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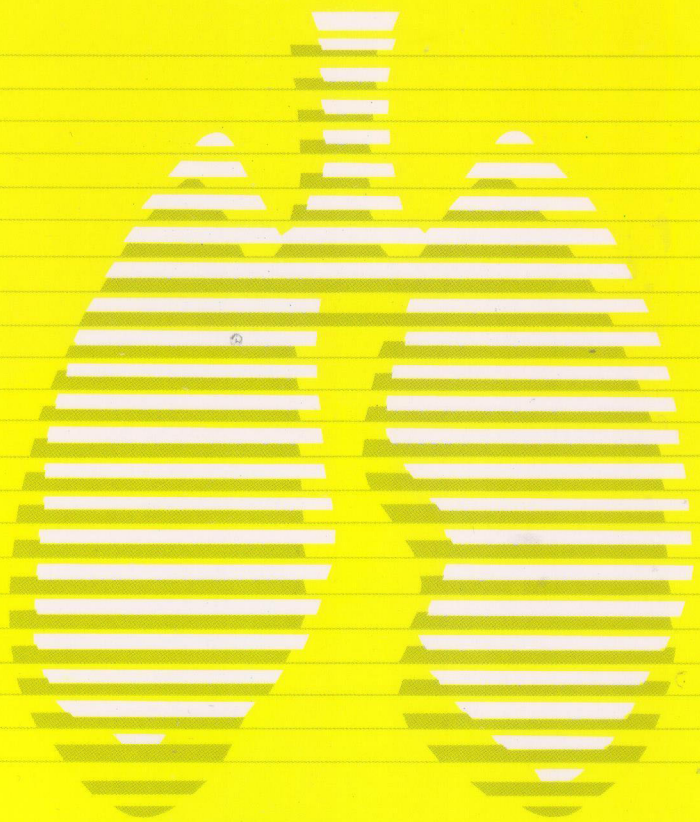

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Orginial Articles

Case Reports

Different Asthma Phenotypes in Adult Asthma: Comparison of Allergic Asthma and Nonallergic Asthma

Chih-Hao Chang, Horng-Chyuan Lin, Meng-Heng Hsieh, Guan-Yuan Chen, Fu-Tsai Chung, Chih-Teng Yu, Han-Pin Kuo

Background: Allergen sensitization is a risk factor for the development of bronchial asthma in adults. However, the relationship between allergen sensitization and lung function in asthma patients is not well understood. This study was conducted to evaluate the relationship between sensitized allergens, total serum immunoglobulin E (IgE) level, and lung function in adult asthmatic patients in northern Taiwan.

Methods: A total of 266 adult Taiwanese patients diagnosed with asthma between January 2003 and December 2004 were enrolled. Age, sex, duration of asthma, pulmonary function tests, total IgE, eosinophilic cationic protein, and specific IgE of ImmunoCAP were recorded. Allergic was defined as the presence of a specific IgE to 1 or more allergens.

Results: There were 161 (60.5%) male and 105 (39.5%) female patients, with a mean age of 60.46 ± 15.40 years. The mean duration of asthma was 13.64 ± 7.35 years. Mite allergens, *Dermatophagoides pteronyssinus* (48.46%) and *Dermatophagoides farina* (49.23%), were the most common indoor allergens. We divided the patients into allergic and nonallergic asthma groups: 164 (61.7%) patients had allergic asthma and 102 (38.3%), nonallergic asthma. Patients with allergic asthma were younger, and had a higher total IgE level and better lung function than the nonallergic asthmatics ($p<0.05$, respectively). Total serum IgE was correlated to peak expiratory flow (PEF) variability ($r=0.3395$, $p<0.0001$) in asthmatic patients. Among allergic asthmatics, the serum total IgE and PEF variability were higher as the number of positive allergen-specific IgE tests increased.

Conclusions: Defining asthma phenotypes as allergic or nonallergic is essential. This study supports the difference between allergic and nonallergic asthma. Patients with allergic asthma were younger and had higher total IgE and better lung function than patients with nonallergic asthma. ***(Thorac Med 2012; 27: 1-12)***

Key words: allergens, asthma, atopy, ImmunoCAP, peak expiratory flow

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Introduction

Asthma is characterized by nonspecific bronchial hyperresponsiveness and airway inflammation, triggered by viral upper respiratory infections, environmental allergens, or other stimuli [1]. Asthma has become more common around the world in recent decades [2-4]. In the United States, over 20 million people are diagnosed with asthma [5]. In Taipei City, the lifetime prevalence of adult bronchial asthma was 7.8% [6]. Therefore, accurate assessments of asthma severity are important to predict functional impairment and guide asthma management.

The Global Initiative for Asthma (GINA) guidelines [1] define asthma severity based on lung function, as measured by forced expiratory volume in 1 second (FEV_1), daytime and nocturnal symptoms, and frequency of rescue bronchodilator use, which do not reflect the heterogeneous characteristics of asthma [7]. Identification of heterogeneity and classification of asthma by phenotype provides a foundation to understand the disease causality and develop therapeutic approaches that lead to improved asthma control and clinical outcomes [8-9].

Allergen sensitization is a significant risk factor for the development of bronchial asthma. According to the definition provided by Johansson [10], "allergic asthma" is the term used to describe asthma mediated by immunologic mechanisms, and "nonallergic asthma" describes that mediated by nonimmunologic types. In allergic asthma, "immunoglobulin E (IgE)-mediated asthma" is used when IgE antibodies initiate an asthmatic reaction.

Researchers have raised concerns about the relationship between allergen sensitization and lung function in asthmatic patients. Romanet-Manent *et al*. [11] demonstrated that the FEV_1 in allergic asthmatics was higher than the FEV_1 in nonallergic asthmatics. In contrast, in a Korean study, Jung *et al*. [12] claimed that there was no difference in FEV_1 between allergic asthma and nonallergic asthma. In Taiwan, mite allergen exposure is the most significant factor associated with asthma [13-16]. However, little is known about the relationship between lung function and sensitization to mite or other allergens.

In this study, we aimed to investigate the clinical characteristics and distribution of common offending allergens, and the association between allergens, total serum IgE levels, and pulmonary function in adult patients with asthma. We also compared the clinical differences between the patients with allergic and nonallergic asthma.

Materials and Methods

Patients

The study was designed as a retrospective review of patient records, with the approval of the Institutional Review Board (IRB), Chang Gung Medical Foundation. Two hundred sixty-six asthmatic adult Taiwanese patients diagnosed with asthma according to the GINA guidelines, and followed up at the outpatient clinics of the Chest Department at Linkou Chang-Gung Memorial Hospital from January 2003 to December 2004 were enrolled. Asthma severity was classified as 1 (mild intermittent), 2 (mild persistent), 3 (moderate persistent), or 4 (severe persistent) according to the National Asthma Education and Prevention Program's (NAEPP) Guidelines for the Diagnosis and Management of Asthma [17].

Pulmonary function tests and methacholine provocation test

Spirometry was undertaken using a flow sensor spirometer, and FEV_1 and forced vital capacity (FVC) were measured. Static lung function data were recorded nearest the time of the outpatient clinic visit between 2003 and 2004. Methacholine inhalation challenge tests were performed with a DeVilbiss model 646 nebulizer, according to the method described in the American Thoracic Society statement [18].

Specific IgE of ImmunoCAP assay

Allergen specific IgE, serum total IgE and eosinophilic cationic protein (ECP) levels were all measured by ImmunoCAP assay. The ImmunoCAP system (Pharmacia CAP system; Uppsala, Sweden) measures specific IgE and provides quantitative measurement of IgE antibodies. The concentration of circulating, allergen-specific IgE antibodies in the serum is measured by the assay, providing an objective determination of the presence and also the extent of IgE-mediated allergy [19]. The specific IgE levels of 6 indoor allergens (*Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df), cockroach, cat dander, dog dander, and *Candida*), 6 outdoor allergens (*Penicillium notatum, Cladosporium herbarum, Aspergillus fumigatus*, ragweed, Bermuda grass, and eucalyptus), and 12 food allergens (egg white, cow's milk, wheat, peanut, soybean, shrimp, codfish, crab, orange, yeast, egg yolk, and mango) were analyzed. A level of ≥ 0.35 KU/L was regarded as positive.

Definition of allergic asthma and nonallergic asthma

Allergic asthma was defined as a positive test for specific IgE (≥ 0.35 kU/l) for at least 1 of the 24 CAP allergens, and nonallergic asthma was defined as no positive results for the CAP allergens.

Statistical analysis

The SPSS (SPSS for Windows, SPSS Inc., Chicago, IL, USA) statistical package was used for statistical analyses. All data are presented as mean ± standard deviation. Tests used were the Student's *t* test or Mann-Whitney test for parametric and nonparametric mean comparisons. The subgroups of gender, and smoking were analyzed by the chi-squared test. Kruskal-Wallis 1-way ANOVA was used to correlate nonparametric categorical data. The relationship between total IgE and clinical characteristics was analyzed using Pearson's correlation. A *p* value less than 0.05 was considered statistically significant.

Results

A total of 266 adult Taiwanese patients with asthma (161 males, 105 females), with a mean age of 60.46 years (range: 19-89 years), were enrolled in this study; 101 (38%) patients had a history of smoking. The total serum IgE level was 243.7 ± 363.3 kU/L, and the ECP value was 9.83 ± 11.02 ug/L. The most common indoor allergens were Dp (48.46%) and Df (49.23%), followed by cockroach (20.00%), and *Candida* (19.23%) (Figure 1). The most common outdoor allergen was *Penicillium notatum* (11.76%), followed by *Aspergillus* (8.56%) and ragweed (8.56%). Shrimp and crab were the most common food allergens, at 30.40% and 25.30%, respectively.

Of the 266 patients, 164 (61.7%) showed positive specific IgE levels to 1 or more CAP allergens and were defined as having allergic

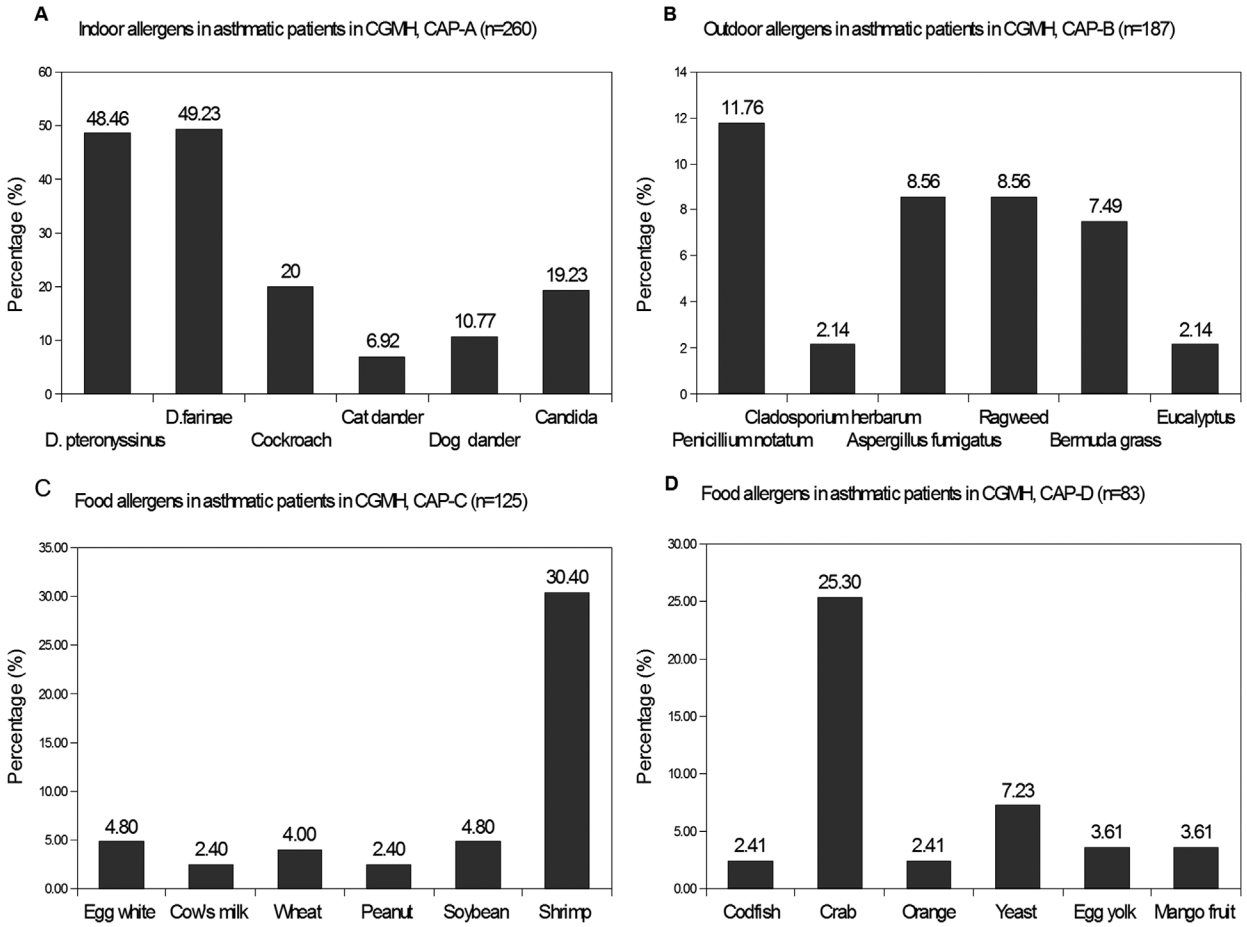

Fig. 1. Environmental allergens in adult asthma patients in northern Taiwan. Indoor allergens (A), outdoor allergens (B), food allergens (C) (D). CGMH: Chang Gung Memorial Hospital.

asthma; the remaining 102 (38.3%) patients had no positive results for any of the CAP allergens and were defined as having nonallergic asthma (Table 1). We compared the clinical characteristics of the allergic and nonallergic groups (Table 1) and found that the patients with allergic asthma were younger than the nonallergic asthmatics (mean age 57.96 ± 16.46 vs. 64.49 ± 12.59 years, respectively). The allergic asthmatics had better FEV_1 percent predicted value, FVC percent predicted value, and peak expiratory flow (PEF), compared with the nonallergic asthmatics (all $p<0.05$) (Table 1). Similarly, the asthma severity score was significantly higher among the nonallergic asthmatics ($p<0.05$) (Table 1). The allergic asthma group had a higher total IgE level and higher PEF variability than the nonallergic asthma group (both $p<0.05$). Total serum IgE was significantly correlated with PEF variability ($r=0.3395$, $p<0.0001$), but not FEV_1 percent predicted value ($r=0.1125$, $p=0.1554$) in the asthmatic patients (Figure 2). Sex, smoking amount, ECP level, FEV_1/FVC ratio, and the provocative concentration causing a 20% fall in FEV_1 (PC20) were not significantly different between the 2 groups (Table 1).

The pulmonary function and laboratory test results of the allergic asthmatics were evaluated

Table 1. Comparison of Characteristics between Allergic and Nonallergic Asthma

	Allergic (n=164, 61.7%)	Nonallergic (n=102, 38.3%)	*p* value
Age (years)	57.96 ± 16.46	64.49 ± 12.59	0.0007
Sex (% of female)	40.85%	37.25%	0.5593
Smoker (%)	37.20%	39.22%	0.7413
Duration of asthma (years)	12.76 ± 7.488	15.04 ± 6.937	0.0138
ECP (ng/l)	10.56 ± 12.92	8.649 ± 6.865	0.1699
Total IgE (kU/L)	338.9 ± 402.8	90.55 ± 214.4	<0.0001
FEV_1, % predicted	66.33 ± 18.59	59.42 ± 22.06	0.0335
FVC, % predicted	71.13 ± 20.87	62.55 ± 19.80	0.0043
FEV_1/FVC, %	70.53 ± 12.25	68.99 ± 13.54	0.4088
PEF variability, %	12.25 ± 6.176	8.688 ± 4.942	<0.0001
PEFR, L/min	316.7 ± 116.8	270.6 ± 117.4	0.0020
PC20	2.634 ± 3.341	2.883 ± 3.762	0.6877
Asthma severity	2.122 ± 0.8347	2.353 ± 0.9081	0.0348

Data are presented as n or mean ± sd.

IgE: immunoglobulin; ECP: eosinophilic cationic protein; FEV_1: forced expiratory volume in 1 second; % predicted: percentage of predicted value; FVC: forced vital capacity; PEFR: peak expiratory flow rate; PC20: provocative concentration causing a 20% fall in FEV_1.

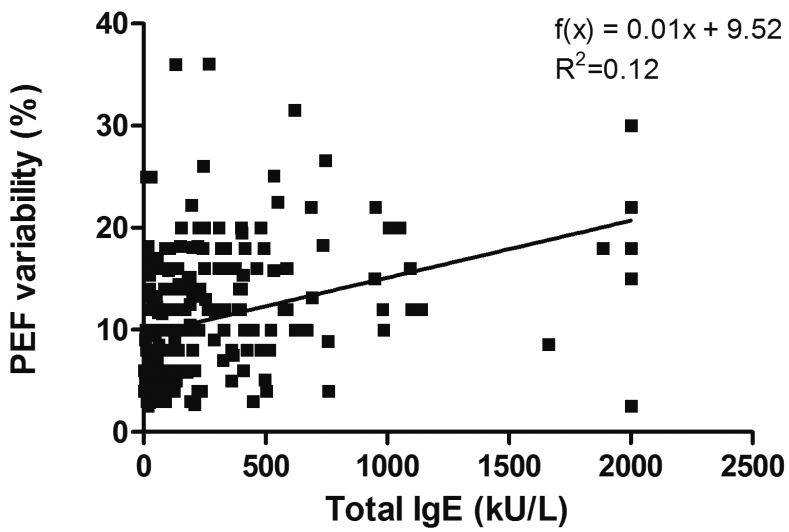

Fig. 2. Correlation of the total serum IgE and PEF variability in all asthma patients (r=0.3395, p<0.0001).

in terms of the number of positive allergens (Table 2). We found that serum total IgE and PEF variability showed higher levels as the number of positive allergen-specific IgE tests increased (both p<0.05) (Table 2, Figure 3). However, there were no significant differences

Table 2. The Impact of Different Numbers of Allergens in Patients with Allergic Asthma

The number of allergens	1,2 (n=69)	3,4 (n=59)	≥5 n=36)	*p* value
Age (years)	61.46 ± 14.56	55.34 ± 17.94	55.53 ± 16.57	0.0660
Sex (% of female)	39.13%	45.76%	36.11%	0.6040
Pulmonary function				
FEV_1, % predicted	64.33 ± 18.03	70.15 ± 19.23	64.22 ± 18.56	0.3469
FVC, % predicted	68.38 ± 23.62	73.56 ± 17.87	71.43 ± 21.57	0.5448
FEV_1/FVC, %	70.84 ± 10.81	70.13 ± 13.67	70.61 ± 12.69	0.9625
PEF variability, %	10.81 ± 6.25	12.27 ± 5.04	14.99 ± 6.92	0.0039
PEFR, L/min	303.3 ± 120.2	324.7 ± 110.4	329.2 ± 121.0	0.4547
Total IgE (kU/L)	206.0 ± 287.4	336.2 ± 273.4	597.9 ± 606.2	<0.0001
ECP (ng/l)	11.23 ± 17.00	10.78 ± 9.711	8.909 ± 7.429	0.6765
PC20	3.423 ± 3.808	2.054 ± 3.490	2.470 ± 2.544	0.3736
Asthma severity	2.072 ± 0.8798	2.136 ± 0.7533	2.194 ± 0.8886	0.7694

Data are presented as n or mean ± sd.

IgE: Immunoglobulin; ECP: eosinophilic cationic protein; FEV_1: forced expiratory volume in 1 second; % predicted: percentage of predicted value; FVC: forced vital capacity; PEFR: peak expiratory flow rate; PC20: provocative concentration causing a 20% fall in FEV_1.

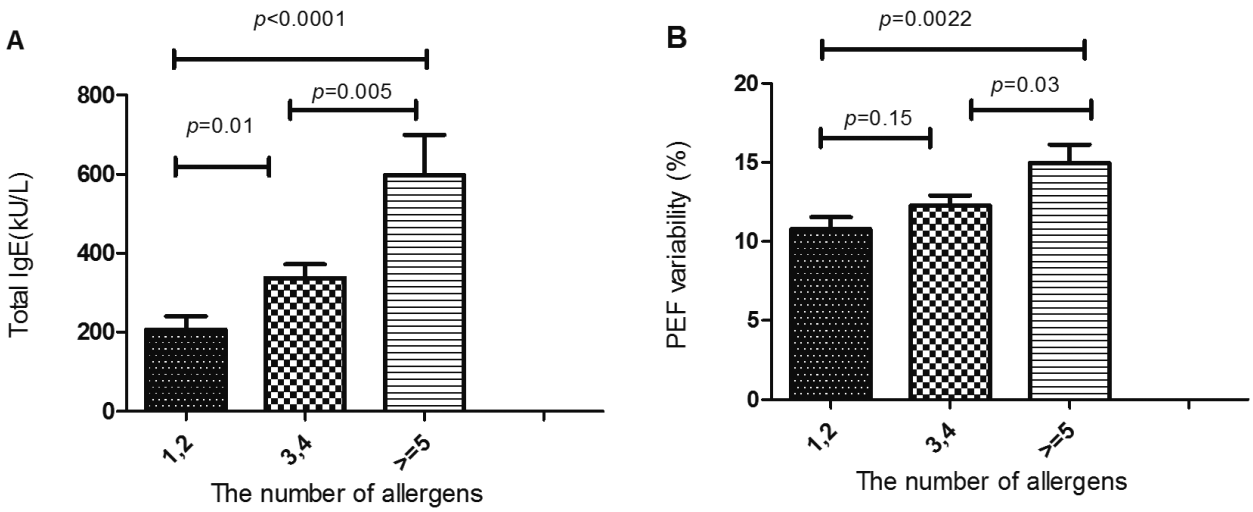

Fig. 3. The serum total IgE (3a) and PEF variability (3b) showed higher levels as the number of positive allergens increased.

in ECP, spirometric value, and asthma severity in patients with different numbers of positive CAP allergens.

To explore the clinical characteristics based on different serum total IgE levels, we divided the allergic asthma patients into high (>200 kU/L), low (≥100 kU/L and <200 kU/L) and normal total IgE level (<100 kU/L) groups. Similarly,

Table 3. The Impact of Total IgE in Patients with Allergic Asthma

Serum total IgE levels	≤100 (n=44)	101-200 (n=39)	>200 (n=81)	*p* value
Age (years)	63.98 ± 13.06	54.21 ± 18.20	56.49 ± 16.55	0.0130
Sex (% of female)	40.91%	38.46%	41.98%	0.9349
Pulmonary function				
FEV_1, % predicted	61.00 ± 21.26	74.00 ± 17.00	65.31 ± 17.30	0.0561
FVC, % predicted	63.19 ± 18.81	78.11 ± 22.53	69.14 ± 20.60	0.0205
FEV_1/FVC, %	68.22 ± 12.99	74.81 ± 11.96	68.98 ± 11.63	0.0455
PEF variability, %	9.129 ± 3.606	12.01 ± 6.030	14.06 ± 6.689	<0.0001
PEFR, L/min	270.5 ± 103.7	344.2 ± 126.1	328.5 ± 113.0	0.0065
The number of allergens	2.477 ± 1.438	3.128 ± 2.041	4.259 ± 3.259	0.0010
ECP (ng/l)	9.650 ± 6.794	7.373 ± 4.767	12.59 ± 17.17	0.1006
PC20	4.378 ± 4.548	2.971 ± 3.547	1.690 ± 2.197	0.0334
Asthma severity	2.159 ± 0.8053	2.077 ± 0.7028	2.123 ± 0.9135	0.9055

Data are presented as n or mean ± sd.

IgE: Immunoglobulin; ECP: eosinophilic cationic protein; FEV_1: forced expiratory volume in 1 second; % predicted: percentage of predicted value; FVC: forced vital capacity; PEFR: peak expiratory flow rate; PC20: provocative concentration causing a 20% fall in FEV_1.

the number of positive allergens and PEF variability showed higher levels as the serum total IgE increased (both $p<0.01$), whereas the PC20 was lower as the serum total IgE increased ($p<0.05$) (Table 3). However, we found that allergic asthmatic patients with a low total IgE level (≥100 kU/L and <200 kU/L) had significantly better pulmonary function (FEV_1 percent predicted value, FVC percent predicted value, FEV_1/FVC ratio and PEF), compared with the allergic asthmatics with a high total IgE level (>200 kU/L) and normal total IgE level (<100 kU/L) (Table 3).

Discussion

There were 3 findings in this study. First, the most common allergens in adult Taiwanese patients with asthma were house dust mites, including Dp and Df. Second, patients with allergic asthma were younger, and had a higher IgE level and better lung function than patients with nonallergic asthmatic. Third, in the investigation of allergic asthmatic patients, higher PEF variability and lower PC20 were found as the serum total IgE and the number of positive allergens increased. In addition, allergic asthmatic patients with a high total serum IgE level (>200 kU/L) had significantly worse lung function than those with a low IgE level, between 100 and 200 kU/L. These findings may indicate that distinguishing asthma phenotypes as allergic or nonallergic is essential, and that as the number of offending allergens increases, or as the level of total serum IgE rises, the patients with allergic asthma have worse pulmonary function.

Mites, including Dp and Df, are the most common allergen in adult asthmatic patients in Taiwan. Similarly, house dust mite sensitization is dominant in patients with asthma in China [20] and South Korea [12]. This might be explained by the fact that dust mites thrive in humid ar-

eas of the world [21]. Since temperature and humidity vary in different geographical areas, physicians should be aware of the prevalent allergens in their location. In Taiwan, studies on allergen sensitization in patients with asthma are usually done with children, and few studies have discussed allergen sensitization in adult asthmatics. In the published literature, the percentage of mite sensitization in adult asthmatic patients in Taiwan was reported to be 45.9% to 63.2% [14-16]. Cockroach is the second most common allergen, with the percentage of sensitization ranging from 17.6% to 38.3%; the third most common allergen has varied in reports. Our study further supports the previous results and offers information on clinical care, as well.

Whether or not allergic asthma and nonallergic asthma have different clinicopathologic features remains debatable. Our study showed that patients with allergic asthma were younger, and had a higher total IgE level and higher FEV_1 than nonallergic asthma patients. These results are consistent with those of Romanet-Manent [11], which showed that allergic asthmatics were younger and had higher FEV_1 than nonallergic asthmatics. It is reasonable that nonallergic asthmatics would be older than allergic asthmatics, because the prevalence of positive allergen sensitization declines after 25 years of age [22]. The baseline lung function percentage predicted did not decrease with age [23]. Moreover, our data revealed that allergic asthmatics had a better FEV_1 percentage predicted and better FVC percentage predicted than nonallergic asthmatics, suggesting that the poor lung function in nonallergic asthmatics cannot be explained by older age. The precise mechanisms of poor lung function and worse outcomes for nonallergic asthma patients are still not well understood. Some evidence has shown that no allergen sensitization may hamper the diagnosis of nonallergic asthma. Bellia *et al*. [24] pointed out that asthmatic patients with a misdiagnosis of chronic obstructive pulmonary disease or with no diagnosis had a lower prevalence of allergies. Delayed diagnosis and treatment of nonallergic asthma may cause a deterioration of lung function. Researchers have also tried to find the pathological difference between the 2 asthmatic subgroups [25-27]. In bronchial biopsies, Amin *et al*. [25] demonstrated that the number of neutrophils was increased in nonallergic asthmatic patients, and the number of T-lymphocytes was higher in allergic asthmatic patients. Therefore, it is possible that the neutrophil-predominant inflammation in nonallergic asthma will cause these patients to become refractory to current standard anti-asthma therapy, such as inhaled corticosteroids. In contrast, it is possible that the T-lymphocyte-mediated airway inflammation in allergic asthma will have a marked response to inhaled steroids, thus resulting in better lung function and less asthma severity. Another possible explanation might be that the treatment for nonallergic asthma is less specific. According to the GINA guidelines, risk factors for asthma include host and environmental factors. Physicians can therefore educate allergic patients to avoid allergen exposure to control their asthma, whereas this is not necessary for nonallergic asthmatics. In this study, we demonstrated the difference between allergic and nonallergic asthma based on clinical parameters such as age, duration of asthma, pulmonary function, and serum total IgE level. However, the difference between allergic and nonallergic asthma still warrants further investigations based on pathological and immunological evidence to disclose the precise mechanisms.

Woodruff and colleagues found that subjects with asthma could be divided into 2 groups: those with Th2 high and Th2 low phenotypes [28]. The asthma subjects in the Th2 high group had increased airway and peripheral blood eosinophils, airway hyperresponsiveness, thickening of the lamina reticularis, and total IgE, which mimic the clinical characteristics of allergic asthma patients in our study. However, it is possible that factors acting through the innate immune pathway, such as environmental exposure to bacterial endotoxins, particulate air pollution, ozone, and persistent infections, may play a role in the Th2 low group of asthma subjects, which is akin to an earlier identification of non-eosinophilic asthma [29]. This group has a relatively poor clinical response to corticosteroids. It is reasonable to suggest that the nonallergic phenotype of asthma in our study might be similar to Th2 low asthma, thus leading to a refractory response to inhaled medications and poor lung function. Therefore, nonallergic asthma potentially represents an important unmet need for specific therapy, such as macrolide therapy [30] or more specific antineutrophil approaches.

Although the precise mechanisms of how offending allergens induce bronchial obstruction and decrease lung function are still not well understood, our observations indicate that as the numbers of sensitized allergens increase, the serum total IgE levels rise significantly in patients with allergic asthma. A previous study showed that serum levels of specific allergens and total IgE were strongly associated with the clinical grade of sensitization and disease severity in allergic patients [31]. IgE has also been shown to be a major contributing factor in the development of bronchial hyperresponsiveness in asthmatics [32]. Moreover, Sears *et al*. [33] investigated the relationship between serum total IgE levels and airway hyperresponsiveness to methacholine in children, and found that the prevalence of diagnosed asthma and airway hyperresponsiveness was related to a higher serum IgE level. This is consistent with our data, in that the number of positive allergens and PEF variability showed higher levels as the serum total IgE increased (both $p<0.01$), whereas the PC20 was lower as the serum total IgE increased ($p<0.05$).

This study has some limitations. First, this is a retrospective cohort study with some missing data. Not all lung function tests were obtained, and not all specific IgE levels were measured in our patients. Second, we did not determine the patterns of infiltrating leukocytes in sputum or the differences in the inflammatory biomarkers contributing to asthmatic phenotypes, in either the allergic or the nonallergic asthma patients in our population. Third, we did not identify treatment outcomes, hospitalization due to asthma exacerbation, or changes in pulmonary function test results after treatment. Fourth, the pulmonary function tests were not taken in the same season. Asthma prevalence and severity may be influenced by climate, temperature, humidity, and residence. Besides, some asthmatic patients had different severities of asthma during the summer and winter. Since measuring the severity of asthma is very complicated, a longitudinal, prospective study to confirm our observation is needed.

In conclusion, this study further supports the idea that allergic and nonallergic asthma are different asthma phenotypes, because patients with allergic asthma were younger, and had higher total IgE and better lung function than patients with nonallergic asthma. Among the allergic asthmatics, as the number of posi-

tive allergens increased, the total serum IgE also increased, thus leading to airway hyperresponsiveness (higher PEF variability and lower PC20). In addition, allergic asthmatic patients with a high total IgE level (>200 kU/L) had a significantly worse lung function than those with an IgE level between 100 and 200 kU/L. This study may provide a more detailed picture of asthma to assist clinical decision-making in asthma control.

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不同表型的成人氣喘：過敏性氣喘與非過敏性氣喘的比較

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前言：過敏原致敏在成人是一個發生氣喘的危險因子。然而，在氣喘病人身上，過敏原致敏和肺功能之間的關係尚未確知。本研究指在探討台灣北部的成人氣喘患者的致敏過敏原、血清總免疫球蛋白E（IgE），以及肺功能之間的關聯。

方法：這個研究收集了266個從2003年1月至2004年12月之間確診為成人哮喘的病人。記錄年齡、性別、氣喘為期、肺功能檢查、血清總免疫球蛋白E、嗜酸性粒細胞陽離子蛋白和ImmunoCAP的特定IgE。過敏性的定義為至少測得一個過敏原的特異性IgE。

結果：有161（60.5%）男性和105（39.5%）女性患者，平均年齡60.46 ± 15.40歲。氣喘為期平均為13.64 ± 7.35年。塵蟎過敏原、屋塵蟎（48.46%）和粉塵蟎（49.23%）是最常見的室內過敏原。我們將患者分為過敏性氣喘與非過敏性氣喘兩組。164（61.7%）患者是過敏性氣喘，102（38.3%）是非過敏性氣喘。過敏性氣喘患者相較與非過敏性氣喘患者，年紀較低，有較高的血清總免疫球蛋白E，與更好的肺功能（$p<0.05$）。氣喘患者的血清總免疫球蛋白E 和尖端呼氣流量（PEF）變異性有相關性（$r=0.3395$，$p<0.0001$）。而過敏性氣喘患者中，血清總免疫球蛋白E和尖端呼氣流量變異性隨著過敏原的特異性IgE數量增加而增加。

結論：區分過敏性氣喘或過敏性是非常重要的，因為兩者是不同的氣喘表型。這項研究顯示過敏性和非過敏性氣喘的不同之處。過敏性氣喘患者年紀較輕，有較高的血清總免疫球蛋白E，以及更好的肺功能。*(胸腔醫學* ***2012; 27: 1-12)***

關鍵詞：過敏原，氣喘，異位性體質，ImmunoCAP，尖端呼氣流量

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Anti-inflammatory Activity and Mucolytic Effect of Ambroxol in Patients with Stable Chronic Bronchitis — A Preliminary Report

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Chronic bronchitis is a clinical disorder characterized by excessive mucus secretions and manifested by chronic or productive cough on most days, for a minimum of 3 months in a year and for not less than 2 successive years. Unfortunately, other disorders with similar manifestations, such as bronchiectasis, tuberculosis, and lung abscess, must be excluded. Patients with predominant asthma or emphysema may fit this definition, and many patients with pathological or physiological hallmarks or chronic bronchitis may not qualify, since they do not cough. Hyper-viscosity and overproduction of sputum often increase morbidity. Mucolytics might alleviate patients' symptoms and improve their daily activity. Ambroxol was first introduced as a mucoactive agent with anti-inflammatory activity. We investigated the benefits of this compound in reducing cytokine concentrations of sputum, sputum viscosity, and pulmonary symptoms in chronic bronchitis patients. Twenty-five chronic bronchitis patients were recruited and 20 completed the study. We found that 2-week oral administration of ambroxol did not improve static lung function (FVC, FEV_1 and FEV_1%) and 6-minute walking test distance. The sputum myeloperoxidase (MPO) activity and IL-8 level were reduced significantly, the sputum TNF-α and IL-1β levels had a tendency to decrease, and the measured sputum viscosity at 1 radian was significantly reduced. These preliminary results support the assumption that ambroxol is a mucolytic agent with anti-inflammatory activity, which might be helpful in terms of sputum clearance and reduction of airway inflammation in chronic bronchitis patients. ***(Thorac Med 2012; 27: 13-20)***

Key words: chronic bronchitis, mucolytics, ambroxol, myeloperoxidase (MPO), IL-8, TNF-α, IL-1β

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Introduction

Chronic bronchitis is a clinical disorder characterized by excessive mucus secretions and manifested by chronic or productive cough on most days, for a minimum of 3 months in a year and for not less than 2 successive years. Unfortunately, other disorders with similar manifestations, such as bronchiectasis, tuberculosis, and lung abscess, must be excluded. Patients with predominant asthma or emphysema may fit this definition, and many patients with pathological or physiological hallmarks or chronic bronchitis may not qualify, since they do not cough [1]. Chronic bronchitis is characterized by excess mucous secretion and airflow obstruction. Since there is no single medication that can treat all the aspects of this illness, most patients require combination therapy. Of the combinations available, oral theophylline, inhaled corticosteroids and inhaled anti-cholinergics and/or bronchodilators supplemented with physiotherapy are the main treatments utilized by these patients [1]. However, sputum hyper-viscosity and overproduction with intractable cough often bothers patients in spite of the treatment. Anti-inflammatory therapy and mucolytics might alleviate the patients' symptoms and improve their daily activity. Ambroxol was introduced as a mucoactive or mucokinetic agent, and also has anti-inflammatory activity [2-5].

Ambroxol was noted to reduce the number of exacerbations and also improve respiratory signs and symptoms in chronic bronchitis in a multicenter double-blind study [6-7]. Similarly, ambroxol reduced mucus viscosity, improved PaO_2 and the chest sound score, and increased tidal volume, PEFR and forced expiratory flow in a single-blinded, randomized study of cystic fibrosis patients [8]. Ambroxol had a tendency to improve mucociliary clearance in chronic bronchitis patients [2], and offered a significant improvement with regard to mucociliary transport in a 2-period cross-over study of hypersecretory bronchitis [3]. However, the anti-inflammatory effect of mucolytic agents such as ambroxol in chronic bronchitis is not yet well-known. In this study, our primary endpoints were to determine the changes in several cytokine levels, such as TNF-α, IL-1β and IL-8, and myeloperoxidase (MPO) activity in sputum and sputum viscosity in chronic bronchitis before and after administration of ambroxol. The secondary endpoints were to determine the changes in spirometry and the 6-minute walking test before and after administration of ambroxol.

Methods

Patients

Twenty-five male patients diagnosed with chronic bronchitis and between 50 and 80 years old were recruited into this study. Their conditions had been stationary without acute exacerbation of disease or upper airway infection for at least 2 months before recruitment. Patients with active pulmonary TB, chronic sinusitis and bronchiectasis were excluded. All patients were conscious, co-operative and able to produce sputum without the aid of chest percussion or postural drainage. Use of oral or inhaled corticosteroids, theophylline, and a regular bronchodilator was allowed without changing the dosage for 1 month prior to the study and during the study period. Rescue bronchodilators were permitted on the basis of "as required". Spirometry was performed before the use of any bronchodilator inhalation. Furthermore, the participants did not have pulmonary instability

(e.g., respiratory rate > 30/min, hypoxemia with SaO_2 < 90% in room air, or hypercapnia with pH < 7.35) or body temperature > 38.5ºC. Patients with co-morbidities, such as liver failure, congestive heart failure, renal failure and active gastroenteral problems were excluded. Female patients that were pregnant or breast-feeding were excluded. Patients with a known hypersensitivity to the test drug were also excluded.

Study design

During their first visit, the patients were evaluated for eligibility to be enrolled in the study. If the patient was eligible for the study and was willing to sign informed consent, he was instructed to take ambroxol (250 mg) 1# tid for 2 weeks. Sputum collection, spirometry and a 6-minute walking test were performed at the beginning and end of the study. There were a total of 3 visits during the study. The protocol was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital and written informed consent was obtained from all patients.

Sputum collection

During the morning of visits 2 and 3, each patient's mouth and tongue were swabbed dry with gauze and the outlets of the salivary glands were occluded by cotton pads. Patients were asked to produce sputum by cough. At least 2 ml of sputum was a suitable amount for both cytokine and viscosity studies. The contaminated saliva was removed with tissue. The sputum was kept in a freezer at -20ºC until viscosity and cytokine measurement was done [9].

Mucus Rheologic Analysis

A controlled stress rotation rheometer (AR500, TA-Instruments, Brussels, Belgium) was used to determine the viscosity of the sputum samples at 1 rad/s, following the manufacturer's instructions.

Measurement of cytokine level

Sputum was digested with 6 M guanidine sulfate in a 37ºC water bath for 30 minutes, and then the sediment was spun with a centrifuge at 950 g for 5 minutes. The supernatant was used for cytokine measurement. An MPO kit (assay range 0.312-20 ng/ml, sensitivity <10 pg/ml) (IBL America, Spring Lake Park, MN, USA), and TNF-α (assay range 0.5-32 pg/ml, sensitivity <0.09 pg/ml), IL-1β (assay range 0.31-20 pg/ml, sensitivity 0.06 pg/ml) and IL-8 (assay range 0.39-25 pg/ml, sensitivity <100 fg/ml) ELISA kits (Invitrogen, Carlsbad, CA, USA) were used according to the manufacturer's instructions.

Spirometry and 6-minute walking test

At the beginning and end of the study period, a Spiroanalyzer ST-350R (Fukuda Sangyo Co Ltd.) was used to measure the best of at least 3 reproducible forced expiratory volumes in one second (FEV_1) and forced vital capacity (FVC) (with a difference within 200 ml or less than 5%) A study nurse conducted a 6-minute walking test at the beginning and end of the study.

Statistics

Data were expressed as means ± standard error of the mean (SEM) of a given number of observations. Student's paired *t*-test was employed for paired data. *P* values of less than 0.05 were considered to be significant for all tests.

Results

Twenty-five patients with chronic bronchitis were recruited and 20 of them completed the study. Three were dropped because they could not accept taking the medication. They thought the ambroxol might have an unknown impact on their health despite assurances of its safety. Another patient consumed only about half of the medication, and 1 patient was not able to produce a measurable amount of sputum. We found that a 2-week oral administration of ambroxol did not improve static lung function (FVC, FEV_1 and FEV_1%) or distance in the 6-minute walking test (Figure 1). The sputum MPO activity and IL-8 level were significantly reduced (1.91 ± 0.15 vs. 1.14 ± 0.13 ng/ml, P=0.006 for MPO; 2.32 ± 0.12 vs. 1.68 ± 0.21pg/ml, P=0.006 for IL-8, N=20 for both) (Figure 2). The sputum TNF-α and IL-1β levels had a tendency to decrease, but not significantly (0.192 ± 0.06 vs. 0.07 ± 0.01, P=0.067 for TNF-α; 0.75 ± 0.18 vs. 0.43 ± 0.11, P=0.133 for IL-1β, N=20 for both) (Figure 2). Viscosity was significantly reduced at 1 radian (2.80 ± 0.13 vs. 1.83 ± 0.08 Pa.s, N=20, P<0.01, Figure 3). No episode of acute deterioration of respiratory function was observed during the study period, and no adverse effects associated with this compound were reported.

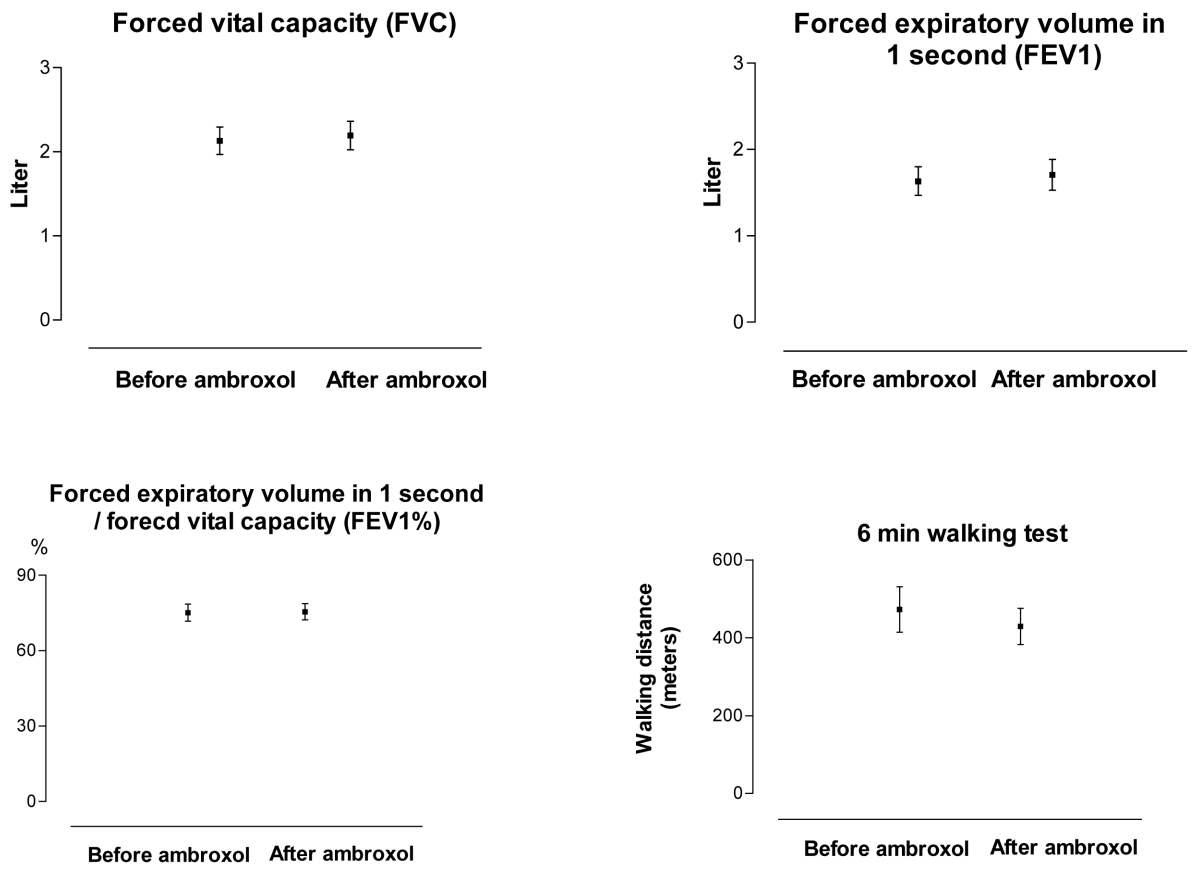

Fig. 1. The results of FEV_1, FEV_1%, FVC and the 6-minute walking test before and after administration of ambroxol are shown. No significant change with regards to pulmonary function tests was observed between groups.

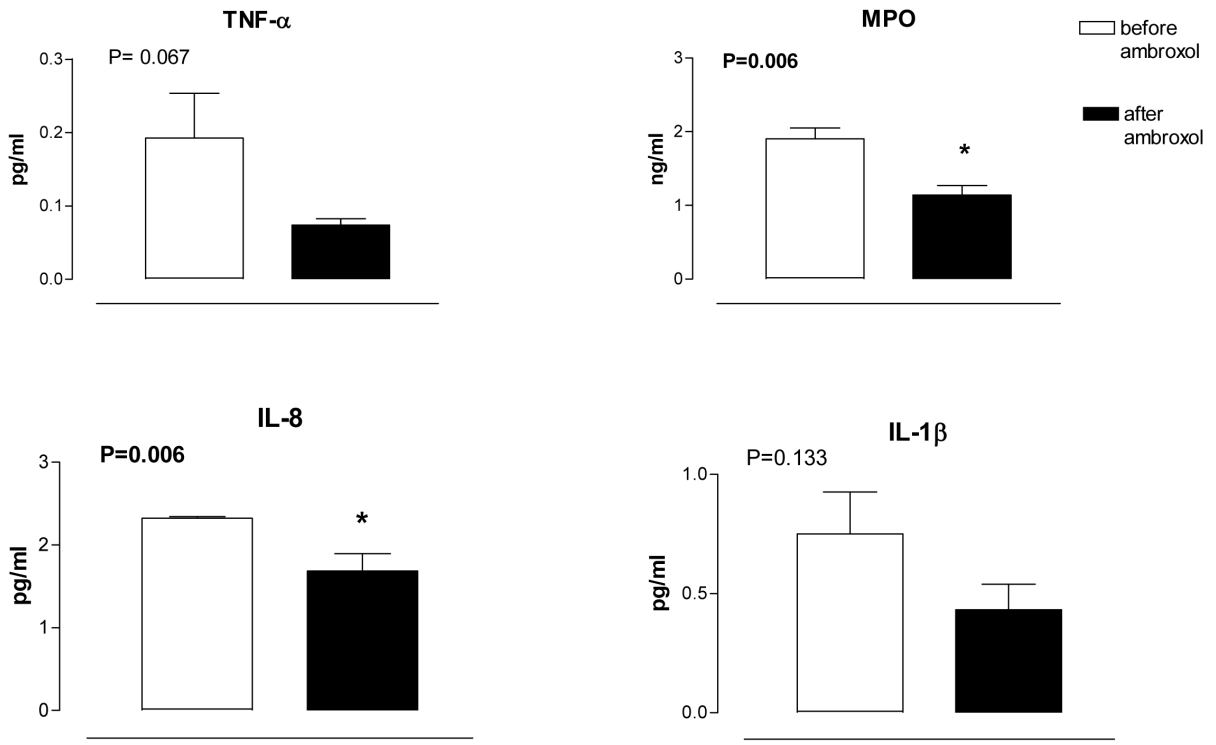

Fig. 2. Myeloperoxidase (MPO) activity, TNF-α, IL-1β and IL-8 levels were measured before and after administration of ambroxol. Significantly reduced levels of MPO and IL-8 were observed after treatment.

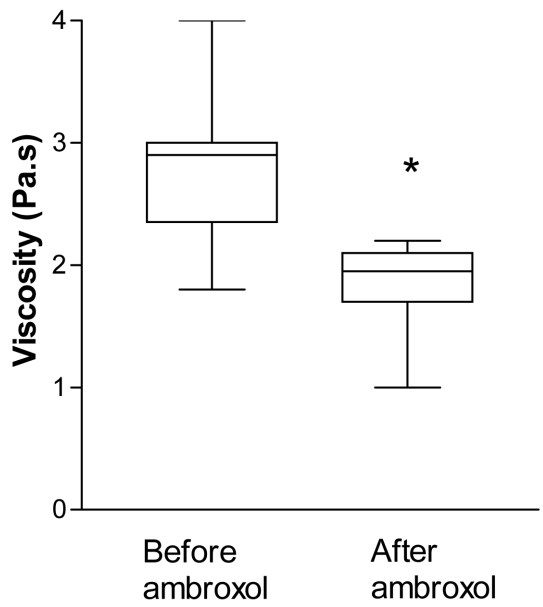

Fig. 3. A significant change in viscosity was observed before and after the administration of ambroxol. (N=20, P<0.01).

Discussion

Mucosolvan, a brand of ambroxol hydrochloride (2-amino-3, 5-dibromobenzyl methyl amino-cyclohexanol hydrochloride) is a hydroxylated metabolite of bromhexine hydrochloride (N-cyclohexyl-N-methyl-2-amino-3, 5-dibromobenzyl) amino-hydrochloride), an earlier benzylamine clinically used as a secretolytic/expectorant. It has been used to treat diseases such as chronic bronchitis or cystic fibrosis, which features abnormal mucus secretion and impaired mucus transport. The pharmacological profile of ambroxol includes secretagogue-like activity, ciliary movement improvement, surfactant stimulation, phospholipase inhibition, and anti-oxidant effects [10].

Ambroxol has been reported in preclinical studies to exhibit an anti-inflammatory effect through the inhibition of TNF-α, IL-2, IFN-γ or IL-1β release from bronchoalveolar mononuclear cells or peripheral mononuclear cells (PMN) [4-5,11]. Also, the spasmolytic activity of clenbuterol is significantly improved in animals pretreated with ambroxol [12]. Ambroxol has been shown to scavenge the oxygen species [13-14], suggesting anti-oxidant activity to protect lung tissue from oxidant-induced lung injury and paraquat intoxication [15]. It was also found that ambroxol inhibited ozone-induced airway hyper-responsiveness in dogs, probably by inhibiting the formation and release of oxygenation products of arachidonic acid from neutrophils [16]. Ambroxol has been shown to protect the lung from damage by peripheral mononuclear cells (PMN) by reducing the chemotaxis of PMN [17].

It was reported that ambroxol decreased the release of elastase and MPO from isolated, activated neutrophils in healthy volunteers [18]. Ambroxol also decreased the release of MPO and lysozyme evoked by 0.5 mg/ml of degraded immunoglobulin G and 1 μM of fMLP in a dose-dependent fashion in another isolated neutrophil model [19].

These results suggested that ambroxol is an anti-inflammatory agent. Our observation of ambroxol in this study showed that it has similar anti-inflammatory effects in reducing significantly the levels of MPO and IL-8 in sputum. Levels of TNF-α and IL-1β also tended to be reduced after treatment with ambroxol. A multicenter double-blind study found that ambroxol reduced the number of exacerbations and improved respiratory signs and symptoms [6-7]. It was further reported that ambroxol reduced mucus viscosity, improved PaO_2 and the chest sound score, and increased tidal volume, PEFR and forced expiratory flow in a single-blind, randomized study of cystic fibrosis patients [8]. However, the change in viscosity was judged by simply examining the patient's eyes rather than using a viscometer. In our study, we measured the viscosity at 1 radian, which reflects the efficacy of ciliary movement *in vivo*. Our results imply that 2 weeks of treatment with ambroxol might increase mucus clearance by ciliary movement. However, we found that patients' lung functions were not altered after 2 weeks of treatment with ambroxol, which might be due to the different treatment period and different population. Ambroxol had a concentration-dependent tendency to improve mucociliary clearance in chronic bronchitis [2] and significantly improve mucociliary transport in a 2-period cross-over study of hyper-secretion bronchitis [3].

In conclusion, we observed that ambroxol significantly reduces the level of TNF-α, IL-8 and MPO in sputum. Sputum viscosity was also significantly reduced at 1 radian. Nevertheless, the duration of this trial was only 2 weeks. Determining whether the effects were lasting would require a longer period of study and additional research. Taken together, these results suggest that ambroxol has an anti-inflammatory activity and mucolytic effect, rather than improving lung function during this period of therapy for chronic bronchitis.

Acknowledgement

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Ambroxol 對慢性支氣管炎病患的化痰與抗發炎效用

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慢性支氣管炎為慢性發炎呼吸道阻塞及黏液過度分泌的疾病，化痰劑可能降低痰液的黏稠度，進而減輕症狀。本研究探討ambroxol對慢性支氣管炎的效用；25個慢性支氣管炎的病人進入本研究，20個病人完成此試驗，經過2週的ambroxol口服後，其肺功能、尖峰氣流速及6分鐘步行測試並無變化；而痰液中巨嗜細胞的myeloperoxidase（MPO）的活性與IL-8的濃度有意義的下降；TNF-α及IL-1ß濃度則略有下降的趨勢。而臨床症狀如咳嗽頻率、咳痰的效能、痰的黃濃色澤及呼吸困難度則有意義的改善；但哮喘發生頻率，夜間睡眠中斷次數及日常生活的活動力無改善，試驗期間並無病人發生急性發作而須住院或到急診治療，也無明顯藥物副作用的報告。本報告的結論為ambroxol是一化痰劑同時也具抗發炎效用，對慢性支氣管炎病人的痰液清除及呼吸道發炎可能有助益。*(胸腔醫學 2012; 27: 13-20)*

關鍵詞：慢性支氣管炎，化痰劑，ambroxol，myeloperoxidase (MPO)，第八細胞素，腫瘤壞死因子，第一乙型細胞素

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Spontaneous Remission in Goodpasture Syndrome and Relapse 5 Years Later — A Case Report

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Goodpasture syndrome is a rare autoimmune disease which has had a poor prognosis in the past. Recovery from severe renal failure due to Goodpasture syndrome is uncommon. Only early detection of this disease can improve the outcome and prevent long-term morbidities. However, some cases will recover spontaneously. In the present case, the initial symptoms and signs were intermittent low-grade fever, chronic cough, and hemoptysis. Chest X-ray showed multiple alveolar patches. No body weight loss and no night sweating were noted. The patient had the same symptoms 5 years previously and they resolved spontaneously. Pulmonary tuberculosis was suspected at that time. This time, hematuria with foamy urine developed during admission, and after renal biopsy and anti-GBM antibody survey, Goodpasture syndrome was diagnosed. The patient's condition improved after immediate treatment with immunosuppressive drugs and hemodialysis, and she was still well after regular follow-up for 12 months. ***(Thorac Med 2012; 27: 21-28)***

Key words: Goodpasture syndrome, spontaneous remission, relapse, anti-GBM

Introduction

The first reported case of Goodpasture syndrome was an 18-year-old male with hemoptysis and renal failure in 1919 [1]. In 1958, Stanton et al. coined the term "Goodpasture syndrome" to categorize patients with pulmonary hemorrhage and glomerulonephritis [2]. Since that time, immune-mediated injury to collagen IV, affecting the function of the epithelia and leading to kidney and lung injury, has been noted [3]. Multiple disorders affecting both the kidney and lung are referred to as pulmonary renal syndrome, and Goodpasture syndrome is a classic example. It comprises the triad of pulmonary hemorrhage, glomerulonephritis and anti-glomerular basement membrane (anti-GBM) antibodies. Patients with "Goodpasture disease" are those who have only glomerulonephritis and anti-GBM membrane antibodies [1]. The associated trigger factors may include tobacco smoking, hydrocarbon solvent exposure, and cocaine abuse [4]. Although Goodpasture syndrome is very rare in the clinical setting, it can cause severe morbidity and mortality. Some cases will spontaneously recover, and this in-

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creases the difficulty of diagnosis [5]. However, early detection of this disease and the use of immunosuppressive medication or hemodialysis will improve patient outcome [4]. Since the early symptoms and signs can be non-specific, physicians should be aware of and able to recognize this disease.

Case Report

A 51-year-old woman who had a history of hypertension suffered from hemoptysis, low-grade fever, chronic dry cough, dyspnea on exertion, fatigue and poor appetite for 1 month. She had had the same symptoms 5 years ago. At that time multiple small nodules in the bilateral lungs were noted on chest computed tomography (CT) and chest X-ray (CXR) (Figures 1, 2A). A series of examinations including sputum acid-fast stain, TB culture, atypical pneumonia titer, fine-needle aspiration, and a serology test for Cryptococcus were performed, but no definite diagnosis was made at that time. Fine needle aspiration showed skeletal muscle and fibroadipose tissue. Urinalysis showed RBC: 2-5 and WBC: 0-2. Serum creatinine was 0.8 mg/dl. The patient did not receive antibiotics or other therapy at that time, and the lesion subsided. She was discharged under stable conditions. Follow-up CXR showed no lesion 3 months later (Figure 2B).

This time, she suffered from intermittent cough with minimal bloody sputum, and the symptoms persisted for 1 month. She denied a

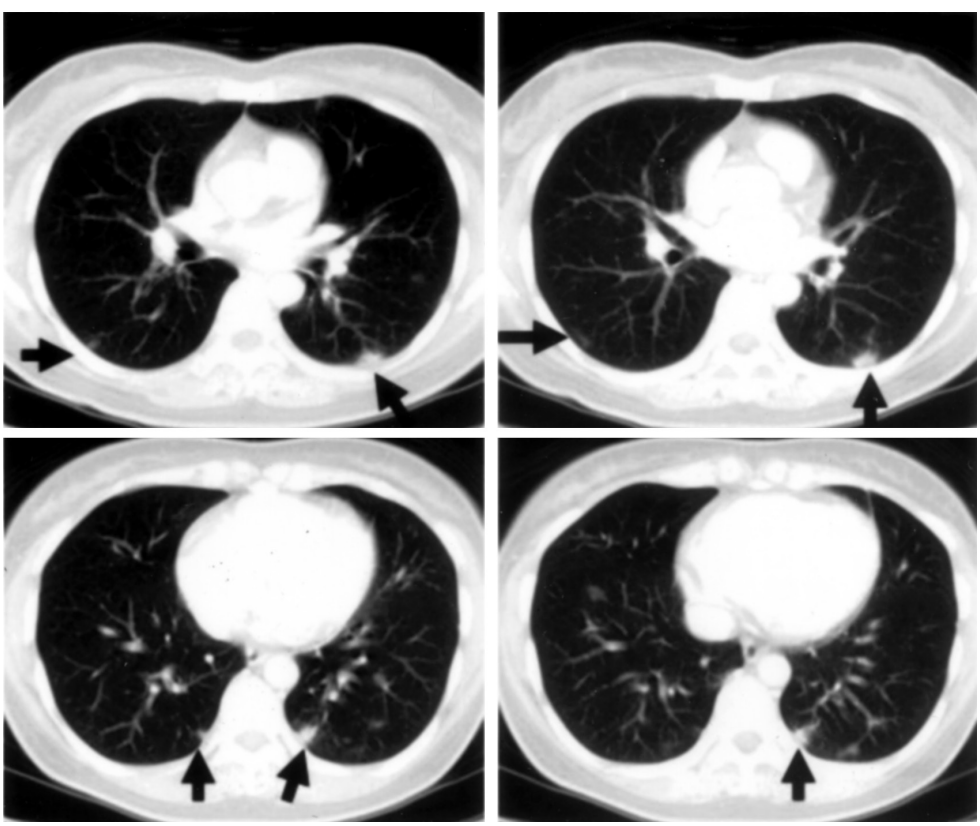
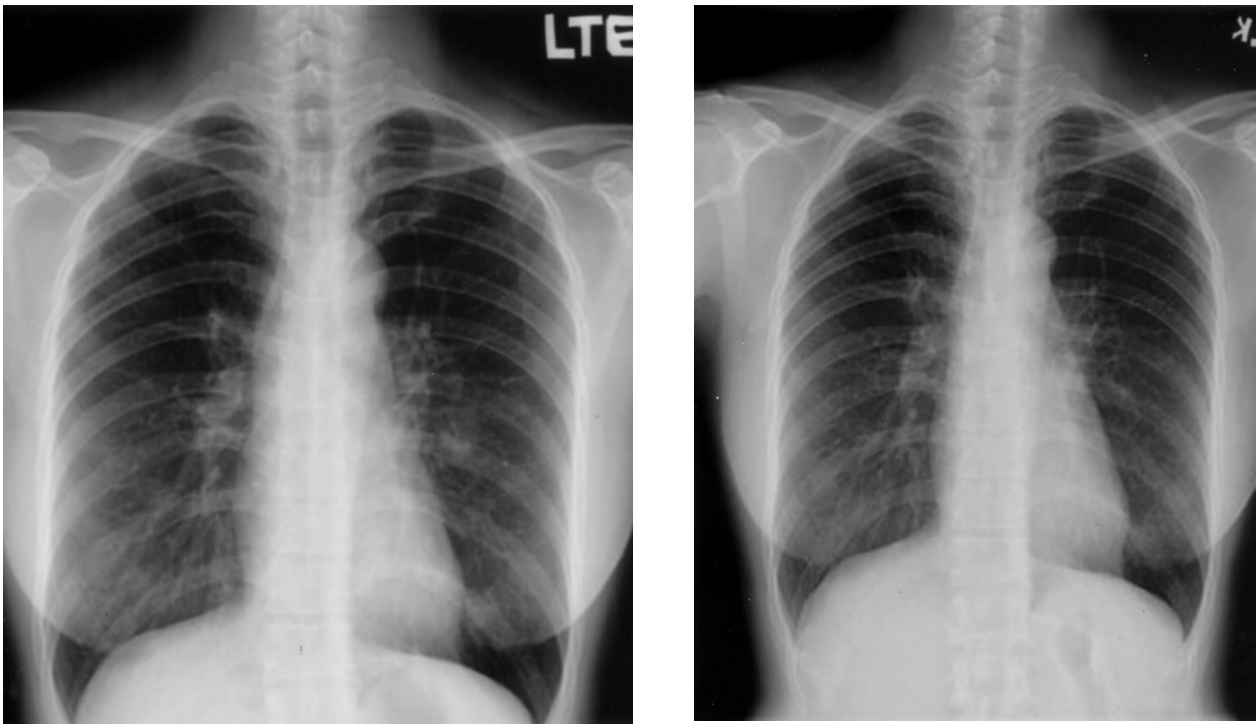


Fig 1. Chest CT revealed some tiny nodules in the LLL and RLL (arrow)

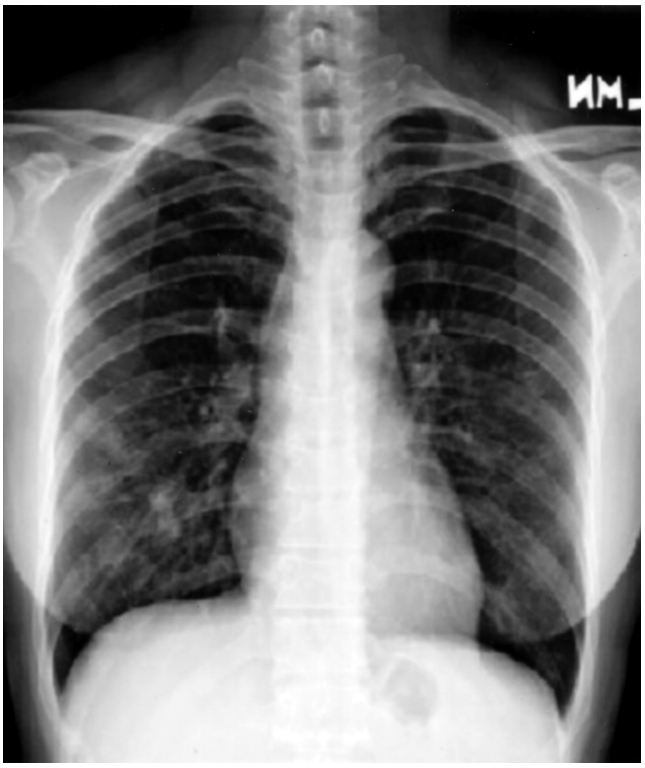


(A) (B)

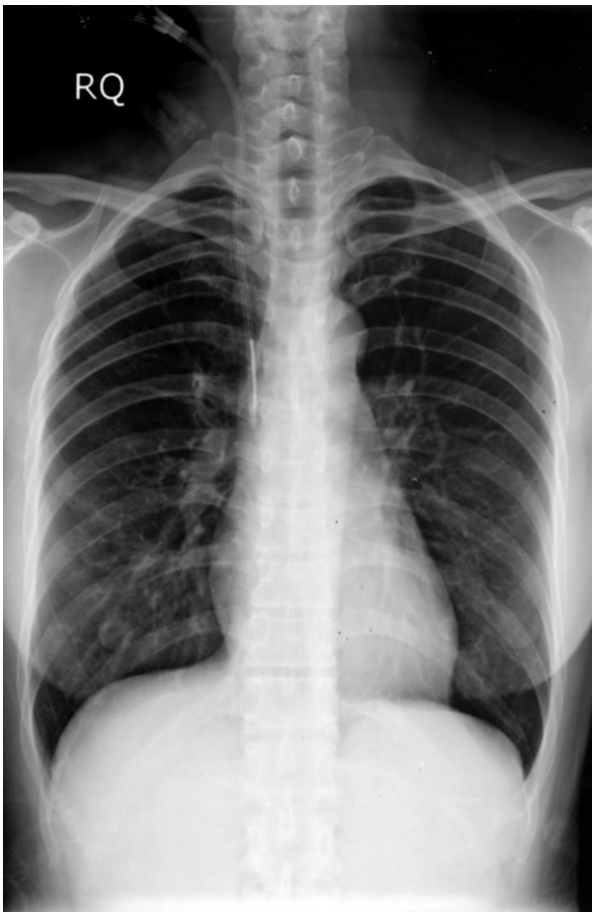
Fig. 2. (A) Some tiny nodules in the LLL; (B) LLL nodules resolved spontaneously 3 months later

history of smoking or hydrocarbon solvent exposure. The sputum was reddish and thick, with an increasing amount in the morning. About 10 days before admission, fever of 38.0-38.2°C began developing especially in the evening, and subsided after the use of antipyretics. The patient went to local clinics for help about 1 week before the present admission, but the symptom persisted. Dyspnea on exertion and mild pain throughout the chest then occurred, so she came to our hospital outpatient department for help. The first CXR showed multiple pulmonary nodules in the bilateral lung fields. Cryptococcal pneumonia and pulmonary tuberculosis (TB) were suspected. Sputum acid-fast stain and serum cryptococcal antigen were checked initially. CXR showed progressive disease 1 week later (Figure 3A), so she was admitted to our section for further evaluation.

Laboratory data showed elevated creatinine of 2.3 mg/dL (normal 0.7-1.4 mg/dL), but no leukocytosis (WBC: 6300/CUMM). Three sets of sputum acid-fast staining were performed and all of them showed negative. Serum cryptococcal antigen showed negative, as well. After admission, the patient complained of foamy urine for several days. The urinalysis showed RBC: (+) and WBC: 5-10 with a granular cast. Hematuria and hemoptysis were present, so we checked the serum anti-neutrophil cytoplasmic antibodies (ANCA) and found ANCA >1:160, anti-GBM (basement membrane antibody) positive, and ANCA (MPO) at 81.5 IU/ml (normal <20 IU/ml). With the clinical impression of pulmonary-renal syndrome, we consulted a nephrologist for renal biopsy. The pathologic find-



(A)



(B)

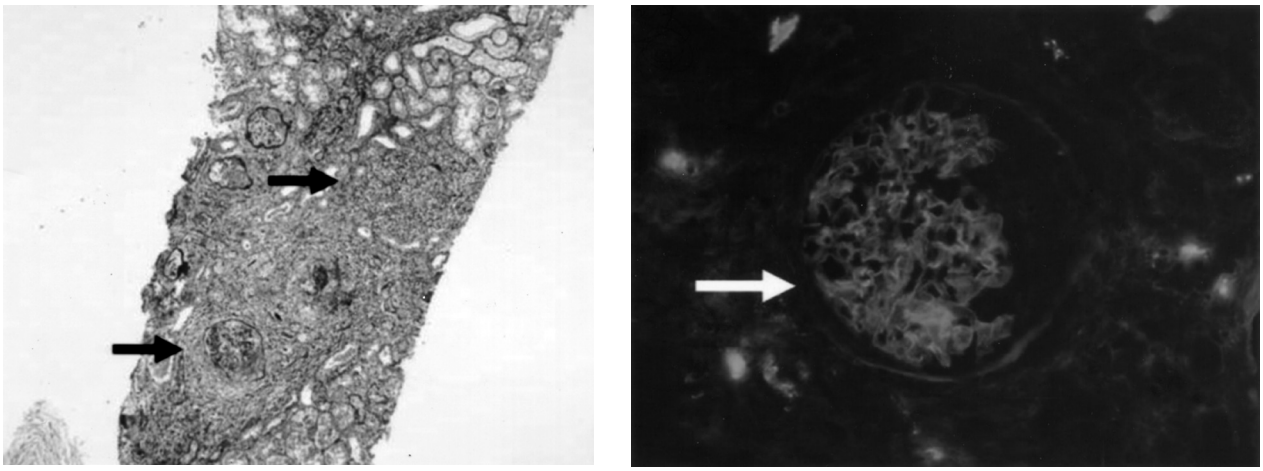
Fig. 3. (A) Multiple nodules in the bilateral lungs; (B) After plasmapheresis and methyprednisolone pulse therapy, the lesion diminished

ing of the biopsy was active crescentic glomerulonephritis, and immunofluorescence showed linear deposition on the basement membrane (Figures 4A, 4B). Goodpasture syndrome with active RPGN (rapid-progressive glomerulonephritis) was diagnosed. Immunosuppressive drugs were administered (dexamethasone 5 mg BID for 1 week, then switched to prednisolone 25 mg QD, plaquenil 200 mg TID for 7 days then tapered to 200 mg BID, and endoxan 50 mg for 2 months). Plasmapheresis was performed 5 times.

After treatment, the patient's creatinine level decreased to 1.6 mg/dL and CXR showed improvement. ANCA (MPO) decreased to 33.2 IU/ml. Follow-up CXR showed the multiple nodules had resolved (Figure 3B). She was subsequently discharged in a stable condition.

Discussion

In this case, we found that Goodpasture syndrome can resolve spontaneously. We know that anti-GBM Ab has been regarded as a pathogenic autoantibody, and that this serum antibody is directed against particular regions of the α3 (IV) chain of collagen IV in the lung and kidney [3]. It may actually be a consequence of T cell-me-



(A) (B)

Fig. 4. (A) Necrotic glomerulus and crescent with PAS stain (100X) (arrow); (B) Immunofluorescence stain (400X) shows immunoglobulin G with linear deposition in the basement membrane (arrow)

diated glomerulonephritis [6]. An animal model revealed a potential tolerance mechanism after autoimmune tissue damage has developed [5]. Early glomerular inflammation may induce resistance to anti-GBM Ab, but the mechanism of action requires further study.

An operational tolerance toward autoantigen can be reestablished. In some cases, autoantibodies disappear spontaneously after 1-3 years [7]. Some recent data have suggested regulatory T lymphocytes can suppress both autoimmune and alloimmune responses. In Goodpasture disease, regulatory CD25+ T cells play a role in inhibiting the autoimmune response. Therefore, it may be helpful to establish a new therapeutic means of inducing hyporesponsiveness in Goodpasture disease [7].

A previous study showed that in many cases of anti-GBM antibody-mediated disease, pulmonary involvement precedes overt renal disease by weeks to years [8]. Pulmonary manifestations appear to occur before renal impairment in most cases. About 82-94% of patients initially presented with hemoptysis, and 50-80% of these patients progressed to develop glomerulonephritis [9]. In our case, the lung manifestation developed 5 years before and renal involvement was noted later. In a case series report, 46% of patients had initial pulmonary involvement with normal serum creatinine. Of these patients, 50% recovered renal function completely, 8% had mild chronic renal insufficiency, and 42% required long-term dialysis or renal transplantation. Overall, renal outcome was excellent in the patients with predominant pulmonary involvement [10]. In our case, the good outcome may be attributed to having the pulmonary manifestation alone at first.

Goodpasture syndrome is a rare autoimmune disease. Due to the low incidence, physicians need to be aware of and able to recognize this disease. In our case, the initial presentation was hemoptysis with abnormal CXR (multiple infiltration with tiny nodules). In Taiwan, there is a moderate incidence of pulmonary TB [11-12]. Pulmonary TB or Cryptococcus is consid-

ered first in Taiwan in cases with hemoptysis with abnormal CXR and intermittent low-grade fever. Goodpasture syndrome should be considered if there is combined renal involvement. In our case, Goodpasture syndrome was diagnosed in out patient when foamy urine and hematuria was noted 5 years after first incidence.

In this case, ANCA was also detected in the serum. Patients with ANCA glomerulonephritis typically present with a broad spectrum of disease activity, from asymptomatic hematuria to rapidly progressive glomerulonephritis [13]. In a prospective study, 70 patients with ANCA glomerulonephritis who were followed up for 2 years had a high rate of hematuria and proteinuria. Of these patients, 24.3% (18/70) needed transient dialysis at onset or during follow-up. Only 4% (3/70) of patients who were followed up for 3 years needed long-term dialysis and 2 of them had pulmonary involvement [14]. In another study, a poor prognosis for renal function was noted in patients who had both anti-GBM and ANCA [15].

In conclusion, Goodpasture syndrome is a rare autoimmune disease which has usually had a poor outcome in the past. Physicians need to pay attention to these patients, especially in the early stage. Lung involvement alone is possible, so we need to be alert for abnormal hemoptysis and multiple nodules on CXR. Spontaneous resolution in Goodpasture syndrome with lung involvement alone is possible, and may be due to self-tolerance of the antibodies. But it is still believed that immunosuppressive drugs or hemofiltration should be administrated as soon as possible. Close follow-up of renal function should be arranged in the later stage of Goodpasture syndrome, due to the high possibility of renal failure.

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自發性緩解的 Goodpasture 症候群於五年後復發：病例報告

戴芳銓　文美卿*　許正園　沈光漢

Goodpasture症候群是一個罕見的自體免疫疾病，在早期這個疾病的預後並不好。而因為這個疾病引起的嚴重腎衰竭很少會恢復，只有早期的發現，才能有較好的預後並避免嚴重的後遺症。但是在少數的病人卻可以看到自發性的恢復。在這個案例，我們可以看到此案例一開始的表現是輕微發燒、慢性咳嗽、咳血以及胸部X光片異常的多處浸潤。但並沒有體重減輕以及夜間盜汗的狀況。這個案例曾在五年前發現過一樣的狀況，並且有被懷疑是肺結核的感染。然而，這次住院中我們有注意到此案例有輕微血尿合併蛋白尿。經過了腎臟切片以及血清抗基底膜抗體（anti-GBM antibody）的檢查，我們確診此個案為Goodpasture症候群。經過立即的免疫抑制藥物以及血漿置換術的處理，此案例的狀況恢復良好並已經在門診追蹤了12個月。*(胸腔醫學* ***2012; 27: 21-28****)*

關鍵詞：Goodpasture症候群，自發性，抗基底膜抗體

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IgG4-Related Sclerosing Disease of the Lung — Case Report

Chih-Heng Kuo, Wen-Hu Hsu, Yi-Chen Yeh*

IgG4-related sclerosing disease is a newly recognized disorder characterized by tissue infiltration of IgG4-positive lymphoplasma cells with or without an elevated serum IgG4 concentration. It was first reported in autoimmune pancreatitis, but may occur in other organ systems, as well.

We report a 47-year-old female patient presenting with an asymptomatic pulmonary nodule. As she refused computed tomography-guided biopsy, and the bronchoscopic cytology report was inconclusive, she underwent surgery under the provisional diagnosis of lung cancer. IgG4-related sclerosing disease of the lung may be easily confused with pulmonary malignancy, and patients often undergo unnecessary surgery. Immunohistochemical staining with the finding of dense IgG4-positive lymphoplasma cell infiltration is essential for the diagnosis. Steroid treatment is usually effective in relieving the symptoms. More study is needed to determine whether steroid treatment is necessary for asymptomatic patients, as in our reported case. ***(Thorac Med 2012; 27: 29-35)***

Key words: IgG4-related sclerosing disease, lymphoplasma cells, pulmonary nodule

Introduction

IgG4-related sclerosing disease is a recently proposed clinical entity characterized by dense infiltration of IgG4-positive plasma cells in involved tissue. IgG4 was initially found to play a role in the pathogenesis and disease activity of autoimmune pancreatitis (AIP). Later, some authors reported that IgG4-related disease may also occur in other organ systems (for example, sclerosing cholangitis, sclerosing cholecystitis, sclerosing sialadenitis, retroperitoneal fibrosis, interstitial nephritis and pulmonary complications.) [1-4].

Pulmonary-related conditions, with or without other organ involvement, may take the form of interstitial lung disease, inflammatory pseudotumor, or lymphomatoid granulomatosis [3,5-6]. Herein, we present a patient with IgG4-related sclerosing disease of the lung mimicking lung cancer on radiographic images.

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Case Report

A 47-year-old woman was found incidentally to have patchy opacity in the left lung field on plain chest X-ray film (Figure 1) during a survey of her newly diagnosed renal cell carcinoma (RCC). She underwent left nephrectomy for her renal malignancy, and pathology reported early-stage RCC. As for the pulmonary lesion, chest computed tomography (CT) showed a speculated nodule in the left upper lobe of the lung with a diameter at the longest point of 2.3 cm (Figure 2). She was suggested to undergo CT-guided biopsy of the lesion, because the possibility of pulmonary malignancy could not be ruled out, but she hesitated.

Follow-up plain chest X-ray film 3 months later showed that the opacity had not regressed. She underwent a bronchoscopic examination to determine the central location of the pulmonary lesion. Bronchoscopy did not show an endobronchial lesion, and brushing cytology performed at the left upper lobe bronchi revealed fibrosis only, with no malignant cells identified. She then came to the surgical outpatient clinic for help. She had no respiratory symptoms, and no fever, chills, weight loss or other complaint was documented. Pulmonary function tests showed that forced expiratory volume in 1 second was 2.46 liters. Normal airway resistance and gas exchange was reported. Tumor markers (CEA, SCC) were checked but not elevated. Whole body F18-deoxyglucose positron emission tomography (FDG PET) showed a mildly increased uptake of FDG at the pulmonary lesion (size: 2.4 cm, SUV max: 2.02) (Figure 3); otherwise, no lymph node spread or distant metastasis was observed.

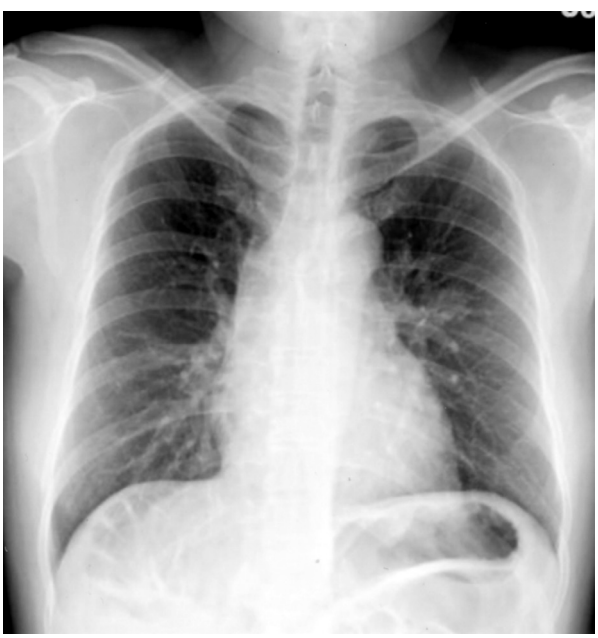

Fig. 1. A ground-glass patchy opacity was located at the left upper lung field, near the left hilum on CXR.

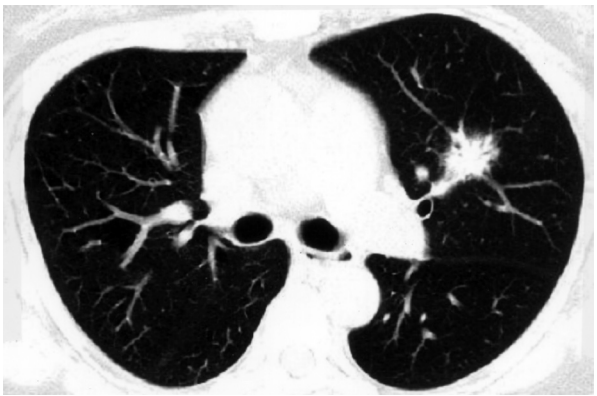

Fig. 2. A spiculated nodule, with minimal air bronchogram, was located centrally at the left upper lobe of the lung on chest CT.

She underwent video-assisted thoracoscopic surgery (VATS) under the provisional diagnosis of lung cancer (4 months after nephrectomy). The lesion was centrally located; wedge resection was attempted but difficult to perform, so left upper lobe lobectomy was performed instead. Under microscopic examination, the nodule showed lymphoplasmacytic cell infiltration intermixed with fibrosis (fibroblast spindle cell proliferation, arranged in a storiform pat-

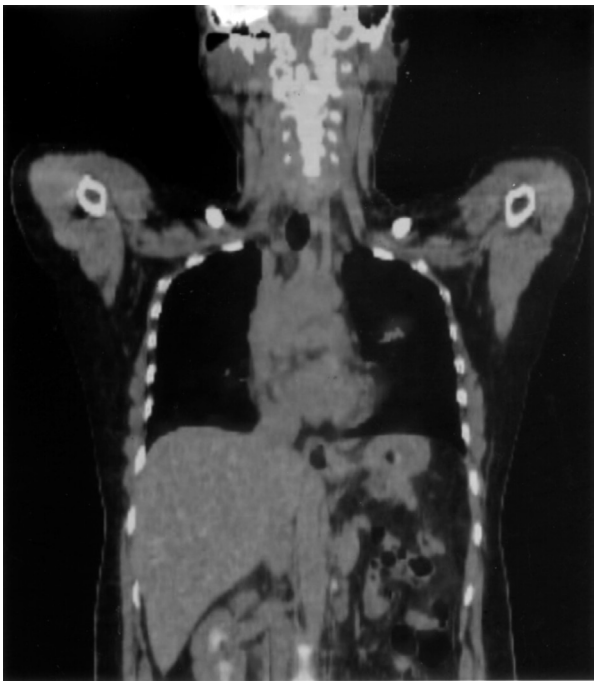

Fig. 3. The lesion on the left upper lobe of the lung showed increased uptake of FDG (SUV max: 2.02) on whole body PET imaging.

tern, histocyte aggregates) and inflammatory cell infiltration (Figure 4). Obliterative phlebitis could also be seen. Special staining showed that the lymphoplasmacytic cells were positive for IgG and IgG4 stains. The Masson's and elastin stains showed increased fibrosis and elastin fibers scattered diffusely throughout the pulmonary nodule. The pathology was compatible with IgG4-related sclerosing disease of the lung.

Serum levels of IgG and IgG4 were checked postoperatively, but were not elevated (IgG: 1140 mg/dl [reference level: 751-1560 mg/dl]; IgG4: 43.2 mg/dl [reference level: 3.9-86.4 mg/dl]). The follow-up chest CT and clinical symptoms were all stable up to 1 year postoperatively (the date of this submission).

Discussion

IgG4 is the rarest of 4 IgG subclasses, and accounts for only 3 to 6% of the total serum IgG concentration. High serum IgG4 levels have been described in a few clinical conditions such as atopic dermatitis, parasitic infestation, pemphigus vulgaris and foliaceus [6].

Yoshida *et al*. first proposed AIP, a condition different from other pancreatic inflammatory diseases or masses, in that serum IgG4 levels are frequently elevated in these patients [18], and a dense infiltration of IgG4-positive plasma cells in the involved pancreas is characteristic. However, this kind of tissue infiltration by IgG4-positive plasma cells is not restricted to the pancreas. Follow-up studies showed this kind of tissue infiltration may occur in a variety of organ systems, and the concept of IgG4-related sclerosing disease as an immunopathologic process with possible multiorgan involvement gradually emerged [9-10]. Some authors have postulated that a possible relationship between this disease and other immunopathologic conditions, such as Sjögren's syndrome, may exist; however, there is as yet no clear evidence [11].

Pulmonary diseases related to IgG4 sclerosing disease have attracted attention recently. They may have various patterns on chest imaging (for example, interstitial pneumonia, consolidative change with air bronchogram, hilar or mediastinal lymph node enlargement, ground-glass opacity or honeycomb lesions). Due to its rare occurrence, the incidence rate of IgG4 sclerosing disease or even that of AIP is unknown. No review series has mentioned the total case number of both conditions as reported in the literature. However, Hirano and associates reported that of 30 patients with AIP, 4 developed IgG4-positive interstitial lung lesions

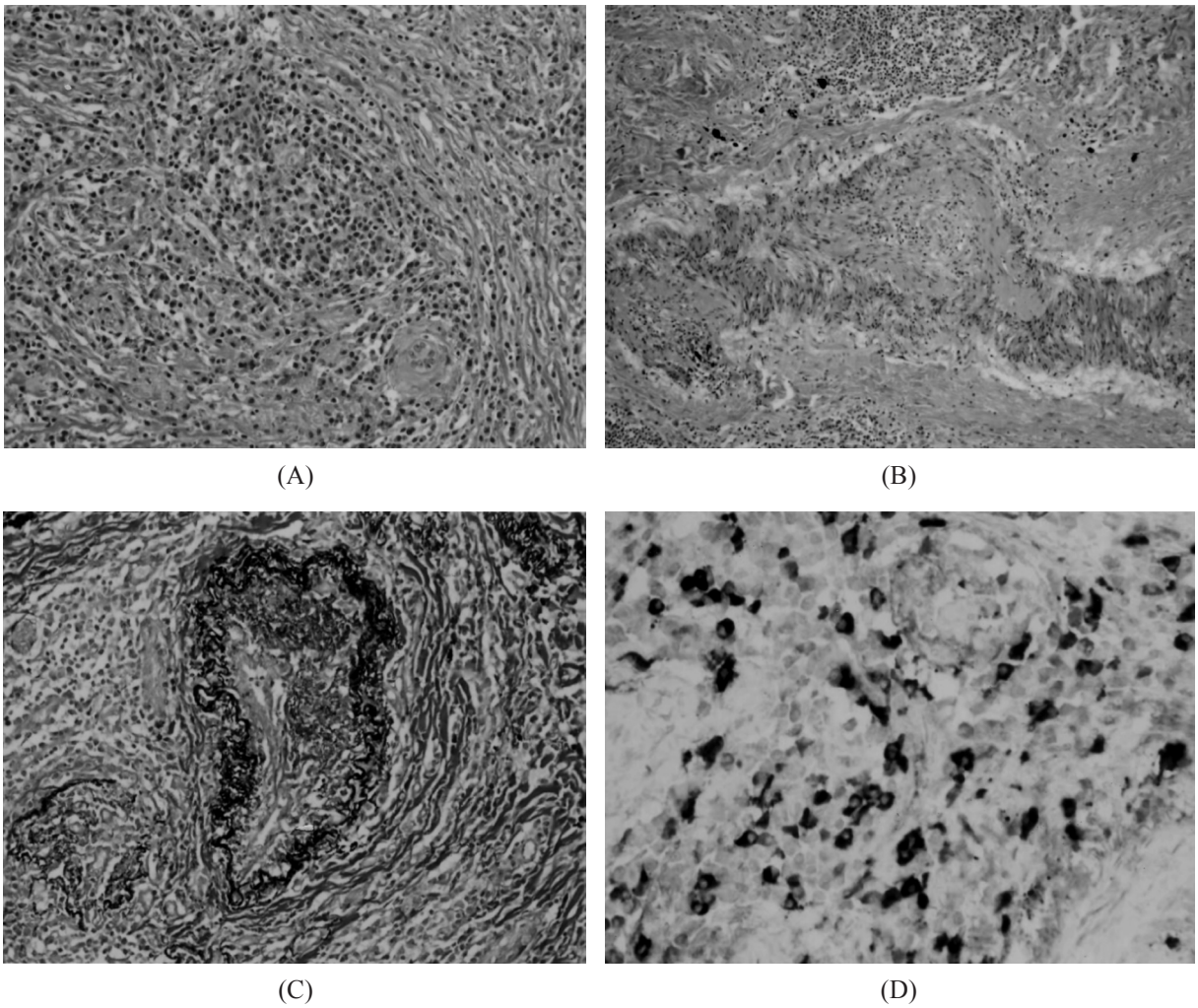

Fig. 4. (A) and (B) showed increased fibroblast proliferation, arranged in a storiform pattern on H & E stain; (C) Sclerotic vasculitis was observed on Masson's elastin stain; (D) IgG4-positive lymphoplasma cell in filtration can be confirmed by IgG4 special staining.

[8]. The respiratory presentation may range from asymptomatic to severe respiratory failure [3,7,10-11]. We reported a patient with IgG4-related sclerosing disease occurring in the lung, and her chest CT images showed a spiculated nodule mimicking lung cancer.

The histological hallmark of IgG4-related sclerosing disease is a dense infiltration of IgG4-positive lymphoplasmacytic cells, accompanied with fibrosis and vasculitis (phlebitis, usually) [6]. In patients with AIP, the pancreas showed swelling, and diffuse stricture of the pancreatic ducts may also be found. In patients with pulmonary involvement, air space consolidation spreading along the bronchovascular bundle, and septal wall thickening or honeycomb changes may be found [8-9]. Some authors suggested the serum IgG/IgG4 concentration may aid in the diagnosis of IgG4-related sclerosing disease; however, positive IgG4 special staining on the lymphoplasmacytic cells alone suffice for the diagnosis [14-15].

In our patient, bronchoscopy with brushing cytology showed fibrosis only, further underscoring the importance of a larger specimen to confirm this disease on histology. CT-guided biopsy or VATS biopsy may provide a larger sample, if the lesion is located at the peripheral zone of the lung [10]. Some authors have suggested that the IgG4 concentration in bronchoalveolar lavage (BAL) may be elevated and help in the diagnosis. Tsushima and associates reported the BAL IgG4 level increased significantly in AIP. Compared with pulmonary sarcoidosis (p<0.01). The BAL IgG4 level was also found to correlate with the serum IgG4 level (p=0.49) [3]. Few reports have mentioned the role of PDG PET imaging in the detection of IgG4 lesions. Hamed and colleagues reported a patient with a multifocal systemic manifestation of IgG4-related sclerosing disease. Hotspots were observed in the submandibular gland, lung, mediastinum and prostate on PET imaging [2]. Out patient's pulmonary lesion was weakly positive on PET imaging. Whether this modality alone or in combination with other examinations, can help identify IgG4 sclerosing lesions requires more study for confirmation.

The patient we reported herein had previous RCC. We conducted exhaustive review of the related literature and could not find a link between IgG4-related sclerosing disease and RCC. However, IgG4-related sclerosing disease manifested as interstitial nephritis has been reported [16].

Corticosteroid is usually effective in relieving respiratory symptoms. Tapering of the dose of steroid may cause symptoms to recur [6,8,10]. Zen *et al* reported the expression of Th2 cytokines and other cytokines was increased in the involved tissue in patients with IgG4-related sclerosing disease [6], so one may postulate that the effectiveness of corticosteroid may lie in the homeostasis of T lymphocytes. Though previous authors have proposed immunogenic or allergic links, these have not yet been proven. Our patient had no symptoms and we did not provide steroid treatment for her in addition to regular follow-up. This strategy has kept her asymptomatic for at least 1 year after operation (till the date of this submission). In conclusion, IgG4-related sclerosing disease is a newly established clinical entity; more investigations are necessary to elucidate its nature and clinical implications.

Acknowledgement

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IgG4 相關之硬化症在肺之表現—病例報告

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IgG4相關之硬化症為一近來發現之病症，特徵是組織中廣泛浸潤許多IgG4染色呈陽性的淋巴漿細胞，可能伴隨血清中IgG4濃度昇高。此病首先在自體免疫胰臟炎的病人上報告過，但其他器官也有可能發生。

我們報告了一位47歲女性，在治療左側腎細胞癌時，意外發現了左上肺結節病灶。由於病人拒絕接受斷層掃描導引之肺穿刺檢查，且支氣管鏡細胞學檢查無具體結果，後來在初步診斷為肺癌下進行肺切除手術。臨床上易誤認為肺惡性腫瘤而接受不必要的手術。在免疫組織化學染色下，IgG4染色呈陽性的淋巴漿細胞廣泛的浸潤是診斷的必要條件。類固醇治療通常有效，可以緩解症狀。至於無症狀病人（如我們報告的病例）是否仍需要類固醇治療，則需更多研究。*(胸腔醫學 **2012; 27: 29-35**)*

關鍵詞：IgG4相關之硬化症，淋巴漿細胞，肺結節

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Wegener's Granulomatosis with Tracheal Involvement and Severe Pulmonary Hemorrhage

Hui-Wen Shih*, Hou-Tai Chang, Cheng-Yu Chang, Shin-Lung Cheng

Wegener's granulomatosis (WG) is a systemic autoimmune vasculitis of small-to-medium-sized vessels. It mainly involves the upper and lower respiratory tracts, the kidneys, skin, and eyes. It can occur at any age and affects both sexes equally. Diffuse pulmonary hemorrhage is an unusual manifestation. Once this occurs, the respiratory condition can deteriorate rapidly, leading to respiratory failure. Early diagnosis and early use of immunosuppressive agents are the main means of managing it. We describe a case of newly diagnosed WG that presented with tracheal involvement and pulmonary hemorrhage. In spite of standard combination therapy with cyclophosphamide and pulse methylprednisolone, the patient still passed away due to severe pulmonary hemorrhage leading to hypoxia and multi-organ failure. ***(Thorac Med 2012; 27: 36-42)***

Key words: Wegener's granulomatosis, pulmonary hemorrhage

Introduction

Wegener's granulomatosis is a systemic autoimmune vasculitis of small-to-medium-sized vessels. It mainly involves the upper and lower respiratory tracts, the kidneys, skin, and eyes. WG can occur at any age and affects both sexes equally. The effects of WG on the subglottis and trachea frequently results in stenosis. Subglottic and tracheal stenosis can lead to respiratory failure or obstructive pneumonitis and is life-threatening. Diffuse pulmonary hemorrhage is an unusual manifestation which incidence was ranged from 7% to 45%. Although once this occurs, the respiratory condition can deteriorate rapidly, leading to respiratory failure. Early diagnosis and the immediate use of immunosuppressive agents can decrease the severity of the disease if a WG patient has pulmonary hemorrhage.

Case Report

A 50-year-old man had suffered from productive cough and hemoptysis for 1 week. Prior to this, he had no fever, chills, or dyspnea. On the first day of admission, his body temperature was 36^{o}C, respiratory rate was 18 breaths per minute, and blood pressure was 134/59 mmHg; his consciousness was clear. No deformity of

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the ears, rhinorrhea, nasal discharge or oral ulcers was found in an ear, nose, and throat examination. There was a patch graft on the nasal side of the bulbar conjunctiva of the right eye. Chest examination revealed crackles in the right lung fields. He had multiple reddish skin ulcerations on both lower legs. According to his medical records, he had received a scleral patch graft with amniotic membrane transplantation in the right eye 1 month before because of scleritis with scleral perforation.

Chest radiography revealed right lower lobe consolidation (Figure 1A). His hemogram and biochemistries were within normal limits. Urinary sediment showed: pH 6.0; 2+ protein; 3+ occult blood; RBC's at 3-5/HPF; WBC's at 3-5/HPF; epithelial cells at 1-3/HFP. He took oral levofloxacin (500 mg per day) for 1 week, but his disease progressed (Figure 1B).

Because of persistent hemoptysis, at bronchoscopy examination was arranged which disclosed endotracheal and endobronchial granulation tissues (Figure 2). Some fresh blood and blood clots were also noted in the right upper bronchus region. A chest computed tomography (CT) scan was performed because of progressive right lung consolidation disclosed multiple cavitary nodules with ground-glass opacities (Figure 3). The pathology of an endobronchial biopsy showed ulcer formation with necrotic debris and granulation tissue formation. A sputum acid fast stain was negative. His serum c-ANCA level (125 u/ml) was higher than the upper limit (<7.00 u/ml). Bilateral sensorineural hearing loss and chronic otits externa were noted after otolaryngologic consultation. Also, his lower leg skin lesions (Figure 4) were biopsied and leukoclastic vasculitis was reported (Figure 5). Wegener's granulomatosis (WG) was highly suspected based on imaging findings, pathology results, and autoimmune profiles.

The patient received a combination of pulse therapy (methylprednisolone at 1000 mg per day; total of 3000 mg) and cyclophosphamide (1000 mg per day). However, the pulmonary hemorrhage deteriorated and he required me-

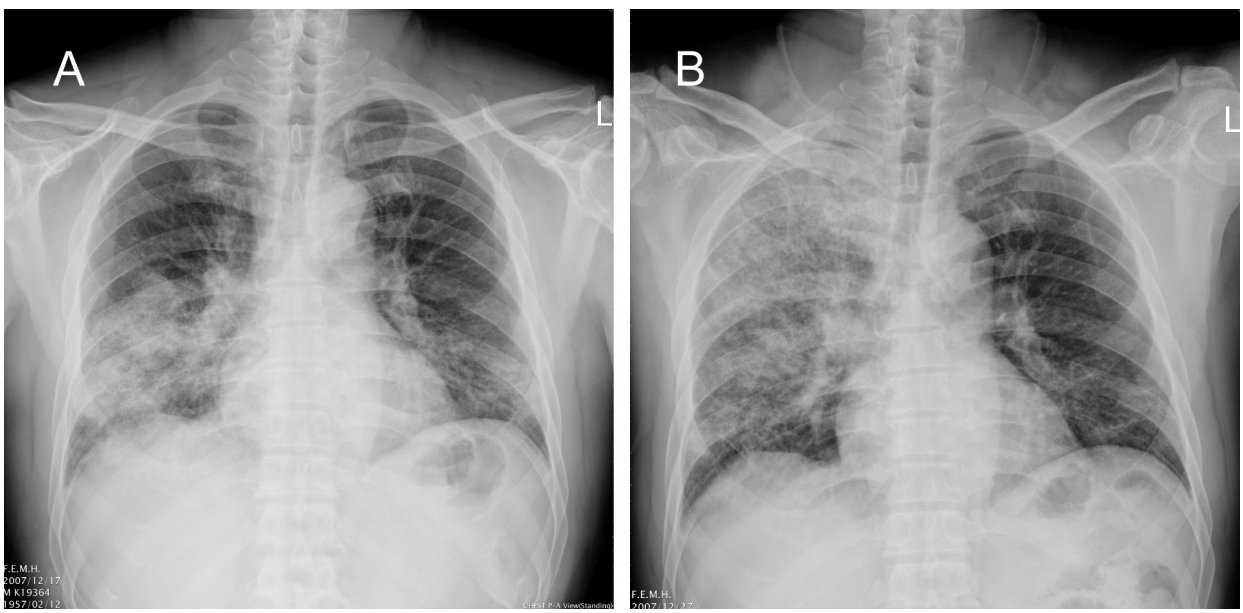

Fig. 1. (A) Chest radiography reveals right lower lung consolidation. (B) Chest radiography showed progressing consolidation after 1 week.

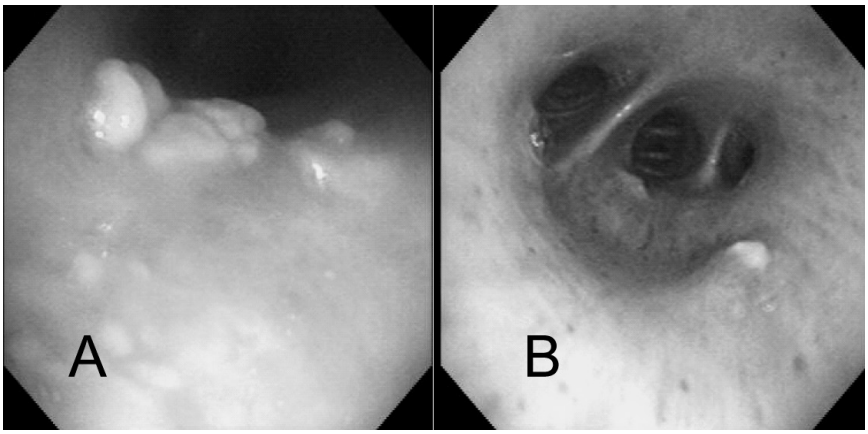

Fig. 2. Bronchoscopy showing endobronchial granulation tissues in the trachea and bilateral main bronchus.

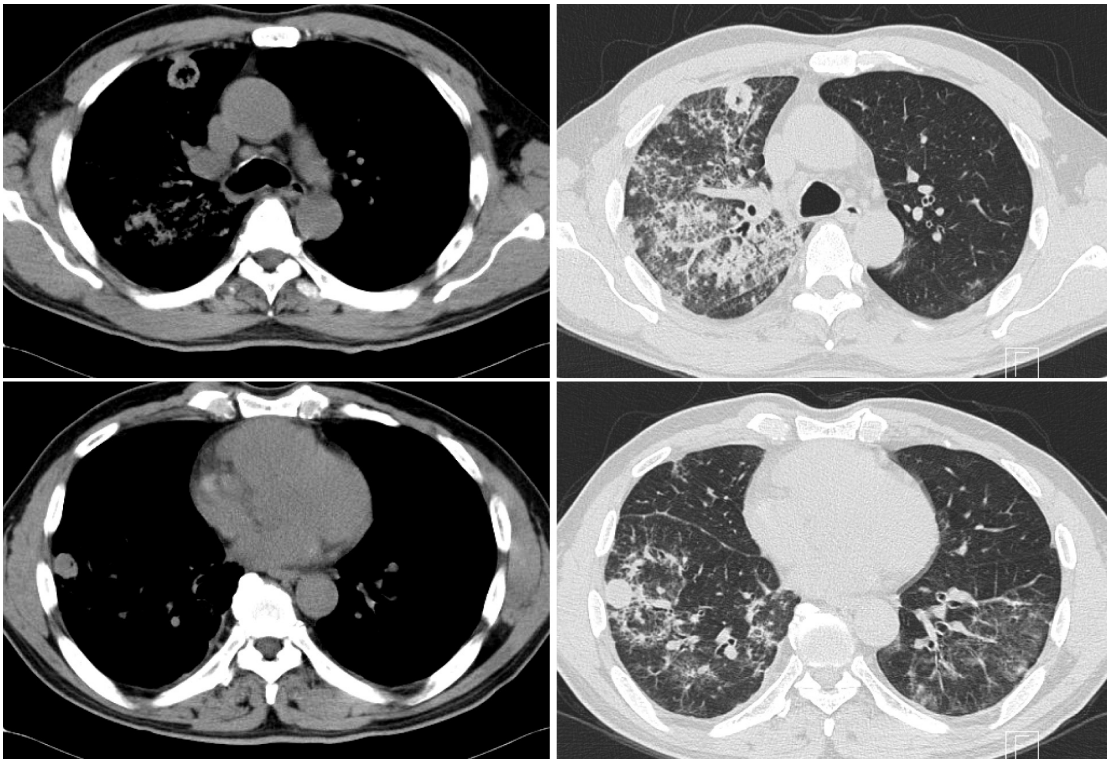

Fig. 3. Chest computed tomography showing multiple cavitary nodules with ground-glass opacities in the right lung zones.

chanical ventilation. While in the intensive care unit, the diffuse pulmonary hemorrhage led to severe hypoxia and multi-organ dysfunction. One week later, he passed away due to multi-organ failure.

Discussion

WG is a systemic autoimmune vasculitis of small-to-medium-sized vessels. It mainly involves the upper and lower respiratory tracts,

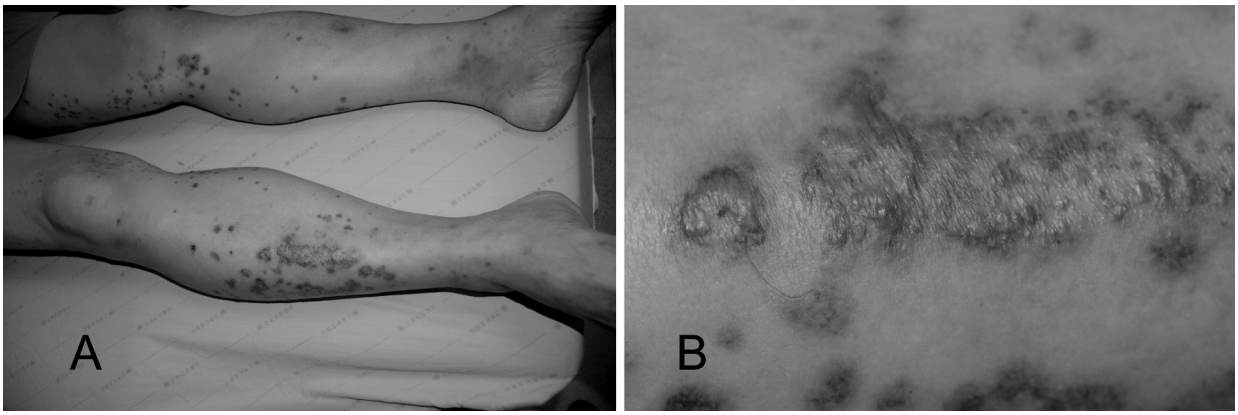

Fig. 4. Multiple dark-red to violaceous non-blanchable palpable papuloplaques are noted on the extremities.

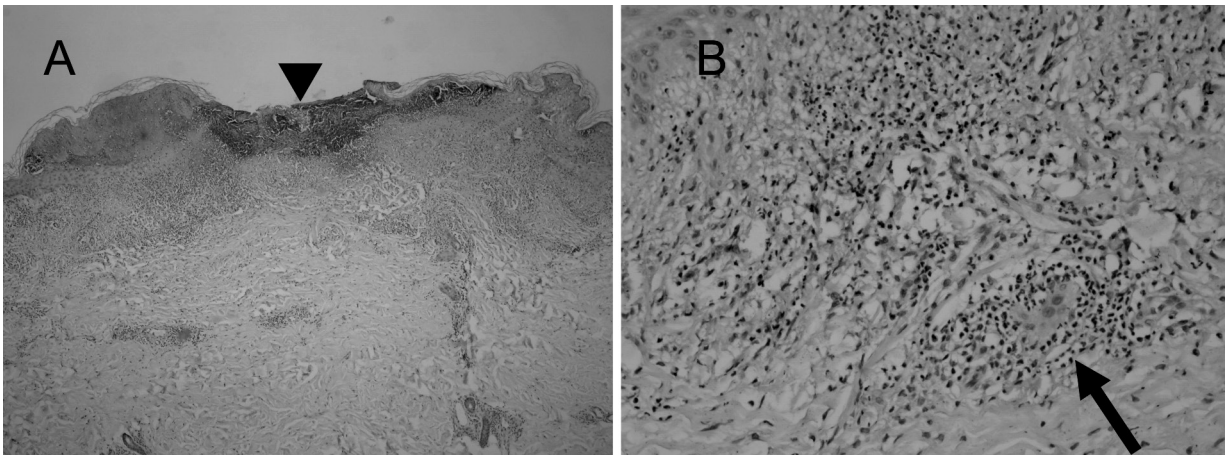

Fig. 5. (A) Skin biopsy showing surface ulceration with crust formation (triangle). (B) Leukocytoclastic vasculitis (arrow).

the kidneys, skin, and eyes. The most common symptoms include persistent rhinorrhea, purulent or bloody nasal discharge, oral or nasal ulcers, dyspnea, cough, and hemoptysis. Other symptoms and signs of affected organs include glomerulonephritis, conjunctivitis, scleritis, skin ulcers, subcutaneous nodules, pericarditis, arthritis, and others [1]. WG can occur at any age and affects both sexes equally [2].

Most of the clinical manifestations of WG are similar regardless of whether onset occurs in childhood or adult. Nevertheless, childhood-onset patients are 5 times more likely to be complicated by subglottis and tracheal stenosis and twice as likely to have a nasal deformity [3]. The effects of WG on the subglottis and trachea frequently results in stenosis. Subglottic and tracheal stenosis can lead to respiratory failure or obstructive pneumonitis and is life-threatening [4-5]. Subglottic stenosis is found in 10% to 20% of WG patients [6]. Pulmonary symptoms develop in about 85% of WG patients [7]. Diffuse pulmonary hemorrhage is an unusual manifestation, although once this occurs, the respiratory condition can deteriorate rapidly, leading to respiratory failure [8]. The

incidence of diffuse pulmonary hemorrhage in WG patients has ranged from 7% to 45%; there was 60% mortality rate with diffuse pulmonary hemorrhage [9]. WG is the most common reason for airway protection and intensive care [10]. In previous reports, lung biopsy of WG patients with pulmonary hemorrhage revealed necrotizing capillaritis [8,11].

The 4 criteria of the American College of Rheumatology for the diagnosis of WG are: (1) abnormal urinary sediment (red cell casts or >5 red blood cells per high-power field); (2) abnormal findings on chest radiograph (nodules, cavities, or fixed infiltrates); (3) oral ulcers or nasal discharge; and (4) granulomatous inflammation on biopsy. The presence of at least 2 of these 4 criteria is associated with a sensitivity of 88.2% and a specificity of 92.0% [12]. A positive cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) is present in 90-95% of active and systemic disease cases and can assist in the diagnosis. However, in limited diseases, positive c-ANCA is seen in only 60-65% of cases [2].

The first step in managing WG is to classify the disease activity. Various systems are used to assess disease activity. The Birmingham Vasculitis Activity Score (BVAS) has been commonly applied with WG patients. BVAS/WG consists of both general symptoms (arthralgia, arthritis, and fever) and the involvement of 8 major organ systems (cutaneous, ear, nose, throat, cardiovascular, gastrointestinal, pulmonary, and renal).

For each site, persistent symptoms or manifestations are given 1 point and new or worsened symptoms are given 2 points. There are 4 possible disease statuses: (1) severe disease/flare (occurrence of any new/worse major item); (2) limited disease/flare (occurrence of any new/worse minor item); (3) persistent disease (presence of ≥1 item representing active disease that has continued since the patient's previous evaluation); and (4) remission (no active disease; either new/worse or persistent items) [13].

The standard therapy for WG is a combination of a glucosteroid and cyclophosphamide. With this combination therapy, the prognosis of WG is remarkably good. More than 90% of patients have marked improvements and about 75% can achieve a complete remission [1]. In addition, some reports have mentioned that prompt plasma exchange [14-15] or double filtration plasmapheresis [16] can improve the pulmonary status. In WG patients, bronchoalveolar lavage with diluted surfactant may be able to treat pulmonary hemorrhage successfully [17]. In conclusion, early diagnosis and the immediate use of immunosuppressive agents can decrease the severity of the disease if a WG patient has pulmonary hemorrhage [18].

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韋格納肉芽腫併發氣管侵犯及嚴重肺出血

施惠雯* 張厚台 張晟瑜 鄭世隆

格納肉芽腫（Wegener's Granulomatosis）是一種壞死型肉芽腫性血管炎，病變主要在小動脈、靜脈及毛細血管，侵犯的器官包含上、下呼吸道，腎臟，眼睛和皮膚。如侵犯氣管，會在氣管內膜形成疤痕組織造成呼吸道狹窄，輕者成阻塞性肺炎，重者則導致呼吸衰竭。合併呼吸道侵犯的韋格納肉芽腫較少併發嚴重肺出血，可是一旦發生，則可能導致立即地呼吸困難和呼吸衰竭。本文報告一例韋格納肉芽腫合併氣管侵犯及嚴重肺出血個案。*(胸腔醫學* ***2012; 27: 36-42)***

關鍵詞：韋格納肉芽腫，肺出血

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Late Onset Non-Infectious Interstitial Lung Disease Following Bone Marrow Transplantation: A Case Report

Mei-Ling Chen, Yung-Hsiang Hsu*, En-Ting Chang**

Late-onset non-infectious pulmonary complications (LONIPCs) occurring more than 3 months after allogeneic stem cell transplantation (allo-SCT) have become recognized as life-threatening complications that reduce the recipient's quality of life. Bronchiolitis obliterans (BO) and bronchiolitis obliterans with organizing pneumonia (BOOP) are most commonly reported. CT-guided transthoracic biopsy has a high diagnostic yield (56-70%) in post-transplant patients with focal, nodular, and peripheral pulmonary lesions with platelet counts above 30 × 10^9/L and good cooperation. The treatment response of LONIPCs to immunosuppressive agents varies. We reported a 35-year-old male who received bone marrow transplantation 21 months previously for relapse of acute lymphoblastic lymphoma, and who had had dry cough for 4 months. The diagnosis of lymphocytic interstitial pneumonia (LIP), a rare presentation of LONIPCs, was made after CT-guided biopsy. The patient responded well to steroid treatment. ***(Thorac Med 2012; 27: 43-48)***

Key words: late-onset noninfectious pulmonary complications (LONIPCs), hematopoietic stem cell transplantation, lymphocytic interstitial pneumonia

Introduction

Hematopoietic stem cell transplantation (HSCT) is potentially curative therapy that has become the standard of care for many hematologic malignancies. But infections, graft-versus-host disease (GVHD), and liver, kidney, and pulmonary complications have been associated with high mortality after allogeneic HSCT [1]. Pulmonary complications developed in 40-60% of recipients, causing 10-40% of transplant-related deaths [2].

The spectrum of pulmonary complications includes infectious and non-infectious conditions which are further classified as early or late onset, depending on whether they occur before or after 100 days post-transplantation. The term "late-onset non-infectious pulmonary complications" (LONIPCs) has been used to refer to events occurring more than 3 months after allogeneic HSCT, and was first reported by Palmas *et al*. in 1998 [3]. But the pathogenesis

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of LONIPCs is still unclear at present. The categorization of LONIPCs has not been defined clearly. Bronchiolitis obliterans (BO) and bronchiolitis obliterans with organizing pneumonia (BOOP) are reported most commonly [3-4].

We present a patient that developed very late-onset lymphocytic interstitial pneumonia (LIP), which is a rare presentation of LONIPCs, following HSCT.

Case Presentation

A 37-year-old male patient who received bone marrow transplantation 21 months previously for relapsing pre-B cell acute lymphoblastic lymphoma (ALL) was admitted due to dry cough for 4 months.

His pre-B cell ALL was diagnosed 10 years ago. It was treated using the GMALL (German Multicenter Study Group for Adult ALL) protocol and the patient achieved complete remission. His lymphoma then relapsed 2 years ago. He underwent allogeneic bone marrow transplantation 21 months previously, and complications such as acute GVHD of the duodenum, colon and skin, and cytomegalovirus (CMV) viremia developed. He was followed regularly and treated with tacrolimus and prophylactic Baktar (sulfamethoxazole and trimethoprim). Chronic GVHD of the oral mucosa also developed 4 months after transplantation.

Four months before this admission, he complained of dry cough which progressed with left-side pleuritic chest pain. A chest roentgenogram showed interstitial infiltrations in the bilateral middle lobes (Figure 1). Surveys for bacterial, viral or tuberculosis infection and autoimmune disease were all negative. His response to Baktar and antitussive therapy was poor. The pulmonary function test showed obstructive

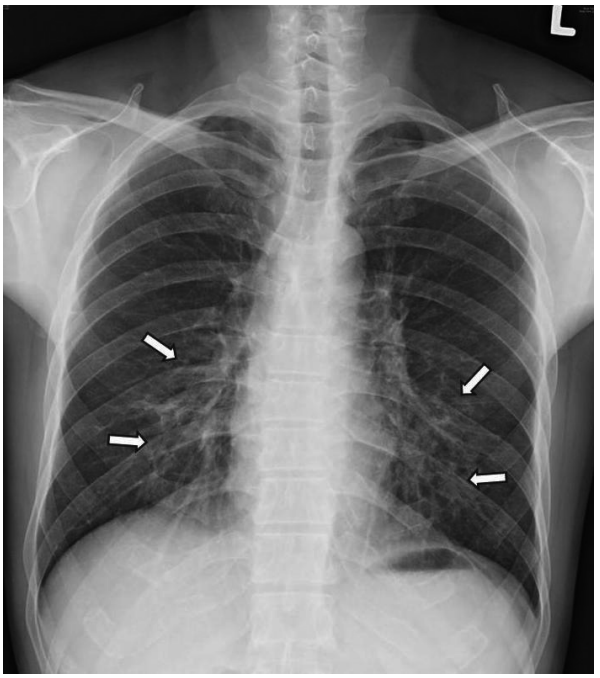

Fig. 1. Chest film shows interstitial infiltration in the bilateral middle lung fields

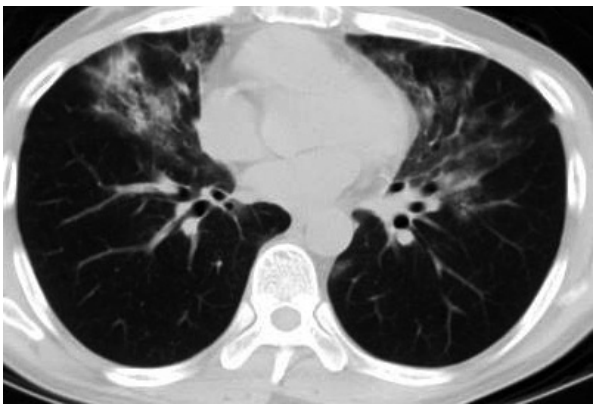

Fig. 2. Chest computed-tomography (CT) revealed ground glass attenuation at the bilateral middle lung fields with consolidation and subpleural fibrosis

lung disease. Chest computed tomography (CT) revealed ground glass attenuation at the bilateral middle lung fields with consolidation and subpleural fibrosis (Figure 2). A CT-guided lung biopsy disclosed a CD3 (+) lymphocyte infiltration in the interstitium. Lymphocytic intersti-

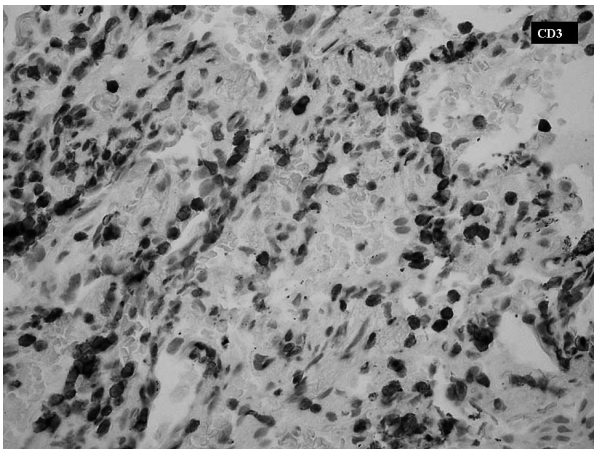

Fig. 3. Immunohistochemistry stain shows CD3-positive lymphocyte infiltration in the lung interstitium (CD3 X 400).

tial pneumonia was then diagnosed (Figure 3). There was no evidence of CMV, *Pneumocystis jirovecii* pneumonia or mycobacterium infection, nor evidence of leukemic relapse. These symptoms are strongly associated with chronic GVHD and are defined as "LONIPCs after stem cell transplantation." The patient was treated with oral prednisolone with an initial dose of 1 mg/kg daily, with symptomatic and radiological improvement.

Discussion

Determining the etiology of new onset pulmonary infiltrations following bone marrow transplantation is very difficult, especially when the infiltrations occur late. LONIPCs is a new disease entity that includes late pulmonary complications in a unique group of patients after HSCT that do not result from an infectious process or relapse of a pre-existing malignancy, as determined by an extensive survey [2-5]. In the present case, the diagnosis of LONIPCs was mainly based on the CT-guided lung biopsy, which is critical in the accurate diagnosis of this disease. The CD3 (+) lymphocyte infiltration in the interstitium, with a negative viral inclusion body and acid-fast stain and an absence of leukemic cell and fibrosis infiltration, indicated a chronic inflammatory process without a causative agent. The microbiological surveys through serological study of CMV, HSV (herpes simplex virus), and mycoplasma, chlamydia, sputum culture of bacteria, mycobacterium, fungus and *Pneumocystis jirovecii* were all negative. These characteristics all meet the diagnosis of LONIPCs.

The incidence of LONIPCs varies widely, ranging between 10% and 26%. BO accounts for the majority of LONIPCs, and LIP is rarely reported [3,5]. Median time for LONIPCs development is about 8-12 months after HSCT, mostly within 1 year. In a literature review, the longest duration until diagnosis of LONIPCs was 1639 days after HSCT and 567 days specifically for lymphocytic pneumonia [3]. In the present case, the duration from HSCT to the diagnosis of LONIPCs was 21 months (722 days), which is longer than in most reported cases. Clinical symptoms are usually insidious at the beginning, as in our patient. Shortness of breath, dyspnea on exertion, cough, long-lasting fever, wheezing, and recurrent pulmonary infections were all reported as alarm symptoms and signs for LONIPCs [5]. Unfortunately, they are not specific and can be present in different type of infections. Therefore, the diagnosis is made on the basis of thoracic high-resolution CT and confirmed by lung biopsy [2,6-7].

The diagnostic approach to the evaluation of a bone marrow recipient with respiratory symptoms and/or pulmonary infiltrates is different from that of a normal host. The patient's condition can deteriorate rapidly, and therefore, invasive procedures are imperative. High-

resolution CT is more sensitive and specific than chest X-ray, and establishes the location and extent of the pulmonary process [2]. The chest CT findings in patients with LONIPCs included ground-glass opacities with or without pleural effusion, and regions of consolidation that could mimic an infectious process. Therefore, the diagnosis of LONIPCs based on clinical criteria may be misleading. The diagnostic yield of bronchoalveolar lavage (BAL) of pulmonary complications accompanying HSCT ranged from 22-55% [6]. The most common pulmonary complications diagnosed by BAL were bacterial pneumonia and diffuse alveolar hemorrhage [8]. Therefore, the role of BAL in LONIPCs is mainly to exclude infectious complications. In fact, Sharm *et al*. observed that only 20% of non-infectious pulmonary complications diagnosed by autopsies in HSCT recipients were recognized and correctly treated antemortem [2,9]. For this reason, biopsy should be performed. Among the different methods used to perform lung biopsy, transbronchial biopsy was reported to be scarcely useful, since it provided a specific diagnosis in less than 20% of patients [10]. Surgical open lung biopsy was the "gold standard" in the diagnosis of pulmonary infiltrations following HSCT, but it is too invasive. CT-guided transthoracic biopsy has a high diagnostic yield (56-70%) in cases of focal, nodular, and peripheral pulmonary lesions with platelet counts above 30×10^9/L and with good cooperation from the patients [6]. The pulmonary infiltrations in our patient were focal with a region of consolidation peripherally, so he was a good candidate for CT-guided biopsy. The complication of CT-guided biopsy is pneumothorax, with an incidence ranging from 15-20%; 6% of cases require chest tube placement. Hemoptysis occurred in 3-5% of cases [6].

Pulmonary function tests are used to characterize non-infectious pulmonary complications after HSCT. An obstructive pattern occurs mostly in obliterative bronchiolitis (OB) and a restrictive pattern could result from thoracic radiation, cytotoxic chemotherapy, pulmonary edema, and in BOOP [11]. Therefore, post-transplant PFT (pulmonary function test) are not generally considered specific, but their role in predicting the development of LONIPCs and mortality due to respiratory insufficiency were highly acceptable [6]. The administration of anti-thymocyte globulin before unrelated donor transplants and slow tapering of cyclosporine after transplant have been shown to prevent chronic GVHD and, therefore, the occurrence of LONIPCs [5].

The reported risk factors for LONIPCs were total body irradiation and the high doses of drugs used in the conditioning regimens, HLA disparity between donor and recipient, and chronic GVHD. Sicca syndrome was also significantly associated with the development of LONIPCs [3-5]. The treatment of LONIPCs is similar to that of chronic GVHD and is based on conventional immunosuppressive drugs, namely cyclosporine and/or prednisolone, but no controlled trials have been conducted to evaluate the best immunosuppressive regimen for LONIPCs. In several review articles, most of the patients with BOOP, interstitial pneumonia and mild airflow limitation at diagnosis responded well to immunosuppressive treatment, while BO patients did not respond to the therapy [3-4].

Conclusion

LONIPCs are an important cause of post-transplantation mortality and morbidity. The

pathogenesis of LONIPCs has not been clearly defined and the presentations have been variable and non-specific. The diagnostic approach should be based on the patient's respiratory condition and types of pulmonary infiltrations. Treatment response is good in most patients with mild or moderate pulmonary functional impairment. In the present study, we reported a patient that developed very late-onset LIP following HSCT and responded well to steroid treatment.

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骨髓移植後遲發性非感染性間質性肺疾病：一病例報告

陳美綾　許永祥*　張恩庭**

造血幹細胞移植後超過3個月所發生的遲發性非感染性肺部併發症（LONIPCs）已成為公認的威脅生命的併發症，並且降低受捐者的生活品質。其中，閉塞性細支氣管炎（BO）以及閉塞性細支氣管炎和肺炎(BOOP)是最常被報導的。在移植後的病人，如果其肺部病變為結節狀、周邊的肺部病變且血小板數量高於30 x 10^9/L以及病人可以配合時，電腦斷層引導下的穿刺活檢具有較高的診斷率（56%～70%）。LONIPC對於治療的反應是不一致的。我們報告一位35歲的男性，接受了骨髓移植，主訴乾咳了4個月。經過電腦斷層引導下穿刺活檢診斷，是淋巴細胞間質性肺炎。這在LONIPC是一種罕見的表現。他對類固醇治療的反應良好。*(胸腔醫學* ***2012; 27: 43-48)***

關鍵詞：遲發性非感染性肺部併發，造血幹細胞移植，淋巴細胞間質性肺炎

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Solitary Squamous Papilloma of Trachea — A Case Report

Mei-Lin Chan, Yi-Chen Yeh*, Wen-Hu Hsu

Squamous papilloma is a benign lesion commonly found on orolaryngeal mucosa and may be associated with HPV type 6 and 11, but is seldom described as a tracheobronchial tumor especially the solitary form. We presented a 39-year-old man with history of laryngeal papillomatosis who suffered from solitary endotracheal squamous papilloma. The endotracheal lesion was pedunculated and about 0.9 cm in size, and resulted in obstruction of the airway. He underwent flexible bronchoscopic Nd-YAG laser ablation under local anesthesia without intubation. This was a rare case based on a literature review since it was a solitary form of endotracheal tumor that underwent bronchoscopic laser ablation without intubation. The clinical manifestations and treatment of these tracheobronchial papillomas are reviewed. ***(Thorac Med 2012; 27: 49-54)***

Key words: Human Papillomavirus (HPV), laryngeal papillomatosis, Nd-YAG laser, solitary squamous papilloma

Introduction

Squamous papillomas are common benign lesions of the oral mucosa and histologically represent an abnormal proliferation of stratified squamous epithelium, supported by a core of fibrovascular tissue. However, they are rarely reported as an endotracheal tumor. Patients with squamous papilloma tend to suffer from recurrence. Herein, we present a case of aryngeal solitary endotracheal squamous papilloma complicated with airway obstruction; the tumor was eliminated with laser ablation.

Case Report

A 39-year-old man had a history of papillomatosis of the vocal cords and oral cavity. He suffered from a gradual development of dyspnea while lying down in the most recent 2 months. In addition, some small granulomas had been expectorated with sputum occasionally in the most recent half year. He visited a hospital, where bronchoscopy revealed an endotracheal lesion, so he then came to our thoracic surgery clinic for a second opinion. Hyperinflation of both lungs was noticed on plain chest film (Figure 1). Another bronchoscopy

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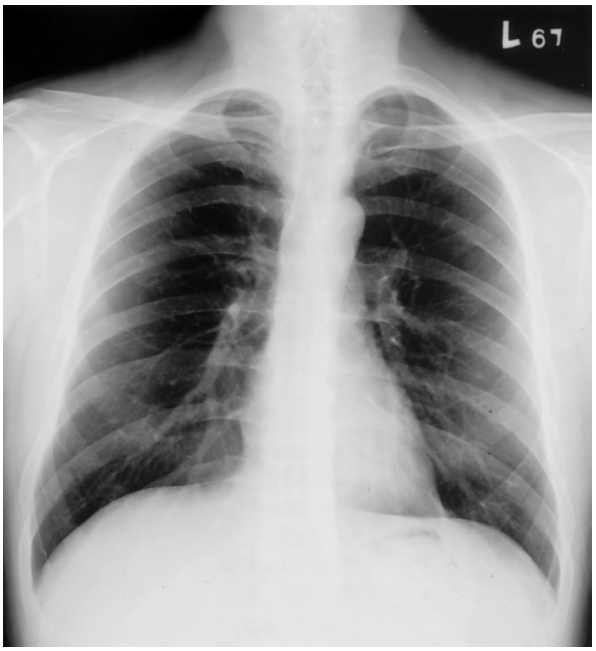
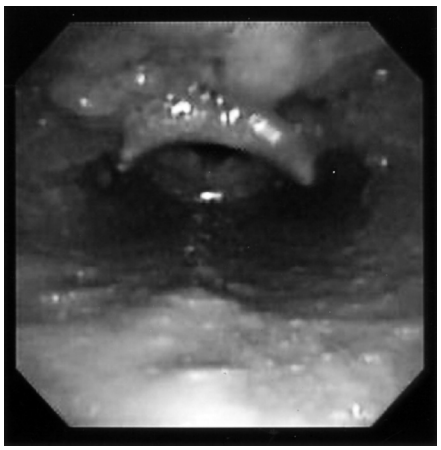
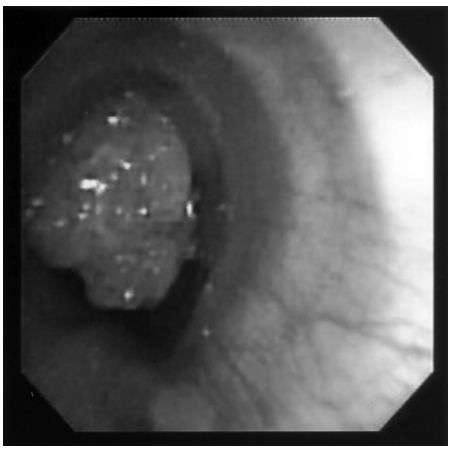


Fig. 1. The plain chest film showed hyperinflation of both lungs

was arranged, which revealed many polyps at the larynx and a pedunculated tumor at the left anterior wall of the trachea (at a level of about 9 cm above the carina and 5 cm below the vocal cord) with movement with breathing (Figure 2). The chest computed tomography showed a 0.9 cm lobulated soft tissue density mass in the trachea (Figure 3). Bronchoscopic biopsy of the lesion revealed papillary outgrowth of the stratified squamous epithelium surrounding fibrous stroma, with marked acanthosis parakeratosis and hyperkeratosis, which is consistent with squamous papilloma (Figure 4). The patient underwent Nd-YAG laser vaporization of the endotracheal tumor under local anesthesia without intubation (Figure 2). The procedure took about



(A)



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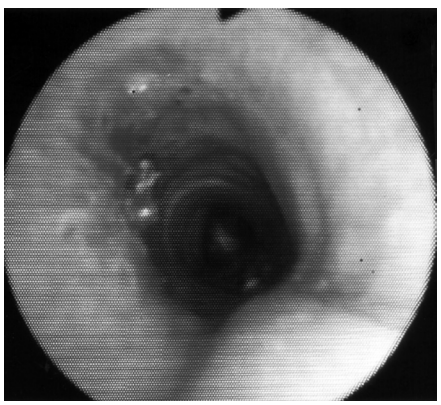

(C)

Fig. 2. (A) Bronchoscopy showed multiple polyps of the larynx. (B) A solitary pedunculated mass on the left anterior tracheal wall. (C) After bronchoscopic Nd-YAG laser ablation, the endotracheal tumor was removed.

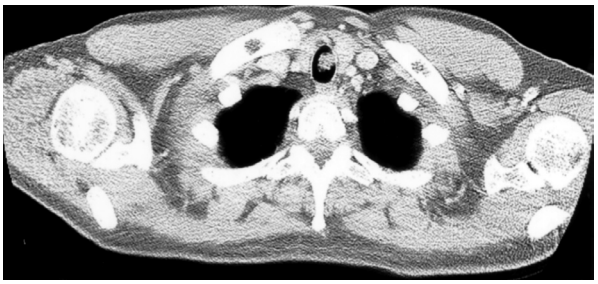

Fig. 3. A 0.9 cm endotracheal tumor with airway obstruction

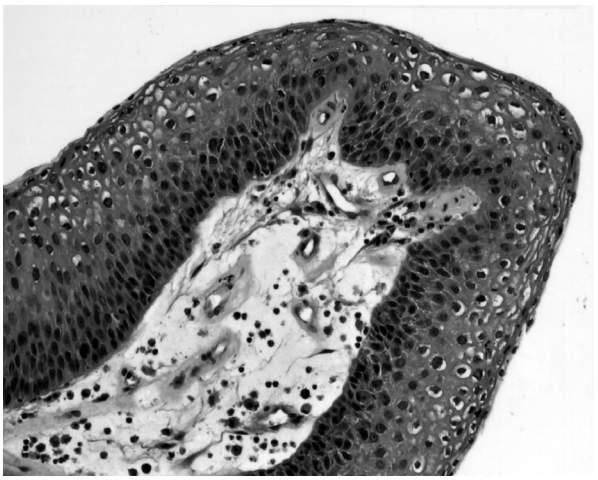

Fig. 4. H&E stain, 200X, Papillary outgrowth of the stratified squamous epithelium surrounding fibrous stroma with marked acanthosis, parakeratosis and hyperkeratosis

30 minutes, and was tolerated well. He then had regular follow-up at our outpatient department.

Discussion

Most respiratory tract tumors are malignant, and benign tumors -- the majority of which are papilloma and harmatoma -- are quite rare. Squamous papillomas are common lesions of the oral mucosa but rarely found in the tracheobronchial tree.

Squamous papilloma is usually a benign innocuous neoplasm that is neither transmissible nor threatening, with a small possibility of malignant transformation, and is characterized by a high rate of recurrence [1-2]. The cause of tracheal papilloma is not well established. Major *et al*. reported an association between squamous papilloma and human papilloma virus (HPV) types 6 and 11 [3], but recent literature has suggested that the presence of HPV may be merely an incidental finding unrelated to the development of a squamous papilloma [3]. It is generally accepted that low-risk HPV type 6 or 11 positivity is associated with a benign clinical course in most cases, whereas high-risk oncogenic HPV16 or 18 is always accompanied by a poor prognosis [4].

Tracheobronchial papillomas have 3 distinct clinical presentations: multiple papillomas, inflammatory polyps or solitary papilloma. Multiple forms are the most common; they occur in the larynx and lower respiratory tract and are associated with HPV. They are also most commonly found in children, although they have been described in adults [5-6]. Multiple papillomas originate primarily in the larynx, with a tracheal incidence of about 2% and lung involvement of <1% [7-8]. They have been divided into juvenile and adult types, because they present distinct clinical courses and different incidences of malignant transformation, based on age at onset and the presence or absence of laryngeal involvement. Inflammatory polyps arise in chronically inflamed mucosa and are caused by chronic irritation. The solitary papilloma is the rarest type. They may go undetected for years, with the highest prevalence in 5th and 6th decades of life. The exact pathophysiology of solitary squamous papilloma has not been determined, although Katial *et al*. reported a case of HPV associated with solitary squamous papilloma complicated by bronchiectasis and bronchial stenosis [9]. Barzo and colleagues observed only 5 cases of solitary papillomas dur-

ing a 21-year period and 15,000 bronchoscopies [10]. All their patients were men and the youngest patient they described was 49 years old.

Our patient had a history of papillomatosis of the larynx combined with solitary endotracheal squamous papilloma. We did not detect whether the DNA of the HPV virus existed in the endotracheal papilloma, so it is hard to tell if the endotracheal papilloma was associated with HPV. When papillomas spread from laryngeal papillomatosis, it is usually in multiple forms. However, this patient had only a solitary papilloma within the trachea, 5 cm below the vocal cord. So the endotracheal papilloma could have either seeded from the laryngeal papillomatosis or originated from the tracheal mucosa. The existence of a solitary papilloma, as opposed to the usual multiple lesions of papillomatosis, is extremely rare. In a review of the literature, we could not find a patient with laryngeal papillomatosis accompanied with solitary tracheobronchial papilloma.

Although squamous papilloma is a benign lesion, a tracheobronchial lesion may cause obstruction of the airway and carry a small possibility of malignant transformation, so this type of lesion should be treated once found. The aim of treatment for tracheobronchial papilloma is to achieve a tumor-free state and maintenance of an airway adequate for breathing, which can be obtained by lesion removal with bronchoscopic laser, electrocauterizer or even anatomic tracheal resection. Long *et al*. reported that 10% of recurrent respiratory papillomatosis cases suffered recurrence within a short period, multisite spread of the disease, or airway compromise by rapid regrowth, and required adjuvant therapies such as cidofovir intralesional injections, photodynamic therapy, pulsed dye laser, indole-3-carbinol and stent implantation, and others [11].

Mohan *et al*. presented a case of recurrent endotracheal papilloma treated with cryosurgery, which has the advantages of less damage to the tracheobronchial cartilage and less stricture formation [12]. The main disadvantage of cryosurgery is that it is not ideal in an emergency situation due to its relatively slow mechanism of action.

For this patient, we chose Nd-YAG laser ablation via flexible bronchoscopy under local anesthesia without endotracheal tube intubation because the papilloma was solitary and pedunculated. The entire procedure was smooth and took only about 30 minutes. No tumor recurrence was found in the 1-month follow-up.

Conclusion

The case presented here is rare for the following reasons. First, the symptoms included small granulomatous expectoration in addition to dyspnea. Second, the patient had a past history of laryngeal papillomatosis, but presented with only solitary endotracheal squamous papilloma. Third, under local anesthesia, the endotracheal squamous papilloma was treated simply and successfully by Nd-YAG laser ablation via flexible bronchoscope without intubation. However, the possibility of local recurrence or even malignant transformation of squamous papilloma should not be neglected. Close follow-up is important.

Acknowledgements

The authors thank Dr. Yeh for providing the pathologic picture and Dr. Hsu for his revision of the article.

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氣管內單一扁平上皮乳突瘤：病例報告

詹梅麟　葉奕成*　許文虎

扁平上皮乳突瘤在口腔咽喉黏膜中是很常見的良性病變，可能與人類乳突病毒（HPV）第6和11型有關聯。但此類病變在氣管或支氣管內相當罕見，特別是單一腫瘤型態的病灶。在此，我們報告了一位39歲有喉部乳突瘤病史之男性病患合併有氣管內單一扁平上皮乳突瘤。此氣管內腫瘤在外型上是具莖狀的，約0.9公分大且合併有氣道之阻塞。病患在局部麻醉沒有接受氣管插管的情況接接受釹雅鉻雷射（Nd-YAG laser）腫瘤切除術。在查閱了文獻後我們發現這一個相當罕見的病例，因為此病患之氣管內扁平上皮乳突瘤是以單一的型態存在；且此病患是在局部麻醉沒有插管的情形下接受軟式支氣管鏡釹雅鉻雷射腫瘤切除術。在查閱了一些文獻後，我們探討了氣管內乳突瘤之臨床表現及其治療方式。*(胸腔醫學* ***2012; 27: 49-54)***

關鍵詞：人類乳突病毒，喉部乳突瘤，釹雅鉻雷射，單一扁平上皮瘤

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Gastric MALT Lymphoma with Secondary Pulmonary Lymphoma: A Case Report

Jing-Quan Zheng, Chi-Mei Zheng, Cheng-Yi Wang, Wei-Jen Ou,
Chin-Yao Lin*, Hen-I Lin

Primary lymphomas of mucosal-associated lymphoid tissue (MALTomas) are rarely encountered in clinical practice. Non-Hodgkin's lymphoma (NHL) accounts for 2-3% of all malignancies, while MALTomas comprise approximately 5% of all NHLs. The simultaneous presentation of gastric MALTomas with pulmonary lymphoma is relatively rare. The radiological appearance of pulmonary lymphoma is also variable. We report the case of a 63-year-old female initially diagnosed with and treated for pulmonary tuberculosis (TB). Due to her persistent cough, chest computed tomography (CT) was done, which revealed findings consistent with pulmonary lymphoma. In addition, the CT scan also showed diffuse thickening of the gastric mucosa wall with a mass lesion. An abdominal CT scan disclosed diffuse thickening of the stomach mucosal wall, with masses that were histopathologically confirmed as gastric MALToma. This case report highlights a common atypical clinical presentation of MALToma, which is easily mistaken to be a chronic inflammatory disease like TB, and reviews its nature, staging, management approach, and outcome. ***(Thorac Med 2012; 27: 55-63)***

Key words: gastric malt lymphoma, *Helicobacter pylori*, pulmonary lymphoma

Introduction

Mucosa-associated lymphoid tissue (MALT) lymphomas (MALTomas) are extra-nodal cancers originating from B cells of the mucosa and sub-mucosa of lymphoid tissue, usually in the stomach and regional lymph nodes [1]. MALTomas account for approximately 8% of all non-Hodgkin's lymphomas and are associated with chronic antigenic stimulation mediated by persistent infection and/or auto-immune mechanisms [2]. Primary pulmonary lymphoma is rare, representing 0.5-1% of primary pulmonary malignancies. Nearly half are identified on the basis of abnormal and incidental radiologic findings [3-5]. Simultaneous findings of pulmonary and gastric lymphoma are clinically uncommon, with very few reported cases [6].

Case Report

A 63-year-old female with a history of

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pulmonary tuberculosis (TB) and treated for 6 months with anti-TB medications complained of a chronic persistent productive cough of a 6-month duration. She visited the chest outpatient department (OPD) because of shortness of breath for 1 month. She had associated abdominal distension, anorexia, indigestion, and generalized malaise. She also reported body weight loss of about 20 kg within the last 6 months. She denied fever, orthopnea, paroxysmal nocturnal dyspnea, or chest pain. She also denied any history of viral hepatitis B. She had a history of gastric ulcer in 1991 with pan-endoscopic findings of chronic gastric ulcers in a kissing ulcer pattern about 3 cm in size located in the upper stomach, but she had irregular treatment. Histopathological examination of a tissue specimen revealed foveolar hyperplasia, and intestinalization with some mixed-type inflammatory cell infiltration. She denied smoking and alcohol drinking.

In the OPD, she was pale-looking but alert, with blood pressure of 115/71 mmHg, heart rate 81/min, respiratory rate 18/min, and body temperature 36.1°C. Chest auscultation revealed diffuse rhonchi. Her abdomen was distended, with slight tenderness in the umbilical region but without rebound tenderness. The liver and spleen were not palpable. A vague soft tissue mass was palpable along the left side of the umbilicus, with hypoactive bowel sounds.

Laboratory data showed anemia (hemoglobin ~8.3 g/dl, hematocrit 26.5) and hypo-albuminemia (albumin 2.4 g/dl). The serum alpha-fetoprotein and carcino-embryonic antigen levels were 2.2 ng/ml and 2.33 ng/ml, respectively, while other laboratory results were within normal limits. Chest x-ray revealed patchy infiltrates at the right upper lobe, reticulo-nodular infiltrates in the bilateral para-hilar regions, and bilateral pleural effusion in the lower lobes (Figure 1). Chest computed tomography (CT) disclosed nodules in the right para-tracheal, sub-carinal, and right hilar region, with irregular consolidation and air-bronchograms in the right upper lobe and some small nodular infiltrations. There was also an associated thickening of the interlobular septae and broncho-vascular bundles in the bilateral lung fields, especially in the lower lobes, with a high degree of suspicion of secondary pulmonary lymphoma (Figure 1).

Incidentally, diffuse thickening of the gastric mucosa wall with masses was also noted (Figure 2). Abdominal CT revealed diffuse thickening of the gastric wall with mass lesions, abdominal and para-aortic lymphadenopathy, and ascites. Pan-endoscopy was performed and showed gastric polypoid tumors with ulceration and bleeding, and gastro-esophageal reflux disease of the lower 1/3 of the esophagus, Los Angeles classification Grade A. Rapid urease test (CLO test) for *Helicobacter pylori* (*H. pylori*) was positive. Histopathology of the tissue specimen revealed lymphoid cells with hyperchromatic round tumor cells diffusely infiltrating the stroma and expanded lip. Immunostaining revealed CD3 focal (+), CD29 (+), ENA focal (+), BCL-2 (+), CD 10 (-), cyclin D1 (-), CD23 (-), CD 5 focal (+), and CD43 focal (+), compatible with MALToma, with possible transformation to another type of lymphoma (intermediate grade) (Figure 4).

Bronchoscopic examination revealed no endobronchial lesion. Atypical cells were found in the bronchial brushing. A whole body tumor scan was done for staging and the images led to a high degree of suspicion of gallium avid lymphomas in the stomach, both lungs, the right salivary gland, and parts of the intestines, mesenteries, and omentum (Figure 3). Bone

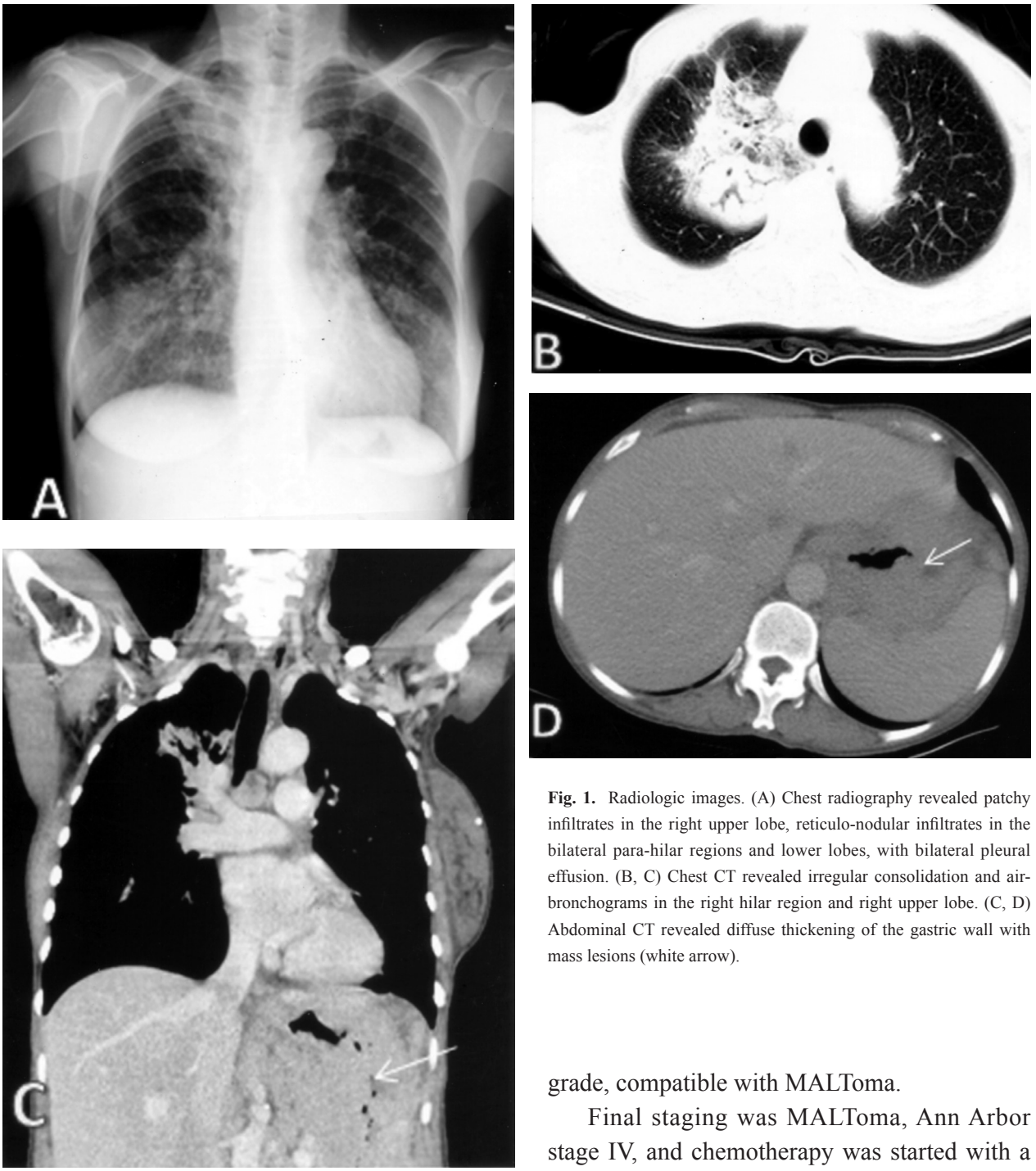

Fig. 1. Radiologic images. (A) Chest radiography revealed patchy infiltrates in the right upper lobe, reticulo-nodular infiltrates in the bilateral para-hilar regions and lower lobes, with bilateral pleural effusion. (B, C) Chest CT revealed irregular consolidation and air-bronchograms in the right hilar region and right upper lobe. (C, D) Abdominal CT revealed diffuse thickening of the gastric wall with mass lesions (white arrow).

marrow biopsy of the left iliac bone also stained for CD 20 (+), CD 5 (-), CD10 (-), CD 23, and cyclin D1 (-), suggesting bone marrow involvement of malignant lymphoma, B cell and low grade, compatible with MALToma.

Final staging was MALToma, Ann Arbor stage IV, and chemotherapy was started with a CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen. However, she had a poor response to chemotherapy after the 6th cycle of the CHOP regimen, and bone marrow failure developed. The patient subsequently died of septic shock.

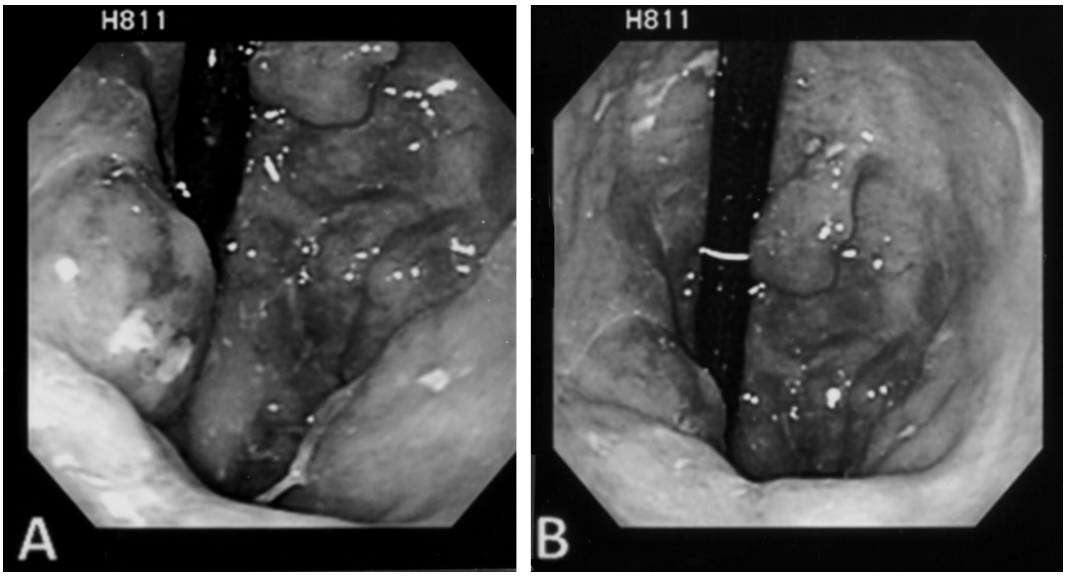

Fig. 2. (A, B) Pan-endoscopy revealed a diffuse nodular and polypoid tumor with ulcer in the gastric body and antrum.

Discussion

Gastric lymphoma is a rare malignancy that accounts for less than 2% of primary gastric cancers [7]. Gastric lymphomas have the highest prevalence in patients over the age of 50, while men are 2 to 3 times more frequently affected than women [2,8]. In 1983, Isaacson and Wright reported an extra-nodal malignant lymphoma arising from MALT, that was found to be a low-grade B-cell lymphoma of the MALT type [9]. MALT includes gut-associated lymphoid tissue (GALT), bronchial/tracheal-associated lymphoid tissue (BALT), nose-associated lymphoid tissue (NALT), and vulvo-vaginal-associated lymphoid tissue (VALT) [10].

MALTomas typically arise from sites normally devoid of lymphoid tissue and are caused by underlying chronic inflammatory disorders (usually autoimmune) that result in an accumulation of lymphoid tissue [1]. MALTomas can occur in other extra-nodal sites, including the stomach, intestines, conjunctiva, salivary glands, thyroid, larynx, lung, breast, kidney, liver, prostate, skin, and dura mater [1,11-13].

Most MALTomas occur as gastric MALTomas (70%). Other common sites include the salivary glands, lungs, and ocular adnexa [1]. Common forms associated with infectious etiologies are gastric MALTomas due to *H. pylori* infection [1,14-15], and ocular adnexal lymphomas associated with *Chlamydophila psittaci* infection [16-17]. MALT lymphomas also preferentially disseminate extra-nodally, especially those of the lungs and stomach [18]. About 69-78% of primary pulmonary lymphoma have been reported as MALT-type lymphomas [3-4].

The majority of both stomach and pulmonary MALToma patients are asymptomatic or present with non-specific symptoms like abdominal pain, sicca syndrome, cough, dyspnea, chest pain, and occasional hemoptysis, with constitutional symptoms like weight loss, fever, night sweats, and fatigue, or with a mass at the site of involvement [4-5,19-22]. These symptoms may last for several weeks to months

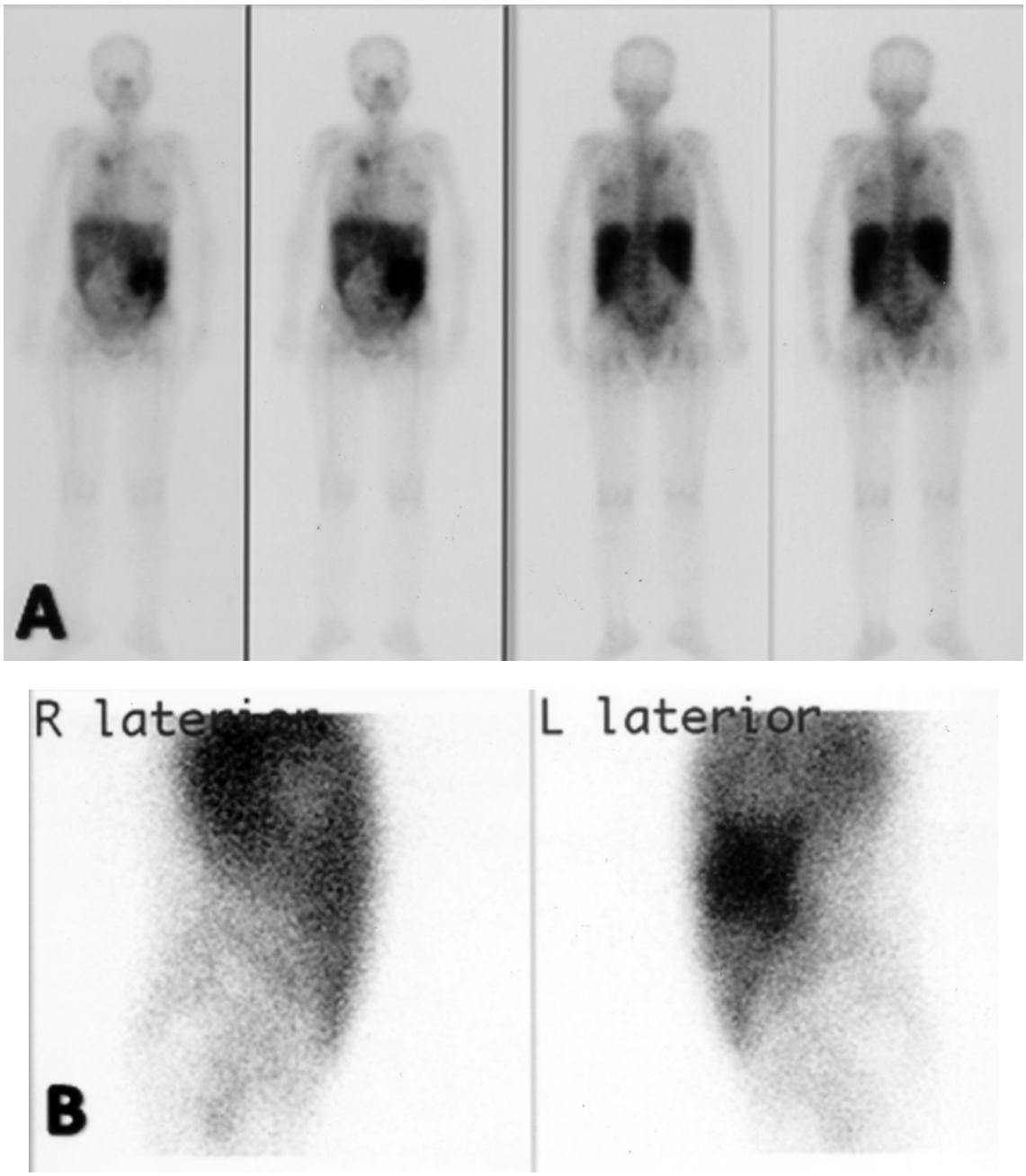

Fig. 3. (A, B) The whole-body tumor scan revealed highly suspicious gallium avid lymphomas in the stomach, both lungs, right salivary gland, and part of the intestines, mesenteries, and omentum.

before definitive diagnosis [3-5]. Nearly half of primary pulmonary MALTomas are identified incidentally in abnormal radiologic findings [3]. Clinically, diffuse sub-mucosal infiltration of the airways by tumor cells results in widespread airway narrowing and presents with obstructive symptoms like dyspnea and wheezing, which may be misdiagnosed as asthma exacerbation [5].

In this case report, the patient was at high

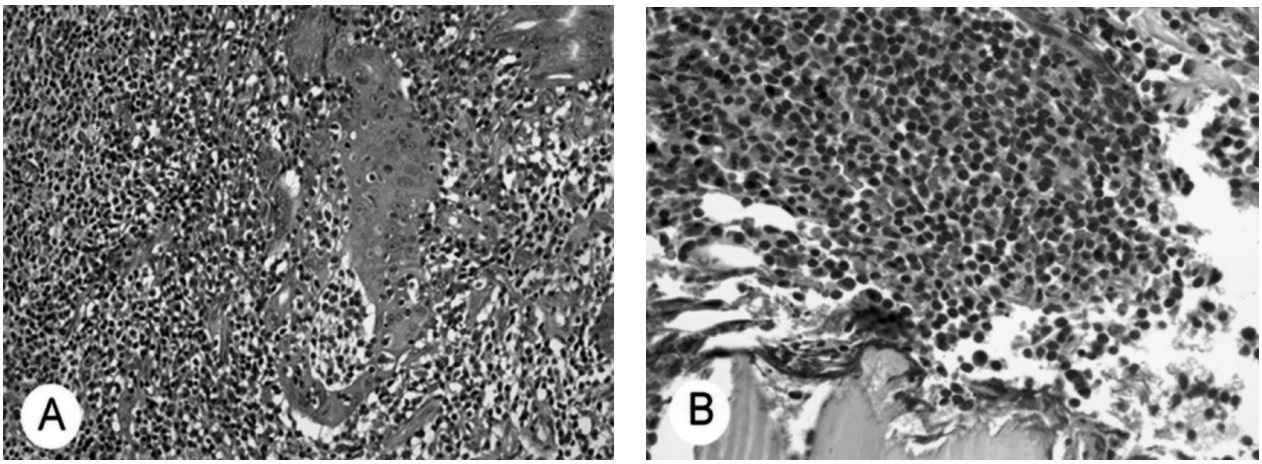

Fig. 4. (A) Diffuse infiltration of lymphocytic cells within the lamina propria and mucosal glands with formation of lympho-epithelial lesion (Hematoxylin-eosin stain, X100). (B) Photomicrography showed involvement of neoplastic lymphoid cells within the marrow spaces. (Hematoxylin-eosin stain, X200).

risk of MALToma due to a history of chronic gastric ulcer since 1991 that was irregularly treated, despite histologic confirmation of foveolar hyperplasia. An *H. pylori* test was not done at that time, however, even though the probability of *H. pylori* infection might have existed then. *H. pylori*-related chronic inflammation may have been an important pathogenesis for gastric MALToma in this patient. The duration of more than 15 years before the MALToma developed in this case reflects the indolent clinical behavior of gastric MALToma. In this case, pulmonary symptoms were also non-specific, hence the initial diagnosis and treatment of pulmonary TB. The gastric MALToma was already at an advanced stage when the diagnosis was made. Extra-gastric MALTomas are significantly prone to dissemination compared with gastric MALTomas [23], and more than 1/3 of patients with non-gastric MALTomas have advanced disease at the time of diagnosis [23-24].

Radiographic features are useful in diagnosing pulmonary MALToma even though the final diagnosis is based on histology and immunohistochemistry [25]. Radiological features are highly variable: it may be a mass, single or multiple, in localized areas of consolidation, or in pleural effusion. Up to 70% of patients have a single or multiple pulmonary nodules or a mass with poorly defined borders, or consolidation with air bronchograms, which differs from other pulmonary diseases [25]. The radiological appearance of this patient also revealed irregular consolidation and air-bronchograms in the right upper lobe, nodular infiltration-associated thickening of the interlobular septae, and broncho-vascular bundles in both lung fields, which led to a high degree of suspicion of pulmonary lymphoma. In addition, bone marrow examination was compatible with MALToma. Thus, the decision was made to start treatment for pulmonary lymphoma without a further mediastinal lymph node biopsy.

Conclusions

Despite the low frequency of transformation of early low-grade gastric MALTomas to

diffuse large B cell lymphomas, both stomach and pulmonary MALTomas may present clinically with non-specific symptoms. This case report highlights a common atypical clinical presentation of MALToma, which is easily mistaken to be a chronic inflammatory disease like TB. A high index of suspicion is necessary, as most cases have incidental findings, delayed and varied treatment, and a poor prognosis.

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罕見胃粘膜相關淋巴組織（MALT）淋巴瘤合併肺部的淋巴瘤：病例報告及文獻回顧

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黏膜相關的淋巴組織之淋巴瘤是一種不常見的緩慢型淋巴瘤。這些低年級淋巴瘤是最常見的診斷為胃。『與黏膜相關的淋巴組織之淋巴瘤』若侵犯至胃部，常與幽門螺旋桿菌（Helicobacter pylori）有關。此種淋巴瘤在診斷時常是局部性的，局限於一定的範圍，較不常侵犯至肺，骨髓，且生長速度緩慢，好發於有自體免疫疾病的人。我們提出一位63歲女性在接受肺結核治療了六個月，因長期咳嗽情形未見改善，來門診救醫時意外發現右上肺葉有疑似「肺部黏膜相關淋巴組織淋巴瘤」。另外腹部電腦斷層檢查，胃鏡檢查顯示胃的黏膜增厚並合併有*Helicobacterpylori*幽門桿菌感染。最後病理學檢查確定診斷為胃黏膜相關的淋巴組織之淋巴瘤。後續檢查顯示淋巴瘤已侵犯至肺和骨髓。我們回溯文獻並對胃和肺黏膜相關的淋巴組織之淋巴瘤的流行病學、臨床、病理、治療、預後做一整理。針對來討論肺黏膜相關淋巴組織淋巴瘤的非典型的臨床症狀，臨床影像相關表現，早期治療的重要性。***(胸腔醫學 2012; 27: 55-63)***

關鍵詞：胃黏膜相關淋巴組織淋巴瘤，幽門桿菌，肺淋巴瘤

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Spontaneous Hemothorax Secondary to Metastatic Thymic Carcinoma

Tsan-Ming Huang, Ching Tzau*, Tai-Kuang Chao**, Chung-Kan Peng***

Thymic carcinoma is a rare anterior mediastinum tumor. Although pleural metastasis is common, thymic carcinoma presenting as spontaneous hemothorax is a rare presentation. We present the case of a 53-year-old man without a past medical history who was admitted from the emergency department for a sudden onset of left chest pain with cold sweating, followed by increasing shortness of breath. A chest roentgenogram taken on admission showed a large amount of pleural effusion on the left side. A diagnostic thoracocentesis yielded bloody pleural fluid, which was consistent with hemothorax in biochemical and cytological studies. Diagnostic video-assisted thoracoscopy showed a left chest wall tumor with bleeding. Limited thoracotomy with resection of the tumor was performed. The histologic report revealed metastatic thymic carcinoma. We also reviewed the literature on thymic carcinoma. ***(Thorac Med 2012; 27: 64-70)***

Key words: spontaneous hemothorax, metastatic thymic carcinoma

Introduction

Thymic neoplasm is the most common primary neoplasm of the anterior mediastinum. Thymic tumors include relatively slow growing thymomas, and more aggressive thymic carcinoma. The usual initial presentation includes cough, chest pain, phrenic nerve palsy, or superior vena cava syndrome [1]. Spontaneous hemothorax as the first presentation in thymic carcinoma is relatively rare. We herein describe such a case.

Case Report

A 65-year-old Taiwanese man with no history of recent trauma or medical history of interest came to our emergency department complaining of a sudden onset of left chest pain in association with cold sweating and increasing dyspnea, especially on exertion, beginning the night before. On physical examination,

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there was nothing of particular note except reduced breathing sounds in the left lower lung zone. There was no jugular vein engorgement or lower limb edema. Blood tests showed a hemoglobin concentration of 13.4 g/dl, hematocrit of 39.0%, white blood cell count of 9.4×10^3 cells/μL (81.3% neutrophils, 11.3% lymphocytes, 6.3% monocytes, 0.3% eosinophils, and 0.3% basophils), and platelet count of 141×10^3 cells/μL. Blood biochemistry findings were as follows: BUN, 23 mg/dl; creatinine, 1.0 mg/dl; sodium, 138 mEq/L; potassium, 4.3 mEq/L. Liver function was within normal limits. Normal sinus rhythm with no ST-T changes on electrocardiography and normal cardiac enzyme levels excluded acute coronary syndrome. The coagulation profiles of prothrombin time and activatd partial thromboplastin time were within normal limits. D-dimer was 283 ng/ml. A chest roentgenogram taken on admission showed left-side pleural effusion with passive atelectasis (Figure 1). A diagnostic thoracocentesis yielded non-clotted bloody pleural fluid, with a RBC count of 4.66×10^6/μL, WBC count of 8600/μL (neutrophils: 61%, lymphocytes: 25%, macrophages: 11%, mesothelial cells: 3%), glucose level of 51 mg/dl, total protein level of 5.3 g/dl, and a LDH level of 1282 U/L, which was consistent with hemothorax. A contrast computed tomographic (CT) scan of his chest excluded aortic dissection, and revealed a 3.6 cm irregular mass with few calcified spots in the anterior mediastinum, favoring a thymic tumor, and a pleural mass about 5.0 cm in size at the left lower hemithorax (Figure 2A & B). Diagnostic video-assisted-thoracoscopy showed a left chest wall tumor with bleeding in situ (Figure 3A). Limited thoracotomy with resection of the tumor was performed. The resected tumor was 8×6×5 cm in size and 160 gm in weight (Figure 3B). The tumor cells were detected by immunohistochemical stain for cytokeratin and CD5, but were negative for TTF-1. The histologic result disclosed low-grade thymic squamous cell carcinoma with pleural metastasis (Figure 4). The patient was classified as having thymic carcinoma, type C, stage IVa. There was no history of muscle weakness, difficulty swallowing, or

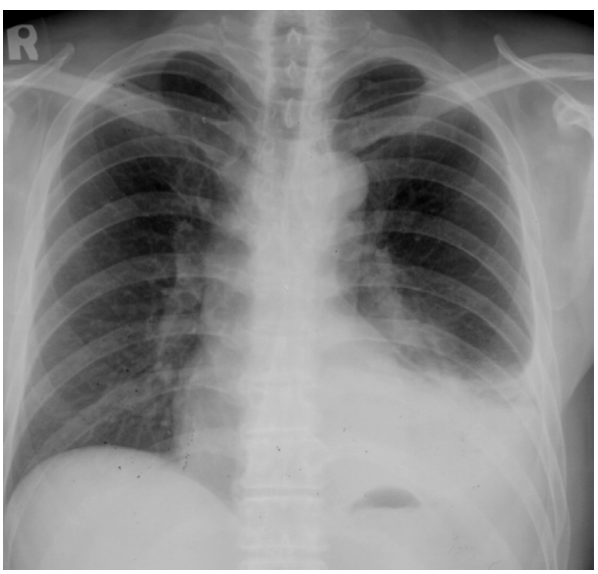

Fig. 1. Chest roentgenogram showing a large amount of pleural effusion on the left with passive atelectasis.

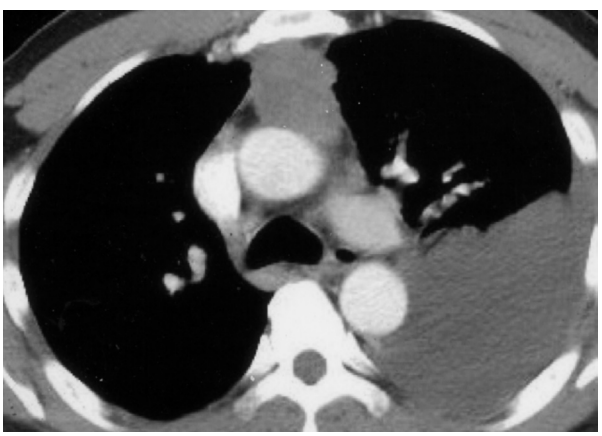

Fig. 2A. Computed tomographic scan of the chest disclosed an irregular mass with few calcified spots in the anterior mediastinum, favoring a thymic tumor.

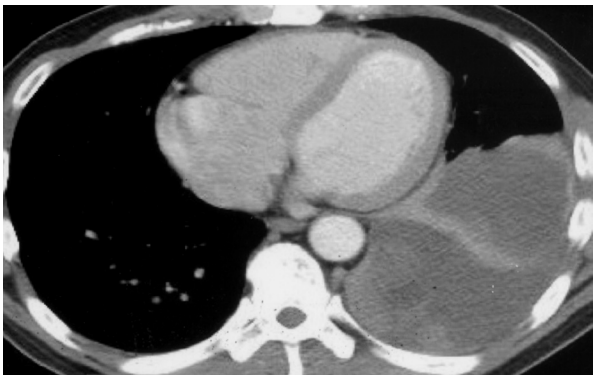

Fig. 2B. Computed tomographic scan of the chest disclosed a pleural mass at the left lower hemithorax.

Fig. 3A. Video-assisted-thoracoscopy showed a left chest wall tumor with rupture in situ.

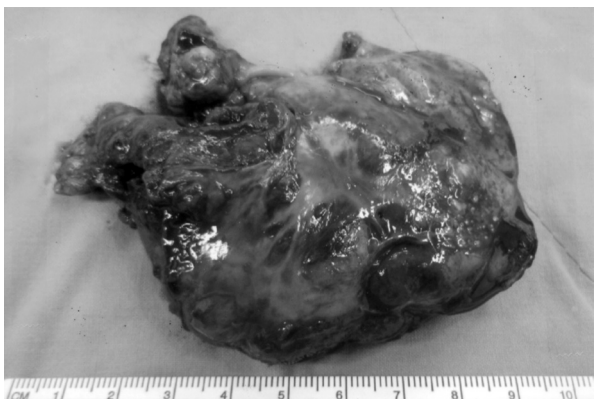

Fig. 3B. The resected tumor was 8×6×5 cm in size and 160 gm in weight.

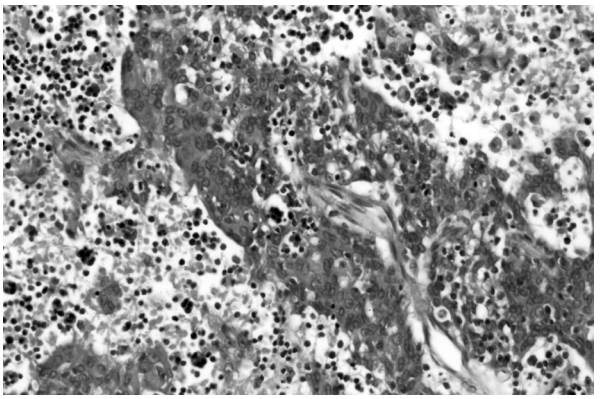

Fig. 4. Syncytial tumor nests with pleomorphic nuclei intermixed with tumor necrosis (hematoxylin & eosin, 400x); consistent with low grade thymic squamous cell carcinoma

ptosis. Myasthenia gravis was excluded. He received the first dose of adjuvant cisplatin-based chemotherapy and radiotherapy during this admission. He was followed-up at the outpatient department with further chemotherapy and radiotherapy, and plans were made for surgical removal of the primary thymic neoplasm.

Discussion

Thymic carcinoma, classified as type C thymoma according to the WHO criteria, accounts for 0.2% to 1.5% of all malignancies [2] and 0.06% of thymic neoplasms [3]. The most common variant is squamous cell carcinoma. The age distribution for thymic carcinoma is broad, and ranges from 10 to 76 years old [4-6]. Nearly 1/3 of patients are asymptomatic at presentation [4-5], and the tumor is often found by routine chest radiography [5]. Thoracic symptoms related to the anterior mediastinal mass effect are chest pain, cough, dyspnea, and other upper respiratory complaints [4-5]. Patients occasionally present with superior vena cava syndrome, hoarseness, and weight loss [5]. Thymic carcinomas have a high frequency of intratho-

racic metastasis. Hung *et al*. found that 12 of 25 patients (48%) had pleural metastasis and 20 of 25 patients (80%) had adjacent cardiovascular invasion [7]. Spontaneous hemothorax as the presenting manifestation of metastatic thymic carcinoma is rarely reported in the literature.

Hemothorax is the accumulation of blood in the pleural cavity. The most common causes of hemothorax are open or closed chest trauma or therapeutic procedures. Non-traumatic spontaneous hemothorax is much less common, and the causes include malignancies, anticoagulant medications, vascular ruptures (aortic dissection, arteriovenous malformations), endometriosis, pulmonary infarctions, adhesions with pneumothorax, and hematologic abnormalities such as hemophilia [8]. In a detailed PubMed search of the English literature available on the subject, spontaneous hemothorax from metastatic malignancies such as angiosarcoma of the scalp, gynecological tumor-like trophoblast tumor, germ-cell carcinoma, melanoma, hepatocellular carcinoma and renal cell carcinoma have been reported [9-14].

Tumors in the anterior mediastinum are difficult to detect, unless they are quite large. More than 90% of patients with thymic carcinoma are not diagnosed until the tumor is in an advanced stage [4-5]. The pleura, innominate vein, pericardium, and lung are the structures most commonly invaded [5]. Our patient did not seek medical help until the development of hemothorax from the metastatic pleural mass. The lack of mediastinal enlargement and the opacity of the pleural fluid on the chest film obscured the diagnosis. The diagnosis was made only when the pleural mass seen on CT was removed by limited thoracotomy and sent for pathology. The definitive diagnosis was metastatic thymic carcinoma, which explained the spontaneous hemothorax with which he presented.

The Masaoka *et al*. staging system [15] is based on the presence or absence of an intact tumor capsule and has been widely used for staging of thymic neoplasm. Blumberg *et al*. reported that Masaoka staging does not appear to predict outcome for patients with thymic carcinoma. Tumor invasion to the innominate vessels is associated with a particularly poor prognosis [16]. Yamakawa *et al*. suggested a TNM classification for staging of thymic carcinomas, which behave in a manner similar to non-small cell carcinoma of the lung. Size and cellular differentiation play an important role [17]. Lymph node involvement and distant metastasis are common. In a previous study of 183 patients with thymic carcinoma, Kondo *et al*. showed that the N factor was one of the predictors of survival in thymic carcinoma. However, the M factor showed less influence on survival than the T or N factors. The 5-year survival for N0, N1, N2, and N3 were 56.0%, 42.1%, 29.3%, and 18.8%, respectively. The 5-year survival for patients with and without distant metastasis was 34.4% and 51.3%, respectively, but the difference was not significant [18].

There are no randomized clinical trials that provide the standard protocol for the management of patients with thymic carcinoma. Low- and high-grade lesions are both managed primarily in accordance with the extent of the disease process. Surgery, radiotherapy and chemotherapy are recommended as the most effective treatment for thymic carcinoma [19]. Complete surgical resection, if possible, following initial neoadjuvant chemoradiation therapy, plus postoperative use of the same modalities, would appear to be the most appropriate approach for patients with advanced disease at the time of initial diagnosis [16,20-21]. In multivariate

analysis, survival was also related to whether or not a complete resection of the tumor had been accomplished [18].

Management of spontaneous hemothorax depends on the severity of hemorrhage and the hemodynamic stability of the patient. Indications for intervention other than thoracostomy include massive hemothroax (>1000 ml), continued bleeding greater than 300 ml in the 1st hour, and bleeding greater than 200 ml/hour for 5 hours. Further intervention may include arterial embolization or video-assisted thoracoscopic surgery [22] in hemodynamically stable patients, and explorative thoracotomy in unstable emergency patients [23].

In summary, although non-traumatic spontaneous hemothorax is commonly due to the complications of anticoagulant therapy and primary vascular bleeding, such as an intrathoracic aneurysmal rupture or a rupture of the subpleural A-V malformation, clinicians should also consider malignant tumor, both primary or metastatic, including metastatic thymic carcinoma, as the possible cause. Early diagnosis, and immediate and appropriate intervention are important for the survival and prognosis of the patient.

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轉移性胸腺癌表現爲自發性血胸

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胸腺癌是罕見的前縱膈腔腫瘤。雖然胸腺癌轉移肋膜常見，以自發性血胸表現為罕見。我們報導一個病例：一位五十三歲的男性，無過去病史，從急診住院，主訴為左側胸痛，合併冒冷汗，以及進階性呼吸困難。胸部X光發現左側大量肋膜積水。診斷性肋膜取液發現血色肋膜液，以生物化學與細胞學檢查，診斷為血胸。診斷性胸腔鏡檢查發現左側胸壁腫瘤併出血。病人接受局限性胸廓切開術及腫瘤切除。病理報告為轉移性胸腺癌。我同時回顧胸腺癌相關文獻。*(胸腔醫學* ***2012; 27: 64-70)***

關鍵詞：自發性血胸，轉移性胸腺癌

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