 Oct; 134(4): 801-7.
21. Ferguson GT, Benoist J. Nasal continuous positive airway pressure in the treatment of tracheobronchomalacia. Am Rev Respir Dis 1993 Feb; 147(2): 457-61.

於慢性阻塞性肺疾病併發急性呼吸衰竭病人意外發現支氣管軟化症：一個病例報告

邱立忠 * 蘇奕豪 ** 高國晉 * 劉劍英 * 楊政達 * 黃建達 *

支氣管軟化症是支氣管在吐氣時管腔狹窄超過 50% 且可能造成呼吸衰竭。先天或後天因素都可能造成支氣管軟化症。後天因素造成支氣管軟化症和氣管內管、氣切、封閉式胸部外傷、肺切除、廣泛性頸部切除手術、放射治療、慢性阻塞性肺疾病、再發性多處軟骨炎、氣管旁血管異常和慢性或反覆性感染有關。我們報告一位 50 歲慢性阻塞性肺疾病男性患者因支氣管軟化症併發高二氧化碳呼吸衰竭。肺功能，氣管鏡和 4D 動態容量肺部電腦斷層診斷為支氣管軟化症。本篇案例報告使我們更加了解吐氣時呼吸道塌陷對慢性阻塞性肺疾病造成之影響。當慢性阻塞性肺疾病患者併發急性呼吸衰竭時，臨床醫師需考慮支氣管軟化症之可能性。*(胸腔醫學 **2012; 27: 349-356**)*

關鍵詞：支氣管軟化症，慢性阻塞性肺疾病，急性呼吸衰竭，4D 動態容量肺部電腦斷層

長庚大學暨林口長庚紀念醫院 * 胸腔內科，** 影像診療科
索取抽印本請聯絡：黃建達醫師，林口長庚紀念醫院 呼吸胸腔內科系 呼吸道疾病科，333 桃園縣龜山鄉復興街 5 號

Rare Metastases of Lung Adenocarcinoma to the Uterine Cervix and Retroperitoneal Lymph Nodes Resulting in Obstructive Uropathy, with a Good Response to Gefitinib

Jiun-Rung Chen*, Tsung-Ying Yang*, Gee-Chen Chang*,**,***,****

Lung adenocarcinoma with metastasis to the uterine cervix is rare, as is ureteral obstruction attributed to metastasis from lung adenocarcinoma. We report a case of lung adenocarcinoma with metastases to both the uterine cervix and retroperitoneal lymph nodes resulting in obstructive uropathy. We used immunohistochemical staining, the epidermal growth factor receptor gene and the clinical course to differentiate lung adenocarcinoma from cervical adenocarcinoma. An excellent response was achieved with first-line gefitinib treatment for 3 months -- both the hydronephrosis and the metastatic cervical tumor had almost disappeared. This is the first case report of metastatic retroperitoneal lymphadenopathy with ureteral obstruction resulting from lung adenocarcinoma treated effectively and safely with gefitinib. ***(Thorac Med 2012; 27: 357-362)***

Key words: lung adenocarcinoma, uterine cervical metastasis, obstructive uropathy, thyroid transcription factor-1, gefitinib

Introduction

Lung adenocarcinoma is the most common histologic type of non-small cell lung cancer (NSCLC). The most frequent metastatic sites include the brain, lung, liver, adrenal glands and skeletal system. Metastasis of lung adenocarcinoma to the uterine cervix is rare. To date, only 3 cases of lung adenocarcinoma with metastasis to the uterine cervix have been reported. Two of these cases occurred as tumor recurrence in patients with a prior diagnosis of lung adenocarcinoma who presented with abnormal vaginal bleeding. They received chemotherapy with paclitaxel and carboplatin, and palliative total abdominal hysterectomy with bilateral salpingo-oophorectomy, respectively [1-2]. The third was an asymptomatic female who underwent a

*Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; **Institute of Biomedical Sciences, National Chung-Hsing University, Taichung, Taiwan; ***School of Medicine, China Medical University, Taichung, Taiwan; ****Department of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan
Address reprint requests to: Dr. Gee-Chen Chang, Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan, No. 160, Chung-Kang Rd., Sec. 3, Taichung, Taiwan, R.O.C. 40705

routine cervical cytology screening that showed malignant cells, and that finally led to the detection of a primary lung adenocarcinoma. She was then treated with erlotinib and died 1 year after diagnosis [3].

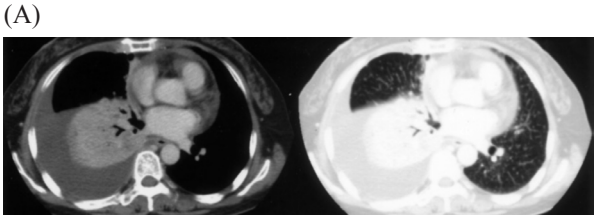
Ureteral obstruction can occur due to a stone, inflammation, infection, injury, developmental anomaly or a tumor. The most common origins of retroperitoneal metastases causing obstructive uropathy are the uterine cervix, prostate, urinary bladder, colon and rectum. To date, few reports regarding ureteral obstruction attributed to metastasis from lung adenocarcinoma have been reported.

Adenocarcinomas compromise approximately 70% of cancers with an unknown primary site, and immunohistochemical staining is helpful in identifying the origin. A great many markers can be used in the evaluation of adenocarcinomas with an unknown primary site, including cytokeratin-7 (CK-7), cytokeratin-20 (CK-20), thyroid transcription factor-1 (TTF-1), thyroglobulin, prostate-specific antigen (PSA), estrogen receptor, and progesterone receptor. However, immunohistochemical staining is not specific enough for definitive identification of the primary site in most cases. Thus, the results of immunohistochemial staining should be interpreted carefully in conjunction with the clinical presentation.

Case Report

A 55-year-old postmenopausal female presented with exertional dyspnea, non-productive cough and right pelvic pain. Chest computed tomography (CT) scan detected a consolidated mass about 6 × 6 cm in the right lower lobe of the lung, with massive right pleural effusion, and multiple lung-to-lung, pleural and liver metastases (Figure 1A). Cytological examination of the pleural effusion revealed adenocarcinoma with strongly positive TTF-1, consistent with adenocarcinoma of the lung. Pelvic CT scan detected multiple enlarged lymph nodes in the lower retroperitoneum causing right-side obstructive uropathy (Figure 2A-B) and enlargement of the uterine endocervix with heterogeneous enhancement (Figure 2C). A subsequent punch biopsy of the uterine endocervix revealed metastatic adenocarcinoma with strongly positive TTF-1 (Figure 3A-B) and only weakly focal positive $p16^{INK4A}$, consistent with a lung origin. The adenocarcinoma cells from the pleural effusion and uterine endocervix had similar cytopathological features (Figure 3B-C). Direct DNA sequencing of the cells from the pleural effusion revealed exon 19 deletion of the epidermal growth factor receptor (*EGFR*) gene. The patient began to receive first-line therapy with gefitinib for stage IV lung adenocarcinoma, with an excellent response. The follow-up chest CT scan after gefitinib treatment for 3 months revealed significant regression of

(A)



(B)

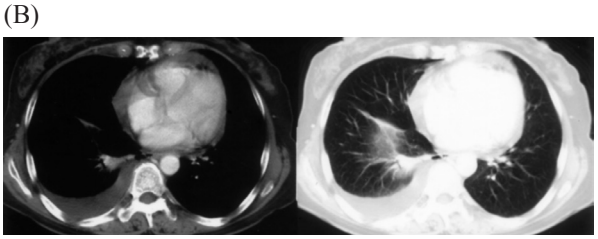


Fig. 1. (A) Chest CT at diagnosis showed a heterogeneous consolidative tumor mass in the right lower lobe of the lung, with pleural metastases, pleural effusion, and bilateral lung metastases. (B) Chest CT showed tumor regression after gefitinib treatment for 3 months.

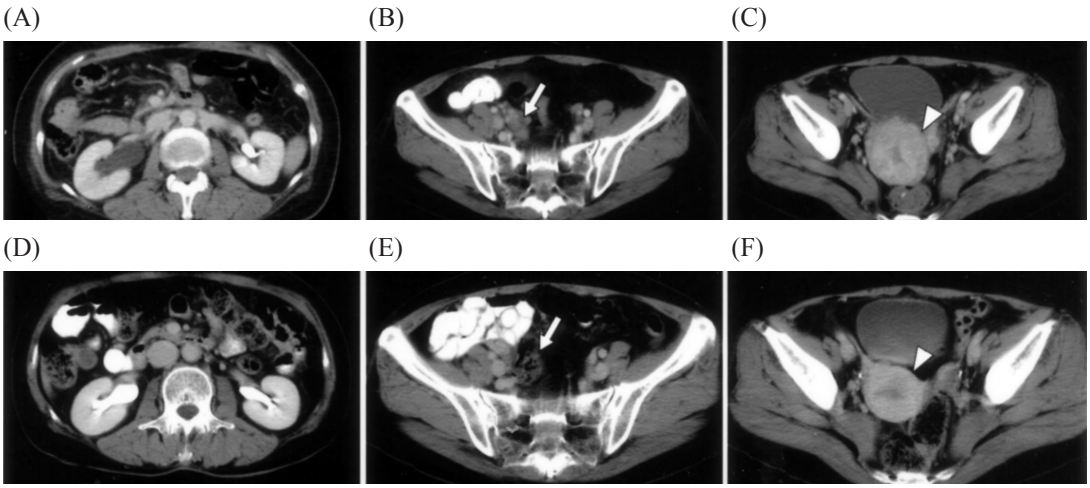


Fig. 2. (A)-(C) Pelvic CT at diagnosis showed right hydronephrosis and hydroureter, right lower retroperitoneal lymph nodes (white arrow), and a uterine cervical tumor (white arrowhead) with heterogeneous enhancement, respectively. (D)-(F) After gefitinib treatment for 3 months, pelvic CT showed improvement in the right obstructive uropathy and regression of the right lower retroperitoneal lymph nodes (white arrow) and the uterine cervical tumor (white arrowhead), respectively.

the lung tumor, pleural effusion and metastatic lesions (Figure 1B). The follow-up pelvic CT scan showed improvement of the right hydronephrosis (Figure 2D), and significant regression of the lower retroperitoneal lymphadenopathy (Figure 2E) and uterine endocervix tumor (Figure 2F). Gefitinib had effectively controlled the disease for 1 year. She then switched to chemotherapy due to disease progression with liver and spinal metastases.

Discussion

Extrauterine malignancy metastatic to the uterine cervix is rare. Most often such cases derive from the female genital organs. Metastases from the gastrointestinal tract and breast have also been reported.

TTF-1 is a relatively specific immunohistochemical test to detect a metastatic adenocarcinoma of lung or thyroid origin [4]. However, weakly positive TTF-1 has been reported in some normal endocervical samples with less than 5% positive labeling. The incidence of strongly positive TTF-1 expression has been reported to be up to 4% in endocervical adenocarcinomas [5]. $P16^{INK4A}$ in immunohistochemical staining is reliable as a sensitive and specific diagnostic marker of cervical adenocarcinoma. However, positive $p16^{INK4A}$ has been reported in 63.3% of adenocarcinomas of the lung with variable degrees of cytoplasmic staining [6]. Cervical cancer has been shown to express moderate to high levels of *EGFR*. However, a phase II trial revealed no objective response to the use of gefitinib as second- or third-line treatment in patients with recurring locoregionally advanced or metastatic cervical cancer [7]. In our case, primary cervical adenocarcinoma was less likely because of the weakly focal positive $p16^{INK4A}$. Moreover, the patient's uterine cervical tumor and right lower retroperitoneal metastatic lymph nodes had almost disappeared after first-line gefitinib treatment. Thus, we confirmed the lung origin of her uterine cervical metastatic adenocarcinoma. Although immunohistochemi-

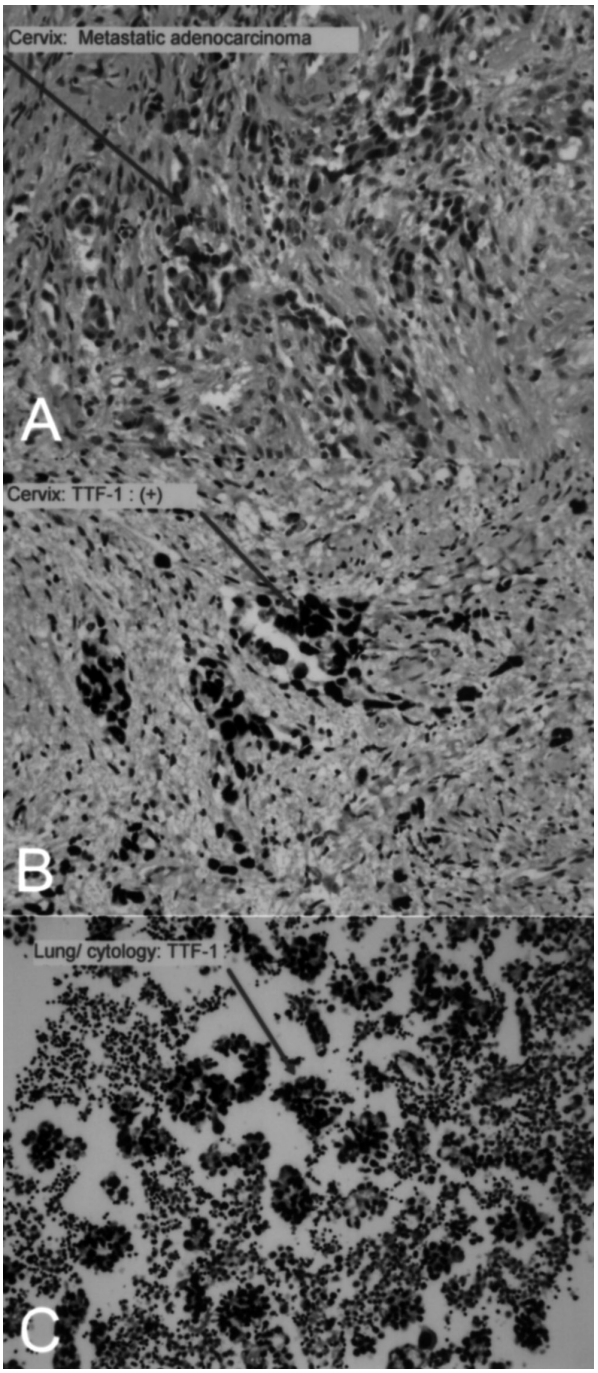


Fig. 3. (A) Microscopic view (hematoxylin and eosin [H&E] stain x 200) showing metastatic adenocarcinoma of the uterine cervix. (B) Microscopic view (immunohistochemical stain x 200) showing TTF-1(+) in the uterine cervical biopsy. (C) Microscopic view (immunohistochemical stain x 100) showing TTF-1(+) in the cytospin preparation of the malignant pleural effusion.

cal analysis helped us to identify the origin of the adenocarcinoma, the application of immunohistochemical analysis in the diagnosis of malignancy should be carefully correlated with the clinical presentation and the course of disease.

EGFR tyrosine kinase inhibitors (TKIs) have shown remarkable activity in the treatment of non-small cell lung cancer (NSCLC) in selected patients. A recent trial reported that *EGFR* TKIs are appropriate for first-line treatment of NSCLC with sensitizing *EGFR* mutations [8]. Our patient was an Asian female, a non-smoker with a TKI-sensitizing *EGFR* mutation – an exon 19 deletion. The above characteristics are predictors of a good response to *EGFR* TKIs, and an excellent response was achieved after first-line gefitinib treatment for 3 months.

The ureteral obstruction secondary to the metastatic retroperitoneal lymphadenopathy subsided after gefitinib treatment. Different measures can be taken to deal with the ureteral obstruction, such as surgery, percutaneous nephrostomy, balloon dilatation and stenting. Treating the underlying malignancy may be considered if there are no urgent complications. However, there is no recommendation in the literature on this subject [9]. Our case is the first reported in which metastatic retroperitoneal lymphadenopathy with ureteral obstruction resulting from lung adenocarcinoma was treated effectively and safely with gefitinib. In this situation, the administration of chemotherapy should be cautious for fear of acute renal failure and urosepsis. *EGFR* TKIs may be a safer and more effective choice for such a complication resulting from lung adenocarcinoma with lymph node metastases in selected patients.

References

1. Hollier LM, Boswank SE, Stringer CA. Adenocarcinoma of the lung metastatic to the uterine cervix: a case report and review of the literature. Int J Gynecol Cancer 1997; 7(6): 490-4.
2. Kai K, Takai N, Nasu K, *et al*. Metastatic uterine cervical cancer originating in the lung: a case report. Gynecol Obstet Invest 2009; 68(4): 269-71.
3. Khan AM, Jain VR, Schlesinger K, *et al*. A rare case of primary lung adenocarcinoma detected by routine liquid-based cervical cytology. Lung Cancer 2007; 58(2): 282-5.
4. Hecht JL, Pinkus JL, Weinstein LJ, *et al*. The value of thyroid transcription factor-1 in cytologic preparations as a marker for metastatic adenocarcinoma of lung origin. Am J Clin Pathol 2001; 116(4): 483-8.
5. Niu HL, Pasha TL, Pawel BR, *et al*. Thyroid transcription factor-1 expression in normal gynecologic tissues and its potential significance. Int J Gynecol Pathol 2009; 28(4): 301-7.
6. Akin H, Yilmazbayhan D, Kilicaslan Z, *et al*. Clinical significance of P16INK4A and retinoblastoma proteins in non-small-cell lung carcinoma. Lung Cancer 2002; 38(3): 253-60.
7. Goncalves A, Fabbro M, Lhomme C, *et al*. A phase II trial to evaluate gefitinib as second- or third-line treatment in patients with recurring locoregionally advanced or metastatic cervical cancer. Gynecol Oncol 2008; 108(1): 42-6.
8. Mok TS, Wu YL, Thongprasert S, *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361(10): 947-57.
9. Hiraki A, Ueoka H, Gemba K, *et al*. Hydronephrosis as a complication of adenocarcinoma of the lung. Anticancer Res 2003; 23(3C): 2915-6.

罕見的肺腺癌轉移至子宮頸及後腹腔淋巴結併阻塞性尿路病變，對 gefitinib 治療反應良好

陳俊榮 * 楊宗穎 * 張基晟 *,**,***,****

肺腺癌很少轉移至子宮頸。此外，肺腺癌也很少造成輸尿管阻塞。我們報告了一個肺腺癌轉移至子宮頸及後腹腔淋巴結併阻塞性尿路病變的個案。我們應用了免疫組織化學染色、表皮生長因子接受器基因及臨床病程來區分是肺腺癌或是子宮頸腺癌。在使用第一線 gefitinib 治療三個月後產生了極佳的反應。水腎及子宮頸轉移性腫瘤幾乎消失了。這是第一個個案報告描述 gefitinib 有效且安全地治療了肺腺癌轉移至後腹腔淋巴結併輸尿管阻塞。*(胸腔醫學 **2012; 27: 357-362**)*

關鍵詞：肺腺癌，子宮頸轉移，阻塞性尿路病變，甲狀腺轉錄因子 -1，愛瑞莎

* 台中榮總 內科部 胸腔內科，** 國立中興大學 生物醫學研究所
*** 中國醫藥大學 醫學院，**** 國立陽明大學 醫學院 醫學系
索取抽印本請聯絡：張基晟醫師，台中榮民總醫院 內科部 胸腔內科，台中市西屯區中港路三段 160 號

Pneumomediastinum as a Presentation of Perforated Sigmoid Diverticulitis – A Case Report

Yau-Lin Wang*, Jeng-Yuan Hsu*,**, Pin-Kuei Fu**

Pneumomediastinum is a sign of aberrant air in the mediastinum. Most cases are caused by respiratory tract or esophageal injury, but rarely originate from perforation of an intestinal organ. We report a diabetic patient taking analgesic medication who presented with diffuse abdominal pain and radiographic findings of pneumomediastinum. The computed tomography of the abdomen and surgical pathology led to the diagnosis of perforated sigmoid diverticulitis. After reviewing the literature, we proposed an integrated algorithm as an adequate differential diagnostic process and document the reasons for delayed diagnosis of this rare presentation of perforated viscus. ***(Thorac Med 2012; 27: 363-369)***

Key words: pneumomediastinum, perforated sigmoid diverticulitis

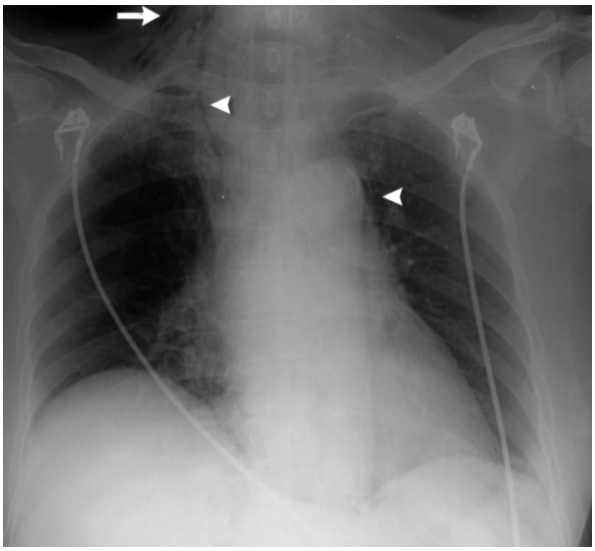
Introduction

Pneumomediastinum (PM), defined as the presence of aberrant air in the mediastinum, is multifactorial and should alert physicians to the need to identify the source of air. The main causes of PM are dissemination of air into the mediastinum from ruptured alveoli or esophageal perforation [1]. PM may be a sign of life-threatening disease, thus an adequate differential diagnosis and management are important in clinical practice. Herein, we present a rare case that was diagnosed as perforated sigmoid diverticulitis with an initial presentation as PM. We also propose an integrated algorithm that physicians can use as an approach with these patients. We review the literature and summarize the factors that may cause delayed diagnosis in cases of perforated viscus, for which PM may be the only initial presentation.

Case Report

A 74-year-old woman with a history of type 2 diabetes mellitus (DM) and peptic ulcer disease presented to the emergency room of a local hospital with diffuse abdominal pain, which she had experienced for 3 days. Prior to this admission, she had received left total knee arthroplasty and took analgesics for pain relief for one month after the operation. Chest radiography obtained in that hospital showed subcuta-

*Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; **Division of Critical Care & Respiratory Therapy, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan
Address reprint requests to: Dr. Pin-Kuei Fu, Division of Critical Care & Respiratory Therapy, Taichung Veterans General Hospital, No. 160, Sec. 3, Taichung Port Road., Taichung 40705, Taiwan



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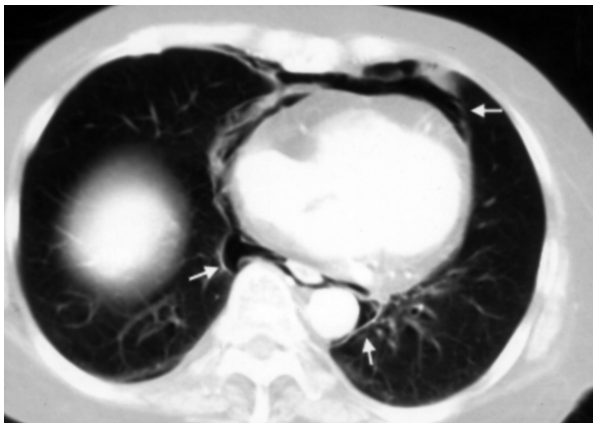
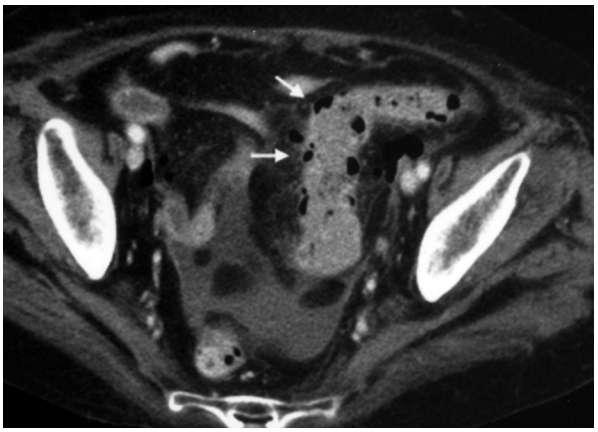


(B)

Fig. 1. Imaging studies of the presented case. (A) Chest radiography showed subcutaneous emphysema on the right side of the neck (arrow) accompanied with pneumomediastinum (PM) (arrow head). (B) Chest computed tomography (CT) demonstrated PM.

neous emphysema on the right side of the neck accompanied with PM (Figure 1A). Computed tomography (CT) of the chest subsequently revealed the presence of free air disseminated into the retroperitoneum and the peri-renal area, but no abnormal fluid accumulation in the mediastinum (Figure 1B). Due to a suspicion of acute mediastinitis, she was transferred to our hospital for further evaluation.

In our hospital, the patient displayed disturbed consciousness and could be awakened only by vigorous physical stimulation. Her temperature was 36.1°C, pulse rate 82 beats per minute, blood pressure 151/83 mmHg, and respiratory rate 16 breaths per minute. Physical examination showed neither hyper-resonance nor adventitious sounds in the bilateral chest. Abdominal palpation revealed diffuse tenderness without obvious rebounding pain. Laboratory tests indicated a white blood cell count (WBC) of 4500/μL with 1% band forms and 82% neutrophils, a hemoglobin (Hb) level of 10.8 g/dl (normal range for women: 11.3-15.3 g/dl), and an elevated C-reactive protein level of 52.03 mg/L (normal range < 0.3 mg/dl). Metabolic acidosis with respiratory compensation (pH: 7.492, PCO_2: 14.6 mmHg, HCO_3^-: 10.9 mmHg) and positive blood ketones (2+) was also noted. In a state of unclear consciousness, the patient was intubated with an endotracheal tube to maintain airway patency. Serial examinations were arranged to differentiate the origin of the PM and find the active infection source. Contrast esophagography excluded esophageal perforation. Upper gastrointestinal endoscopic investigation showed no obvious viscus perforation, but revealed duodenal diverticulum at the bulb, reflux esophagitis, Los Angeles Classification grade A, and circular ulcer formation at the antrum. Nasopharyngeal fiberoscopy showed intact mucosa from the nasopharynx to the hypopharynx, without any bulging mass or abscess formation. The patient was then transferred to the intensive care unit (ICU) for further management. Two days after admission, a CT of the abdomen was arranged due to diffuse abdominal tenderness. The images showed much extra-luminal free gas and fluid accumulation around the recto-sigmoid colon, which



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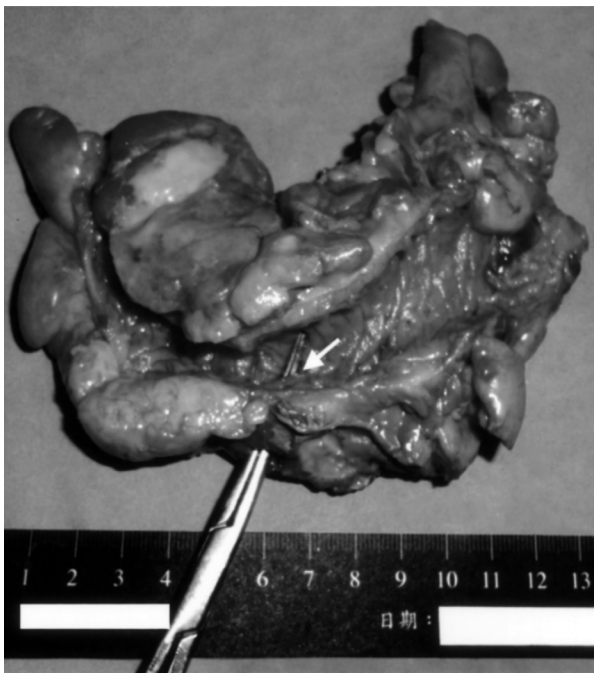


(B)

Fig. 2. Imaging study and surgical findings of the present case. (A) Abdominal CT showed much extra-luminal free gas and fluid accumulation around the recto-sigmoid colon. (B) Surgical intervention disclosed a perforated sigmoid colon. Arrow indicates a fistula penetrating out from the lumen of the sigmoid colon.

suggested acute bowel perforation (Figure 2A). Surgical intervention disclosed diverticulitis with perforation of the sigmoid colon (Figure 2B) accompanied with pus accumulation in the pelvic cavity and segmental infiltration of the small intestine, which resulted in poor perfusion. Hartmann's procedure and segmental resection of the small intestine (about 30 cm in length) were performed. Histopathology reported a perforated ulcer in the sigmoid colon (Figure 3) with abscess formation and suppurative peritonitis. However, even with aggressive postoperative care in the ICU, her condition deteriorated progressively and she expired on the 20th postoperative day due to septic shock.

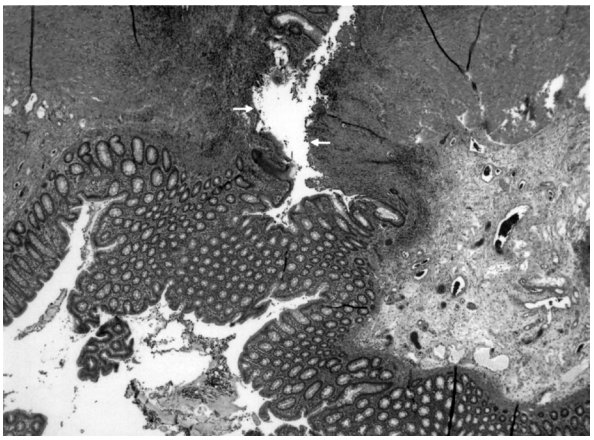


Fig. 3. Histopathology reported a perforated ulcer of the sigmoid colon (H&E stain 40X).

Discussion

The mediastinum is a thoracic chamber that contains various organs and structures, including the trachea, esophagus, heart, thoracic duct, thymus, lymph nodes, vessels and nerves, but no free air. Thus, any aberrant air present in the mediastinum, termed PM, should alert physicians to the need to identify the source of the air. The sources of PM can be classified as follows: upper respiratory tract, intra-thoracic airways, lung parenchyma, gastrointestinal tract, external to the body, and infection with gas-producing organisms [2]. According to the statistical data in the literature [1,3], ventilator-

associated barotrauma and traumatic injury to the chest are the most common causes of PM. PM can also be caused by invasive medical techniques, thus a detailed review of received medical procedures is important to exclude iatrogenic causes. In addition to the traumatic and iatrogenic causes of aberrant air, PM can, in rare cases, originate from non-traumatic, non-iatrogenic conditions, such as head and neck infectious disease, intra-pulmonary parenchymal or cavitary disease, and intra-abdominal viscus perforation. Since non-traumatic and non-iatrogenic causes of PM are rare and complicated, we proposed an integrated algorithm (Figure 4) to help physicians differentiate these difficult cases. As in the present case, by following the algorithm to make the differential diagnosis, the life-threatening surgical conditions might be detected sooner and the outcome of the patient changed.

Since PM may be a sign of life-threatening disease, it is important to identify the source of the air and initiate early medical or surgical intervention. Invasive investigations, including bronchoscopy, gastrointestinal endoscopy and esophagography, are usually performed to search for the source of the air leak. However, Haam *et al*. [3] suggested that precise history-taking and physical examination are preferable to invasive techniques such as esophagography and esophagoscopy for patients with no evidence of mediastinitis or a history of esophageal injury. In our reported case, the major clinical symptom was diffuse abdominal pain. This presentation of the abdomen should remind physicians that the source of the air leak is below, not above, the diaphragm. Thus, CT of the abdomen should be considered as the first step to rule out perforation of the intra-abdominal viscus. In addition, after early identification of the source of the aberrant air, the patient's outcome may be improved with surgical intervention in the emergency room.

We have reviewed and summarized the previously published reports of cases defined as "PM secondary to intra-abdominal disease", which excluded iatrogenic causes, such as endoscopic procedures (Table 1). In these cases, we found that very few of the patients sought medical help immediately; and even for those who were admitted to the hospital, the physicians tended to ignore the warning signs. We identified 2 possible reasons for the delayed diagnosis of PM secondary to intra-abdominal disease. First, most of the patients were immunodeficient, with poorly controlled diabetes and/or autoimmune disease, and they often took steroids and analgesics concurrently. This immunocompromised status and the use of steroids and analgesics may have led to an inappropriate inflammatory response when the patients suffered from an infectious disease, and masked or attenuated the clinical symptoms and signs, such as fever, chills or pain. Second, PM secondary to intra-abdominal disease is not associated with intraperitoneal inflammation or clinical peritoneal rebound pain because the perforated viscus is located in the retroperitoneal space. Therefore, physicians tend to subjectively and objectively disregard such a surgical emergency due to the lack of significant warning sings.

In summary, early and accurate diagnosis of PM secondary to intra-abdominal disease is challenging, especially in diabetic and immunodeficient patients who are taking steroid and analgesics concurrently. Herein, we presented a rare case of PM secondary to perforated sigmoid colon and proposed an integrated algorithm to help in the differential diagnosis. From

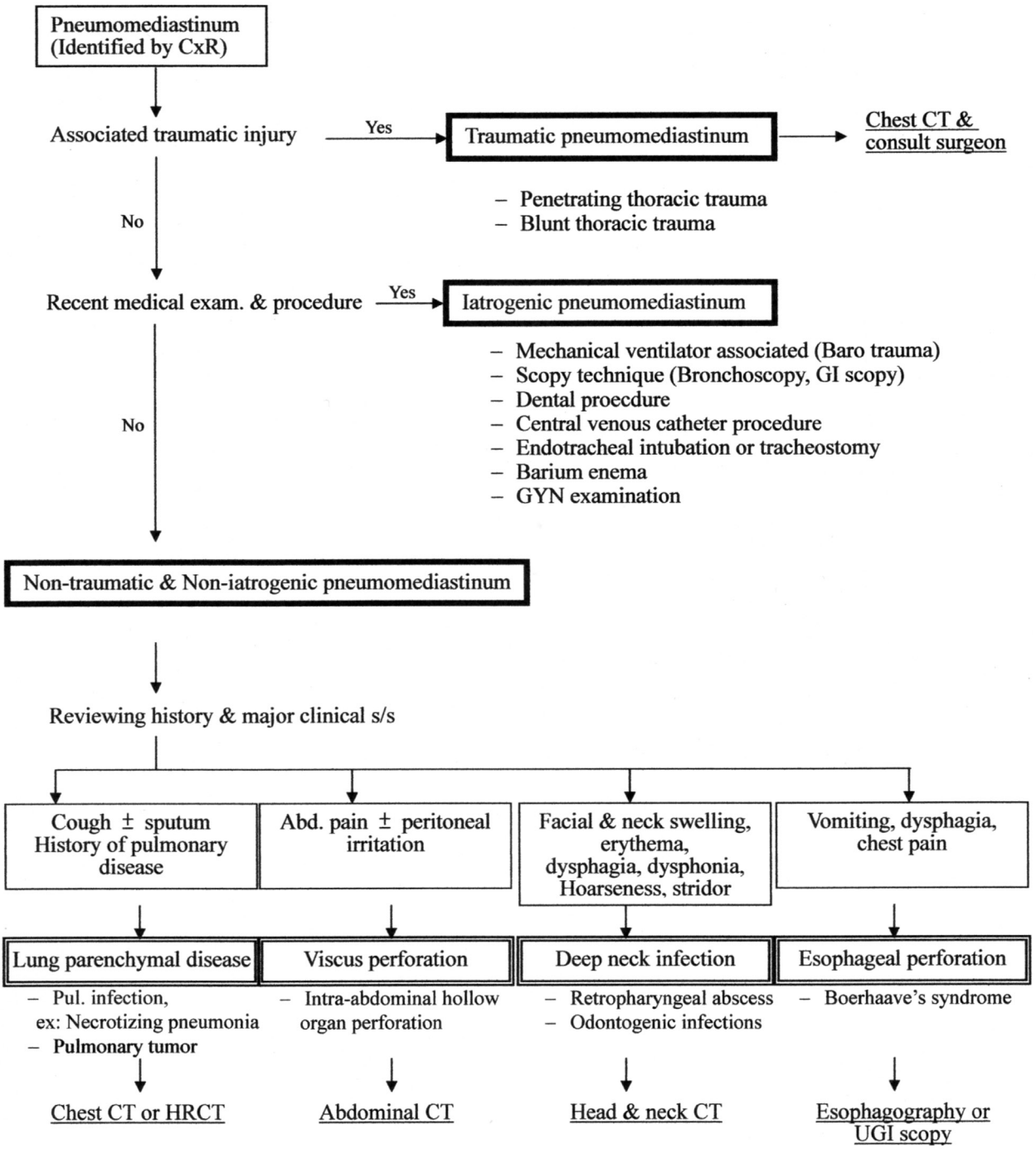


Fig. 4. An integrated algorithm for the differential diagnosis of PM.

a review of the literature, we have deduced 2 reasons why physicians would ignore this surgical emergency. Early awareness of this rare condition will expedite the diagnosis and treatment, and thus minimize morbidity and mortality.

Table 1. Summary of case reports of pneumomediastinum secondary to intra-abdominal disease, excluding those with iatrogenic causes

Author (year)	Age/Sex	Past history	Medication	Fever	Abdominal tenderness	Peritoneal sign
Mogan *et al*. (1980) [4]	16/F	Ulcerative colitis	Steroid	N	Y	Y
Hur *et al*. (1995) [5]	67/F	Diabetes	NA	N	Y	N
Alvares *et al*. (1997) [6]	26/M	Ulcerative colitis	Steroid	Y	N	N
van Oers *et al*. (2000) [7]	66/M	NA	NA	Y	Y	NA
Besic *et al*. (2004) [8]	50/F	Breast cancer	Steroid	Y	Y	N
Farah *et al*. (2009) [9]	60/F	VKH syn	Steroid	Y	Y	N
Choi (2011) [10]	59/M	NA	Analgesic	Y	Y	N
Lee *et al*. (2010) [11]	63/M	NA	Analgesic	N	Y	Y
Present case (2012)	74/F	Diabetes	Analgesic	N	Y	N

NA: not available; M: Male; F: Female; VKH syn: Vogt-Koyanagi-Harada syndrome

References

1. Caceres M, Braud RL, Maekawa R, *et al*. Secondary pneumomediastinum: a retrospective comparative analysis. Lung 2009; 187: 341-6.
2. David RP, Pneumomediastinum and Mediastinitis. Robert JM, Murray and Nadel's Textbook of Respiratory Medicine, 5th ed, Philadelphia, PA, Saunders/Elsevier, 2010: 1836-58.
3. Haam SJ, Lee JG, Kim DJ, *et al*. Oesophagography and oesophagoscopy are not necessary in patients with spontaneous pneumomediastinum. Emerg Med J 2010; 27: 29-31.
4. Mogan GR, Sachar DB, Bauer J, *et al*. Toxic megacolon in ulcerative colitis complicated by pneumomediastinum: report of two cases. Gastroenterol 1980; 79: 559-62.
5. Hur T, Chen Y, Shu GH, *et al*. Spontaneous cervical subcutaneous and mediastinal emphysema secondary to occult sigmoid diverticulitis. Eur Respir J 1995; 8: 2188-90.
6. Alvares JF, Dhawan PS, Tibrewala S, *et al*. Retroperitoneal perforation in ulcerative colitis with mediastinal and subcutaneous emphysema. J Clin Gastroenterol 1997; 25: 453-5.
7. van Oers JA, Ponssen HH, Hesp WL. Pneumopericardium, pneumomediastinum, pericarditis and mediastinal abscess secondary to diverticulitis of the sigmoid. Intensive Care Med 2000; 26: 1867-8.
8. Besic N, Zgajnar J, Kocijancic I. Pneumomediastinum, pneumopericardium, and pneumoperitoneum caused by peridiverticulitis of the colon: report of a case. Dis Colon Rectum 2004; 47: 766-8.
9. Farah R, Makhoul N. Pneumomediastinum as a presenting symptom of perforated sigmoid cancer: a case report. Cases J 2009; 2: 7356.
10. Choi PW. Pneumomediastinum caused by colonic diverticulitis perforation. J Korean Surg Soc 2011; 80 Suppl 1: S17-20.
11. Lee HS, Kuo PH. Pneumomediastinum and subcutaneous emphysema secondary to perforated duodenal ulcer: a case report and literature review. Thorac Med 2010; 25: 294-8.

乙狀結腸憩室炎破裂導致之縱膈腔氣腫—病歷報告

王耀麟 * 許正園 *,** 傅彬貴 **

縱膈腔氣腫起因於異常空氣出現在縱膈腔組織內，於多數情況下是由呼吸道或食道損傷所引起，但少數是從腹腔腸道器官穿孔所導致。我們報告一位糖尿病患者，有服用止痛藥之病史，此次以瀰漫性腹痛之表現且胸部放射線檢查發現有縱膈腔氣腫。經腹部斷層掃描及病理診斷為乙狀結腸憩室穿孔。透過文獻審查，我們提出了一個整合之鑑別診斷流程，並提出兩個於此類病人中延誤正確診斷的理由。*(胸腔醫學 2012; 27: 363-369)*

關鍵詞：縱膈腔氣腫，乙狀結腸憩室穿孔

台中榮民總醫院 內科部 胸腔內科 *，台中榮民總醫院 內科部 呼吸治療科 **
索取抽印本請聯絡：傅彬貴醫師，台中榮民總醫院 內科部 呼吸治療科，台中市中港路三段 160 號

Common Variable Immunodeficiency – A Case Report with Emphasis on the Diagnostic Clues and Treatment Response

Shu-Lan Hsu*, Kuo-Sheng Fan*, Yen-Hsien Lee*,**, Hsing-Chun Chen*, Chun-Liang Lai*,**

Common variable immunodeficiency (CVID) encompasses a group of heterogeneous conditions linked by a lack of immunoglobulin production and primary antibody failure. CVID has a broad range of clinical symptoms with the involvement of multiple organs, especially the respiratory system. The mean onset of symptoms in patients with CVID is in their 3rd decade of life. Given the complexity and rarity of the disease, the diagnosis of CVID is often delayed for a mean of 8.9 years. We herein report a 24-year-old female patient with CVID manifesting with migratory pneumonia, splenomegaly, and persistently elevated liver enzymes. The disease was suspected due to the presence of hypoglobulinemia, and confirmed by low serum levels of IgG, IgM, and IgA. Her splenomegaly was attributed to CVID-related lymphoproliferative disorder. The spleen regressed to normal size after intravenous immunoglobulin supplementation. This case emphasizes the need for a high index of clinical suspicion for CVID in patients presenting with recurrent sinopulmonary infections and/or an impaired capacity to produce specific antibodies in response to infection, such as chronic hepatitis C. Early diagnosis is needed to prevent significant morbidity and mortality and to improve the prognosis in these patients. ***(Thorac Med 2012; 27: 370-376)***

Key words: common variable immunodeficiency, hepatitis C, intravenous immunoglobulin, migratory pneumonia, splenomegaly

Introduction

Common variable immunodeficiency (CVID), also known as acquired hypogammaglobulinemia, is a primary immunodeficiency resulting from B-cell differentiation failure and impaired secretion of immunoglobulins. The prevalence of CVID ranges from 1/50,000 to 1/200,000, with a reported incidence of 1/75,000 live births in Western countries [1]. The onset age of clinical symptoms in CVID ranged from 3 to 79 years, with mean ages of 23 years and 28 years in male and female patients, respectively, which differs from X-linked

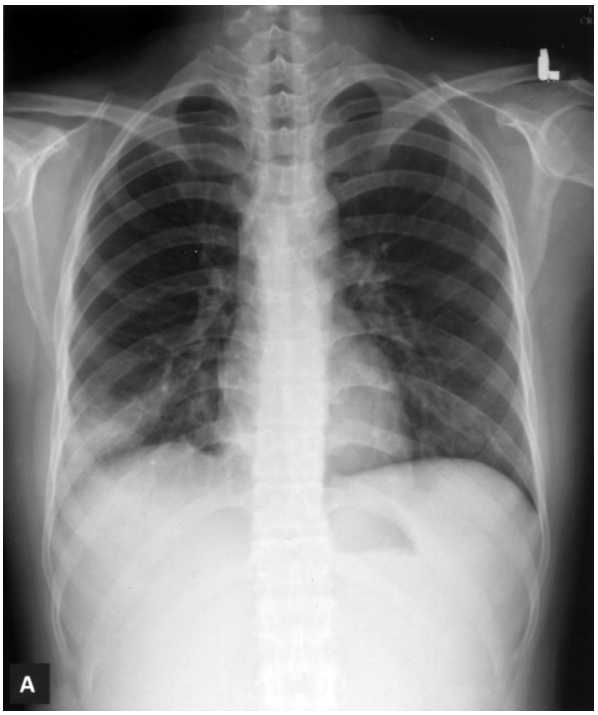
*Division of Pulmonary and Critical Care, Department of Internal Medicine, Buddhist Dalin Tzu Chi General Hospital, Chiayi, Taiwan; **School of Medicine, Buddhist Tzu Chi University, Hualien, Taiwan
Address reprint requests to: Dr. Chun-Liang Lai, Division of Pulmonary and Critical Care, Department of Internal Medicine, Buddhist Dalin Tzu Chi General Hospital, No. 2, Ming-Sheng Road, Dalin Town, Chiayi, 62247, Taiwan

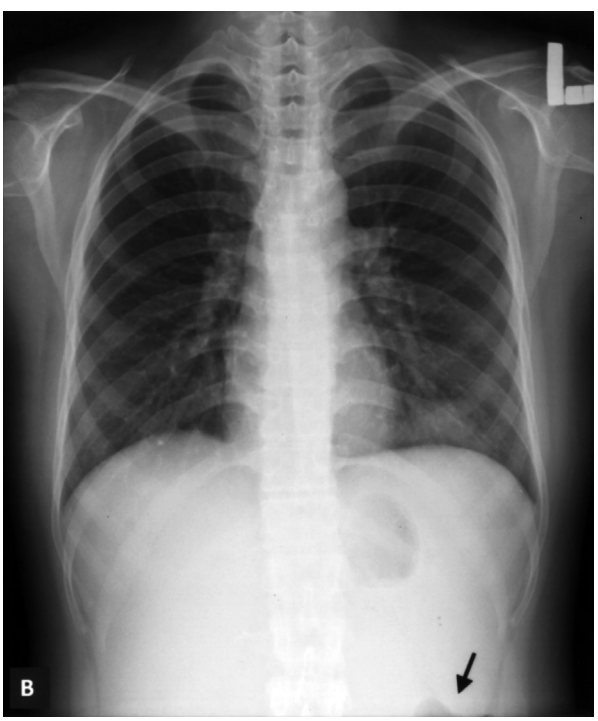
immunodeficiency disorders [2]. CVID has a broad range of clinical manifestations, including recurrent sinopulmonary infections and chronic lung disease, autoimmune diseases, gastrointestinal disorders, granulomatous infiltrative diseases, lymphoproliferative disorders, lymphoma and/or solid tumors. Because of its rarity, onset in adulthood, and involvement of multiple organs, the diagnosis is commonly missed in general clinical practice, with an average delay of 8.9 years [3]. We herein report a 24-year-old woman who manifested initially with migratory lung patches and chronic hepatitis, and in whom the diagnosis of CVID was delayed for 1 decade and that of chronic hepatitis C for 2-3 years. Clinical clues for the diagnosis of and treatment strategy for this rare disease are also discussed.

Case Report

A 24-year-old housewife, a never-smoker, presented to this hospital with high fever and yellowish productive cough for 1 day. The patient had a past medical history of bronchiectasis status post-right middle lobe lobectomy at age 14 and gall bladder stone status post-cholecystectomy at age 16. During the previous 8 years, she had had several episodes of lung infection treated at other hospitals uneventfully. She was also known to have elevated serum liver enzymes with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of more than 3-fold the upper reference limit for 2-3 years. Hepatitis B surface antigen, surface and core antibodies (Ab), and hepatitis A and C Ab were all nonreactive. Three months prior to this admission, she had another episode of pneumonia in the right lower lobe, with sputum culture yielding *Streptococcus pneumoniae* (Figure 1A). On her 2nd admission to this hospital, she was found to have left lower lobe pneumonia (Figure 1B). On physical examination, splenomegaly was discovered. Her white blood cell (WBC) count was elevated, at 10,000/mm3; with 70.9% segment forms, and 20.9% lymphocytes. Abdominal echography showed splenomegaly (a longitudinal diameter of 13.4 cm) and the liver was relatively enlarged (15.5 cm at the right lobe). We started intravenous moxifloxacin therapy. Sputum culture yielded *Haemophilus influenzae*. A series of workups was arranged in order to survey the etiology of her repeated infections. There was no congenital anomaly in her aero-digestive system. The anti-human immunodeficiency virus antibody was nonreactive. However, hypoglobulinemia was detected with a serum globulin level as low as 1.3 mg/dl [reference level: 2.3-3.5 mg/dl]. Primary immunodeficiency was suspected. Further survey of immunoglobulin levels showed IgG: <33.3 mg/dl [reference level: 694-1618 mg/dl], IgM: 11.4 mg/dl [reference level: 60-263 mg/dl], and IgA: <6.67 mg/dl [reference level: 68-378 mg/dl]. Her blood B and T cell numbers were within normal limits (Figure 2). The ratio of CD4 and CD8 was slightly below the lower normal limit. The immunoglobulin levels of her parents were all within normal ranges. Hence x-linked hypogammaglobulinemia was excluded. She was then diagnosed with CVID. Due to the nature of the ineffective Ab production in this disease, we reconsidered the possibility of viral hepatitis C for her abnormal liver enzymes, despite the fact that her serum anti-hepatitis C virus (HCV) Ab was negative. Direct detection of serum HCV RNA yielded 80 copies/ml, and confirmed the presence of HCV infection.

The patient then started intravenous immunoglobulin (IVIG) replacement therapy. The





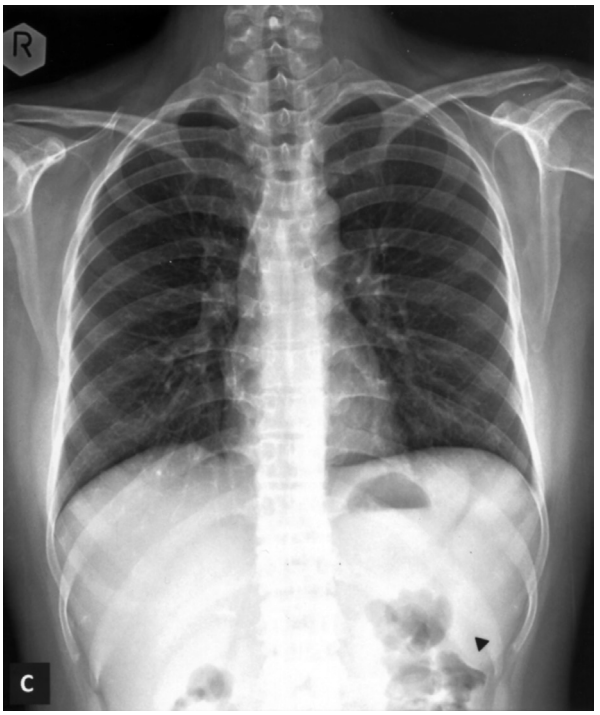


Fig. 1. A 24-year-old woman had with migratory pneumonia within 3 months with different causal microorganisms as pneumococcus in the right lower lobe (A) and *Haemophilus influenzae* in the left lower lobe (B). Splenomegaly was indentified on the 2nd chest radiography (B, arrows). After intravenous immunoglobulin replacement for her CVID, regression of splenomegaly could be detected on the follow-up chest film (C, arrowhead).

initial dose was 200 mg/kg every 4 weeks, and was escalated to maintain a trough level of serum IgG above 400-500 mg/dl. After 15 months of IVIG treatment, her splenomegaly regressed (Figure 1C), with echography measuring a longitudinal diameter of 7.3 cm. She had no recurrent pneumonia in the following 10 years.

Discussion

CVID results from the failure of B-cell differentiation, plasma cell development, and/or impaired immunoglobulin secretion. The etiology in the vast majority of cases of CVID is unknown. Recent studies reported that defects in the genes that encode inducible T-cell costimulator (ICOS) [4], transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) [5-6], CD19 [7], B cell

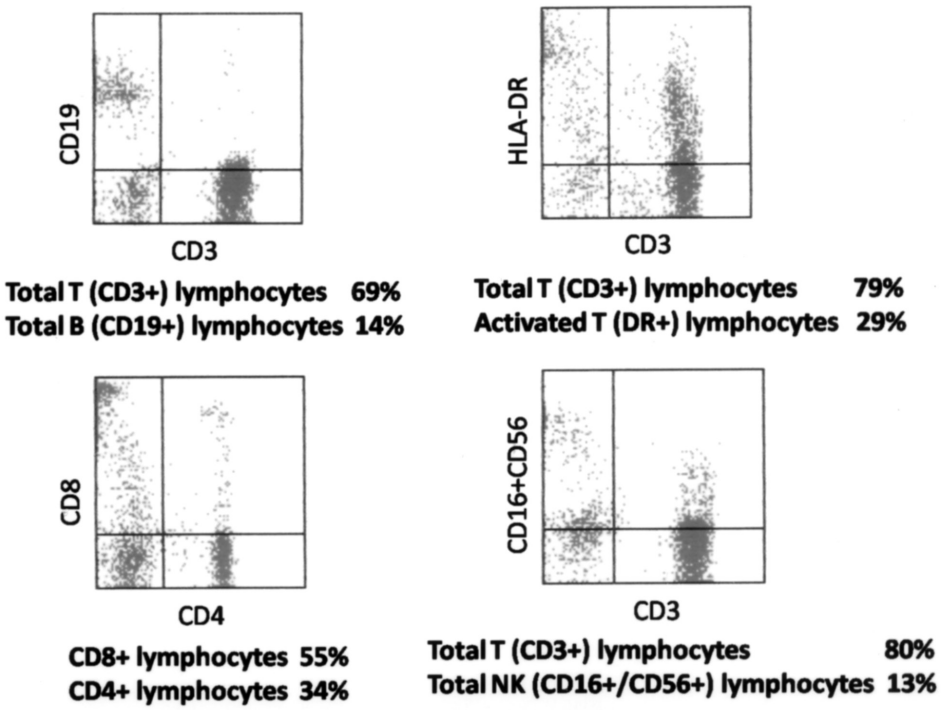
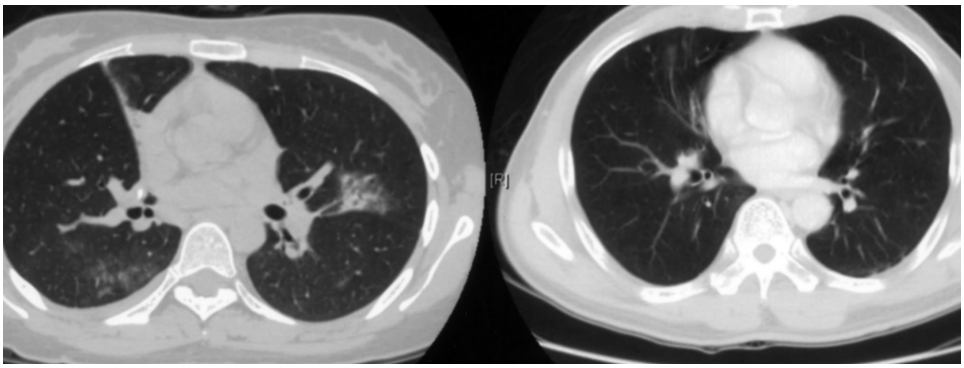


Fig. 2. The proportions of lymphocytes in the blood of this female patient with CVID were: T lymphocytes (CD3+): 76% (average) (reference range 50-84%), B lymphocytes (CD19+): 14% (reference range 5-18%), and natural killer (NK) cells (CD16+/CD56+): 13% (reference range 7-40%). The CD4 (helper)/CD8 (suppressor/cytotoxic) ratio was 0.62 (reference range 0.7-2.3).

activating factor receptor (BAFFR) [8], CD81 [9], CD20 [10], or CD21 may be related to the disease [11]. Patients with CVID due to polymorphisms in TACI, the most common genetic abnormalities occurring in approximately 7% of patients with CVID, are more likely to have autoimmune disease and splenomegaly [12]. But genetic alterations in TACI and their immunological and clinical relevance are still incompletely understood. In a mice study, deletion of Tnfrsf13b, the gene encoding TACI, resulted in an impaired response to thymus-independent antigens and a halt of lymphocyte maturation, which abolishes the immunoglobulin switching to IgA, IgE, and IgG1. Ineffective production of Ab might be a stimulator to lymphoproliferation [13].

CVID has variable clinical presentations involving multiple organs. The most common manifestation is recurrent bacterial infections which involve the sinuses and respiratory tract, leading to sinusitis, otitis media, bronchitis, bronchiectasis, and/or pneumonia (Figure 3A). Common pathogens include encapsulated (*Hemophilus influenzae*, *Streptococcus pneumoniae*) or atypical (Mycoplasma spp.) bacteria [14]. Gastrointestinal tract infections with pathogens (*Campylobacter jejuni*, Salmonella spp., *Giardia lamblia*) are also common. The prevalence of hepatitis is increased in CVID, occurring in approximately 12% of patients [2]. Because of impaired immunoglobulin production, it is nearly impossible to detect any antiviral Ab in patients with CVID who also have



(A) (B)

Fig. 3. The bronchiectasis in patients with CVID is nonspecific. It can be diffused or localized, as shown in this case (A), which involved several lobes. In another patient (B), on the other hand, only the right middle lobe was found to have cylindrical bronchiectasis.

viral hepatitis. The diagnosis of viral hepatitis in such patients may require methods to detect viral particles directly, such as measuring HCV RNA, as in the present case. In our case, the diagnosis of CVID was delayed up to 10 years, even though apparent clinical clues, including her repeated infections with encapsulated pathogens (implying a humoral immunity dysfunction) and persistently elevated liver enzymes due to HCV-related hepatitis but masked by negative serology (anti-HCV Ab) study, were present. The majority of CVID patients have their disease onset in adulthood, which differs from X-linked immunodeficiencies in children. Non-pediatric physicians may be less alert or unfamiliar with this disease. In addition, the disease is so rare physicians would not consider it a first priority. As a result of our increased awareness, we subsequently diagnosed 2 other patients with CVID. One of these 2 patients had only mild bronchiectasis (Figure 3B) without significant infections before diagnosis. The clue to his CVID was the hypoglobulinemia found incidentally in the physical check-up. The other patient had severe bronchiectasis and respiratory impairment at the diagnosis. The definitive diagnosis of CVID requires a serum IgG level less than 2 standard deviations from the mean for age-adjusted standardized reference, a low serum IgA or IgM level, and impaired capacity to make a specific Ab in response to immunization or infection, in addition to the exclusion of other primary or secondary Ab deficiencies. B-cell numbers are variable in CVID.

The mainstay of treatment for CVID is IVIG. The target trough level should be kept above 400-500 mg/dl, which is achieved by infusing a dose of 200-400 mg/kg every 2-4 weeks. The dosage varies from patient to patient, and IgG levels should be checked periodically to attain a targeted trough level. Several studies have demonstrated the benefit of regular IVIG replacement therapy in protecting against lower respiratory infections [3] and to decrease mortality [15-16]. However, there is no report in the English-language literature on whether IVIG can reverse splenomegaly, and return the spleen to a normal size. In this case, we witnessed the regression of splenomegaly and no relapse of the lower respiratory tract infection.

The long-term outcome may require further observation.

Conclusion

The case presented here emphasizes the need for a high index of clinical suspicion for CVID in patients presenting with recurrent sinopulmonary infections or an impaired capacity to make specific Ab in response to immunization or infection (such as anti-HCV-Ab-negative chronic hepatitis C infection). Although IVIG treatment brings improvement to these patients, early diagnosis is crucial to prevent significant morbidity and mortality and to improve the prognosis.

References

1. Park MA, Li JT, Hagan JB, *et al*. Common variable immunodeficiency: a new look at an old disease. Lancet 2008; 372: 489-502.
2. Cunningham-Rundles C, Bodian C., Common variable immunodeficiency. Clinical and immunological features of 248 patients. Clin Immunol 1999; 92(1): 34-48.
3. Quinti I, Soresina A, Spadaro G, *et al*. Italian Primary Immunodeficiency Network. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol 2007; 27(3): 308-16.
4. Grimbacher B, Hutloff A, Schlesier M, *et al*. Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. Nat Immunol 2003; 4(3): 261-8.
5. Castigli E, Wilson SA, Garibyan L, *et al*. TACI is mutant in common variable immunodeficiency and IgA deficiency. Nat Genet 2005; 37(8): 829-34.
6. Salzer U, Maul-Pavicic A, Cunningham-Rundles C, *et al*. ICOS deficiency in patients with common variable immunodeficiency. Clin Immunol 2004; 113(3): 234-40.
7. van Zelm MC, Reisli I, van der Burg M, *et al*. An antibody-deficiency syndrome due to mutations in the CD19 gene. N Engl J Med 2006; 354(18): 1901-12.
8. Wehr C, Kivioja T, Schmitt C, *et al*. The EUROclass trial: Defining subgroups in common variable immunodeficiency. Blood 2008; 111(1): 77-85.
9. van Zelm MC, Smet J, Adams B, *et al*. CD81 gene defect in humans disrupts CD19 complex formation and leads to antibody deficiency. J Clin Invest 2010; 120(4): 1265-74.
10. Kuijpers TW, Bende RJ, Baars PA, *et al*. CD20 deficiency in humans results in impaired T cell-independent antibody responses. J Clin Invest 2010; 120(1): 214-22.
11. Thiel J, Kimmiq L, Salzer U, *et al*. Genetic CD21 deficiency is associated with hypogammaglobulinemia. J Allergy Clin Immunol 2012; 129(3): 801-10.
12. Cunningham-Rundles C, Autoimmune manifestations in common variable immunodeficiency. J Clin Immunol 2008; Suppl 1: S42-5.
13. Salzer U, Chapel HM, Webster AD, *et al*. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. Nat Genet 2005; 37(8): 820-8.
14. Oksenhendler E, Gerard L, Fieschi C, *et al*. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis 2008; 46(10): 1547-54.
15. Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. J Allergy Clin Immunol 2002; 109(6): 1001-4.
16. Resnick ES, Moshier EL, Godbold JH, *et al*. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood 2012; 119(7): 1650-7.

常見性變異性免疫缺乏症—強調診斷線索及治療反應之病例報告

許舒嵐 * 范國聖 * 李彥憲 *,** 陳信均 * 賴俊良 *,**

常見性變異性免疫缺乏症代表一群變異性高的族群，他們無法製造免疫球蛋白並使原發性抗體失效。它有許多臨床症候，會影響多重器官特別是呼吸系統。常見性變異性免疫缺乏症發生年齡多在 30 歲上下，但因疾病複雜度，平均被延誤診斷時間長達 8.9 年。本文報告一 24 歲年輕女性有遊走性肺炎，脾腫大，和持續性肝指數異常，因實驗室檢查發現球蛋白指數低下，懷疑是常見性變異性免疫缺乏症，並經由 IgG、IgM、IgA 數目低下確診。此病人的脾腫大，懷疑和常見性變異性免疫缺乏症相關的淋巴增生疾病有關，且再經免疫球蛋白治療之後，脾腫大回復至正常大小。此臨床病例強調當病人有反覆性鼻竇與呼吸道感染，以及對於感染症無法產生相對應抗體，如 C 型肝炎時，應高度懷疑此病，早期診斷才可避免嚴重的後遺症並改善預後。*(胸腔醫學 **2012; 27: 370-376**)*

關鍵詞：常見性變異性免疫缺乏症，遊走性肺炎，脾腫大，靜脈注射型免疫球蛋白

* 大林慈濟醫院　內科部　胸腔內科，** 佛教慈濟大學
索取抽印本請聯絡：賴俊良醫師，大林慈濟醫院　內科部　胸腔內科，62247 嘉義縣大林鎮民生路 2 號

Disseminated *Penicillium marneffei* Infection in a Patient without HIV Infection: A Case Report

Chu-Yun Huang*, Tsan-Chieh Liao**, Lei-Chi Wang***, Chun-Ku Chen**,
Jia-Yih Feng*,****, Yu-Chin Lee*,*****

Penicillium marneffei infection is a fungal infection which often occurs in immunocompromised hosts, especially HIV-infected patients. Although both immunocompetent and immunocompromised patients can be infected, disseminated *Penicillium marneffei* is extremely rare in non-HIV patients. We report an HIV-negative patient who developed disseminated *Penicillium marneffei* infection that included the lung, lymph node, and bone, with the initial presentation of fever, night sweating, body weight loss and refractory pulmonary infiltrates. Grocott's Methenamine Silver stain-positive fungi were identified in specimens from transbronchial, lymph node and bone marrow biopsies. *Penicillium marneffei* was confirmed by fungal culture from sputum, bronchoalveolar lavage fluid, transbronchial lung biopsy, mediastinal lymph node biopsy, and bone marrow biopsy. After treatment with intravenous amphotericin B followed by oral itraconazole for 10 weeks, the clinical symptoms and pulmonary infiltrates resolved completely. ***(Thorac Med 2012; 27: 377-385)***

Key words: bone marrow, fever, non-HIV, *Penicillium marneffei*, pneumonia

Introduction

Penicillium marneffei (*P. marneffei*) is an emerging opportunistic fungal pathogen, and infection by this pathogen is an important cause of morbidity and mortality in human immunodeficiency virus (HIV)-infected patients, especially in Southeast Asia [1]. It also occurs occasionally in immunosuppressed patients who have had travel-related exposure to this organism [1]. *P marneffei* is endemic in Burma (Myanmar), Cambodia, Southern China, Indonesia, Laos, Malaysia, Thailand and Vietnam [2]. Although both immunocompetent and immunocompromised patients can be infected, it is extremely rare to find systemic infections in HIV-negative patients. The clinical manifestations of *P. marneffei* infection have included cough, fever, weight loss, anemia, skin lesions, lymphadenopathy, and hepatomegaly [3]. Because of its non-specific presentations, the diagnosis of *P. marneffei* infection is frequently de-

*Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; **Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan; ***Department of Pathology, Taipei Veterans General Hospital, Taipei, Taiwan; ****Institute of Clinical Medicine; *****School of Medicine, National Yang-Ming University, Taipei, Taiwan
Address reprint requests to: Dr. Jia-Yih Feng, Department of Chest Medicine, Taipei Veterans General Hospital, #201, Section 2, Shih-Pai Road, Taipei 11217, Taiwan

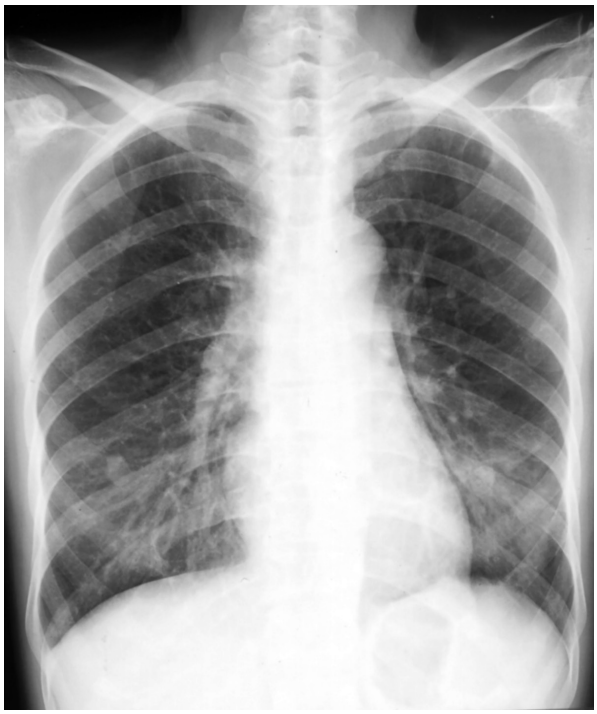
layed, especially in non-HIV-infected patients.

Case Report

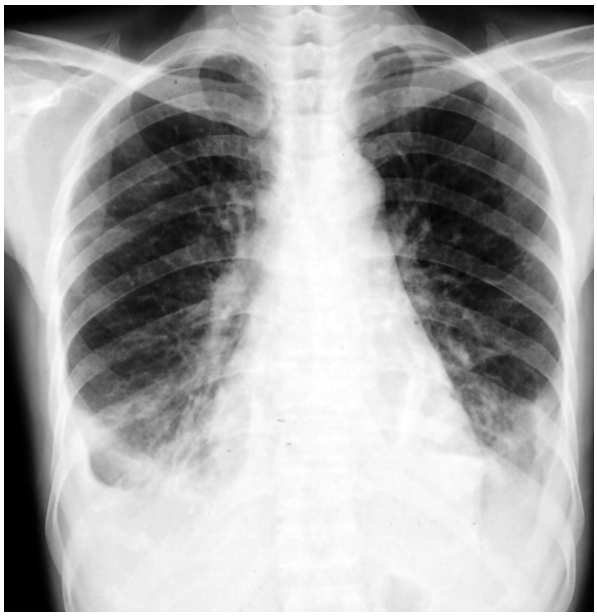
A 48-year-old woman presented to our hospital with low-grade fever and night sweating for more than 1 month. She also complained of body weight loss of approximately 3 kilograms within 1 month. The patient did not smoke and denied recent travel. She also denied having a prior history of systemic diseases, and had had an active lifestyle until 1 year ago. She suffered from 2 episodes of community-acquired pneumonia about 1 year and 6 months, respectively, prior to this admission. Due to the symptoms/signs as described above, she was admitted to another hospital about 3 weeks before coming to our institution, under the impression of atypical pneumonia. She received parenteral antibiotics, but her symptoms persisted. She was then transferred to our hospital and admitted for further evaluation.

Upon arrival, the patient appeared pale and ill-looking. Her vital signs were as follows: heart rate, 115/min; respiratory rate, 20/min; blood pressure, 106/54 mmHg; body temperature, 38.3°C. Physical examination revealed pale conjunctiva and fine crackles in the left lower lung fields. No skin lesions could be found. The laboratory test results were: WBC, 17,200/cumm; hemoglobin, 9.1 mg/dL; platelet, 554,000/cumm; C-reactive protein level, 9.36 mg/dL. Chest radiograph revealed increased infiltrates in the bilateral lower lung fields (Figure 1A). Chest computed tomography (CT) showed localized alveolar infiltration in the left lower lobe with multiple confluent mediastinal lymphadenopathy with rim enhancement (Figure 2). The patient received amoxicillin/clavulanic acid and azithromycin initially as empirical treatment, but the symptoms of intermittent fever persisted. Serology tests for atypical pathogens, including *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydophylla pneumoniae*, were all negative. Acid-fast bacilli were not found in the sputum, and sputum culture showed no growth of bacteria. The ELISA screening test for HIV was checked twice, and also revealed negative results. Serum titers of autoantibodies were not elevated and the analyses of lymphocyte subpopulations also showed normal distributions. Parenteral levofloxacin was administered later, but the chest radiographs revealed that infiltrates in the bilateral lower lung fields were in progression, with an accumulation of pleural effusion (Figure 1B).

The patient then underwent bronchoalveolar lavage (BAL) and transbronchial lung biopsy of the left lower lobe. Mediastinoscopy was arranged for mediastinal lymph nodes biopsy. Cytological examination of the BAL fluid (BALF) disclosed Grocott's Methenamine Silver (GMS) stain-positive non-budding bisected fungus spores (Figure 3). The histopathologic examination of specimens from transbronchial lung biopsy and lymph node biopsy demonstrated granulation tissue with the presence of numerous GMS-positive yeast forms of microorganisms within the cytoplasm of macrophages and extracellular tissue. A centrally located transverse septum, which was consistent with *P. marneffei*, could also be identified (Figure 4). Fungal cultures of the sputum, BALF, and tissue specimens from transbronchial lung biopsy and mediastinal lymph node biopsy showed growth of *P. marneffei* (Figure 5). In order to exclude occult hematological malignancy, bone marrow biopsy was also performed. GMS stain-positive yeast was found in the bone marrow biopsy specimens and *P. marneffei* was isolated



(A)



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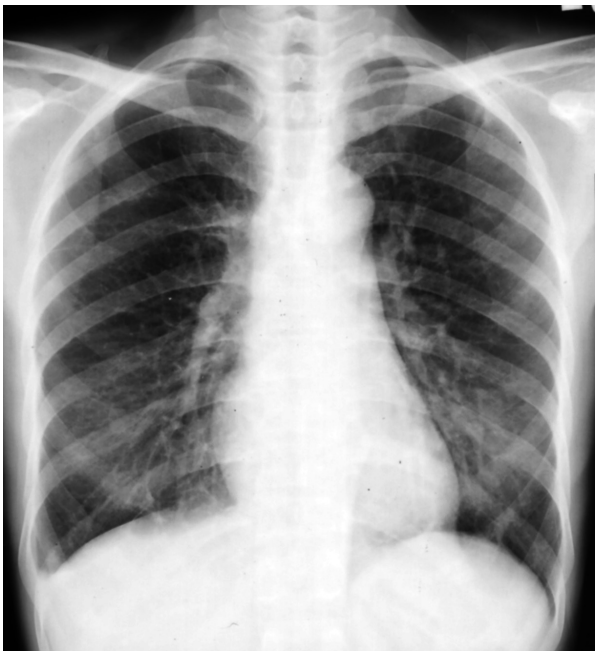


(C)

Fig. 1. (A) Chest radiograph on the day of admission showed localized infiltrates in the bilateral lower lung fields. (B) Chest radiograph on the 10th day showed progressive change with accumulation of pleural effusion. (C) Chest radiograph after completion of intravenous amphotericin B followed by oral itraconazole for 10 weeks showed total resolution of pulmonary infiltrates.

from cultures of bone marrow aspirates.

With a diagnosis of disseminated *P. marneffei* infection with lung, lymph node and bone marrow involvement, the patient received intravenous amphotericin B (0.6 mg/kg) for 2 weeks, followed by oral itraconazole 400 mg daily for 10 weeks. The pulmonary infiltrates on chest radiographs improved completely (Figure 1C). The clinical symptoms of intermittent fever, night sweating, and body weight loss also subsided.

Discussion

P. marneffei was first isolated from the bamboo rat in Vietnam in 1956, and the first case of human infection was described in a man with Hodgkin's lymphoma in 1973. *P. marneffei* can cause infection in immunocompetent patients, but prefers immunocompromised hosts and has

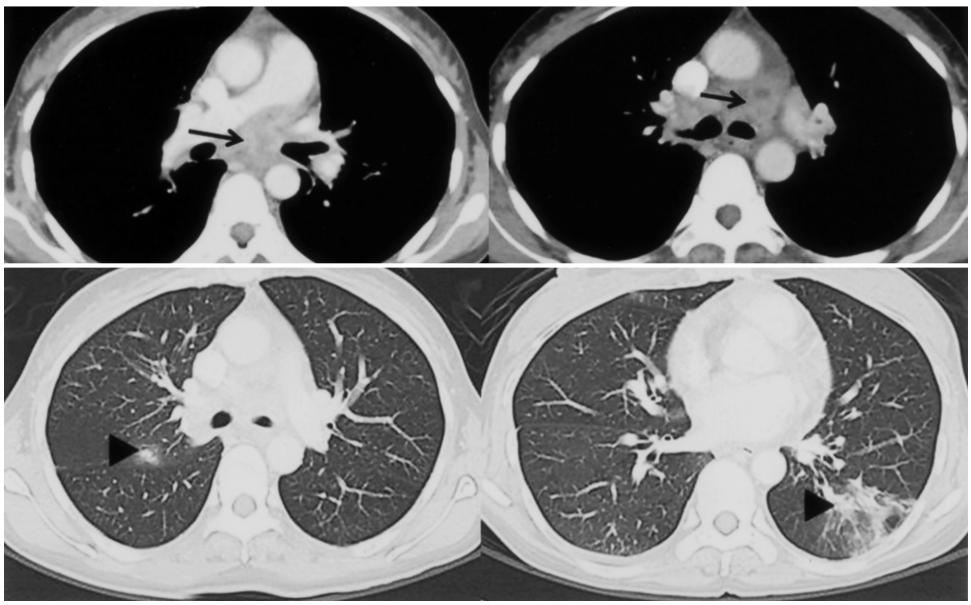
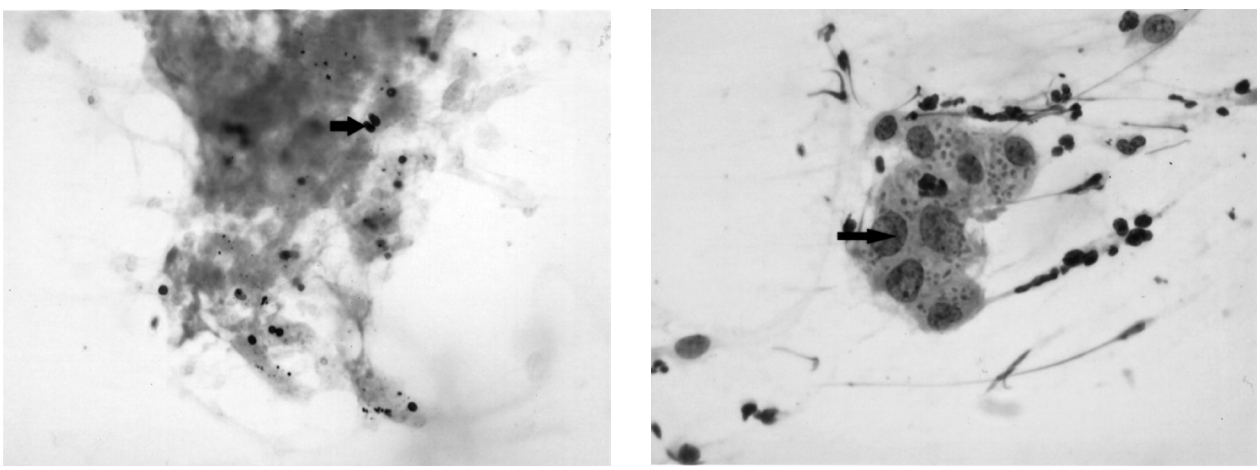


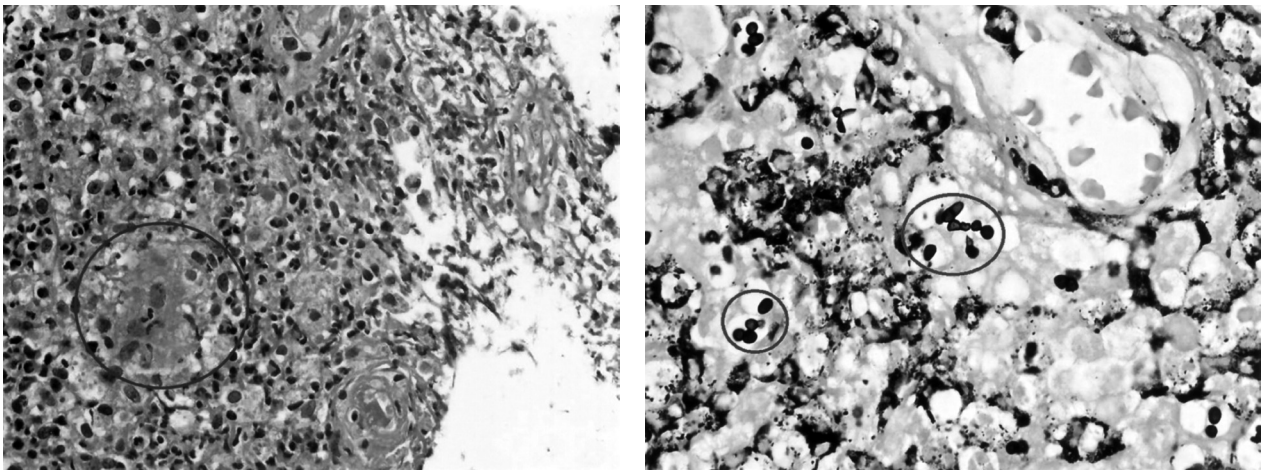
Fig. 2. Chest computed tomography on the day of admission showed confluent mediastinal lymphadenopathy with rim enhancement (arrow) and localized alveolar infiltrates in the left lower lobe (arrow head).



(A) (B)

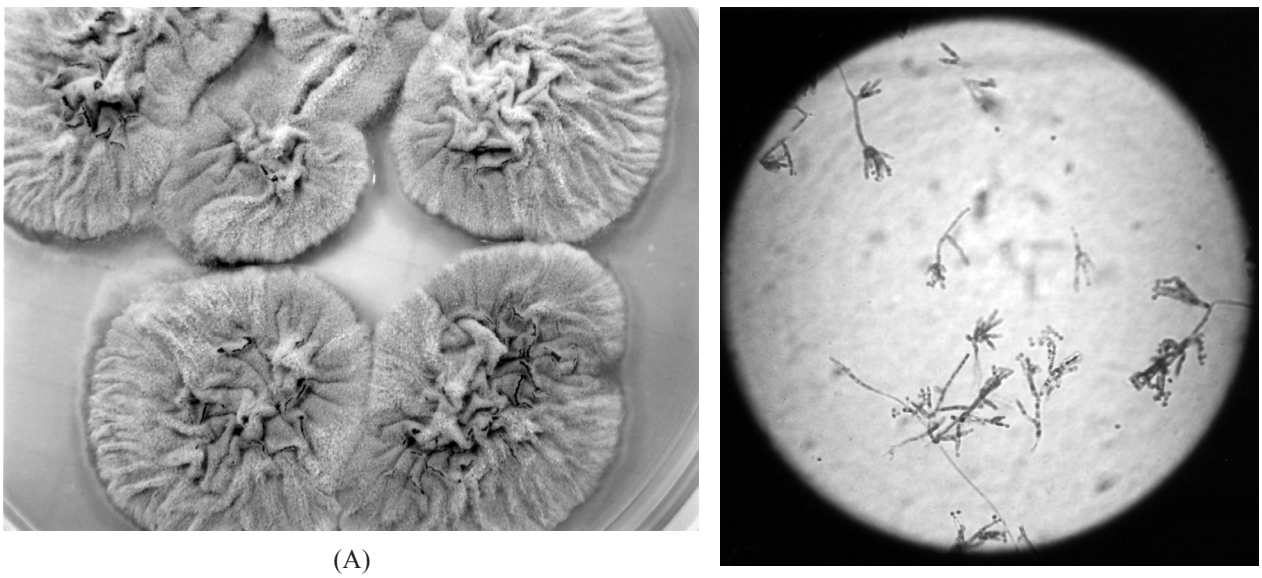
Fig. 3. Cytological examination of bronchoalveolar lavage fluid. (A) Grocott's methenamine silver (GMS) stain showed non-budding bisected fungus spores (arrow). (x400) (B) Papanicolaou stain showed centrally located transverse septum within the yeast (arrow). (X400)

become an important opportunistic pathogen in HIV-positive individuals in Asian countries [3-4]. As the HIV/AIDS epidemic has spread, the prevalence of *P. marneffei* infection also has increased in countries in the region, including Vietnam, India, Taiwan, Malaysia, Cambodia, and the provinces of Guangxi and Guangdong in China [5-7]. Reports of *P. marneffei* infection in Taiwan are relatively scarce. Hsueh *et al*. described 24 patients with *P. marneffei* infection from 1987 through 1998. Of these 24 patients, 16 had AIDS and 20 had disseminated *P.*



(A) (B)

Fig. 4. Histopathological examination of transbronchial lung biopsy. (A) Hematoxylin and eosin (H&E) stain showed acute inflammation with granulation tissue (circle). (x100) (B) Grocott's methenamine silver (GMS) stain showed numerous yeast forms of microorganisms within the cytoplasm of macrophages and extracellular tissue (circle). (X200)



(A) (B)

Fig. 5. Culture from transbronchial lung biopsy revealed growth of *P. marneffei*. (A) *P. marneffei* grows as mold and exhibits diffusible red pigment when growing on Sabouraud's glucose agar medium at 25°C. (B) Conidiophores of *P. marneffei* bearing phialides and chains of conidia at 37°C.

marneffei infection. In addition, 17 of 24 cases were diagnosed from 1996 through 1998, which indicated an increasing trend of *P. marneffei* infection in Taiwan [8].

Patients with *P. marneffei* infection commonly present with symptoms and signs of infection involving the reticuloendothelial system, including generalized lymphadenopathy,

hepatomegaly, and splenomegaly [9-10]. Anemia is the most common laboratory finding, and was also found in our patient. Non-specific respiratory symptoms, including cough, dyspnea, and chest pain may be present as well. Approximately 1/3 of patients may exhibit gastrointestinal symptoms, such as diarrhea [11-12]. The skin lesions of *P. marneffei*, which occur on the face, upper trunk, and extremities, may manifest as papules, pustules, abscesses, nodules, or ulcers. In HIV-infected individuals, the skin lesions typically are umbilicated papules that resemble those of molluscum contagiosum [13], whereas in individuals not infected with HIV, abscesses are a more common manifestation of cutaneous involvement.

Radiographic features of pulmonary *P. marneffei* infection are diverse and non-specific. In a series of 30 cases reported by Supparatpinyo *et al*., the abnormal chest radiographic findings included diffuse reticulonodular infiltration (13 cases), localized alveolar infiltration (12 cases), diffuse alveolar infiltration (3 cases), and localized interstitial infiltration (1 case) [2]. Localized reticular infiltration and cavitary lesion were also reported by Deesomchok and colleagues [12]. In these reports, diffuse reticulonodular infiltration seems to be the most common presentation in chest radiographs. In our case, the initial chest radiograph showed localized alveolar infiltration in the left lower lobe of the lung. The nonspecific findings in the chest radiograph again highlight the importance of histopathological examination and taking cultures to make an accurate diagnosis and exclude the possibility of other microorganisms, such as mycobacterium or other fungal infections.

Diagnosis of *P. marneffei* infection is confirmed by the identification of the organism from smear, culture, or histopathological sections. Supparatpinyo reported that bone marrow culture was the most sensitive (100%) in diagnosing *P. marneffei* infection, followed by skin biopsy cultures (90%) and blood cultures (76%) [2,11]. *P. marneffei* can be seen in histopathological sections stained with hematoxylin and eosin (H&E), GMS, or periodic acid-Schiff stain (PAS). The mold-to-yeast conversion is a diagnostic characteristic of *P. marneffei*. In our case, the presence of GMS-positive fungus with typical pathological features of *P. marneffei* within macrophages in specimens from both BALF and mediastinal lymph node biopsy, transbronchial lung biopsy, and bone marrow biopsy confirmed the diagnosis. The centrally located transverse septum can be clearly identified and differentiated from *Histoplasma capsulatum*. The fungal cultures of sputum, transbronchial lung biopsy, BAL fluid, and bone marrow aspirate also revealed growth of *P. marneffei*.

Patients with *P. marneffei* infection always suffer high mortality, especially those who are misdiagnosed at an early stage or left untreated. Previous studies demonstrated the high susceptibility of *P. marneffei* to miconazole, itraconazole, ketoconazole, and flucytosine, and its intermediate susceptibility to amphotericin B. Treatment with amphotericin B (0.6 mg/kg) for 2 weeks followed by oral itraconazole 400 mg daily for 10 weeks resulted in excellent responsiveness [13-14]. In our case, the patient was treated by intravenous amphotericin B for 2 weeks followed by oral itraconazole for 10 weeks. The clinical symptoms and pulmonary lesions resolved completely, which suggested that such a therapy is effective for disseminated *P. marneffei* infection.

Although *P. marneffei* infection was most frequently found in HIV-positive individuals, it may infect non-HIV individuals as well. In pre-

vious reports, *P. marneffei* infections were found in patients with lymphoma, renal transplant recipients, systemic lupus erythematosus patients, and those receiving corticosteroid therapy or undergoing allogeneic bone marrow transplantation [10,15-17]. The authors believed that the infection was related to a cell-mediated immunity defect in these patients [10,15,18]. In our case, the ELISA screening test for HIV was checked twice with negative results. Autoimmune diseases were unlikely as no characteristic clinical presentation was identified and serum titers of autoantibodies were not elevated. Occult hematological malignancy was also excluded by mediastinal lymph node biopsy and bone marrow biopsy. The analyses of lymphocyte subpopulations also showed normal distributions. Given the fact that the patient suffered from disseminated *P. marneffei* infections combined with 2 episodes of community acquired pneumonia within 1 year prior to this admission, certain unidentifiable defects in cellular immunity remained highly possible.

Conclusions

P. marneffei infection is an important cause of morbidity and mortality in HIV-infected patients in Southeast Asia, and is occasionally found in immunosuppressed patients who have had travel-related exposure to this organism. It may also occur in patients without definite underlying diseases that are associated with immune defects. The diagnosis of *P. marneffei* infection depends on characteristic histopathological findings with fungus cultures, and timely antifungal therapy is crucial to reduce the morbidity and mortality. However, a proper diagnosis is frequently delayed, especially in non-HIV-infected patients. The case presented herein demonstrates the importance of clinical suspicion in making an early diagnosis. The possibility of *P. marneffei* infection should be kept in mind in endemic areas, even in patients with competent immune functions.

References

1. Ranjana K, Pryokumar K, Singh T, *et al*. Disseminated *Penicillium marneffei* infection among HIV-infected patients in Manipur State, India. J Infect 2002; 45: 268-71.
2. Supparatpinyo K, Khamwan C, Baosoung V, *et al*. Disseminated *Penicillium marneffei* infection in Southeast Asia. Lancet 1994; 344: 110-13.
3. Vanittanakom N, Cooper CR, Fisher MC, *et al*. *Penicillium marneffei* infection and recent advances in the epidemiology and molecular biology aspects. Clin Micro viol Rev 2006; 19: 95-110.
4. Deng Z, Ribas JL, Gibson DW, *et al*. Infections caused by *Penicillium marneffei* in China and Southeast Asia: review of eighteen published cases and report of four more Chinese cases. Rev Infect Dis 1998; 10: 640-52.
5. Louthrenoo W, Thamprasert K, Sirisanthana T, *et al*. Osteoarticular penicilliosis marneffei. A report of eight cases and review of the literature. Br J Rheumatol 1994; 33: 1145-50.
6. Chariyalertsak S, Sirisanthana T, Saengwinloey O, *et al*. Clinical presentation and risk behaviors of patients with acquired immunodeficiency syndrome in Thailand, 1994-1998: regional variation and temporal trends. Clin Infect Dis 2001; 32: 955-62.
7. Xi L, Lu C, Zhou X, *et al*. Fifteen cases of penicilliosis in Guangdong, China. Mycopathologia 2004; 158: 151-5.
8. Hsueh PR, Teng LJ, Hung CC, *et al*. Molecular evidence for strain dissemination of *Penicillium marneffei*: an emerging pathogen in Taiwan. J Infect Dis 2000; 181: 1706-12.
9. Duing TA. Infection due to *Penicillium marneffei*, an emerging pathogen: review of 155 reported cases. Clin Infect Dis 1996; 23: 125-30.
10. Luo DQ, Chen MC, Liu JH, *et al*. Disseminated *Penicillium Marneffei* Infection in an SLE patient: a case report and literature review. Nycopathologia 2001; 171: 191-6.
11. Heath TC, Patel A, Fisher D, *et al*. Disseminated *Penici-*

llium marneffei: presenting illness of advanced HIV infection; a clinicopathological review, illustrated by a case report. Pathology 1995; 27: 101-5.

12. Deesomchok A, Tanprawate S. A 12-case series of *Penicillium marneffei* pneumonia. J Med Assoc Thai 2006; 89: 441-7.
13. Supparatpinyo K, Chiewchanvit S, Hirunsri P, *et al*. An efficacy study of itraconazole in the treatment of *Penicillium marneffei* infection. J Med Assoc Thai 1992; 75: 688-91.
14. Sirianthana T, Supparatpinyo K, Perriens J, *et al*. Amphotericin B and itraconazole for treatment of disseminated *Penicillium marneffei* infection in human immunodeficiency virus-infected patients. Clin Infect Dis 1998; 26: 1107-10.
15. Lo CY, Chan DT, Yuen KY, *et al*. *Penicillium marneffei* infection in a patient with SLE. Lupus 1995; 4: 229-31.
16. Wang JL, Hung CC, Chang SC, *et al*. Disseminated *Penicillium marneffei* infection in a renal-transplant recipient successfully treated with liposomal amphotericin B. Transplantation 2003; 7: 1136-7.
17. Woo PC, Lau SK, Lau CC, *et al*. *Penicillium marneffei* fungaemia in an allogeneic bone marrow transplant recipient. Bone Marrow Transplantation 2005; 35: 831-3.
18. Deesomchok A, Tanprawate S. A 12-case series of *Penicillium marneffei* pneumonia. J Med Assoc Thai 2006; 89: 441-7.

非愛滋病毒感染全身性馬爾尼菲青黴菌者之個案報告：一病例報告

黃筑筠 * 廖贊傑 ** 王蕾琪 *** 陳俊谷 ** 馮嘉毅 *,**** 李毓芹 *,*****

馬爾尼菲青黴菌是一種常發生在免疫不全宿主的黴菌感染，特別好發在 HIV 陽性的患者。雖然在免疫健全或是免疫不全的人都可能造成感染，全身性馬爾尼菲青黴菌卻很少發生在 HIV 陰性的病人。東南亞地區，包括台灣、泰國、印尼與大陸地區都屬於馬爾尼菲青黴菌的流行區。我們報告一位 HIV 陰性且無旅遊史的病人受到全身性馬爾尼菲青黴菌的感染，受影響部位包括肺部、淋巴結、和骨髓。一開始的症狀包括發燒、夜間盜汗、體重減輕和持續的肺部浸潤。我們從支氣管穿刺切片、支氣管肺泡沖洗液、淋巴結切片及骨髓切片可以發現 Grocott's Methenamine Slive（GMS）染色呈現陽性的酵母菌樣病原菌；此外從病患的痰液、支氣管肺泡沖洗液、經支氣管穿刺切片、縱膈腔淋巴切片及骨髓切片的黴菌培養均可培養出馬爾尼菲青黴菌。經針劑 amphotericin B 治療二星期及口服 itraconazole 十週治療後，病患的臨床症狀及肺部浸潤均有顯著改善。*(胸腔醫學 **2012; 27: 377-385**)*

關鍵詞：骨髓，發燒，HIV 陰性，馬爾尼菲青黴菌，肺炎

* 台北榮民總醫院 胸腔部，** 台北榮民總醫院 放射部，*** 台北榮民總醫院 病理部
**** 國立陽明大學臨床醫學研究所，***** 國立陽明大學醫學系
索取抽印本請聯絡：馮嘉毅醫師，台北榮民總醫院 胸腔部，台北市 112 北投區石牌路二段 201 號

Paroxysmal Sympathetic Hyperactivity: Two Case Reports

Tung-Han Wu, Wen-Kuang Yu, Yen-Wen Chen, Jia-Horng Wang

Paroxysmal sympathetic hyperactivity (PSH) is a syndrome characterized by episodes of hyperthermia, diaphoresis, agitation, dystonia, and increased blood pressure (BP), respiratory rate (RR), and heart rate (HR). Most cases are found after brain injury, although a few cases have had no brain injury. The exact mechanism is still not clear, but PSH can be treated by opioids, gabapentin, benzodiazepines, centrally acting α-agonists, and β-antagonists, bromocriptine, and intrathecal baclofen, instead of anti-epileptics, antibiotics, or antipyretics, in most cases. Delayed diagnosis and management of PSH may increase morbidity and mortality. We present 2 cases and review the literature on PSH. Accurate diagnosis and appropriate treatment can reduce the number of ventilator days and shorten the hospital course, and even improve the clinical outcome. Therefore, the differential diagnosis and management of patients presenting with hyperthermia, dystonia, tachypnea, and tachycardia are very important in daily practice in the intensive care unit. ***(Thorac Med 2012; 27: 386-391)***

Key words: paroxysmal sympathetic hyperactivity, dystonia, hyperthermia, tachycardia, tachypnea

Introduction

Paroxysmal sympathetic hyperactivity (PSH) is a syndrome with paroxysmal autonomic nervous system over-activity [1]. The classical features of PSH are hyperthermia, diaphoresis, agitation, dystonia, and increased blood pressure (BP), respiratory rate (RR), and heart rate (HR) [1-6]. At least 10 different names are used for the same condition, and include sympathetic storming, dysautonomia, paroxysmal autonomic instability with dystonia (PAID), central autonomic dysfunction, acute midbrain syndrome, hypothalamic-midbrain dysregulation syndrome, fever of central origin, hyperpyrexia associated with muscle contraction, etc. [2]. A recent review revealed several types of acquired brain injury preceding PSH onset: traumatic brain injury (TBI; 79.4%), hypoxic brain injury (9.7%), stroke (5.4%), and hydrocephalus (2.6%); other causes were rare [5]. The incidence of PSH in the subgroup of survivors of severe TBI has been estimated at 8% to 33% [1-7]. In series studies, patients with PSH have poorer outcomes and greater healthcare costs, and it is believed that inaccurate di-

Department of Respiratory Therapy, Taipei Veterans General Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Jia-Horng Wang, Department of Respiratory Therapy, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Rd., Taipei 11217, Taiwan

agnosis and delayed management may contribute to these results [1-6]. We present herein the cases of 2 patients with PSH and fewer ventilator days after a correct diagnosis was reached and adequate management provided.

Case Report

Case 1

A 15-year-old boy denied any previous systemic disease. He was involved in a traffic accident and was sent to a local hospital with the initial Glasgow coma scale of $E_1V_1M_1$. Brain CT revealed contusion intracranial hemorrhage, acute subdural hemorrhage, and severe brain swelling in the right frontal-temporal-parietal area, and emergency craniotomy was performed at once. In addition, a subdural-peritoneal shunt was used for subdural effusion 15 days later. The level of consciousness returned to $E_4V_TM_{5\sim6}$ after surgery. Because of difficulty weaning from the ventilator, he was transferred to our respiratory therapy intensive care unit (RTCU) for further weaning on day 26 after the accident.

After admission to the RTCU, intermittent seizures accompanied with fever, tachypnea, and tachycardia were observed and meningitis was highly suspected, but lumbar puncture showed no evidence of meningitis on day 34. The neurologist was consulted for the refractory seizure and suggested the use of midazolam (dormicum) continuous infusion and anti-epileptics, such as phenytoin (Dilantin) and levetiracetam (Keppra). The seizure activity seemed to be under control with the medication. Electroencephalography (EEG) revealed no epileptic activity on day 50. Two days later, an episode of fever, tachypnea, tachycardia, seizure, and diaphoresis was observed during the ventilator weaning process. The neurologist was consulted again and suggested the use of clonazepam (Rivotril). However, the clinical condition did not improve. PSH was suspected, so we prescribed a β-blocker (Inderal) and morphine; the clinical condition then improved dramatically (see Figure 1). Successful extubation was performed 6 days later (day 58). His level of consciousness returned to $E_4V_4M_6$. He was finally transferred to a chronic care unit for further rehabilitation.

Case 2

A 74-year-old male had a history of hypertension, atrial fibrillation, and hyperlipidemia. He was admitted to a local hospital due to right middle cerebral artery (MCA) infarction with the initial presentation of clear consciousness and a sudden onset of weakness in the left extremities. A change in consciousness ($E_1V_1M_{1\sim2}$) was noted on day 5 after admission, and brain CT showed severe brain edema. Emergency decompressive craniectomy was performed, but there was no improvement in consciousness after the operation. Repeated brain CT revealed hemorrhagic infarction of the right MCA territory with communicating hydrocephalus; the patient then received ventriculoperitoneal shunting on day 24. Due to his poor condition, he was transferred to our neurology ward for further management on day 28, at the family's request.

After admission, the initial level of consciousness was $E_1V_1M_{1\sim2}$. Anti-epileptics and glycerol were prescribed for his epilepsy and increased intracranial pressure. He was transferred to the RTCU for further ventilator weaning on day 38. Tracheostomy was performed on day 44. Recurrent episodes of tachycardia (180-200/min), tachypnea (35-40/min), high

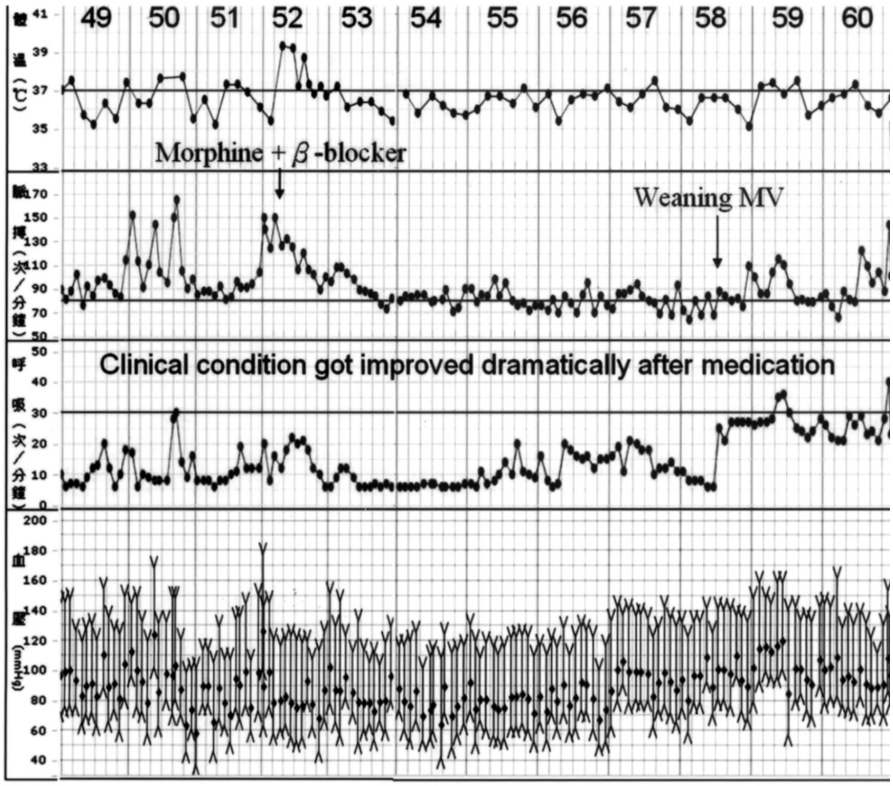


Fig. 1. The TPR (temperature, pulse rate, respiratory rate, and blood pressure) sheet of case 1. On day 52, we prescribed a β-blocker (Inderal) and morphine, and the clinical condition improved dramatically. Successful extubation was performed 6 days later (day 58)

BP (systolic BP around 160-180 mmHg), diaphoresis, seizure, and low grade fever (37.6°C) were found on day 71. Based on previous experience, PSH was highly suspected. Therefore, medication with a β-blocker and morphine was prescribed, and the condition improved dramatically (see Figure 2). The patient was successfully weaned from the ventilator after 6 days (day 77), and was finally transferred to a chronic care unit for further rehabilitation.

Discussion

Two cases of PSH were reported herein. The diagnosis of PSH was supported by the history of brain injury, paroxysmal elevation of sympathetic tones (high BP, tachycardia, tachypnea), diaphoresis and fever without evident focus [1-7]. The possibility of epilepsy was excluded by EEG examination in case 1.

Although a final consensus on the pathogenesis of PSH has not yet been reached, current opinion has it that transient structural or functional disconnection in the brain may lead to injury in the central inhibitory pathway and subsequently cause sympathetic hyperactivity [12]. Other critical conditions associated with sympathetic activation include sepsis, malignant hyperthermia, withdrawal syndrome, epilepsy, etc. These conditions can be differentiated from PSH by their characteristic clinical and laboratory presentations. Without a doubt, PSH is a diagnosis of exclusion. The 8 symptoms/signs criteria recommended by Blackman *et al*. [3]

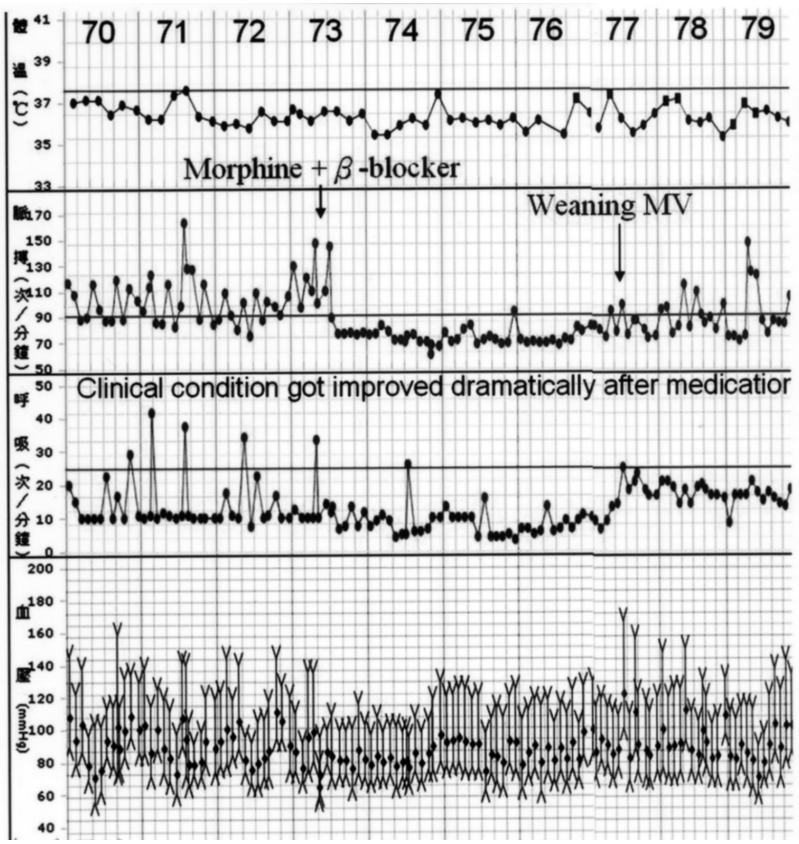


Fig. 2. The TPR (temperature, pulse rate, respiratory rate, and blood pressure) sheet of case 2. On day 73, medication with a β-blocker and morphine was prescribed, and the condition improved dramatically. Successful ventilator weaning was achieved 6 days later (day 77).

may be more objective, but this is still far from a consensus.

The pivotal matter following the diagnosis of PSH is the pharmacological management. A limited amount of data support the use of a muscle relaxant or anticonvulsant for dystonia, centrally acting α-agonists and β-blockers for sympathetic activity and appropriate sedative and morphine treatment for general control [12]. Hyperbaric oxygen therapy is reported to be effective, as well [9]. In our case, timely consideration of PSH was accompanied with an adjustment of medication, which led to the liberation of our patients from mechanical ventilation support within 1 week.

Conclusion

The diagnosis of PSH is frequently missed, with a consequent delay in appropriate treatment. This diagnosis should be taken into consideration when encountering patients with any kind of brain injury with recurrent episodes of fever, tachypnea, tachycardia, agitation, seizure and elevated BP. Accurate diagnosis and appropriate treatment can reduce the number of ventilator days and ICU days, shorten the hospital course, and improve the clinical outcome.

References

1. Baguley IJ, Nicholls JL, Felmingham KL, *et al*. Dysautonomia after traumatic brain injury: A forgotten syndrome? J Neurol, Neurosurg & Psychiat 1999; 67: 39-43.
2. Perkes IE, Menon DK, Baguley IJ, *et al*. Paroxysmal sympathetic hyperactivity after acquired brain injury: a review of diagnostic criteria. Brain Inj 2011; 25(10): 925-32. Review.
3. Blackman JA, Patrick PD, Buck ML, *et al*. Paroxysmal autonomic instability with dystonia after brain injury. Arch Neurol 2004; 61: 321-8.
4. Hendricks HT, Heeren AH, Vos PE. Dysautonomia after severe traumatic brain injury. Eur J Neurol 2010; 17: 1172-7.
5. Perkes, I., Baguley, I., Nott, M., *et al*. A review of paroxysmal sympathetic hyperactivity after acquired brain injury. Annals of Neurol 2010; 68: 126-35.
6. Baguley IJ, Heriseanu RE, Cameron ID, *et al*. A critical review of the pathophysiology of dysautonomia following traumatic brain injury. Neurocrit Care 2008; 8: 293-300.
7. Baguley IJ, Slewa-Younan S, Heriseanu RE, *et al*. The incidence of dysautonomia and its relationship with autonomic arousal following traumatic brain injury. Brain Inj 2007; 21: 1175-81.
8. Lv LQ, Hou LJ, Yu MK, *et al*. Risk factors related to dysautonomia after severe traumatic brain injury. J Trauma 2011 Sep; 71(3): 538-42.
9. Lv LQ, Hou LJ, Yu MK, *et al*. Hyperbaric oxygen therapy in the management of paroxysmal sympathetic hyperactivity after severe traumatic brain injury: a report of 6 cases. Arch Phys Med Rehabil 2011 Sep; 92(9): 1515-8.
10. Rabinstein AA. Paroxysmal sympathetic hyperactivity in the neurological intensive care unit. Neurol Res 2007; 29: 680-2.
11. Baguley IJ, Cameron ID, Green AM, *et al*. Pharmacological management of dysautonomia following traumatic brain injury. Brain Inj 2004; 18: 409-17.
12. Baguley IJ. The excitatory: inhibitory ratio model (EIR model): an integrative explanation of acute autonomic overactivity syndromes. Med Hypotheses 2008; 70: 26-35.
13. Perkes IE, Baguley IJ. Current understanding of dysautonomia after severe acquired brain injury. Adv Clin Neurosci Rehabil 2008; 8: 10-1.
14. Baguley IJ, Heriseanu RE, Nott MT, *et al*. Dysautonomia following severe traumatic brain injury: evidence of persisting overresponsiveness to afferent stimuli. Am J Phys Med Rehabil 2009; 88: 615-22.

陣發性交感神經過度活化：兩則病例報告

吳東翰　余文光　陳燕溫　王家弘

陣發性交感神經過度活化（Paroxysmal sympathetic hyperactivity, PSH）是一種以陣發性的體溫增高、冒汗、躁動、肌肉張力異常、血壓變高、呼吸變快及心跳變快的症候群。絕大多數的病例報告都是在腦部損傷之後發生，只有少數病例沒有腦部損傷。明確的致病機轉到現在仍不清楚，大多數的病患對於嗎啡類、gabapentin、benzodiazepine、中樞作用 α- 致效劑與 β- 阻斷劑、bromocriptine 與脊髓腔內注射 baclofen 等藥物有效，而對一般抗癲癇藥物、抗生素或退燒藥效果較差，對陣發性交感神經過度活化的延遲診斷與處置可能會增加死亡率與罹病率，我們提出兩則病例報告並回顧陣發性交感神經過度活化相關文獻。正確的診斷與適當的處置能夠減少呼吸器使用天數與住院天數，甚至是預後，故對於加護病房內呈現體溫增高、肌肉張力異常、呼吸變快及心跳變快病人的鑑別診斷與處置是相當重要的。*(胸腔醫學* ***2012; 27: 386-391)***

關鍵詞：陣發性交感神經過度活化，肌肉張力異常，體溫增高，心跳變快，呼吸變快

台北榮民總醫院　呼吸治療科
索取抽印本請聯絡：王家弘醫師，台北榮民總醫院　呼吸治療科，112 台北市北投區石牌路 2 段 201 號

Hypersensitivity Pneumonitis Presenting as Fever of Unknown Origin – A Case Presentation and Review of the Literature

Fu-Kang Chang*, Fang-Chi Lin*,**, Shi-Chuan Chang*,***

Hypersensitivity pneumonitis (HP) is a pulmonary disorder with symptoms of fever, dyspnea and cough resulting from exposure to an antigen to which the subject has been previously sensitized. The clinical symptoms are very similar to pyogenic infection. Detailed history-taking and a high index of suspicion are mandatory in aiding the diagnosis of HP. Herein, we reported a patient with HP with the initial presentation of intermittent fever, general malaise, and body weight loss. Comprehensive surveys for infectious diseases, autoimmune diseases and malignancies were carried out at a local hospital and a medical center, and yielded negative results. Despite undergoing open lung biopsy, no definite diagnosis was made. Bronchoalveolar lavage (BAL) was done at our hospital and lymphocytic alveolitis was suggested by the cytological smear of the BAL fluid (BALF). Based on the clinical presentation, contact history, cytological findings of the BALF and pathological findings of lung biopsy obtained from other hospitals, HP was highly suspected. The patient underwent pulse therapy with methyprednisolone and maintenance with a low-dose steroid. Fever subsided gradually and the follow-up chest radiograph demonstrated marked regression of the pulmonary lesions. ***(Thorac Med 2012; 27: 392-400)***

Key words: hypersensitivity pneumonitis, fever of unknown origin, bronchoalveolar lavage

Introduction

Fever of unknown origin (FUO) has been defined as follows: (1) a temperature greater than 38.3°C (101°F) on several occasions, (2) illness of more than 3 weeks duration, and (3) failure to reach a diagnosis despite 1 week of inpatient investigation [1]. The common causes of FUO are infections, malignancies, and collagen vascular diseases. A diagnosis of FUO will be delayed in cases with other rare etiologies. Herein, we report a patient with hypersensitivity pneumonitis (HP) presenting with FUO, and highlight that HP should be included in the list of differential diagnoses for FUO.

*Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; **School of Medicine, National Yang-Ming University, Taipei, Taiwan; ***Institute of Emergency and Critical Care Medicine, National Yang-Ming University, Taipei, Taiwan
Address reprint requests to: Dr. Shi-Chuan Chang, Department of Chest Medicine, Taipei Veterans General Hospital, No. 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan

Case Presentation

A 41-year-old man was an air-conditioning renovation technician. He was a non-smoker and had been robust in the past. He denied a recent travel history or animal contact history. He suffered from intermittent high fever, up to 39°C, and general malaise for several weeks before seeking medical help in May 2011. He also complained of cough with scanty sputum, but denied dyspnea on exertion. He was then admitted to a local hospital. Although no definite infection focus was found, infectious diseases could not be ruled out clinically. The patient was treated with empiric antibiotics; the fever subsided, and the patient was discharged 5 days later. However, fever quickly recurred when the patient went back to work. In addition, a loss of body weight of about 8 kg was noted within 1 month after discharge. The patient then visited a medical center, and was admitted in June 2011.

Physical examination revealed a man of medium stature. His vital signs were as follows: blood pressure, 110/70 mmHg; heart rate, 82 beats/min; respiratory rate, 16 breaths/min. Arterial oxygen saturation was 94% as measured by pulse oximetry in room air. Chest auscultation disclosed bilateral basal crackles. The complete blood cell count results were as follows: hemoglobin, 12.4 g/dL; white blood cell count, 2800/μL; and platelet count, 81000/μL. Abnormal findings in laboratory tests included an elevation of blood C-reactive protein (CRP, 6.89 mg/dL, reference value <0.5 mg/dL) alanine aminotransferase (ALT, 314 U/L; reference values, 0-40 U/L) and aspartate aminotransferase (AST, 292 U/L; reference values, 5-45 U/L). A chest x-ray film (CXR) showed interstitial infiltrates in bilateral lower lung fields (Figure 1). Hepatitis markers were checked because of abnormal liver function, but showed negative results. Sonography of the abdomen revealed hepatosplenomegaly with mild fatty liver. The results of Legionella urine antigen, blood mycoplasma antibody titer, sputum acid-fast stain and blood interferon gamma rapid assay for tuberculosis yielded negative results. A survey for FUO caused by microorganisms including Q fever, scrub typhus or typhus was done, and yielded negative results. Bone marrow aspiration was performed due to pancytopenia, and the cytology and pathology reported myelodysplastic syndrome. Ceftriaxone and doxycycline were administrated due to suspected atypical infection. He was discharged after the fever subsided.

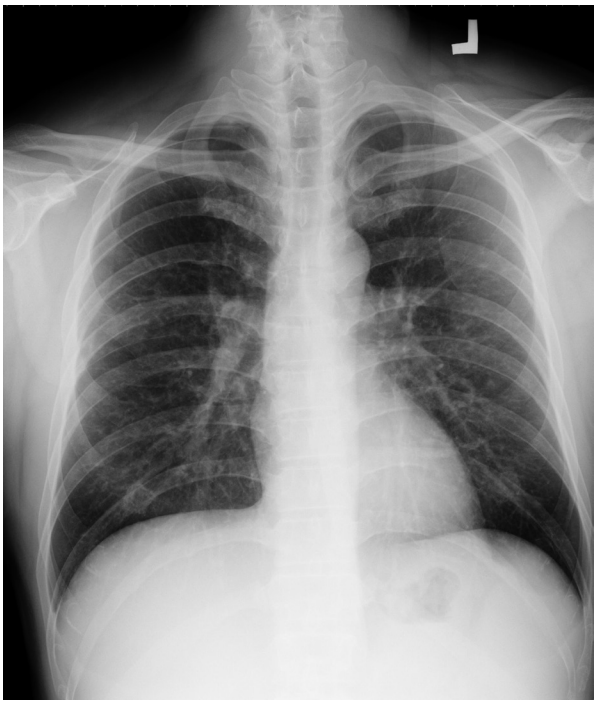


Fig. 1. CXR taken on 12 June 2011 reveals interstitial infiltrates in bilateral lower lung fields

However, the fever recurred when the patient returned to work, so he was admitted to the medical center again in June 2011. During this hospitalization, a complete blood cell count

revealed the following: hemoglobin, 12.2 g/dL; white blood cell count, 3800/μL; platelet count, 95000/μL. Blood ALT and AST returned to normal values (36 U/L and 26 U/L). Blood levels of anti-nuclear antibody (ANA) and rheumatic factor were within normal limits. However, a follow-up CXR showed progression of pulmonary lesions (Figure 2). High-resolution computed tomography (HRCT) of the chest revealed pulmonary infiltrates with ground-glass opacity and diffuse centrilobular nodules in the middle and lower lungs, with sparing of the costophrenic areas (Figure 3).

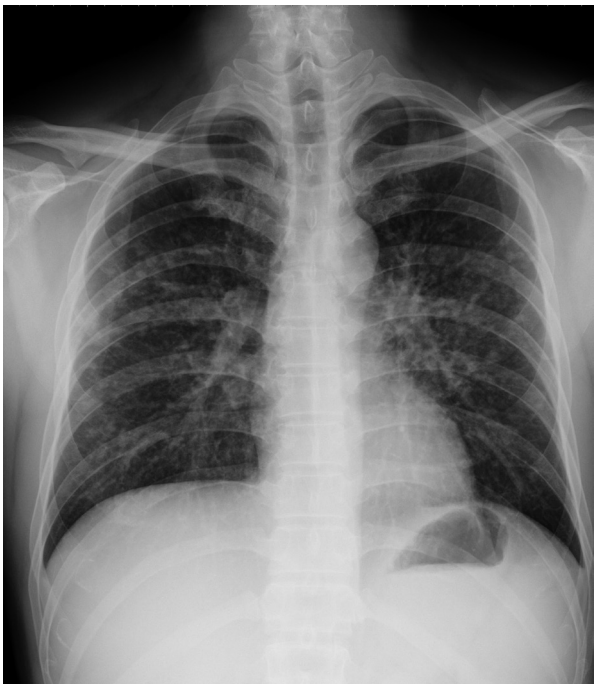


Fig. 2. CXR on 28 June 2011 shows progression of pulmonary lesions.

Pulmonary function testing revealed normal ventilator function (forced expiratory volume in 1 second (FEV_1), 3.94 L, 112% of normal predicted value; forced vital capacity (FVC), 4.3L, 99% of normal predicted value; FEV_1/FVC ratio, 91%) and a reduction of pulmonary diffusion capacity for single-breath carbon monoxide (59% of normal predicted value).

As atypical pneumonia was suspected, diagnostic bronchoalveolar lavage (BAL) was performed on 15 July 2011. The microbiologic cultures of the BAL fluid (BALF) yielded no growth. Since no definite diagnosis was made, the patient underwent open lung biopsy by video-assisted thoracic surgery (VATS) on 25 July 2011. The pathologic examination findings revealed bronchopneumonia. A therapeutic trial with anti-tuberculosis medications was suggested by the physicians. However, the patient refused and was admitted to our hospital for further management.

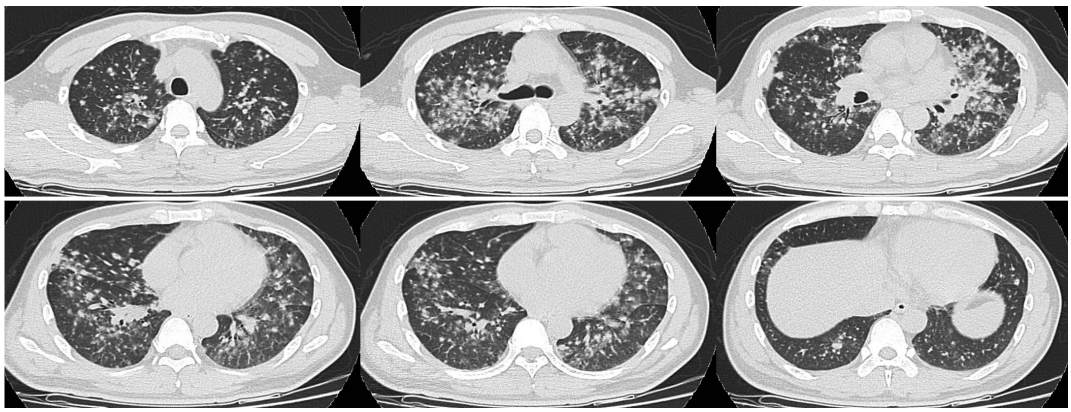
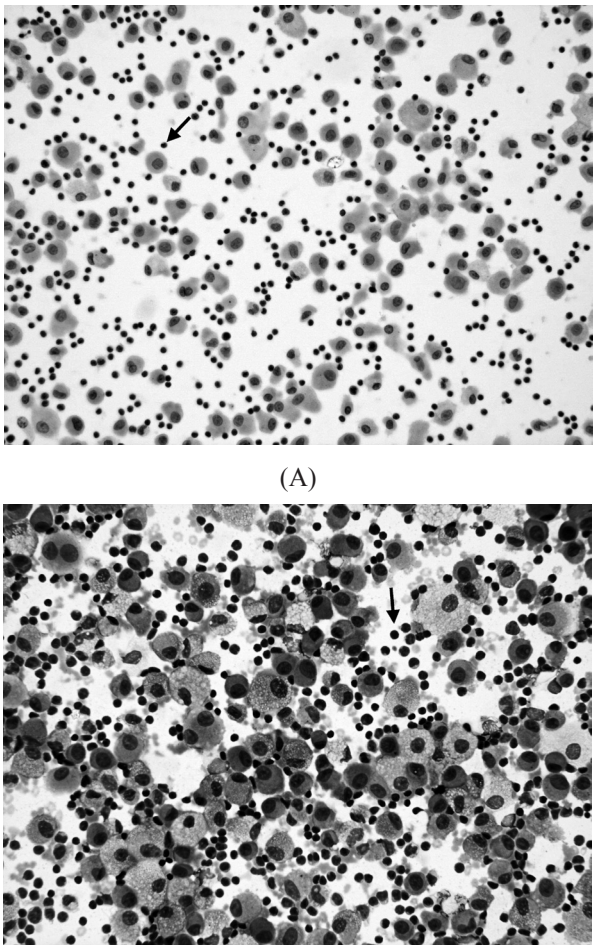


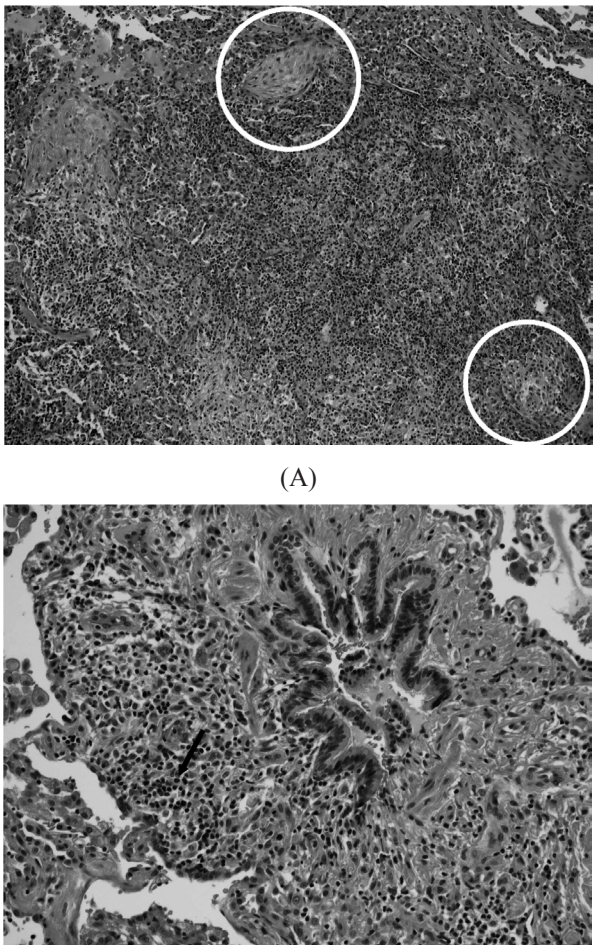
Fig. 3. Thoracic HRCT shows pulmonary infiltrates with ground-glass opacity and diffuse centrilobular nodules (11 July 2011)



(A)

(B)

Fig. 4. Cytological examination of BALF reveals marked lymphocytosis (A). Papanicolaou stain, X 200. (B). Liu stain X 400



(A)

(B)

Fig. 5. Pathological findings of lung biopsy specimens. (A) Hematoxylin and eosin satin, X 100, reveals poorly-formed non-necrotizing granulomas within the nodules (B) Hematoxylin and eosin satin, X 200, reveals several bronchiolocentric nodules composed of lymphoplasmacytic infiltrates.

Under the impression of HP, the patient underwent diagnostic BAL again on 25 August 2011, and cytological smears of the BALF showed marked lymphocytosis (>40%, Figure 4). The results of lymphocyte subpopulations in the BALF were as follows: CD4-positive T cells, 79.5%; CD8-positive T cells, 5.0%. The cytological smears and microbiologic cultures of the BALF yielded negative results for the detection of microorganisms. Suspecting HP, the patient received pulse therapy with methylprednisolone 1000 mg/day for 3 days, followed by oral prednisolone 5 mg per day, and the fever subsided gradually. The surgical lung biopsy specimens taken at another medical center were borrowed from that center, and demonstrated several bronchiolocentric nodules composed of lymphoplasmacytic infiltrates with foamy macrophages and non-necrotizing granuloma within the nodules, which were highly suggestive of HP (Figure 5). After a careful history-taking, bird excreta appeared to be the most probable

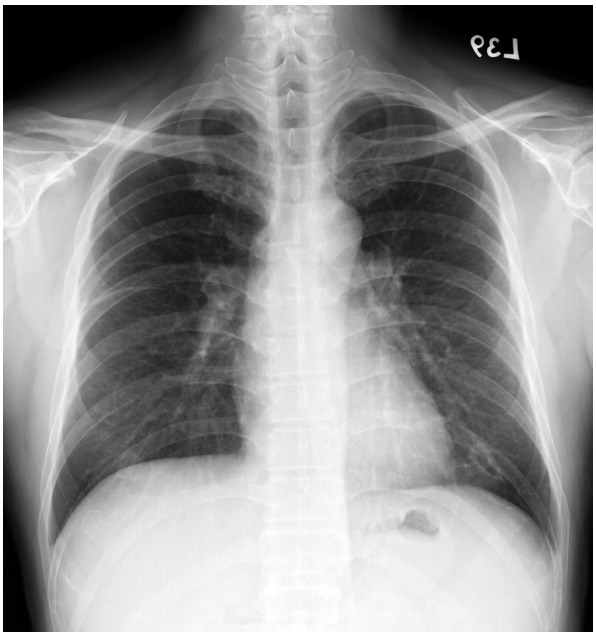


Fig. 6. CXR obtained on 22 October 2011 after steroid treatment shows regression of pulmonary lesions.

offending antigen. Because of this, the patient was strongly suggested to wear a high efficiency mask during work, or else quit the job. A follow-up CXR 2 months after steroid treatment revealed regression of the pulmonary lesions; there was no fever recurrence after discharge from our hospital (Figure 6).

Discussion

HP is a pulmonary disorder with symptoms of fever, dyspnea and cough resulting from the inhalation of an antigen to which the subject has been previously sensitized. A wide spectrum of antigens may trigger the development of HP. The case presented herein would be called "bird breeders disease" traditionally, because the symptoms of HP developed on several occasions when the patient was exposed to bird excreta. However, because of industrial development and urbanization in the modern era, there are many organic and inorganic materials that could be offending antigens for HP. Therefore, the clinical presentations of HP may vary widely. In this regard, making the diagnosis of HP appears to be a difficult challenge for physicians. A high index of suspicion would be the mainstay for a diagnosis of HP, particularly in patients with repeated attacks of similar symptoms.

HP is caused by the inhalation of an antigen that triggers a complex immunologic response at the site of antigen deposition within the lungs. This immunologic inflammatory response and the attempts by the host to repair the damage may lead to a progressive deposition of fibrotic tissue, which may result in permanent damage and dysfunction, leading to pulmonary disability or death.

HP can be categorized clinically into 3 different forms [1]. Acute HP typically occurs after high-level, intermittent exposure to the offending antigen over a short period. Subacute HP is characterized by the gradual development of symptoms that may occur during weeks to months after repeated low-level antigen exposure. Chronic HP involves a continuous long-term, low-level antigen exposure leading to irreversible pulmonary damage without major acute attacks. The clinical manifestations of HP are protean depending on the intensity and frequency of offending antigen exposure. Fever is uncommon in HP, and may develop in about 15% of these patients [2].

FUO is defined as follows: a temperature higher than 38.3°C on several occasions, a fever lasting more than 3 weeks, and failure to reach a diagnosis despite 1 week of inpatient investigation [3]. The 4 categories of potential etiologies of FUO are -- classic, nosocomial, immune-deficient, and human immunosuppres-

sive virus (HIV)-associated. Each group has a unique list of differential diagnoses [4]. The most common causes of classic FUO are infection, malignancy, and collagen vascular diseases [4]. However, many unrelated pathologic conditions can present as FUO. It is not uncommon to fail to reach a definitive diagnosis of patients with FUO, and about 20% of cases remain undiagnosed. Our reported patient presented with intermittent fever lasting more than 3 weeks. A series of examinations were performed throughout the period of fever, and the results did not favor infectious disease, malignancy or collagen vascular diseases. As such, our case fulfilled the criteria of FUO.

HP can be a rare clinical cause of episodic FUO [5]. A number of diagnostic criteria recommendations for HP have been published [6]. None of these sets of criteria has been validated. Their diagnostic accuracy is therefore unknown. Of these, the diagnostic criteria established by Schuyler in 1997 are used widely in normal daily practice (Table 1) [7]. The major criteria include (1) symptoms compatible with HP; (2) evidence of exposure to the offending antigen; (3) image findings compatible with HP on CXR or HRCT; (4) alveolar lymphocytosis shown on cytological smears of BALF; (5) pulmonary histological changes compatible with HP and (6) a positive "natural challenge". Our reported patient had recurrent clinical symptoms consistent with HP. The CXR and HRCT revealed reticulonodular lesions and pulmonary infiltrates with ground glass opacity in bilateral lung fields, which were compatible with the imaging characteristics of HP (Figures 2-3) The patient underwent BAL, and marked lymphocytosis was shown in the cytological smears of the BALF (over 40%, Figure 4). The pathological examination of the lung biopsied specimens revealed bronchiolocentric nodules composed of lymphoplasmacytic infiltrates with foamy

Table 1. Diagnostic criteria for hypersensitivity pneumonitis (HP), modified from the criteria reported by Schuyler in 1997 (Chest 1997; 111: 534-6)

Major criteria (4 major criteria should be presented)
1. History of symptoms compatible with HP
2. Evidence of exposure to the offending antigen by history or through detection of bronchoalveolar lavage fluid antibody in serum
3. Changes characteristic of HP on chest radiograph (reticulonodular infiltrates, linear opacities) or high-resolution computed tomography of the chest (ground-glass opacities, micronodules, honeycombing, linear opacities, air-trapping)
4. Demonstration of bronchoalveolar lavage fluid lymphocytosis, if bronchoalveolar lavage analysis is performed
5. Demonstration of histological changes consistent with HP, if lung biopsy is performed, such as alveolitis, non-caseating granulomas, giant cells, foamy alveolar macrophages or fibrosis
6. Positive "natural challenge" that produces symptoms and objective abnormalities either through controlled inhalational challenge or after re-exposure to the offending environment
Minor criteria (2 minor criteria should be presented)
1. Bibasilar rales
2. Decreased diffusion capacity
3. Arterial hypoxemia either at rest or with exercise

macrophages, and non-necrotizing granuloma within the nodules highly suggestive of HP (Figure 5). Finally, the patient developed similar symptoms on several occasions when he returned to work and was exposed to bird excreta, which was compatible with a "natural challenge". Therefore, our patient fulfilled the 5 major criteria, and also fulfilled 2 minor criteria (1) bibasilar rales and (2) decreased pulmonary diffusing capacity. As a consequence, the diagnosis of HP was conclusive.

A predominance of CD8+ T lymphocytes and a CD4+/CD8+ ratio less than 1.0 in the BALF is often observed in HP, whereas a predominance of CD4+ lymphocytosis and a high CD4+/CD8+ ratio in the BALF is related to sarcoidosis. It is suggested that lymphocytosis and the CD4+/CD8+ ratio in the BALF can be used to differentiate HP from sarcoidosis. However, the argument has been challenged because the CD4/CD8 ratio in the BALF of HP can increase to the levels seen in sarcoidosis. Recent studies suggest that this low CD4+/CD8+ ratio is found in the chronic form of HP and in asymptomatic individuals, whereas a predominance of CD4+ T cells is found in the acute phase of the disease. In addition, the CD4+/CD8+ ratio also depends on the type and dose of inhaled antigen, as well as the duration of this antigenic exposure [8-9]. Our patient had alveolar lymphocytosis with CD4+ T cell predominance in the BALF, highly suggestive of the acute to subacute phase of HP.

The mainstays of treatment of HP are early diagnosis and the avoidance of further exposure to the causative agents. Steroid appears to be the only pharmacologic treatment for HP, however, the dose and duration of corticosteroid treatment when needed remain unclear. A randomized placebo-controlled trial [10] involving 36 patients with acute farmer's lung randomized to receive either 40 mg of prednisolone tapered over 8 weeks or placebo reported that corticosteroids might hasten recovery from the acute stage of HP, but had a limited beneficial effect on long-term prognosis. Subacute stages of HP may require higher doses of corticosteroid for several months. Pulse therapy with intravenous infusion of corticosteroid was reported to be effective in a patient with severe summer-type hypersensitivity pneumonitis [11]. Our clinical experience indicates that oral corticosteroid is less effective in treating HP, particularly in those with severe HP. Our patient underwent pulse therapy with intravenous methyprednisolone followed by oral prednisolone, and promising results were had.

Conclusion

The present case fulfills the diagnostic criteria for HP on the basis of medical history, clinical features, evidence of exposure to the antigen, compatible imaging findings on CXRs and HRCT, demonstration of lymphocytosis in the BALF, and compatible histological changes with a positive natural challenge test and a good response to steroid treatment. Therefore, HP should be added to the list of differential diagnoses of a patient with FUO. A high index of suspicion and detailed history-taking is mandatory in HP patients, since prevention of further exposure to the offending antigens is crucial for avoiding recurrence.

References

1. Patel AM, Ryeu JH, Reed CH. Hypersensitivity pneumonitis: Current concepts and future questions. J Allergy Clin Immunol 2001; 108: 661-70.

2. Selman M, Lacasse Y, Pardo A. Hypersensitivity pneumonitis caused by fungi. Proc Am Thorac Soc 2010; 7: 229-36.
3. Ergönül O, Willke A, Azap A, *et al*. Revised definition of fever of unknown origin: limitations and opportunities. J Infect Jan 2005; 50(1): 1-5.
4. Roth AR, Basello GM. Approach to the adult patient with fever of unknown origin. Am Fam Physician 2003 Dec 1; 68(11): 2223-8.
5. Hirschmann JV, Pipavath SN, Godwin JD. Hypersensitivity pneumonitis: A historical, clinical, and radiologic review. Radiographics 2009 Nov; 29(7): 1921-38.
6. Lacasse Y, Cormier Y. Hypersensitivity pneumonitis. Orphanet J Rare Dis 2006; 1: 25-34.
7. Schuyler M, Cormier Y. The diagnosis of hypersensitivity pneumonitis. Chest 1997; 111: 534-6.
8. Sharma OP, Fujimura N. Hypersensitivity pneumonitis: A non-infectious granulomatosis. Semin Respir Infect 1995; 10: 96-106.
9. Girard M, Lacasse Y, Cormier Y. Hypersensitivity pneumonitis. Allergy 2009; 64: 322-34.
10. Kokkarinen JI, Tukiainen HO, Terho EO. Effect of corticosteroid treatment on the recovery of pulmonary function in farmer's lung. Am Rev Respir Dis 1992; 145: 3-5.
11. Arai M, Kawada H, Kaburagi T, *et al*. A case of severe summer-type hypersensitivity pneumonitis treated with high-dose administration of steroid. Nihon Kyobu Shikkan Gakkai Zasshi 1991; Nov; 29(11): 1457-63.

以不明熱表現的過敏性肺炎：病例報告

張富康 * 林芳綺 *,** 張西川 *,***

過敏性肺炎是一種因吸入過敏原後而引發一連串免疫反應導致的肺部疾病。臨床表現與感染性肺炎非常相似，都會出現發燒、咳嗽、呼吸困難等現象。臨床上的高度懷疑以及詳盡的病史詢問方能有效的獲得診斷，並且避免再次的接觸到過敏原而復發。我們提出一位過敏性肺炎以不明熱表現的患者。此病患起初的臨床表現為發燒、全身無力、體重減輕。經過在地區醫院和醫學中心的反覆住院，詳盡的進行感染性疾病、自體免疫疾病、惡性腫瘤方面的檢查仍無明確病因。甚至進行肺部外科病理檢查仍無診斷。我們進行了支氣管鏡肺泡沖洗術，在肺泡沖洗液的細胞學檢查中看到了明顯的淋巴球增多。並回溯了病患的接觸病史發現他工作時會接觸到鳥類排泄物。根據臨床症狀、接觸病史、肺泡沖洗液細胞學檢查、肺部外科病理標本等的結果，高度懷疑病患罹患過敏性肺炎。經由類固醇的治療過後，病患的發燒緩解了，影像學上肺部的病灶也消失了。*(胸腔醫學 **2012; 27: 392-400**)*

關鍵詞：過敏性肺炎，不明熱，支氣管肺泡沖洗術

* 台北榮民總醫院 胸腔部，** 國立陽明大學醫學院，*** 國立陽明大學重症醫學研究所
索取抽印本請聯絡：張西川醫師，台北榮民總醫院 胸腔部，台北市 112 北投區石牌路二段 201 號