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Orginial Articles

Case Reports

Amoxicillin Modulates Leukosequestration and Proinflammatory Cytokine Release in Airway of Patients with Bronchiectasis

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Background: Bronchiectasis is a chronic airway disease of diverse etiology, characterised by persistent bacterial colonization, bronchial inflammation, and progressive tissue damage. Neutrophil influx with oxidants and pro-inflammatory cytokines production not only provides phagocytic protection from microbes, but is also implicated in further airway inflammation. This study was designed to investigate whether amoxicillin affects neutrophil-mediated airway inflammation in bronchiectasis.

Methods: A 2-week course of therapy with amoxicillin (250 mg, 4 times per day) or duracef (250 mg, twice per day) was administered for bronchiectasis patients. Twenty-one bronchiectasis patients in stable condition after adequate chest care and hydration were enrolled in a randomized fashion. The neutrophil cellularity in 3 ml induced sputum was counted before and after treatment. The sputum IL-8 and TNF-α levels were measured using the ELISA method. Leukocyte adhesion molecules CD11b/CD18 and DCFH in induced sputum were determined by flow cytometric assay.

Results: The total cell count of neutrophils in 3 ml induced sputum was significantly reduced in patients receiving amoxicillin from 14.4 ± 5.1 to 9.3 ± 5.2 ($x10^6$ cells) ($p < 0.05$). There was no change in total cell counts in the duracef group ($p = 0.13$). Amoxicillin significantly decreased the TNF-α and IL-8 levels in a supernatant of sputum, from 168.7 ± 65.6 pg/ml to 50.3 ± 26.8 pg/ml ($p < 0.01$), and from 9538.4 ± 1650.1 pg/ml to 5664.4 ± 1384.4 pg/ml ($p < 0.01$), respectively, whereas the TNF-α and IL-8 levels in the duracef group did not significantly change after treatment.

In the amoxicillin group, the change in the sputum IL-8 level was significantly related to the change in the total cell count of leukocytes ($r = 0.67$, $n = 11$, $p < 0.05$). There was also a significant correlation between the percentage of change in the sputum IL-8 level and total cell counts of leukocytes after antibiotic therapy in the amoxicillin group ($r = 0.76$, $n = 11$, $p < 0.01$). The expression of CD11b, CD18 and DCFH did not significantly change after treatment in both groups.

Conclusion: Different antibiotics have different effects on patients with bronchiectasis. Amoxicillin downregulates the TNF-α and IL-8 levels in sputum, thus leading to a decrease of airway neutrophil sequestration and preventing further airway damage. ***(Thorac Med 2006; 21: 392-405)***

Key words: bronchiectasis, amoxicillin, neutrophil, tumor necrosis factor-α, interleukin-8

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Introduction

Bronchiectasis is a disease involving recurrent pulmonary infections and chronic airway inflammation that causes destruction of the ciliated epithelium and submucosa with elastic and muscular tissue degeneration [1]. Dense polymorphonuclear neutrophil (PMN) infiltrates in the airways is a characteristic of bronchiectasis, and significantly increases during airway infection, thus exaggerating the inflammatory burden [2]. Recruitment or sequestration of neutrophils appears to be a crucial response of the host against bacterial and fungal invasion [3-4]. When the mucociliary clearance and alveolar macrophages are overwhelmed, the rapid influx of neutrophils from the lung vasculature, releasing substantial amounts of reactive oxygen metabolites, together with hydrogen peroxide (H2O2), hypochlorous acid (HOCl) and hydroxyl radical (OH·), accounts for a large part of PMN microbicidal activity [5]. However, activated PMNs in the bronchial lumen are also capable of releasing pro-inflammatory mediators, including IL-8 and TNF-α [6], which when combined with toxic oxygen radical species, including H2O2 and $O2^-$ [7], may also subsequently lead to epithelial injury and impairment of mucociliary clearance [8], and increase mucus secretion. In particular, the chemotaxis, transendothelial and transepithelial migration, as well as phagocytosis and degranulation of PMNs, are regulated by the expression of adhesion molecules on PMNs, especially β-2 integrins (CD11/CD18) [9]. Thus, a fine-tuned regulation of neutrophil activation may occur after the adherence of neutrophils to epithelial cells. Moreover, the adherence between leukocytes and epithelial cells may perpetuate the activation of leukocytes by the production of pro-inflammatory cytokines from the epithelial cells, leading to mucus hypersecretion. Therefore, the initiation of PMN adherence and oxidant production, and then the decrease in pro-inflammatory cytokine production in patients with bronchiectasis may be of therapeutic significance.

Antibiotic therapy is the mainstay treatment for infective exacerbations in bronchiectasis [10]. Broncicctasis runs a chronic course and patients are given short-term antibiotics intermittently for clinical exacerbations. Besides the respective interactions between antibiotics and between the immune system and bacteria, antibiotics also directly interact with the immune system [11]. Agents which potentiate neutrophil function and interfere with pro-inflammatory cytokine release may have a beneficial effect on the development and progression of such disease. Amoxicillin has also been widely used in the treatment of excess sputum production in chronic bronchitis. Recent reports have revealed that amoxicillin could be a immunodepressing antibiotic through its neutralizing effect on cytokine production [11]. Therefore, amoxicillin may have a potential role in the neutrophil-regulated host defences and neutrophil-derived airway inflammatory responses in patients with bronchiectasis.

Neutrophils are recruited in abundance in the airways in bronchiectasis, as shown by sputum cytology [12]. Previous studies [13] have reported that cellular and biochemical analysis of induced sputum is feasible in healthy and asthmatic subjects. Therefore, the changes in neutrophil activity and cytokine level in induced sputum in the airways of bronchiectasis patients provide the responses to antibiotic therapy.

The present study was designed to investigate the immunomodulatory effects of amoxicillin on airway neutrophil sequestration and the associated cytokine production in patients with bronchiectasis.

Methods

Patients

Twenty-one patients (11 men and 10 women) with bronchiectasis were enrolled in this study. Bronchiectasis was diagnosed by history and clinical symptoms, as well as chest X-ray and/or computerized tomography scan of the thorax. Bronchiectasis was a result of prior pneumonia in 16 patients and prior tuberculosis (TB) in 5 patients. None of them had immunoglobulin deficiency or immotile cilia syndrome. All patients had suffered from a production of mucopurulent sputum of more than 30 ml/day at home, for at least 3 weeks before the study, with clinically significant symptoms of cough. Their ages ranged from 52 to 68 (a mean of 59.8 ± 5.1) years. All subjects received regular postural drainage and chest care before the study. They were conscious, co-operative, and able to produce an effective cough. Patients with other active pulmonary or systemic disorders were excluded. No oral or inhaled corticosteroids, non-steroid anti-inflammatory agents or maintenance antibiotics were used at least 4 weeks before the study. Theophylline was used throughout the study without changing the dosage, and inhaled β2-agonists were permitted on an "as required" basis. Moreover, the patients had not had a pulmonary (respiratory rate > 30/min, severe hypoxemia with SaO2 < 90% in room air or hypercapnia with pH < 7.35) or systemic (high fever, body temperature > 38.5°C, chills or bacteremia) exacerbation in the past 4 weeks. Female patients were not pregnant or breast feeding. Patients with a known hypersensitivity to any of the constituents of the test drugs were excluded.

Study design and antibiotic treatment

The subjects were randomly divided into 2 groups: 11 patients used amoxicillin (250 mg orally 4 times per day) and 10 patients served as a control group, continuing to take duracef (250 mg orally 2 times per day). The treatment period consisted of 14 consecutive days for each group.

At the baseline of the study period, all patients underwent a pulmonary function test. The best of at least 3 attempts at reproducible forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) (with a difference within 200 ml or less than 5%) were measured by a Spiroanalyzer ST-350R (Fukuda Sangyo. Co Ltd. Chiba, Japan). Before the start and end of treatment, sputum was collected for analysis. Maintenance treatment, such as postural drainage and chest care, continued at home without a change throughout the study period.

Twenty-three patients were initially recruited for this study. One male (aged 56) in the amoxicillin group, and 1 female (aged 57 years) in the duracef group dropped out due to incomplete sputum study (the male patient) and massive hemoptysis (the female patient) during the study period. Totally, 11 patients (7 men and 4 women) in the amoxicillin group and 10 patients (4 men and 6 women) in the duracef group completed the entire course of treatment. Their characteristics, initial clinical assessments and sputum cellularity are presented in Table 1. The protocol was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital, and informed consent was obtained from all patients.

Sputum collection

On the morning of day 1 (the start) and the morning of day 15 (the end) of the study, the patients' mouth and tongue were swabbed dry with a gauze, and the outlets of the salivary glands were occluded by cotton pads. After receiving postural drainage and chest percussion, the

Table 1. Characteristics of patients and their sputum cellurity and cytokines level before and after therapy

	Amoxicillin Group (n = 11)		Duracef Group (n = 10)	
Age (yrs)	60.3 ± 5.4		59.3 ± 4.4	
Sex (M/F)	7 / 4		4 / 6	
Total Numbers of Involved Lobes on CxR	2.8 ± 0.4		2.5 ± 0.3	
Cause of bronchiectasis (n)				
prior pneumonia	9		7	
prior tuberculosis	2		3	
FEV1, L (% pred)	1.37 ± 0.20 (57.0 ± 7.3)		1.42 ± 0.22 (54.6 ± 8.4)	
FVC, L (% pred)	1.94 ± 0.21 (70.6 ± 7.3)		2.09 ± 0.18 (71.9 ± 7.5)	
	Pre-Treatment	Post-Treatment	Pre-Treatment	Post-Treatment
Cellurity in sputum				
Total cell count (x 10^6 PMNs/3 ml)	14.4 ± 5.1	9.3 ± 5.2**	18.8 ± 7.1	23.7 ± 13.0
Viability (%)	94.6 ± 0.8	94.8 ± 1.2	97.0 ± 1.0	97.3 ± 1.0

Definitions of abbreviation: PMNs = polymorphic neutrophils; TNF-α = tumor necrosis factor-α; IL-8 = interleukine-8.

* Values are mean ± SEM;

** $p < 0.05$, compared with pretreatment level.

patients inhaled nebulized sterile 3% saline solution for 20 minutes from an ultrasonic neubulizer (Ultra-NEB'99, DEVILBISS Co. Pascay-Meslay, France), the reservoir of which was filled with 3% saline solution (100 ml). The patients were asked to cough and the sputum was collected and sent for analysis. The sputum production was collected under the supervision of our rehabilitative therapeutist in a hospital set-up.

Sputum Processing

Preparation of the supernatant Three milliliters of sputum were diluted 1:3 with Hanks' balanced salt solution (HBSS), vortexed briefly, and centrifuged for 5 minutes at 2000 rpm. The supernatants were collected and stored at –80°C for cytokine analysis.

Preparation of the cellular component (neutrophils) The pellet containing the cells was washed twice by suspension in Ca- and Mg-free HBSS containing 10% fetal calf serum (FCS), mixing gently by vortex mixer, and then centrifuging for 5 minutes at 2000 rpm. The pellet was suspended again in 10 ml HBSS with 10% FCS, and the suspension was filtrated through a nylon mesh (with a 60 μm hole size) to yield the neutrophils. This suspension of neutrophils was at least 95% pure, using Liu's stain. The cell counts were measured by a hemocytocounter. The viability of neutrophils was determined by trypan blue dye exclusion.

Cytokine assay in the supernatant of induced sputum

interleukin-8 (IL-8) The immunoreactivity of IL-8 in supernatants was measured by a sandwich-ELISA method, using a commercial-kit (Bender MedSystems Vienna, Austria, Europe). The IL-8/NAP-1 ELISA was an assay for the quantitative detection of IL-8/NAP-1 levels in cell culture supernatants, human serum,

plasma, and amniotic or other body fluids. An anti-IL-8/NAP-1 monoclonal coating antibody was adsorbed into microwells. IL-8/NAP-1 present in the sample or standard bound to antibodies adsorbed to the microwells. A HRP-conjugated polyclonal anti-IL-8/NAP-1 antibody was added and bound to IL-8/NAP-1 captured by the first antibody. Following incubation, unbound enzyme conjugated anti-IL-8/NAP-1 was removed during a wash step, and substrate solution reactive with HRP was added to the wells. A colored product was formed in proportion to the amount of IL-8/NAP-1 present in the sample. The reaction was terminated by the addition of acid, and absorbance was measured at 450 nm. A standard curve was prepared.

Tumor necrosis factor-α (TNF-α) The TNF-α level in supernatants was also measured by an ELISA method, using a commercial-kit (Bender MedSystems Vienna, Austria, Europe). An anti-TNF-α monoclonal coating antibody was adsorbed into microwells. TNF-α present in the sample or standard bound to antibodies adsorbed to the microwells. A HRP-conjugated polyclonal anti-TNF-α antibody was added and bound to TNF-α captured by the first antibody. Following incubation, unbound enzyme conjugated anti-TNF-α was removed during a wash step, and substrate solution reactive with HRP was added to the wells. A colored product was formed in proportion to the amount of TNF-α present in the sample. The reaction was terminated by the addition of acid, and absorbance was measured at 450 nm. A standard curve was prepared.

Analysis of adhesion molecule expression on neutrophils

For the analysis of the increased plasma membrane expression of CD11b, CD18 and ICAM-1 on neutrophils (1 ml, 10^6 cells/ml), immunofluorescence flow cytometry was performed by staining cells with 5 μL monoclonal mouse antibody to human and 5 μL FITC-conjugated F (ab)'2 rabbit anti-mouse IgG (DAKOPATTS a/s, Denmark). Analysis was accomplished with a FACScan (Becton Dickinson, Mountain View, CA) by gating 10,000 counts in the neutrophil region of the forward and right angular scattergrams and using the nonbinding IgG1 as a control. Results were expressed as the mean of fluorescence intensities (M.F.I) of patient samples, taking the mean channel number of the positive cells in arbitrary units of log amplified green fluorescent signals.

Analysis of oxidative metabolism capacity in neutrophil

intracellular hydrogen peroxide production The individual leukocyte respiratory burst response was assessed using 2'.7' dichlorofluorescin diacetate (DCFH-DA) and flow cytometry [14]. In brief, after incubation in the presence or absence of stimulation, neutrophils were pelleted and resuspended in PBS containing 5 mM glucose and 0.1% gelatin, but lacking $Ca^{2+}$and Mg^{2+} (PBSg) at 10^5 cells/ml, and then loaded with DCFH-DA (1 μM) for 15 min at 37°C with shaking. Cells were washed twice with PBSg and transferred to an ice bath, then were further incubated with PE-conjugated anti-CD11b/CD18 (Beton Dickinson, Mountain View, CA, USA) for 20 min at 4°C, and subsequently analyzed by flow cytometry after 2 extensive washings with cold PBSg containing 10% FCS.

Flow cytometric analysis

Analysis was performed with a FAScan flow cytometer (Becton Dickson, Mountain View, CA) equipped with a 5 W argon ion laser at 300 MW with a 75 high voltage setting and an excitation

wavelength of 488 nm. The emitted light was collected through 488 nm and 550 nm dichroic filters. A 525-nm band-pass filter was used for gating fluorescence emission, and a 570-nm long-pass filter for scattering emission. All fluorescence was measured using logarithmic amplification. Granulocytes were identified based on forward angle light scatter and log 90° scatter parameters. Ten μl of propidium iodide were added to each sample to distinguish leukocytes from nonviable cells. After stimulation, the cells might have had a different forward angle and side (90°) light scatter, which required a change in the gates. In cases of dual-color analysis, overlap of the green fluorescence and PE emission spectra was eliminated by electronic substration. For the histogram, 5000 leukocytes were analyzed. The FACScan cytometer was always operated at the same settings.

Statistical analysis

Data are presented as mean ± standard error of the mean (SEM). One-way analysis of variance for mixed design was used to compare the values of more than 2 different experimental groups. If variance among groups was noted, a Bonferroni test wa used to determine significant differences between specific points within groups. Comparisons of only 2 different time points were made with a paired *t* test. For data with uneven variation, a Mann- Whitney *U* test (2-tailed) or Wilcoxon signed ranks test was used for unpaired or paired experimental/baseline values, respectively. The relationships between IL-8 and TNF-α, as well as changes in IL-8 and total cell counts in the amoxicillin group, CD11b M.F.I. and CD18 M.F.I., and changes in CD11b M.F.I. and CD18 M.F.I. after treatment with amoxicillin, were sought by Spearman's rank correlation test. Significance was set at $p < 0.05$.

Results

Baseline data of the study subjects

There were no significant differences in baseline data between the 2 groups in terms of age, sex, lobar involvement of bronchiectasis on chest X-ray [15], pulmonary functions (FEV_1 and FVC), and sputum cellularities (total cell count and viability) (Table 1). All bacterial culture of sputa before and after treatment showed no particular pattern for specific pathogens, such as pseudomonas. All bacterial cultures from our patients grew mixed flora, which, in our laboratory, meant that the colony counts for specific pathogens were too low to reach clinical significance.

Effect on cellularity in induced sputum

The total cell count of neutrophils in 3 ml induced sputum was significantly reduced in patients receiving amoxicillin, from 14.4 ± 5.1 to 9.3 ± 5.2 (x 10^6 cells) ($p < 0.05$). The total cell counts in the duracef group did not change ($p = 0.13$) (Table 1). The viability did not significantly change in either group. The viabilities of neutrophils before and after treatment in both groups were all above 94%.

Effect on cytokine levels in induced sputum

Amoxicillin significantly decreased the TNF-α level in the supernatants of sputum (from 168.7 ± 65.6 pg/ml to 50.3 ± 26.8 pg/ml; $p < 0.01$), whereas the TNF-α level in the duracef group did not significantly change after treatment (from 173.2 ± 47.6 pg/ml to 117.3 ± 30.9 pg/ml; $p > 0.05$) (Figure 1).

Similiary, amoxicillin also significantly decreased the IL-8 level in supernatants of sputum (from 9538.4 ± 1650.1 pg/ml to 5664.4 ± 1384.4 pg/ml; $p < 0.01$), whereas the IL-8 level

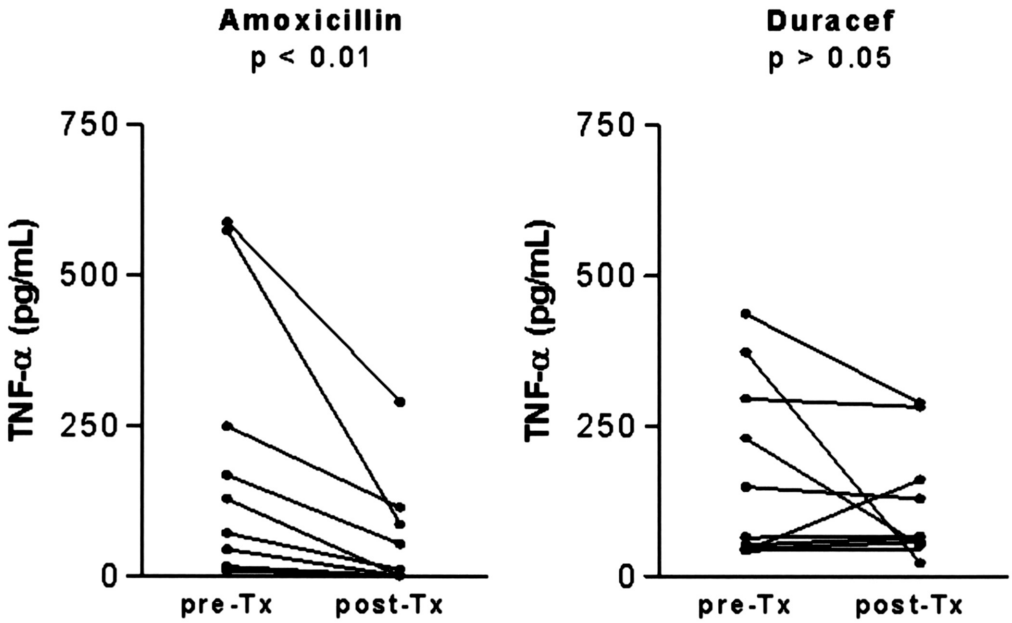

Fig. 1. The effect of amoxicillin (n=11) or duracef (n=10) on the expression of TNF-α before and after treatment in patients with bronchiectasis. The significance is indicated.

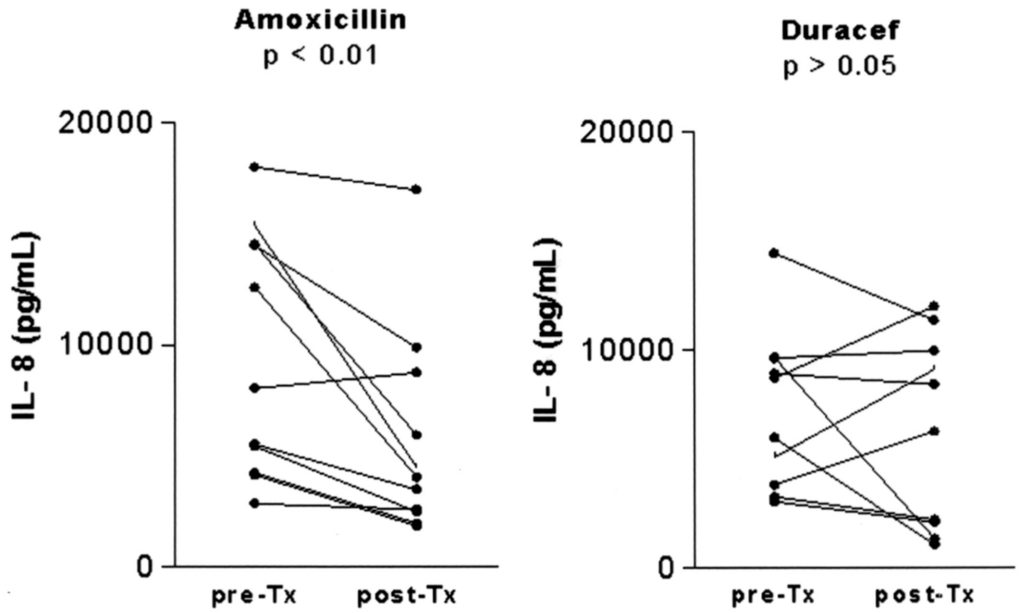

Fig. 2. The effect of amoxicillin (n=11) or duracef (n=10) on the expression of IL-8 before and after treatment in patients with bronchiectasis. The significance is indicated.

in the duracef group did not significantly change after treatment (from 7233.2 ± 1150.64 pg/ml to 6364.1 ± 1372.3 pg/ml; $p > 0.05$) (Figure 2).

In the amoxicillin group, the change in the sputum IL-8 level was significantly related to the change in the total cell count of leukocytes (r =

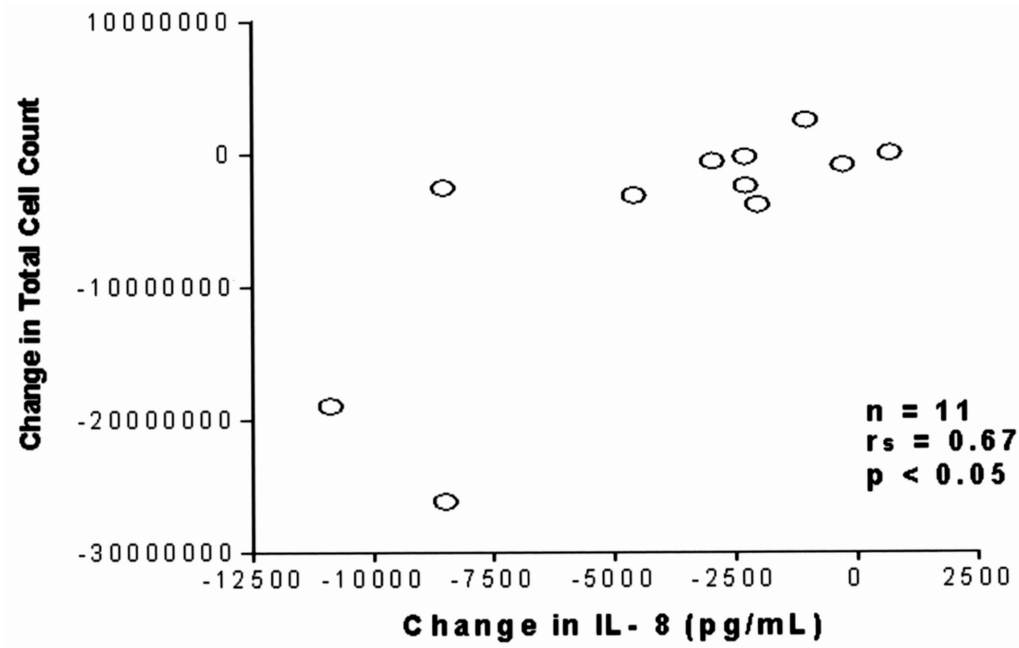

Fig. 3. The relationship between change in total cell counts of leukocytes and interleukin-8 (IL-8) level in induced sputum before and after therapy in patients receiving amoxicillin. The significance is indicated.

0.67, n = 11, $p < 0.05$) (Figure 3). There was also a significant correlation between the percentage of change in the sputum IL-8 level and total cell counts of leukocytes after antibiotic therapy in the amoxicillin group (r = 0.76, n = 11, $p < 0.01$) (Figure 4).

Effect on adhesion molecular (β2-integrin) expression of airway neutrophils

There was a trend toward a decrease in CD11b, CD18 in neutrophils in the amoxicillin groups (from 309.9 ± 43.6 to 270.6 ± 32.6 and 264.3 ± 37.2 to 215.9 ± 33.7) [expressed as mean fluorescence intensity (M.F.I.) of 10000 cells], although it was not signficantly different. The expression of leukocyte adhesion molecules CD11b and CD18 in induced sputum in the duracef group showed no significance (308.2 ± 19.8 to 325.9 ± 19.8 and 280.2 ± 19.3 to 277.6 ± 14.9) (Figure 5).

Effect on intracellular oxidative metabolism of airway neutrophils

The mean DCF fluorescence intensity of neutrophils in induced sputum, representing the airway oxidative metabolism of patients receiving amoxicillin, also showed a decreasing trend (673.7 ± 183.3 to 567.1 ± 158.0) after treatment, although it did not reach statistical significance; there was no significant change in the duracef group (495.6 ± 141.0 to 531.2 ± 129.9; $p > 0.05$) (Figure 5).

Patients tolerated antibiotics well, without any complaints. No acute infective exacerbation was found in either group during the 2-week therapy. No study subjects developed infection in the week following therapy.

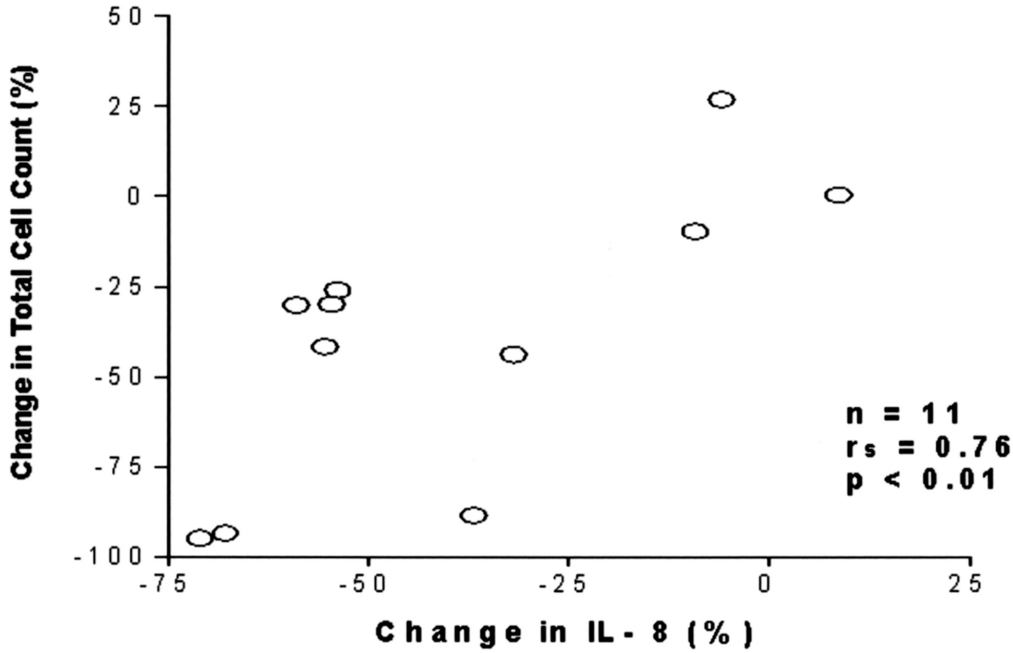

Fig. 4. The relationship between percentage change in total cell counts of leukocytes and interleukin-8 (IL-8) level in induced sputum before and after therapy in patients receiving amoxicillin. The significance is indicated.

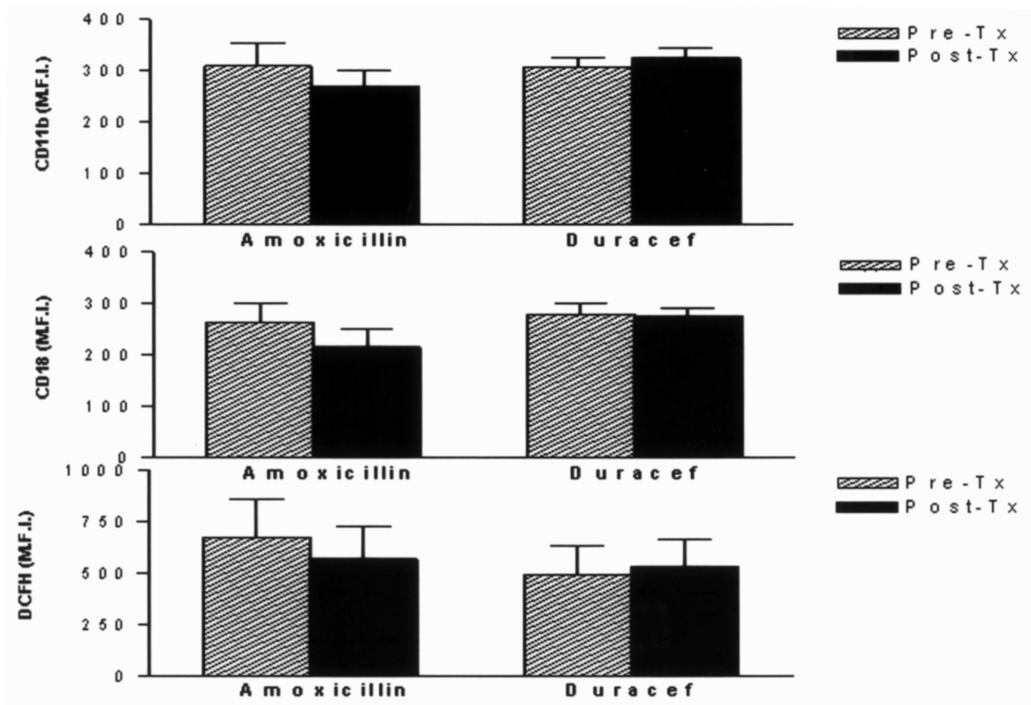

Fig. 5. The changes in leukocyte CD11b, CD18 and intracellular hydrogen peroxide [expressed by mean DCF fluorescence intensity (M.F.I.)] in patients after receiving (post-Tx) amoxicillen (n=11) or duracef (n=10), compared with the pre-treatment values (pre-Tx). The mean ± SEM values and the stastistical significance are indicated.

Discussion

Bronchiectasis is a chronic airway disease of diverse etiology, which is characterised by persistent bacterial colonization, bronchial inflammation, and progressive tissue damage [1]. The load of colonized bacteria is often associated with the production of large volumes of purulent sputum containing neutrophils [10, 16]. Neutrophil influx with reactive oxygen species and pro-inflammatory cytokines production not only provides opsonophagocytic protection from microbes [3], but is also implicated in further airway inflammation [17]. Aside from regular chest physiotherapy, current therapy with an emphasis on frequent courses of antibiotics [18] is still not able to gain a satisfactory understanding of their pharmacologic mechanisms. The present study demonstrated that amoxicillin was clinically useful in patients with bronchiectasis through its reduction of the level of pro-inflammatory cytokines, including TNF-α and IL-8, and associated total neutrophil counts in induced sputum, thus leading to a decrease in further airway injury in bronchiectasis. In contrast, duracef did not affect neutrophil activity and cytokine production in bronchiectasis.

Neutrophils mediate host defenses and tissue damage through the production of ROI and performed proteins (proteases and antibiotic proteins), which synergize for a fully destructive response [5]. Neutrophil-derived protease has been shown to stimulate interleukin-8 (IL-8) released by epithelial cells, thereby enhancing recruitment, and to inactivate the neutrophil C3Bi receptor, thus reducing the opsonophagocytic function of the cells. Janice *et al*. [19] reported that IL-8 is an important chemoattractant and presents a high concentration in the sputum of patients with chronic inflammatory airway diseases, such as bronchiectasis and cystic fibrosis. TNF-α has been implicated in the pathogenesis of many inflammatory airway diseases, such as asthma. TNF-α is known to upregulate the expression of cell adhesion molecules on endothelial cells in vitro [20] and also enhance extracellular proteolysis by neutrophils, thus leading to disease progression in bronchiectasis. Therefore, therapeutic antibiotics which reduce the IL-8 and TNF-α in the lung may have a potentially beneficial effect on disease progression in patients with bronchiectasis. Amoxicillin is used worldwide in the treatment of chronic inflammatory airway diseases. The present study demonstrated that amoxicillin, given via the oral route for 2 weeks, reduced the level of IL-8 and TNF-α in induced sputum from patients with bronchiectasis, suggesting that this antibiotic may profoundly suppress inflammatory reactions and resultant tissue injury.

The source of the IL-8 and TNF-α found in the sputum of our patients is unknown. Vera *et al*. [6] concluded that there were increased concentrations of IL-8 and TNF-α in induced sputum from patients with chronic obstructive pulmonary disease, thus leading to airway inflammation. These concentrations might be produced by the many inflammatory cells that are present in the airways, such as neutrophils and monocytes. The cellular source of IL-8 may be macrophages, neutrophils, or epithelial cells, and the TNF-α may be derived from macrophages, mast cells, or other inflammatory cells. [6, 20]. TNF-α was reported to increase IL-8 production from epithelial cells and neitrophils. The existence of a baseline high concentration of IL-8 and TNF-α in sputum suggested that epithelial cells may be another major source of IL-8 and TNF-α. A study specifically designed to address the effect of an antibiotic (amoxicillin) on the cytokine expression of differ-

ent airway cells is needed.

Neutrophil recruitment in the airway is the hallmark of bronchiectasis. IL-8 is a chemotactic cytokine with the main actions of neutrophil recruitment and activation. Pin *et al*. [21] concluded that cell counts in induced sputum could be used to investigate airway inflammation. There is increasing evidence that amoxicillin could be an immunodepressing antibiotic through a neutral effect on cytokine production [11]. Therefore, the action of amoxicillin in decreasing the neutrophil count in the sputum from patients with bronchiectasis may be through its direct effect on the inhibition of IL-8 release from airway epithelial cells.

Currie *et al*. [22] reported in their study that amoxicillin reduced the prurulent sputum volume in patients with bronchiectasis, and may improve morbidity. This double-blind randomized study, investigating the clinical improvement with amoxicillin treatment, found that there was no bactericidal effect, because the sputum culture showed no important changes in the bacterial flora and concentration of *Haemophilus spp*. after amoxicillin treatment. They suggested that amoxicillin may significantly reduce the host inflammatory response in patients with bronchiectasis. Data in the present study showed that amoxicillin modulates TNF-α and IL-8, and reduces the neutrophil count in the airway of patients with bronchiectasis.

PMNs are paramount in host response mechanisms against bacteria and fungi [23]. The ability of PMNs to combat infectious agents in the lung is due to a number of specific activities, including chemostaxis, adherence to vessel endothelium and airway epithelium, and transmigration to tissues, as well as phagocytosis and microbial killing [3]. Genetic deficiencies in cellular CD11b/CD18 are associated with the decreased mobilization of neutrophils to sites of infection and increased susceptibility to infection, reflecting the importance of CD11b/CD18 in several adherence-dependent neutrophil inflammatory and host defense functions [24]. Neutrophils sequestrated at the airways with infection and inflammation will exert their microbicidal action via ingestion and the subsequent destruction of invading micro-organisms via the change in reactive oxygen intermediates (ROI) [23]. Shappell *et al*. [25-26] also suggested that H2O2 production is adherence-dependent and mediated by the expression of Mac-1 (CD11b/CD18). In the present study, amoxicillin in the treatment of patients with bronchiectasis did not statistically decrease the expression of leukocyte β2 integrins (CD11b/CD18) on neutrophils, and the production of ROI (H2O2) by neutrophils in induced sputum; however, amoxicillin showed a greater trend toward lowering the β2 integrins (CD11b/CD18) on neutrophils, and the production of ROI (H2O2) by neutrophils, than duracef, suggesting that amoxicillin exerts a potential role in bronchiectasis by blocking the neutrophil adherence and migration to airways to produce opsonophagocytic protection. Perhaps a large scale study is needed to confirm this point.

Sampling airway secretions by means of bronchoscopy has a number of disadvantages. Previous reports [13], with an emphasis on induced sputum, had concluded that the analysis of induced sputum was a useful noninvasive method to reveal changes in inflammatory cells and markers which were similar to those reported in bronchoalveolar lavage fluid. Many studies have demonstrated that determining the IL-8 level in sputum was a good means of evaluating chronic inflammatory airway disease [19]. That is why we selected to measure the changes in neutrophil functions and cytokines in induced sputum as the responses of antibiotic therapy for airway infec-

tion and inflammation.

Taken together, the antibiotics had some effect on the patients with bronchiectasis. Amoxicillin downregulated the TNF-α and IL-8 levels in sputum. It may have decreased the total cell counts of leukocytes in sputum by means of decreasing the IL-8 expression. Through these processes, amoxicillin decreased airway neutrophil sequestration to prevent further airway damage. Our conclusion provides a new therapeutic direction in bronchiectasis treatment.

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Amoxicillin 調節支氣管擴張病人之呼吸道內白血球及前發炎細胞素之表現

鍾福財　林鴻銓

目的：探討 Amoxicillin 調節支氣管擴張病人之呼吸道內中性球及前發炎細胞素之表現。

方法：21 位穩定支氣管擴張病人隨機分為兩組，分別接受為期兩週之 Amoxicillin (250 毫克每天四次)或 duracef (250 毫克每天兩次)治療；比較治療前後，痰液內中性球數量，及 TNF-α 與 IL-8 濃度；並分析中性球附著分子表現及氧化代謝能力。

結果：接受 Amoxicillin 治療組，治療前後痰液內中性球數量(14.4 ± 5.1 降到 9.3 ± 5.2)(× 10^6 細胞) ($p < 0.05$)及 TNF-α (168.7 ± 65.6 pg/ml 降到 50.3 ± 26.8 pg/ml) ($p < 0.01$)與 IL-8 (9538.4 ± 1650.1 pg/ml 降到 5664.4 ± 1384.4 pg/ml) ($p < 0.01$)濃度皆呈現顯著減少。同時痰液內 IL-8 降低量與中性球減少數之絕對值($r = 0.67$, $n = 11$, $p < 0.05$)與相對值($r = 0.76$, $n = 11$, $p < 0.01$)皆呈現正相關。接受 duracef 治療組，治療前後則無顯著變化。而痰液內中性球附著分子表現及氧化代謝能力，兩組皆無顯著變化。

結論：Amoxicillin 可藉由調節支氣管擴張病人痰液內 TNF-α 與 IL-8 濃度，以減少呼吸道內中性球數量，及可能對呼吸道的損傷。*(胸腔醫學* ***2006; 21: 392-405****)*

關鍵詞：支氣管擴張， Amoxicillin ，中性球，腫瘤壞死因子-α ，細胞間素-8

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Levels of sTREM (Soluble Triggering Receptor Expressed on Myeloid Cells)-1 in Pleural Effusion as an Indicator of Pulmonary Bacterial Infection

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Background: The presence of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in bronchoalveolar fluid in patients receiving mechanical ventilation can be an indicator of pneumonia. The diagnostic role of sTREM-1 in pleural effusion for patients with pulmonary bacterial infection is still uncertain.

Methods: We performed a prospective observational study. A total of 25 patients were enrolled and divided into 2 groups: 13 with bacterial parapneumonic effusion and 12 with transudative effusion. The sTREM-1 concentration in pleural effusion was measured by a sandwich enzyme-linked immunosorbent assay. Unpaired Student's t tests were used to compare the differences between the groups. Receiver operator characteristic analysis was performed to determine the optimal cut-off value.

Results: Levels of sTREM-1 in pleural effusion were significantly higher in parapneumonic effusion than in transudative effusion (p = 0.023). The optimal diagnostic value of sTREM-1 in discriminating parapneumonic from transudative pleural effusion was set at 29.69 pg/mL, with a sensitivity and specificity of 75% and 100%, respectively.

Conclusions: A higher concentration of sTREM-1 in pleural effusion is a useful indicator for the detection of bacterial parapneumonic effusion. Further studies are warranted to clarify its role in discriminating different pathogens and predicting patient outcomes. ***(Thorac Med 2006; 21: 406-412)***

Key words: soluble triggering receptor expressed on myeloid cells, pleural effusion

Introduction

Many biological markers have been studied in the assessment and differential diagnosis of infectious diseases [1-2]. In addition to traditional inflammatory parameters such as C-reactive protein (CRP) and white blood cell (WBC) counts, a newly discovered receptor expressed on the surface of neutrophils and a subset of monocytes, known as the triggering receptor expressed on myeloid cells (TREM)-1, was identified as detecting the acute inflammatory response to microbial

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products [3]. A soluble form of TREM-1 (sTREM-1) is released from the activated phagocytes and can be measured in various body fluids. The presence of sTREM-1 in bronchoalveolar fluid from mechanically ventilated patients has been shown to be a good indicator of infectious pneumonia [4].

The development of pleural effusion (PE) is a common manifestation of pulmonary disease. Parapneumonic effusions might occur in 20-40% of patients who are hospitalized due to pneumonia [5]. The classical biochemical markers, such as pH, glucose, protein, and lactate dehydrogenase (LDH), are not always effective for differentiating between the different types of effusions, particularly between infectious and non-infectious diseases [6]. Thus, it would be paramount to investigate other markers that can establish a more accurate diagnosis between these 2 types of pleural effusion. For this study, we prospectively investigated the diagnostic value of sTREM-1 levels in pleural effusion for the purpose of discriminating parapneumonic from transudative effusion.

Materials and Methods

From September to December 2005, we prospectively enrolled 33 patients admitted to National Taiwan University Hospital (NTUH) with clinically significant pleural effusion detected either by chest radiography or ultrasonography. Specimens of pleural effusion were measured through routine workups (cells counts, differential classification and biochemistry), microbiological cultures (bacteria, tuberculosis and fungus), and cytological analysis. Patients were excluded from this study for any of the following: (a) unproved diagnosis; (b) hemothorax; (c) proved non-bacterial pulmonary infection; or (d) malignant pleural effusion.

Parapneumonic effusion was diagnosed according to the existence of pleural effusion associated with the clinical and biochemical features of pneumonia, fulfilling at least 3 of the following criteria: (a) fever up to 37.5^{o}C; (b) pulmonary infiltrations seen in chest radiography; (c) purulent airway secretions; (d) WBC counts >12000 mm^{3}; and (e) positive sputum culture results for bacteria. Exudative and transudative effusions were diagnosed according to Light's criteria [7]. The following clinical data were collected for each patient: age, sex, admission diagnosis, underlying diseases or conditions, and serum infection parameters, including white blood counts with or without CRP.

After obtaining informed consent from patients or next of kin, pleural effusion was collected by thoracentesis and centrifuged at 4^{o}C, separated into aliquots and stored at -80^{o}C until the day of assay. Concentrations of sTREM-1 in pleural effusion were determined by a sandwich enzyme-linked immunosorbent assay. In short, 96-well goat anti-mouse IgG coated plates (R&D Systems, Minneapolis, Minn., USA) were incubated overnight at room temperature with 400 ng per well mouse anti-human TREM-1 captured antibody (R&D Systems). The plates were then washed with 0.05% Tween 20 in phosphate-buffered saline. Samples and standards were diluted in phosphate-buffered saline containing 20% fetal calf serum and incubated for 2 h. Human recombinant sTREM-1 was used as the standard (R&D Systems). After 3 washes, 40 ng per well biotinylated goat anti-human TREM-1 (R&D Systems) was added for 2 h at room temperature. After 3 washes, bound sTREM-1 was detected with peroxidase-conjugated streptavidin (R&D Systems) and ortho-phenylenediamine as the substrate. The color reaction was stopped after

10 min with 2 N H2SO4, and the absorbance was read at 450 and 560 nm for wavelength correction. All measurements were performed in duplicate and in a blinded fashion.

For statistical analysis, data were expressed as mean ± SD with range, and in the case of a skewed distribution, a median was used with range. We used a Chi-square test for categorical variables and a Fisher's exact test, if appropriate, along with a Student's *t* test for continuous variables. To determine the optimal cut-off value for discriminating parapneumonic from transudative effusion, the receiver operator characteristics (ROC) model was used for analysis. Statistical analyses were performed with the SPSS-10 computer software program (SPSS, Inc., Chicago, IL). A *p* value of less than 0.05 was considered statistically significant.

Results

During the 3-month study period, 25 patients were enrolled. The parapneumonic effusion group consisted of 13 patients with a mean age of 72.0 (range, 54-86) years, and a male percentage of 85%. The transudative effusion group consisted of 12 patients with a mean age of 67.5 (range, 49-90) years, and a male percentage of 75%. Laboratory measurements, as shown in Table 1, including total WBC counts in both serum and effusion, neutrophil and lymphocyte counts in the effusion, and WBC and CRP in the serum, did not demonstrate a significant difference between the 2 groups.

The mean concentration of sTREM-1 in the pleural effusion of the parapneumonic group was 184.70 ± 210.28 pg/mL, and that in the transudative group was 30.26 ± 47.75 pg/mL. The difference between these 2 groups was statistically significant ($p = 0.022$) (Figure 1). Using ROC analysis, the Wilcoxon estimate (95% CI) of the area under the ROC curve (AUC) was 0.885 (0.683 to 1) (Figure 2). The optimal cut-off value was determined to be 29.69 pg/mL, with a diagnostic sensitivity of 100% and a specificity of 75%.

Table 1. Characteristics of the 25 patients

	Parapneumonic n=13	Transudative n=12	*p* value
Age (years)	72.0 ± 11.3 (13,54-86)	67.5 ± 13.6 (12,49-90)	*p*=0.380
Male	11/13 (85%)	9/12 (75%)	*p*=0.849
WBC (E)	1600 ± 2057 (13,200-7400)	1285 ± 2796 (12,25-10000)	*p*=0.753
Lymphocyte (E)	405 ± 537 (13,60-2047)	622 ± 1454 (12,21-5200)	*p*=0.634
Neutrophil (E)	1048 ± 1982 (13,40-6910)	416.8 ± 865 (12,0-3000)	*p*=0.311
WBC (S)	15617 ± 14372 (13,1570-46840)	8091 ± 4959 (12,330-17440)	*p*=0.096
CRP (S)	7.4 ± 9.3 (8,2-9.8)	3.6 ± 2.4 (5,0.81-7.29)	*p*=0.300

*Data are presented as No./total (%) or mean ± SD (No., range)

*E = effusion; S = serum

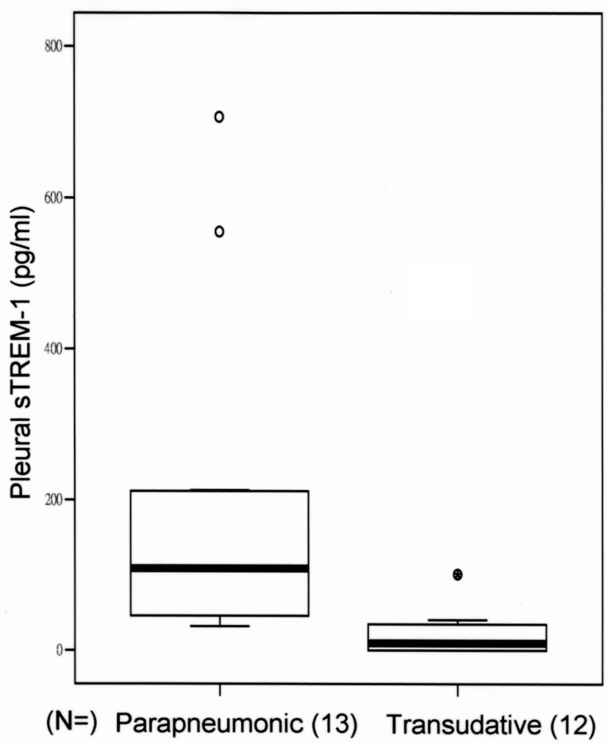

Fig. 1. Levels of soluble triggering receptor expressed on myeloid cells (sTREM-1) in the pleural effusion of 13 patients with pneumonic effusion and 12 patients with transudative effusion.
Legends: Individual values are plotted, and the bars represent the means of the values. $p < 0.001$ for the comparison between the groups of patients with parapneumonic and transudative effusion.

Discussion

The results of this study revealed significantly increased sTREM-1 levels in bacterial parapneumonic effusions as compared to transudative effusions, which could indicate the need for close follow-up up to detect its progression to complicated effusion, and the need for an urgent application of pleural drainage.

However, median sTREM-1 levels in both groups were higher than the recommended cut-off level of 5 pg/mL in BAL fluid with pneumonia [4], although they were much lower than the cut-off level of 60 ng/mL in plasma with sepsis [8]. A reasonable explanation is that flashed water diluted the sTREM-1 concentration in the BAL fluid, and high levels in the serum reflected the severe inflammatory response in patients with sepsis. To date, no published studies have addressed the impact of sTREM-1 levels in the detection of bacterial parapneumonic effusion. Concerning the usefulness of the sTREM-1 concentration as a diagnostic parameter in pleural effusion, we used a cut-off level of 29.69 ng/mL for differentiating between bacterial parapneumonic and transudative effusion.

According to the new classification by Light [9], a typical uncomplicated parapneumonic effusion includes the following: a negative Gram stain and culture, and the following biochemical data: pH >7.2, glucose >40 mg/dL, and LDH less than two-thirds of the serum upper reference limit. When LDH rises to greater than 3 times the serum upper reference limit and/or pH falls to less than the level of 7.0-7.2, and the results of bacteriological analysis are negative, the effusion is borderline complicated and must be closely followed up to detect its progression to complicated (pH <7.0 and/or glucose <40 mg/dl, or a positive Gram stain or culture), in which tubal thoracostomy or surgical intervention for drainage is indicated. Thus, a new biomarker for the local inflammatory response is needed, one that can be used as an indicator for the detection and management of parapneumonic effusion.

Various molecules, such as CRP, interleukin-6 (IL-6), IL-8, soluble intercellular adhesion molecule-1 (sICAM-1), soluble fas ligand (sFasL), neutrophil elastase (NE), polymorphonuclear elastase (PMN-E), myeloperoxidase (MPO) and procalcitonin (PCT) have been used as diagnostic tools for discriminating infectious and non-infectious pleural effusions [10-18]. However, none of them have gained wide clinical accep-

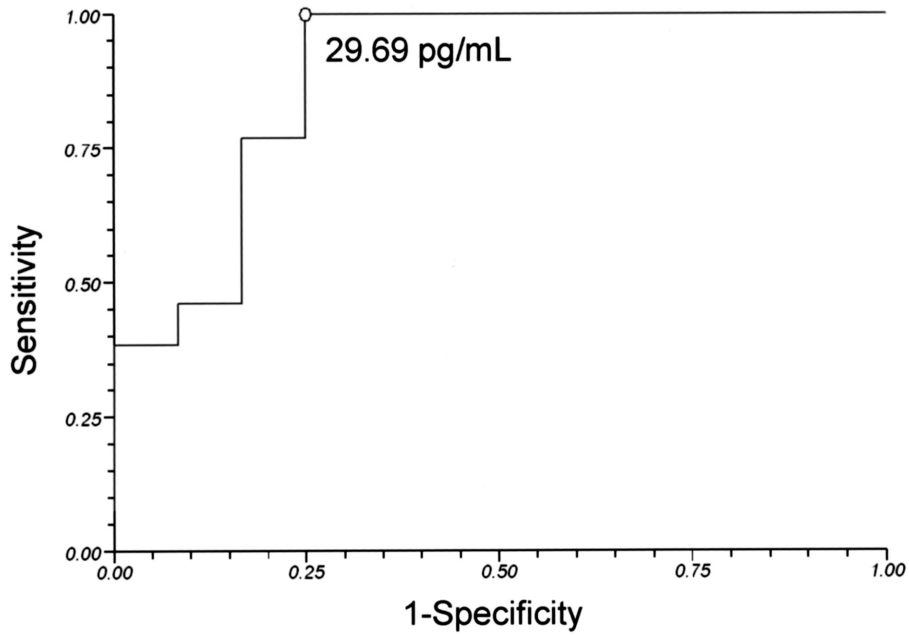

Fig. 2. Receiver operating characteristic curves for cut-off levels of soluble triggering receptor expressed on myeloid cells (sTREM-1) in pleural effusion, for differentiating between parapneumonic and transudative effusion.
Legend: Areas under the receiver operating characteristic curves were 0.885 (95% confidence interval, 0.683 to 1) for a cut-off value of 29.69 pg per milliliter of sTREM-1 in pleural effusion.

tance because the clinical significance of these variables is unclear, and most of the findings have not been confirmed in large series studies.

TREM-1 is a cell surface molecule expressed on granulocytes, monocytes, and a subset of macrophages. Like other cell-surface receptors, TREM-1 has a short intracellular domain, and, when bound to its still unidentified ligand, it activates a signal-transduction molecule called DAP12 and triggers the secretion of inflammatory cytokines, amplifying the host response to bacterial stimuli [3, 19]. Human tissues infected with bacteria are infiltrated with neutrophils and macrophages that express high levels of TREM-1. Conversely, TREM-1 is only weakly expressed in samples from patients with noninfectious inflammatory disorders [3]. The sTREM-1 is released from the activated phagocytes, and its presence in bronchoalveolar lavage fluid has recently been demonstrated as a good indicator of infectious pneumonia in mechanically ventilated patients [4]. Plasma levels of sTREM-1 have also been shown to be helpful in identifying critically ill patients suffering from infection [8]. Such a biological marker is able to distinguish the inflammatory response to infection from noninfectious inflammation, which should be considered of clinical use. Furthermore, elevated levels were observed in the bacterial parapneumonic group in this study, compared with the transudative group. However, other microbial infections, such as tuberculosis or fungal infection, were not included in this study.

In conclusion, our results indicate that pleural fluid sTREM-1 determination is one of the parameters for discriminating between parapneumonic and transudative effusion. With the establishing of a differentiating cut-off point at 29.69

pg/mL, higher sTREM-1 values would suggest an infectious process, probably of bacterial origin, and could indicate the need for thoracentesis and/or the urgent application of pleural drainage. Further studies are warranted to clarify its role in discriminating different pathogens and predicting patient outcomes.

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肋膜積液中骨髓細胞表達的可溶解觸發受體（sTREM-1）值可做爲肺部細菌感染的指標

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背景：在支氣管肺泡灌洗液中，骨髓細胞表達的可溶解觸發受體（sTREM-1）的有無，可作為接受呼吸器患者是否有肺部感染的指標。但是在肋膜積液中，sTREM-1 值所扮演的的角色尚未明朗。

方法：這是一個前瞻性的觀察研究，總共有 25 位患者分為兩組為研究對象。13 位為細菌性肺炎相關肋膜積液及 12 位為滲出性肋膜積液的患者。我們利用酵素連結免疫吸附分析的方法測出肋膜積液中 sTREM-1 的濃度。統計上則是利用 *t*-test 來比較兩組的差異，並利用 ROC 曲線分析來決定兩組的臨界值，

結果：在肺炎相關的肋膜積液中 sTREM-1 濃度值比滲出性的肋膜積液為高 ($p = 0.023$)。在肋膜積液中，sTREM-1 的最佳診斷臨界值為 29.69 pg/ml ，以用來區分細菌性肺炎相關或滲出性的肋膜積液，其靈敏度及特異度分別為 75% 及 100% 。

結論：在細菌性肺炎相關的肋膜積液中 sTREM-1 有較高的濃度，並可作為其指標。對於 sTREM-1 值在其他菌種的感染及病患預後的影響則需進一步的研究來釐清。*(胸腔醫學* ***2006; 21: 406-412)***

關鍵詞：骨髓細胞表達的可溶解觸發受體（sTREM-1），肋膜積液

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Clinical Characteristics and Outcome in Adult Patients with Pneumococcal Empyema

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Background: Pneumococcus is the leading cause of pneumonia. However, little data exists concerning the clinical characteristics and risk factors associated with pneumococcal empyema, a common complication of pneumococcal pneumonia.

Patients and Methods: This study retrospectively reviewed the data of 20 adult patients with culture-proven pneumococcal empyema who were hospitalized at Chang Gung Memorial Hospital, Taipei, from November 1998 to May 2005. Baseline characteristics, underlying diseases, outcome parameter and antibiotic insusceptibility rates were analyzed. Additionally, outcome parameters for 2 groups— the community-acquired empyema (CAE) group (n=12) and the hospital-acquired empyema (HAE) group (n=8)—were compared.

Results: Patients with HAE had a higher pulse rate, higher pH value and lower PaO2 of arterial blood gas than the CAE patients (p=0.073, 0.024 and 0.055, respectively). Malignancy, which was the most common underlying disease for both groups, was more common in the HAE group (87.5%, n=8) than in the CAE group (33%, n=12) (p=0.017). The most common malignant diseases were lung, head, and neck cancer. Duration of parenteral antibiotics therapy, duration of fever, and duration of hospital stay were longer in the HAE group than in the CAE group (all p <0.05, respectively). The antibiotic insusceptibility rates of penicillin, cefuroxime, ceftriaxone and vancomycin were not significantly different between the CAE and HAE group (all p>0.2).

Conclusion: Patients with HAE had poorer outcomes than those with CAE. Underlying malignancies were a major risk factor for HAE. ***(Thorac Med 2006; 21: 413-421)***

Key words: pneumococcal empyema, pleural effusion, malignancy, antibiotics, susceptibility

Introduction

Streptococcus pneumoniae, the most common bacterial pathogen causing community-acquired pneumonia in both adults and children, results in an estimated 500,000 cases of pneumonia each year [1]. The pneumococcus (*Streptococcus pneumoniae*) is also the most common etiological agent in community-acquired pneumonia in adult hospitalized patients in Taiwan [2], and is the leading cause of hospital-acquired pneumonia in hospitalized patients not in inten-

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sive care unit (ICU) [3].

In a previous clinical study, 4.5% of adult patients developed culture-proven empyema after pneumococcal pneumonia [4]. In hospital-acquired cases, empyema also frequently occurred after chest surgery or thoracocentesis, or due to a subdiaphragmatic pathogenic condition or congestive heart failure complicated with aspiration pneumonia [5]. Thoracic empyema has an overall mortality rate of up to 20% [6]. Despite increasing antimicrobial resistance, little data exist regarding the risk factors for pneumococcal empyema. A previous study indicated that hospital-acquired empyema (HAE) has a higher mortality rate than community-acquired empyema (CAE) [5]. However, data elucidating the different clinical characteristics of CAE and HAE are limited. Some studies showed that malignancy is a common underlying disease among patients with invasive *Streptococcus pneumoniae* infection [7]. No study has determined whether malignancy predisposes patients to respiratory tract and pleural infection, or even the malignancies that are likely related to pneumococcal empyema.

This study compared the initial clinical characteristics, underlying diseases, antibiotic susceptibility, treatment and clinical outcomes of community-acquired empyema (CAE) and hospital-acquired empyema (HAE) caused by *Streptococcus pneumoniae*. This study also describes the characteristics of cancer patients with pneumococcal empyema.

Patients and Methods

Data was obtained for 20 patients, aged 18 or older, with pleural effusion and culture-proven pneumococcal empyema, and hospitalized at Chang Gung Memorial Hospital, Taiwan, between November 1998 and May 2005. Cases were chosen according to the availability of patient charts. The data was representative of the first presentation of pneumococcal empyema for all patients. CAE was defined as an acute infection in the pleural space diagnosed within the first 48 hours of admission. HAE was defined as thoracic empyema that occured >48 hours after admission—not incubating at the time of admission.

Pleural fluid specimens were obtained using thoracocentesis or during tubal thoracotomy. Pneumococcal empyema was considered present when a finding of pleural effusion on a chest radiograph was coupled with any of the following: culture or Gram staining of pleural fluid positive for *Streptococcus pneumoniae*; pleural fluid with a pH of <7.2; a lactate dehydrogenase level of >1000 IU/mL; glucose level of <20 mg/dL; protein level of >3000 mg/dL; and/or white blood cell count (WBC) of >50,000 cells/mL [8-9].

Susceptibility of isolates to penicillin, cefuroxime, ceftriaxone was determined by microdilution. Susceptibility to vancomycin was determined by the disk diffusion method, according to the National Committee for Clinical Laboratory Standards, 2000. Isolates in the intermediate or resistant categories were considered non-susceptible.

The following data were collected for each patient: age; predisposing factors including important underlying diseases and associated medical conditions; vital signs on arrival; hematological and biochemical investigative results; pathogens isolated from effusion specimens; treatment details, including the regimen and duration of antibiotic therapy, and invasive drainage procedures and surgery; and patient outcome, including duration of antibiotics therapy, closed drainage, fever, ICU stay, and hospital stay.

Statistical analysis was performed using

SPSS 10.0 for Windows and GraphPad Prism 4. Continuous variables were compared using the Student's independent samples t- test. Proportions were compared using the chi-square test (2-tailed, confidence interval (CI) 95%). A value of $p<0.05$ was considered statistically significant.

Results

Twenty adults, 15 males (75%) and 5 females (25%), were enrolled in this study. No subject had a documented history of pneumococcal vaccination or a stay in a nursing home. Twelve (60%) subjects had CAE and 8 (40%) had HAE. The average hospital stay before diagnosis of CAE and HAE was 0.5 ± 0.9 days and 17.4 ± 8.9 days. Table 1 presents a summary of the clinical characteristics for both groups. The mean ages of the patients in the CAE and HAE groups were 59.9 ± 16.8 years and 55.9 ± 14.7 years, respectively. The male-to-female ratio in both groups was 3: 1. The HAE patients had a lower pH of arterial blood gas than the CAE patients (p=0.024). Although the HAE patiens had a lower PaO2 value than the CAE patients, the difference was not statistically significant (p=0.055). The remaining characteristics of the 2 groups, including clinical signs, hemograms, and biochemistry data,

Table 1. Patient Characteristics

Parameters	CAE (n=12)	HAE (n=8)	*p* value
Gender (M:F)	9:3	6:2	
Age (years)	59.9 ± 16.8	55.9 ± 14.7	0.591
Clinical signs (initial presentations)			
Body temperature (°C)	37.0 ± 0.9	36.9 ± 1.2	0.771
Conscious level (Coma scale)	15.0 ± 0.0	15.0 ± 0.0	1.000
Pulse rate (rate/min)	105.8 ± 17.0	120.4 ± 20.1	0.073
Respiratory rate (rate/min)	22.7 ± 4.9	22.3 ± 4.1	0.845
Systolic blood pressure (mmHg)	112.8 ± 36.0	119.1 ± 13.1	0.659
Hemograms			
White blood cell count (10^3/μl)	12.9 ± 12.0	13.7 ± 5.4	0.376
Neutrophil (%)	75.2 ± 25.0	77.8 ± 16.7	0.402
Hematocrit (%)	32.3 ± 4.1	34.7 ± 5.4	0.132
Platelet (10^3/μl)	284.5 ± 128.2	285.1 ± 116.2	0.496
Biochemistry			
Albumin (g/dl)	2.7 ± 0.8	2.6 ± 0.5	0.779
Sugar (mg/dl)	179.2 ± 163.8	192.0 ± 53.8	0.869
Basic urea nitrogen (mg/dl)	30.2 ± 19.7	20.9 ± 10.1	0.239
Serum sodium (mmol/liter)	134.3 ± 5.3	133.6 ± 9.3	0.829
Baseline Arterial blood gas (ABG) analysis			
pH	7.30 ± 0.18	7.47 ± 0.09	0.024
PaO_2 (mmHg)	68.18 ± 18.11	91.44 ± 35.67	0.055
$PaCO_2$ (mmHg)	44.1 ± 27.10	31.3 ± 6.03	0.193
HCO_3^- (meq/L)	20.1 ± 8.17	21.95 ± 5.45	0.346

PaO_2: partial pressure of arterial oxygen; $PaCO_2$: partial pressure of arterial carbon dioxide; HCO_3^-: arterial bicarbonate

Table 2. Underlying Diseases of all Patients in Both Groups

Parameters	CAE (n=12)	HAE (n=8)	*p* value
Malignancy	4 (33.3%)	7 (87.5%)	0.017
Lung cancer	1 (8.3%)	3 (37.5%)	0.110
Buccal cancer	0 (0%)	1 (12.5%)	0.209
Laryngeal cancer	0 (0%)	1 (12.5%)	0.209
Esophageal cancer	0 (0%)	1 (12.5%)	0.209
Hepatocellular carcinoma	0 (0%)	1 (12.5%)	0.209
T-lymphoblastic lymphoma	0 (0%)	1 (12.5%)	0.209
Mesothelioma	1 (8.3%)	0 (0%)	0.402
Malignant hemangiopericytoma	1 (8.3%)	0 (0%)	0.402
Rectal cancer, Duke D	1 (8.3%)	0 (0%)	0.402
Chronic obstructive airway disease	2 (16.7%)	0 (0%)	0.224
Asthma	1 (8.3%)	1 (12.5%)	0.761
Bronchiectasis	1 (8.3%)	0 (0%)	0.402
Diabetes mellitus	3 (25.0%)	1 (12.5%)	0.494
Congestive heart failure	3 (25.0%)	0 (0%)	0.125
Steroid use	2 (16.7%)	2 (25.0%)	0.648

were not statistically different.

Table 2 lists the underlying diseases of both patient groups. Of the 12 CAE patients, 4 (33.3%) had a history of malignancy (3 with progressive cancer and 1 with a history of malignant hemangiopericytoma who was in a disease-free status). Of the 8 HAE patients, 7 (87.5%) had a history of cancer (6 with cancer currently in progression and 1 with lung cancer status following pneumonectomy); the only patient without a history of cancer was diagnosed with hepatocellular carcinoma 27 months after the empyema episode. The prevalence of other comorbidities, including asthma, diabetes mellitus, steroid use (found in both groups) or bronchiectasis and congestive heart failure (found only in patients with community-acquired empyema), were not significantly different between the 2 groups. No patient in this study had a history of cerebrovascular accidents or renal disease.

Of the 11 patients with underlying neoplastic diseases, 2 (18.1%) were disease-free (1 with malignant hemangiopericytoma and lung metastasis status following surgery, radiotherapy and chemotherapy; 1 with lung cancer following pneumonectomy) and 9 had active neoplastic diseases. The mortality rate was 33% in the patients with active neoplastic diseases. The average interval from diagnosis of cancer to culture-proven empyema was 20.25 ± 20.80 months (range, 0.5-53 months). Seven of 9 patients had received chemotherapy. None of these 9 patients had leukopenia when diagnosed with pneumococcal empyema.

Table 3 presents the treatment and clinical outcome of the CAE and HAE patients. After culture-proven empyema was diagnosed, the HAE patients had a longer duration of parenteral antibiotics therapy, duration of fever and duration of hospital stay, than the CAE patients (all $p< 0.05$, respectively). The duration required for closed drainage (either by chest tube or by pig-

tail catheter) was not significantly different between the 2 groups. Three patients with CAE did not receive closed drainage: 1 declined closed drainage and recovered after many instances of chest tapping; 1 died due to rapidly progressing pneumonia with septic shock before closed drainage could be performed, 1 had only a very small amount of empyema and died due to upper gastrointestinal bleeding. One patient with HAE did not receive closed drainage because tumor bleeding developed suddenly after diagnosis of empyema and the patient died. Seven (58.3%) of 12 patients in the CAE groups and 6 (75%) of 8 patients in the HAE groups were transferred to an ICU, and the average hospital stay was 8.3 ± 17.0 days and 15.1 ± 18.3 days, respectively. No patient received intrapleural fibrinolytic agents. Mortality rates during hospitalization were 16.7% (2/12) in the CAE group (1 patient without a history of cancer died due to septic shock and 1 with a history of hemangiopericytoma died due to upper gastrointestinal bleeding), and 37.5% (3/8) in the HAE group (1 with esophageal cancer died due to multiple organ failure, 1 with buccal cancer died due to tumor bleeding, and 1 with triple cancer died due to arrhythmia).

The insusceptible rates for penicillin, cefuroxime, ceftriaxone, and vancomycin were 41.7%, 33.3%, 0%, and 0%, respectively, for the CAE patients (Table 4), and 62.5%, 50%, 12.5%, and 0%, respectively, for the HAE patients (Table 4). In the patients with susceptible and insusceptible isolates to penicillin, cefuroxime and ceftriaxone, the mortality rates were 30% (3/10) and 20% (2/10), 25% (3/12) and 25% (2/8), 21.1% (4/19) and 100% (1/1), respectively (p=0.605, 1.000, and 0.076, respectively).

Discussion

Pneumococcus is a major cause of community-acquired infections, and there is increasing interest in its role in the epidemiology of hospital-acquired infections [10]. Most studies analyzing pneumococcal infections have focused on lung infection, either community-acquired or hospital-acquired pneumonia. This study is the first to highlight the different characteristics and outcomes associated with CAE and HAE caused by pneumococcus. Retrospective analysis of patient data showed that HAE patients had poorer outcomes than CAE patients, leading to longer fever duration, antibiotic use, and subsequent hospital stay for the HAE patients. Underlying malignancy was a major risk factor for HAE. Once patients developed an invasive pneumococcal disease, such as HAE or CAE, antibiotic susceptibility did not influence patient the outcome.

In adults with pneumococcal pneumonia, pleural effusion can occur in up to 57% of cases [11]. Most cases of pleural effusion resolve spontaneously without the need for further intervention. However, because of the interplay of a number of host and microbial factors, pleural effusion can progress to empyema (a collection of purulent material in the pleural space). Pleural empyema is the most common complication of bacterial pneumonia. Examination of pleural fluid parameters helps determine the presence of an empyema and the need for drainage. Pleural empyema in pneumococcal pneumonia has an incidence of 2% to 8% [12]. Unfortunately, there have been no controlled prospective trials with children that compare the outcome of different treatment strategies for empyema.

Fever, tachycardia, tachypnea and leukocytosis commonly present in patients with systemic inflammatory response syndrome. In this study, baseline tachycardia and mild tachypnea were identified in both the CAE and HAE groups; how-

Table 3. Treatment and Clinical Outcome of Patients in Both Groups

Parameters	CAE (n=12)	HAE (n=8)	*p* value
Duration of antibiotics therapy (days)	23.2 ± 10.2	36.8 ± 15.6	0.030
Duration of drainage (days)	16.2 ± 9.8 (n=9)	24.1 ± 16.4 (n=7)	0.248
Duration of fever (days)	8.8 ± 8.6	21.6 ± 14.2	0.022
ICU stay (days)	8.3 ± 17.0 (n=7)	15.1 ± 18.3 (n=6)	0.604
Hospital stay (days)	27.5 ± 14.3	48.0 ± 18.2	0.012
Mortality rate	16.7% (2/12)	37% (3/8)	0.292

Table 4. Insusceptibility to Antibiotics Rate in Both Groups

Antibiotics	CAE	HAE	*p* value
Penicillin	41.6%	62.5%	0.361
Cefuroxime	33.3%	50%	0.456
Ceftriaxone	0%	12.5%	0.209
Vancomycin	0%	0%	-

ever, the mean body temperature on arrival was normal. Lack of fever (>38°C) has been associated with a high in-hospital mortality rate among CAE patients [13]. Therefore, excluding pneumococcal empyema for patients with pneumococcal pneumonia and pleural effusion is important even when the patient is initially afebrile. Similarly, initial arterial blood gas analysis indicated that the HAE patients had a higher pH and PaO2 than the CAE patients (p=0.024 and 0.055, respectively). A review of the chest films showed that 11 (91.7%) of the 12 CAE patients had pneumonic patches, and only 4 (50%) of the 8 HAE patients had pneumonic patches when empyema was identified (p=0.035). Since HAE was not necessarily a complication of pneumonia, the lung parenchyma and airways were minimally involved initially in some cases.

In the CAE group, 2 patients had chronic obstructive pulmonary disease (COPD), 1 had bronchiectasis and 3 had congestive heart failure. In contrast, no patient had COPD, bronchiectasis, or congestive heart failure in the HAE group. This difference in underlying diseases may account for the blood gas data which showed that the CAE group had more severe acidosis and hypoxemia than the HAE group. Despite the better arterial blood gas data, the HAE group had worse outcomes than the CAE group, suggesting that an underlying airway disease and heart function may not be the major determinants of pneumococcal empyema. A further study with a larger number of patients than that in this study is needed to determine the clinical significance.

Outcomes were poor for pneumococcal infection [4] and empyema [14] in patients with major underlying diseases. This study recognized that the prevalence of cancer was higher (87.5%) among the HAE patients than the CAE patients (33.3%) (p=0.017). Several possible reasons may account for the increased susceptibility to empyema of patients with malignant diseases. First, these patients need hospitalization for chemotherapy, radiotherapy and surgery; consequently, they are often exposed to the risk of nosocomial infections. Besides, the primary sites of cancer of the patients in this study were the intrathoracic organs, such as the lungs, esophagus and pleura. Some cases with a primary site outside the thorax had lung metastases. Most of these patients had undergone invasive procedures for intrathoracic lesions. Previous lung surgery is an important risk factor for infection [15-16]. Moreover, an endobronchial lesion is also a predisposing factor for

an empyema. A pre-existing fluid accumulation, either malignant pleural effusion or transudates secondary to hypoalbuminemia or volume reduction, also contributed to bacterial translocation. Bone marrow suppression after chemotherapy was considered an etiology of an immunocompromised status; however, no patient in this study group had leukopenia. Compared with the CAE patients, the HAE patients had a longer duration of fever, period of parenteral antibiotic therapy, and length of hospital stay. Based on this study and the literature [14], we propose that underlying malignancy should be the major precipitating factor for HAE.

The rates of insusceptiblity to penicillin and cefuroxime were higher in this study. Several previous studies had demonstrated that insusceptibility to penicillin is not associated with higher mortality for patients with pneumococcal infections [4]. In this study, no statistically significant difference existed for insusceptibility rates between the CAE and HAP patients, suggesting that antibiotic insusceptibility did not influence patient outcome. This finding is somewhat consistent with those of a previous study of pneumococcal pneumonia [4].

No patients in this study had received a pneumococcus vaccine before the episode of pneumococcal pneumonia. Schultz reviewed 230 pediatric patients hospitalized for empyema, and concluded that after universal use of the pneumococcal conjugate vaccine, the number of patients with empyema and the prevalence of pneumococcus decreased [17]. In an era when vaccines against pneumococcal disease are available, understanding the epidemiology of serious pneumococcal infections is important to planning strategies that prevent invasive diseases and remaining vigilant regarding changes in serotype distribution. The recently licensed 7-valent pneumococcal conjugate vaccine (Prevnar; Wyeth-Lederle Vaccines) recommended for universal use for children <23 months of age does not contain serotype 1 [18]. However, the licensed 23-valent polysaccharide vaccines and the investigational 9-valent and 11-valent pneumococcal conjugate vaccines containing serotype 1 have also been available recently [19]. Since malignant disease is a major risk factor of pneumococcal empyema, vaccines may be considered for patients with cancer, especially those with an intrathoracic origin involvement or lung metastases.

The major limitations of this study are as follows (1). The study used a retrospective design. (2) Culture-negative cases were excluded; only patients with pleural effusion culture-proven pneumococcal empyema were enrolled. However, determining that a patient has pneumococcal empyema in culture-negative cases is difficult. (3) There were too few patients in this series. A prospective, large-scale study is needed to confirm the findings reported herein.

In conclusion, the HAE patients, compared to the CAE patients, had a longer period of fever, and required a longer hospital stay and parenteral administration of antibiotics. Further studies are needed to determine whether the difference in mortality rates between CAE and HAE is statistically significant. Underlying malignancies were a major risk factor for HAE.

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肺炎球菌導致之膿胸在成年病患的臨床特徵及預後

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背景：肺炎球菌是肺炎最重要的致病菌。雖然膿胸是肺炎的常見併發症，目前針對肺炎球菌造成的膿胸的臨床表現及危險因子的討論並不多。

方法：回溯研究在 1998 年 11 月至 2005 年 5 月間，在台北長庚醫院住院 時，肋膜腔積液檢體中培養出肺炎球菌的 20 位成年病患，其基本資料，潛在疾病及對抗生素不敏感的比例。病患被分成社區感染膿胸（n=12）及院內感染膿胸（n=8）兩組，其治療結果亦經比較。

結果：院內感染膿胸的病患，相較於社區感染膿胸的病患，在患病初始，有較快的心搏速率，動脈血有較高的 pH 值及氧氣分壓（分別為 p=0.073 ， 0.024 及 0.055）。惡性腫瘤在兩組都是最重要的危險因子，而在院內感染膿胸的病患更為常見（社區感染 33％，院內感染 87.5％， p=0.017）。惡性腫瘤原發部位以肺及頭頸部為主。院內感染膿胸需使用抗生素的時間較長，發燒及住院時間也較（p<0.05）長。兩組菌株對 penicillin ， cefuroxime ， ceftriaxone 及 vancomycin 的不敏感比例無顯著差別（p>0.2）。

結論：肺炎球菌導致的膿胸病患中，院內感染者有較差的預後。惡性腫瘤是主要的危險因子，在院內感染膿胸者盛行率更高。*(胸腔醫學* ***2006; 21: 413-421)***

關鍵詞：肺炎球菌，膿胸，肋膜，惡性腫瘤，抗生素，敏感性

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Prognosis of Patients with DM/PM Requiring Intensive Care due to Acute Respiratory Failure

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Background: The prognosis of patients with dermatomyositis/polymyositis (DM/PM) requiring intensive care for acute respiratory failure has not been reported. A retrospective study was conducted to analyze the clinical course and outcome of these patients.

Methods: Medical records were reviewed for patients admitted to the intensive care unit from January 1985 to December 2004. The diagnosis of DM/PM was based upon Bohan and Peter's criteria, and those patients with respiratory failure as the indication for ICU admission were enrolled.

Results: Nineteen patients with DM/PM were admitted to the ICU because of respiratory failure during the study period. Eight patients were diagnosed with interstitial lung disease. Respiratory failure developed within a mean of 14 months after the diagnosis of DM/PM. The causes of respiratory failure were: pneumonia (n=14), interstitial lung disease (ILD) (n=5), ventilatory failure (n=2), and acute lung edema (n=1). The most common complications were septic shock (n=16), followed by ARDS (n=13), and acute renal failure (n=9). Twelve patients died, with a mortality rate of 63%. The causes of death were: pneumonia (n=6), septic shock (n=3), ILD with respiratory failure (n=2), and hepatic failure (n=1). Ninety-two percent of the expired patients and all of those with ILD developed ARDS. ILD patients were often refractory to immunosuppressive treatment while patients with ventilatory failure had a good response to therapy.

Conclusion: Patients with DM/PM and respiratory failure requiring ICU admission had an extremely high mortality rate, and most died of pneumonia. ***(Thorac Med 2006; 21: 422-432)***

Key words: dermatomyositis, polymyositis, respiratory failure

Introduction

Dermatomyositis (DM) and polymyositis (PM) are overlapping diseases characterized by an inflammation of the skeletal muscles resulting in symmetrical weakness (principally of the limb girdle, neck, and pharynx) and a characteristic skin rash. Both DM and PM share common features with connective tissue diseases, and are usually classified together [1]. PM and DM are considered to be associated with morbidity and mortality rates as high as 50%, and principally

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related to life-threatening muscle weakness, cardiac and lung complications, and malignancy [2].

Up to 45% of PM/DM patients develop pulmonary involvement, such as infection, aspiration pneumonia, malignancy and drug-induced pneumonitis. Chronic respiratory failure due to respiratory muscle weakness and acute or chronic interstitial lung disease (ILD) has been identified as the most frequent and characteristic lung complication of DM/PM. ILD complicates DM/PM in 5-30% of cases and may lead to life-threatening complications, i.e., ventilatory failure, secondary pulmonary arterial hypertension, or cor pulmonale. The presence of ILD in patients with myositis affects the prognosis and contributes substantially to morbidity and mortality [2-6].

This retrospective study was undertaken to characterize the clinical course and outcome of DM/PM patients who were admitted to the intensive care unit (ICU) in our hospital because of acute respiratory failure.

Patients and Methods

Patient population

A computer-aided search was conducted to identify all patients seen at National Taiwan University Hospital during the period from January 1, 1985 to December 31, 2004 with records coded for the diagnosis of DM or PM. Patients were considered acceptable for inclusion in the study if they had fulfilled the diagnostic criteria for DM/PM and developed acute respiratory failure requiring mechanical ventilation. The criteria for the diagnosis of DM/PM were based upon those of Bohan and Peter [1]: (1) symmetrical proximal muscle weakness, (2) elevated serum muscle enzymes, (3) myopathic changes on electromyography (EMG), (4) typical histological findings on muscle biopsy, and (5) characteristic dermatologic manifestations (heliotrope rash, periungual erythema, Gottron's papules, and poikiloderma). Confidence limits were defined as follows: definite, probable, and possible, according to the number of fulfilled criteria (at least 4, 3, or 2, respectively, including skin rash for the diagnosis of dermatomyositis). Patients admitted to the ICU for post-surgery care, those with no need for mechanical ventilation, or those aged less than 18 years were excluded.

Data collection

The clinical data were collected from the medical chart records, which included the clinical history, physical examination, laboratory test results, radiographic findings, biopsy results, EMG, and pre-ICU treatment course. Presenting signs and symptoms were recorded from the first medical encounter which eventually lead to a diagnosis of DM/PM. For the ICU course, the reasons for ICU admission, duration of stay in the ICU and total hospital admission, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, treatment, laboratory results, survival, and complications were all reviewed.

Pulmonary involvement

Pulmonary involvement was systemically investigated in relation to initial symptoms, chest radiographs, pulmonary function tests (PFT), lung biopsy, and cultures of respiratory tract specimens. Interstitial lung disease (ILD) was diagnosed based on the presence of radiological abnormalities with respiratory symptoms (dyspnea, nonproductive cough, hypoxemia, "velcro"-like crackles on chest auscultation) and/or restrictive ventilatory defects. The radiographic signs of ILD on HRCT included parenchymal micronodules and nodules, linear opacities, irregularity of the interfaces between peripheral pleura and aerated

lung parenchyma, ground-glass opacities, honeycombing, and traction bronchiectases or bronchioloectases [7-9].

Statistical Analysis

Data are presented using mean ± SD for continuous variables and percentages for categorical variables. Comparisons involving continuous data were done using the Wilcoxon rank sum test. For group comparisons involving binary data, we used Fisher's exact test. The results were regarded as significant when the p value was < 0.05.

Results

Clinical features and laboratory findings. During the study period, 166 patients (PM=81, DM=85) were diagnosed with DM/PM and 28 were admitted to the ICU. Nine patients were excluded because of post-operative care (n=2), complete atrioventricular block (n=2), diabetic ketoacidosis (n=1), intracranial hemorrhage with deep coma, cryptococcal meningitis with confused consciousness (n=1), and expired on admission to the ICU after cardiopulmonary resuscitation (n=2). Nineteen patients satisfied the enrollment criteria; they included 7 males and 12 females, aged 55.6 ± 16.2 years. Ten patients were diagnosed as PM and the other 9 were DM. Demographics, and the symptoms and signs of the patients at the initial presentation are summarized in Table 1. Skeletal muscle biopsy performed in 15 cases was able to confirm the diagnosis of myositis in 11 cases. Of these, skin biopsies of 2 patients suggested the diagnosis of DM. EMG performed in 18 cases contributed to the diagnosis in all of them. Three patients with thyroid disease were under regular medical treatment and were in a euthyroid status when DM/PM was diagnosed (Table 1). The only patient with malignancy was diagnosed as having non-Hodgkin's lymphoma 2 years after the diagnosis of DM.

The mean interval between the onset of initial symptoms and the diagnosis of DM/PM was 2.9 months (range, 0-12 months). The most common initial symptoms were proximal muscle weakness (n=12) followed by skin rash (n=8). Most people (79%) had weakness at the time of diagnosis, as well as dysphagia (42%). Video-pharyngoesophagography was performed in 3 of these patients and confirmed a swallowing dysfunction. One of the patients also complained of dysarthria. Among the 8 patients with ILD, dyspnea and skin rash were the most frequent initial symptoms (5/8). Pulmonary symptoms preceded the onset of skin/musculoskeletal symptoms in 2 cases (interval, 12.5 and 14 months, respectively), and occurred after skin/musculoskeletal lesions in 4 (interval 6.4 ± 5.1 months, range 0.5-12 months).

The laboratory findings at the initial diagnosis were elevated CK (84%), LDH (84%), transaminase (79%), and erythrocyte sediment rate (85%) (Table 2). A greater number of non-ILD patients had elevated CK and anti-nuclear antibody compared to the ILD patients (91% vs. 75 %, p=0.74 and 73% vs. 38%, p>0.18, respectively). Serum anti-Jo-1 antibody was checked in only 6 patients (3 with ILD), but none of them were positive.

The HRCT findings of the patients are summarized in Table 2. Irregular linear and ground-glass opacities were present in all patients in the ILD group. Four ILD patients had a CT presentation compatible with usual interstitial pneumonia. PFT was performed in 6 ILD patients and 4 non-ILD patients. Among the 6 ILD patients, 5 showed restrictive ventilatory defects (mild, n=3; moderate, n=2) and diffusion impairment (mild, n=3; severe, n=2). Other findings included resting hypoxemia (n=1), and a mild to moderate de-

Table 1. General characteristics of the patient population

Patients / Sex/Age	Diagnosis /accuracy*	Comorbidities	Symptom duration (mo)	Initial symptoms	Follow-up duration (mo)
ILD (+)					
1/ F/68	PM/p	VHD, Sjorgren's syndrome, PBC	2	Dyspnea	14.5
2/ M/53	DM/p	dm	1	Weakness, rash	3.4
3/ M/41	DM/p	-	0.75	Weakness, rash	12.2
4/ M/69	DM/d	CAD, hypothyroidism	2	Weakness, dyspnea	48.2
5/ M/69	DM/p	-	3.5	Weakness, dyspnea	2.7
6/ F/36	DM/p	-	3	Rash	8.2
7/ F/50	DM/p	-	6	Rash	6.0
8/ F/76	PM/d	HTN, asthma	0.5	Dyspnea	16.2
ILD (-)					
9/ F/59	PM/d	dm	1.5	Weakness	19
10/F/69	PM/d	HTN	0.3	Weakness	6.2
11/ F/70	PM/d	TB destructive lung with cor pulmonale, dm	4	Weakness	40.7
12/M/41	PM/p	HTM, dm, chronic steroid	NA	Weakness	129.5
13/ F/36	PM/d	Hypothyroidism	6	Weakness	17.3
14/ F/70	DM/p	Asthma, hyperthyroidism	2	Weakness, rash	8.6
15/ F/62	DM/p	Lymphoma	12	Weakness, rash	24
16/F/34	DM/p	-	4	Rash	50.2
17/F/22	PM/d	SLE	1	Weakness	43.3
18/M/73	PM/d	HTN	0.5	Weakness, rash	2.5
19/M/59	PM/p	-	2	Weakness	15.5

* Diagnostic accuracy is based on Bohan and Peter criteria for DM/PM, p: probable, d: definite.

CAD: coronary artery disease, DM: diabetic mellitus, HTN: hypertension, NA: not available, PBC: primary biliary cirrhosis, RF: rheumatoid factor, SLE: systemic lupus erythematosus, VHD: valvular heart disease.

crease in Pimax and Pemax (n=1). The 2 patients with asthma showed a moderate obstructive ventilatory defect. Two non-ILD patients with a restrictive ventilatory defect later developed ventilatory failure and hypercapnia.

Lung pathology. Surgical (thoracotomy, n=3; video-assisted thoracoscopic, n=1) or transbronchial (TBLB, n=3) lung biopsy was available for 7 patients. The hisotopathological finding was diffuse alveolar damage in 2 patients, honeycomb lung in 1, interstitial fibrosis (by TBLB) in 2, PCP in 1, and alveolar cell hyperplasia in 1 patient. All except for 1 patient received lung biopsy after ICU admission.

Immunosuppressive therapy before ICU admission. All patients had taken corticosteroids before admission to the ICU, usually in the form of oral prednisone (most commonly 40-60 mg/d). Fourteen patients (ILD=5, non-ILD =9) also underwent concomitant immunosuppressive therapy and hydroxychloroquine was the most frequently prescribed agent (ILD=5, non-ILD =5). Three non-ILD patients received methylprednisolone pulse (1000 mg/d for 3 days)

Table 2. Laboratory and HRCT findings of DM/PM patients

	Number positive /number tested (%)	Serum level, median (range)
Laboratory findings[a]		
Raisied CK (U/L)	16/19 (84)	1976 (260-18440)
Raised LDH (U/L)	16/19 (84)	963.5 (519-3170)
Raised transaminase (U/L)	15/19 (79)	102 (38-562)
Raised ESR	11/13 (85)	
Positive ANA	11/19 (58)	
Positive RF	3/19 (16)	
Positive anti-Jo-1 antibody	0/6 (0)	
HRCT findings		
Irregular linear opacity[b]	9/16 (50)	
Ground-glass opacity[b]	10/16 (63)	
Honeycombing	5/16 (31)	
Consolidations	4/16 (25)	
Others[c]	6/16 (38)	
Pulmonary function test		
Restrictive	7/10 (70)	
Obstructive	1/10 (10)	
Mixed	1/10 (10)	
Impaired DLCo	8/10 (80)	
Outcomes		
Expired	12/19 (63)	
Complete recovery	2/19 (11)	
Improved with extubation	2/19 (11)	
Improved with tracheostomy	3/19 (16)	

[a] At initial diagnosis of DM/PM.

[b] These findings presented in all patients with the diagnosis of ILD.

[c] These HRCT findings included bronchiectasis in 2 patients, pleural effusion in 5, and pneumothorax in 1 patient.

therapy, 2 of them for refractory muscle weakness and 1 for SLE-related nephrotic syndrome. The latter also received pulse cyclophosphamide. Patient number 9 was given IVIG in addition to pulse steroid treatment.

In the ILD group, only 1 patient with muscle weakness responded to treatment. ILD progressed in 2 patients, despite treatment, and was stable in 2 other. In the non-ILD group, the musculoskeletal symptoms of 9 patients (weakness and arthralgia) showed good response to immunosuppressive agents. However, 5 of them had disease flare-up after tapering steroid during the treatment course.

ICU course and outcome. The patients developed respiratory failure in a mean of 14 months (range 0-120 months) from initial diagnosis (ILD vs. non-ILD, 10.5 ± 13.8 mo vs. 16.5± 34.6 mo, $p>0.05$). Causes of respiratory failure and complications in the ICU are shown in Table 3. Comparisons between the ILD and non-ILD patients and the survivors and non-survivors are also lis-

Table 3. Comparisons between ILD/non-ILD patients and survivors and non-survivors in the ICU

ICU admission	Total	ILD		*p*	Outcomes		*p*
	n=19(%)	Yes (n=8)	No (n=11)		Non-survivors (n=12)	Survivors (n=7)	
Age	55.6±16.2	57.8±14.8	54.1±17.7	0.838	61.1±18.2	46.3±17.6	0.099
Sex (M/F)	7/12	4/4	3/8	0.377	6/6	1/6	0.173
Diagnosis (DM/PM)	9/10	6/2	3/8	0.070	7/5	2/5	0.35
Causes for respiratory failure							
Pneumonia	12 (63)	3	9	0.074	7	5	0.656
Worsened ILD	5 (26)	5	0		5	0	
Muscle weakness	2 (11)	0	2		0	2	
Acute lung edema	1 (5)	0	1		0	1	
Complications							
Septic shock	16 (84)	7	9	1	11	5	0.528
ARDS	13 (68)	8	5	0.018	11	2	0.01
ARF	9 (47)	5	4	0.87	7	2	0.85
MOF	8 (42)	6	2	0.024	8	0	
Pneumothorax/ Pneumomediastinum	6 (32)	5	1	0.041	5	1	0.888
Hepatic failure	1 (5)	1	0		1	0	
Laboratory findings (median, range)							
Albumin (g/dl)	2.85(1.8-4.5)	2.9(1.8-4)	2.7(2.2-4.5)	0.89	2.65(1.8-4)	3(2.3-4.5)	0.147
CK (U/L)	187 (24-1247)	260.5 (26-806)	146 (24-1247)	0.443	214 (26-806)	79 (24-338)	0.387
LDH (U/L)	1175 (552-3438)	1131 (552-3438)	1386 (9-2450)	0.865	1131 (102-3438)	1155.5 (83-2063)	0.566
AST (U/L)	81.5 (21-1182b)	144 (32-1182)	66.5 (21-98)	0.178	72.5 (27-1182)	65 (13-98)	0.086
ALT (U/L)	33.5 (9-450)	70 (33-450)	27 (9-118)	0.1	52 (27-450)	15 (5-118)	0.086
Steroid dose mg/d, medium(range)	0 (0-240)	120 (20-240)	60 (0-120)	0.048	80 (0-240)	40 (8-80)	0.156
APACHE II score	18.3±5.4	17.8±2.6	18.6±6.9	0.9	19.6±5.6	16.0±4.5	0.285
LOS, ICU (days)	30.0±25.0	23.3±11.7	34.9±31.1	0.274	34.1±27.1	28.0±21.0	0.22
LOS, hospital (days)	81.8±70	72.8±54.1	88.3±81.6	0.649	70.2±45.6	101.7±100.8	0.866
Mortality	12 (63)	8	4	0.013			

ted. The APACHE II scores were not significantly different between the ILD and non-ILD patients, or the survivors and non-survivors. There was a significant difference in the incidence of acute respiratory distress syndrome (ARDS), multiorgan failure, and pneumothorax / pneumomediastinum between the ILD and non-ILD patients. Only the incidence of ARDS was significantly different between the survivors and non-survivors. The causes of death were: pneumonia (n=6), septic shock (n=3), ILD with respiratory failure (n=2), and hepatic failure (n=1). Overall, the ICU

mortality rate was 63%, and the ILD group had higher mortality than the non-ILD group (p= 0.013).

Treatment in the ICU. All patients except 2 received intravenous methylprednisolone during their ICU stay. Steroid was not given to these 2 patients because of tuberculosis infection. The dose of methylprednisolone was higher in the ILD group than in the non-ILD group (p=0.048) (Table 3). Other immunosuppressive treatment included pulse cyclophosphamide (n=3), intravenous immunoglobulin (n=2), methotrexate (n=2), azathioprine (n=1), and hydroxychloroquine (n=4).

Patient 2, 3, 6, and 7 had no respiratory symptoms at the time of DM/PM diagnosis, although there was interstitial lung infiltration on the chest-X-ray. These patients developed rapidly progressing respiratory distress with a mean interval of 13 days between the onset of dyspnea and intubation (range, –15 to 60 days). All 4 patients were refractory to immunosuppressive treatment and subsequently died of respiratory failure. Patient 10 received pulse steroid therapy for initially suspected ILD until lung biopsy proved PCP. In the non-ILD group, the 2 patients with respiratory muscle weakness had a good response to immunosuppressive therapy.

Laboratory findings in the ICU Elevated se-rum LDH, CK, and transaminases were observed on ICU admission (Table 3). Other abnormal laboratory data included leukocytosis (WBC>10,000/μl) in 53% of patients, anemia (Hb<12 g/dl) in 74%, hypoalbuminemia in 84%, and elevated CRP in 82%. Compared to their initial laboratory data, patients who died had lower serum CK (214 vs. 2689 U/L, p=0.029) and albumin (2.65 vs. 3.1 g/dl, p=0.038), and higher LDH (1131 vs.755 U/L, p=0.04) values when they were admitted to the ICU. Similarly, lower CK (260.5 vs.2226 U/L, p=0.05) and higher LDH (1131 vs. 638 U/L, p=0.017) on ICU admission were also observed in the ILD patients. These patients tended to develop severe infection with mycobacterial species (n=3), fungemia (n=3), and bacteremia (n=3).

Discussion

This study highlights the high mortality rate (63%) of DM/PM patients who developed acute respiratory failure: 100% in the ILD group and 36% in the non-ILD grroup. Pneumonia (50%) was the most common cause of death, followed by septic shock (25%). We speculated that respiratory failure is a feature associated with a poor prognosis, regardless of the etiology.

In previous series analyzing the survival of DM/PM patients, lung complications were one of the most common causes of death. In the series of Marie and Hachulla, pulmonary involvement was considered as a poor prognostic factor and caused the deterioration and death of 71% of patients, including 55% with aspiration pneumonia and 19% with ILD [2]. In a recent retrospective study of 81 DM/PM patients, 50 (61%) presented pulmonary involvement. ILD was present in 32 (39%) patients, and 5 of them developed devastating acute interstitial pneumonia. Eighteen (22%) patients presented restrictive myopathic lung disease. Their study revealed that patients with restrictive myopathic lung disease had a good prognosis [6]. The main difference between our study and previous ones is that we focused especially on DM/PM patients who developed acute respiratory failure. In this group of patients, pneumonia (including aspiration pneumonia) was the most common cause of respiratory failure (63%), followed by exacerbation of ILD (26%), and ventilatory failure (11%). ARDS developed

in 68% of our patients and 92% of them died. It is possible that the use of immunosuppressive agents and aspiration predisposes to the development of pneumonia [10]. The integrity of the host's pulmonary defense mechanism is a critical factor in assessing the risk of pneumonia. Our patients were all immunocompromised hosts and were at high risk for pneumonia-associated mortality because of previous steroid treatment, comorbidity like heart and renal disease, preexisting pulmonary disease, and mechanical ventilation.

Only 4 (21%) patients in our series developed aspiration pneumonia, and 3 of them died. Because aspiration pneumonia was mainly secondary to DM/PM-related esophageal motor dysfunction and ventilatory insufficiency, and often occurred early in the disease course, a search for both esophageal involvement and ventilatory insufficiency should be performed during the initial evaluation of these patients. This evaluation should include: (1) esophageal manometry; (2) video-pharyngoesophagography; (3) PFT; and (4) a chest radiograph. Aggressive therapy for patients with clinical/subclinical esophageal involvement may be required, but would have short-term efficacy [2, 11].

Our data demonstrated that once DM/PM patients with ILD developed acute respiratory failure, they had a much worse outcome. The high mortality of our ILD patients might be due to several reasons. First, most of our ILD patients had a pulmonary function test and HRCT only when pulmonary symptoms presented, which hindered early detection of ILD. Second, the immunosuppressive therapy usually was not given until ARDS had developed or a lung biopsy had been done. Thus there was a delay in immunosuppressive therapy. Third, though not all our ILD patients had an available lung pathology, most of them had HRCT findings compatible with usual interstitial pneumonitis or DAD, which according to previous studies [3-4, 12] had a less favorable prognosis and was often refractory to aggressive treatment. Other reported factors related to the poor outcome of ILD include rapidly progressive-ILD (RP-ILD), initial diffusing capacity of carbon monoxide <45%, and neutrophil alveolitis [4-6, 13]. Four DM patients in our series developed RP-ILD. They had relatively mild muscle weakness, but an acute onset of respiratory symptoms. They were refractory to aggressive corticosteroid and immunosuppressive treatment and all died within 3 months after the onset of pulmonary symptoms. Two of them had DAD on lung biopsy. These findings were comparable with those of previous reports [13-15]. Most reports of RP-ILD patients with myositis were usually of amyopathic dermatomyositis (ADM). Factors that reported to be associated with RP-ILD include less muscle weakness and a lower frequency of autoantibody (ANA of anti-Jo1 antibody), lower serum creatine kinase/lactate dehydrogenase levels, and a higher CD4+/CD8+ T-lymphocyte ratio in the peripheral blood [6, 13].

Besides ILD, other differential diagnoses of bilateral diffuse lung infiltration, e.g., drug-related or infectious pneumonia (such as PCP or viral pneumonia), should always be considered [16], since the treatment strategy is different between ILD/drug-induced pneumonitis and infectious pneumonia. One of our patients was treated for ILD on initial admission to the ICU, but was later proven to have PCP by lung biopsy via VATS. The patient died of refractory hypoxemia and sepsis, despite adequate antibiotic use. Plain chest radiography as well as standard laboratory tests usually fail to differentiate interstitial pneumonitis and pulmonary infection. High-resolution CT of the lungs, serum endotoxin, and

serum beta-D-glucan have been found to be useful for differentiating the conditions associated with respiratory failure in DM/PM patients [17]. Although muscle enzymes, especially creatinine phosphokinase, are usually considered a valuable parameter for diagnosis and monitoring clinical activity and response to treatment [1], our ILD patients and patients with aspiration pneumonia and hypoventilatory failure had only mildly elevated or normal serum CK levels on admission to the ICU compared to their initial diagnosis of the disease.

Corticosteroid treatment alone is often not sufficient to improve ILD and other immunosuppressive agents are frequently required. The most often used drugs with reported beneficial effects on lung function are cyclophosphamide, cyclosporine A, azathioprine, and methotrexate [4, 18-19]. Early institution of pulse intravenous cyclophosphamide in combination with pulse methylprednisolone [18] or intravenous immunoglobulin [20] has been reported to be beneficial in patients with RP-ILD. All our RP-ILD patients were refractory to treatment. The lung conditions of the remaining ILD patients were transiently stabilized by the treatment; however, they tended to develop severe infection (fungal infection and systemic mycobacterial tuberculosis) after strong immunosuppressive treatment. According to some reports, the reasons for the limited number of patients that respond to these therapies could be related to differing histopathologies of ILD, suggesting different disease mechanisms. Furthermore, the response rate may be higher when treatment is initiated early in the course of the disease, before irreversible changes have developed.

In conclusion, respiratory failure is a poor prognostic factor for DM/PM patients in the ICU. The DM/PM patients with respiratory failure who were admitted to the ICU in this series had a high mortality rate. The most common cause of death was pneumonia followed by progression of ILD. The most common complication was septic shock. Once patients developed ARDS, they had an extremely high mortality rate. The levels of muscle enzymes did not reflect the severity of the disease. Early systemic investigation of pulmonary and esophageal involvement is necessary at the time DM/PM is diagnosed. Aggressive immunosuppressive treatment should be given as early as possible in the presence of lung involvement.

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皮肌炎及多發性肌炎病人因急性呼吸衰竭需要加護醫療之預後

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背景：目前為止，尚沒有關於皮肌炎 (dermatomyositis) 及多發性肌炎 (polymyositis) 病人因急性呼吸衰竭需要加護醫療之預後之報告。本文以回溯性分析此類病人的臨床病程及預後。

方法：我們回顧自 1985 年 1 月至 2004 年 12 月間，曾住進加護病房病人的醫療紀錄，將診斷符合皮肌炎 / 多發性肌炎，並且發生呼吸衰竭而住到加護病房的病人納入研究。皮肌炎 / 多發性肌炎之診斷，是根據 Bohan 及 Peter 二人所訂定的診斷條件。

結果：在研究期間，共有 19 位診斷為皮肌炎 / 多發性肌炎病人，因呼吸衰竭住到加護病房。其中有 8 位病人被診斷有皮肌炎 / 多發性肌炎相關之間質性肺病。呼吸衰竭的發生，平均在皮肌炎 / 多發性肌炎診斷後的 14 個月發生。導致呼吸衰竭的原因有：肺炎 (n=14)，間質性肺病 (n=5)，通氣衰竭 (ventilatory failure) (n=2)，及急性肺水腫 (n=1)。最常發生的併發症為敗血性休克 (n=16)，其次為急性呼吸窘迫症候群 (n=13) 及急性腎衰竭 (n=9)。共有 12 位病患死亡，死亡率 63% 。其死因包括：肺炎 (n=7)、敗血性休克 (n=3)、間質性肺病併發呼吸衰竭 (n=2)、肝衰竭 (n=1)。死亡病人中， 92% 發生急性呼吸窘迫症候群； 而所有間質性肺病之患者，均發生急性呼吸窘迫症候群。後者常對免疫抑制治療無效； 反之那些因通氣衰竭的病患，對治療則有不錯的反應。

結論：皮肌炎 / 多發性肌炎病人，併發呼吸衰竭而需要加護醫療照顧者，死亡率極高，最常見的死因為肺炎。*(胸腔醫學* ***2006; 21: 422-432)***

關鍵詞：皮肌炎，多發性肌炎，呼吸衰竭

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Pulmonary Leptospirosis after Mountain Climbing in Southern Taiwan: A Case Report

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Leptospirosis is a worldwide zoonotic disease, more prevent in tropical and subtropical regions. It usually occurs in subjects with occupational exposure, such as those involved in rice farming, and occasionally in those who participate in recreational activities in wilderness areas. The clinical features of leptospirosis vary widely, ranging from self-limited anicteric illness to severe pulmonary hemorrhage, jaundice, acute renal failure, and even death. A diagnosis of leptospirosis may be difficult, particularly in those without occupational exposure, because of a lack of specific clinical features and radiographic findings. We report a 61-year-old male who was transferred to our hospital due to fever, hemoptysis, and abnormal CXR findings. The patient was treated for community-acquired pneumonia, but with a poor response. Due to his history of recent wilderness recreation, leptospirosis was highly suspected, and subsequently confirmed by serological testing. The patient responded well to penicillin treatment. ***(Thorac Med 2006; 21: 433-438)***

Key words: leptospirosis, jaundice, acute renal failure

Introduction

Leptospirosis is a zoonotic disease caused by Leptospira. Dark-field or phase-contrast microscopy of wet preparations is required for direct visualization of Leptospira, since the bacteria stain poorly [1]. Leptospirosis is a disease of the environment; transmission depends on exposure to the infected urine of carrier mammals, either directly or indirectly via contamination of the soil or water. The disease is divided into 2 classic forms: anicteric and icteric, based on whether or not there is a presence of jaundice. The anicteric form is more common and less severe, whereas the icteric form has a more complicated clinical course. Pulmonary involvement has been reported to be a poor prognostic factor, but the incidence of pulmonary involvement in the icteric and anicteric forms is still a matter of controversy [2]. We report a male adult who was initially diagnosed with community-acquired pneumonia, based on the clinical features of fever, cough and hemoptysis, and bilateral pulmonary infiltrates shown on chest radiographs. A history of wilderness activity prompted us to render a diagnosis of leptospirosis. The patient recovered rapidly after peni-

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cillin therapy.

Case Report

A 61-year-old male suffered from chills, fever and cough with blood-tinged sputum for 1 week. He visited local clinics and was transferred to our emergency room (ER) because of abnormal findings on chest X-ray film (CXR).

The patient denied major medical diseases, and had quit smoking 10 years previous. One week before this admission, the patient climbed a mountain in southern Taiwan with his family. Physical examination at the ER revealed no remarkable findings, except for rales in the bilateral lungs on auscultation, and multiple reddish papules on the 4 limbs. No visible cutaneous skin wounds or eschar were noted. The vital signs were as follows: blood pressure, 156/92 mmHg; heart rate, 112 beat/min; respiratory rate, 20/min; body temperature, 36.7°C. Complete blood count showed a total leukocyte count of 16.1×10^9/L, with a differential count of 70% neutrophils and 13% lymphocytes. The blood biochemistry data were as follows: blood urea nitrogen, 56 mg/dL; creatinine, 2.0 mg/dL; alanine aminotransferase, 59 U/L; C-reactive protein, 7.57 mg/dL; sodium, 145 mg/dL; potassium, 4.4 mg/dL; glucose, 587 mg/dL (non-fasting); lactate dehydrogenase, 393 U/L; total bilirubin, 1.09 mg/dL. The CXR revealed pulmonary infiltrates in both lung fields (Figure 1). Results of arterial blood gas analysis in room air were as follows: pH, 7.42; PaO_2, 51.7 mmHg; PCO_2, 30.6 mmHg.

He was admitted the day after arriving at the ER under the impression of community-acquired pneumonia, and empiric antibiotics with moxifloxacin were given to cover the possible bacteria and pathogens responsible for the atypical pneumonia. Low-grade fever of about 38°C persisted for 3 days after admission. Thoracic high resolution computed tomography (HRCT) performed on the first day of hospitalization revealed diffuse ground-glass opacities in both lower lungs (Figure 2). Atypical or unusual pneumonia caused by zoonotic pathogens were highly suspected, because of a recent history of mountain climbing. Serological tests for mycoplasma, legionella,

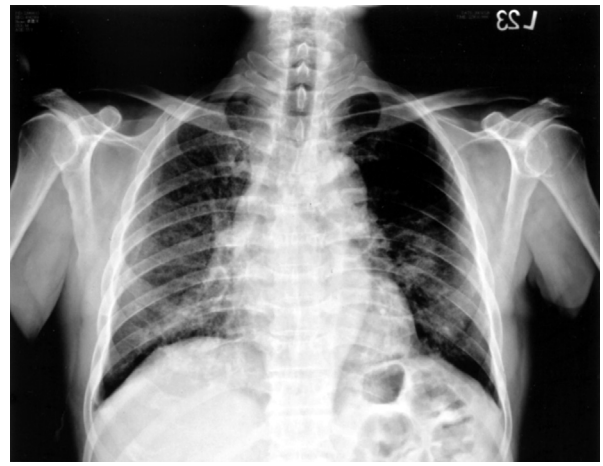

Fig. 1. Chest X-ray film shows bilateral infiltrates, especially in the lower lungs.

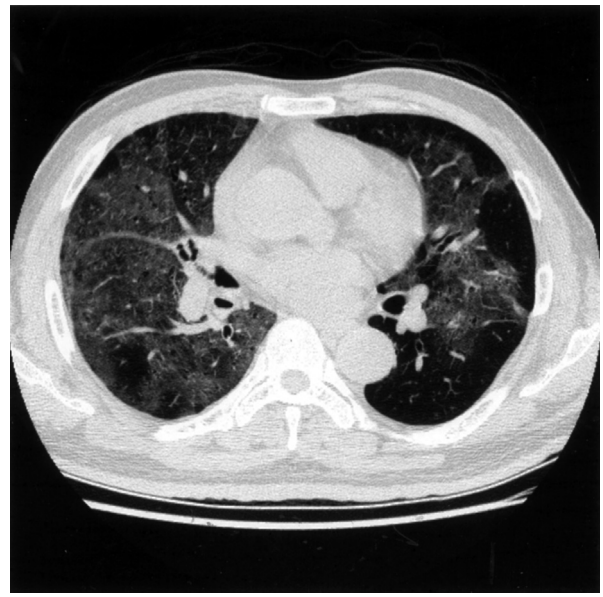

Fig. 2. Highresolution computed tomography of the chest reveals ground-glass opacities in the lower lungs.

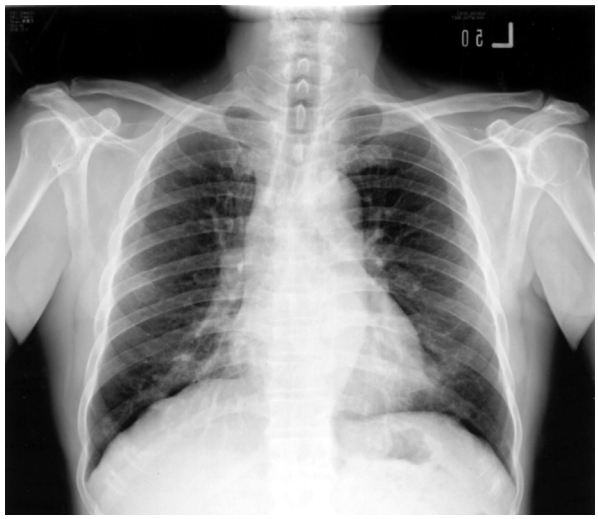

Fig. 3. Chest X-ray film shows marked improvement 6 days after penicillin-G treatment.

cytomegalovirus immunoglobulin M, and scrub typhi yielded negative results. Cryptococcus antigen and legionella antigen were undetectable. The microscopic agglutination test (MAT) against *Leptospira tarassovi* was positive, with a titer of 1:400 on the fourth hospitalization day. Accordingly, penicillin-G was administered. In addition, diabetes mellitus was diagnosed based on the fasting glucose (157 mg/dL) and hemoglobin A1c (9.7 %) findings. Six days after penicillin-G treatment, the CXR showed marked improvement (Figure 3). The patient was discharged on the eleventh day of hospitalization.

Discussion

Leptospirosis is a worldwide zoonotic disease, more prevalent in the tropical and subtropical regions. The common clinical features of leptospirosis include fever, headache, conjunctivitis, myalgia, and jaundice [3]. The main organs involved are the liver, the central nervous system, the kidney, skeletal muscles, and the lungs [4]. The rate of pulmonary involvement has varied wildly, with a range of 20-70% [3, 5-7], based on respiratory symptoms.

In patients with leptospirosis, CXR abnormalities might be observed around the third to seventh day after the onset of symptoms. The initial findings are multiple, predominantly nodular densities, ranging from 1 to 7 mm in diameter. Large confluent areas of air-space consolidation develop subsequently. Finally, the lesions resolve gradually with a diffuse, ill-defined, ground glass appearance [6]. In most patients, the CXR shows bilateral peripheral lesions rather than a lobar or segmental distribution. HRCT of the chest is superior to CXR in evaluating the extent of lung involvement. The common radiographic findings include extensive, bilateral ground-glass opacities in involved lobes, areas of consolidation, or centrilobular nodules [8]. However, these imaging findings are not specific for the pulmonary lesions of leptospirosis.

Pulmonary lesions are primarily hemorrhagic rather than inflammatory. Pathologically, petechiae are found distributed throughout the lungs and the tracheobronchial trees. Extensive pulmonary hemorrhage and edema may be observed in advanced disease [9-10]. Acute respiratory distress syndrome (ARDS) and alveolar hemorrhage are 2 of the most fatal conditions in leptospirosis. Patients with severe pulmonary involvement and major hemoptysis can die in less than 24 hours without appropriate management [7, 11]. Yersin and colleagues reported that pulmonary hemorrhage was a main cause of death in hospitalized patients with leptospirosis in Seychelles [12]. Accordingly, a rapid diagnosis is mandatory for leptospirosis patients with pulmonary involvement.

Diagnosis of leptospirosis can be made either by demonstrating the organism or by serological tests that detect leptospiral antibodies. The defini-

tive diagnostic test is the recovery of leptospires from clinical specimens, either by culture, which is insensitive and slow, by immunohistochemical staining, or by demonstrating the presence of leptospiral DNA by PCR [13]. Serology is the most frequently used diagnostic approach for leptospirosis. The microscopic agglutination test (MAT) is the standard reference test for the serological diagnosis of leptospires, because of its high sensitivity and specificity [14]. In the current CDC case definition, a titer of ≥ 200 is used to define a probable case with a clinically compatible illness. A 4-fold or greater rise in titer between paired sera confirms the diagnosis [15].

There remains some controversy about whether antimicrobial treatment of leptospirosis should be initiated. However, most experts are reluctant to withhold antimicrobial treatment when clinical findings and epidemiological exposure history suggest leptospirosis [16]. Several case series indicated that the duration of illness was shortened in leptospirosis patients when appropriate antibiotic therapy (penicillin G 6 million units/day in divided doses, or doxycycline 100 mg twice daily) was administered during the initial phase of the illness (within 2-4 days) [17-18]. Once ARDS developed, promising results with the timely use of mechanical ventilation using lung protective strategies were reported in a prospective randomized study of 8 patients with leptospirosis-associated ARDS in Brazil [7]. Jarisch-Herxheimer reactions have been reported after penicillin therapy in leptospirosis [19]. This reaction describes the release of endotoxin when large numbers of organisms are killed by antibiotics. However, the apparently low risk should not preclude the use of penicillin in leptospirosis [20].

In conclusion, leptospirosis may present as a disease with multi-organ involvement. Occasionally, pulmonary involvement may be the initial presentation. Leptospirosis should be added into a list of differential diagnoses when a patient is presented with compatible clinical features and imaging findings, as well as a history of recent recreation or work in the wilderness. Early use of penicillin or doxycyline may shorten the clinical course and prevent mortality.

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南台灣爬山旅遊後所引起的肺部鉤端螺旋體病：病例報告

施穎銘　張西川 **　杜瑞煌 *

鉤端螺旋體病 (leptospirosis) 是一種全球性人畜共通疾病，在熱帶或亞熱帶地區較盛行，通常發生在戶外工作者如農夫，或是到野外從事休閒活動的人。被感染病人的臨床表現，可從無症狀、自限性無黃疸熱病到嚴重肺出血、黃疸、急性腎衰竭或甚至死亡。肺部侵犯的臨床表徵，包括：發燒、咳嗽、咳血和胸部 X 片出現以肺周邊分布為主的細小結節 (micronodule)、毛玻璃狀 (ground-glass)、實質化 (consolidation) 的病灶。若病人有上述表徵加上野外活動的接觸史，臨床上對治療社區性肺炎的經驗療法反應不佳，則要懷疑被鉤端螺旋體感染的可能，尤其在亞熱帶的台灣。

我們在此報告一位 61 歲男性病人，因發燒、咳血及胸部 X 光片異常被轉診到本院急診。初時，被當成社區性肺炎治療，病人持續發燒，在確認病人有野外活動的暴露史，經血清抗體檢查後確立診斷為鉤端螺旋體病。病人在接受盤尼西林 (penicillin) 治療後病況迅速好轉，痊癒出院。*(胸腔醫學* ***2006; 21: 433-438)***

關鍵詞：鉤端螺旋體，黃疸，急性腎衰竭

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Post-ictal Neurogenic Pulmonary Edema — A Case Report

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Neurogenic pulmonary edema (NPE) is a rare or easily underdiagnosed pulmonary complication that occurs after central nervous system damage. The prognosis of survivors is good, and they usually recover rapidly if neurological insult is controlled. We report a case of NPE that developed after a seizure attack. The patient had no respiratory symptoms at presentation, but the NPE was found incidentally by radiographic study, and the patient recovered spontaneously within 96 hours. NPE should be on the list of differential diagnoses in patients with bilateral alveolar infiltration after a neurological event. Aggressive respiratory support is indicated for severe cases; however, general supportive care is adequate for most patients, and the radiographic infiltration usually resolves rapidly and spontaneously. ***(Thorac Med 2006; 21: 439-443)***

Key words: neurogenic pulmonary edema, seizure

Introduction

Neurogenic pulmonary edema (NPE) is a rare or easily underdiagnosed pulmonary disease. The pathogenesis relates to a change in pulmonary hydrostatic pressure and capillary permeability associated with increased intracranial pressure following seizure, head trauma, stroke, intracranial hemorrhage, and infection. The mortality rate of NPE is around 9.5%, and the prognosis of survivors is good; they usually recover rapidly if neurological insult is controlled [1]. We report the case of a patient who developed NPE soon after a seizure attack, and recovered within 96 hours, without treatment.

Case Report

A 35-year-old female had had epilepsy since 9 years of age, and was referred to the Department of Neurology of this institute in 2000. Brain magnetic resonance imaging showed right mesial temporal sclerosis and an electroencephalogram revealed spikes in the right mesial temporal area. She underwent craniotomy for temporal lobectomy and hippocampectomy, and was regularly followed up at our outpatient clinic.

On this occasion, she suffered from a generalized tonic-clonic seizure episode with transient loss of consciousness, and was sent to our Emergency Department immediately. On arrival, phy-

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sical examination revealed clear consciousness, stable vital signs without respiratory distress, and clear breathing sounds. Electrocardiogram revealed normal sinus rhythm without chamber dilation or ischemic change. The chest radiograph showed bilateral alveolar infiltration, predominantly in the right perihilar area, without cardiomegaly or pleural effusion (Figure 1). The laboratory examination revealed a white blood cell count of 15300 /mm^3 with 92.1% neutrophils and 4.1% lymphocytes, and C-reactive protein was 0.91 mg/dl. Chest computed tomography was performed 2 hours after the chest radiograph, and demonstrated patchy ground glass opacifications at bilateral perihilar regions, which were more prominent on the right side (Figure 2). The patient refused admission and asked for discharge. During the 4-hour stay at the Emergency Department, she received only supportive care, and neither antibiotics nor diuretics were prescribed. She came back and visited our outpatient clinic 4 days later. A follow-up chest radiograph was taken and revealed nearly complete resolution (Figure 3).

Discussion

NPE is an unusual complication after central nerve system damage, and was first described by

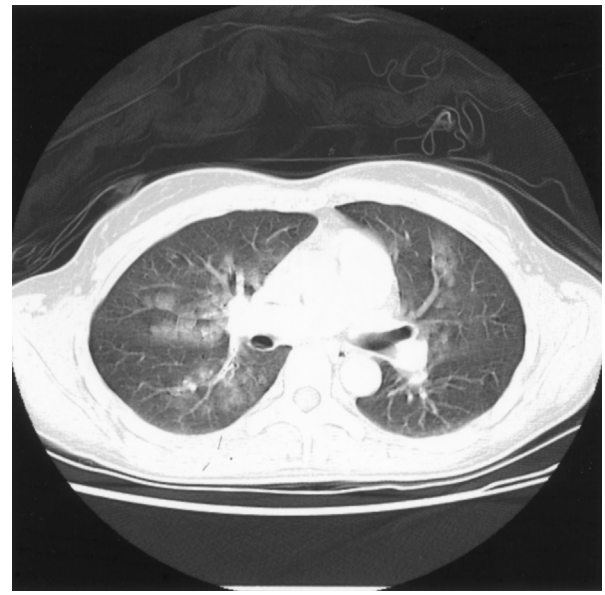

Fig. 2. Chest computed tomography shows patchy ground glass opacifications at bilateral perihilar regions, more prominent on the right side.

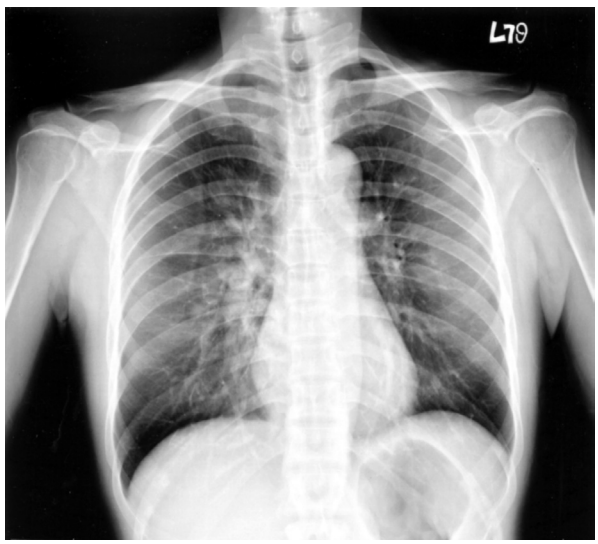

Fig. 1. Chest radiograph revealing bilateral alveolar infiltration predominantly in the right perihilar area without cardiomegaly and pleural effusion.

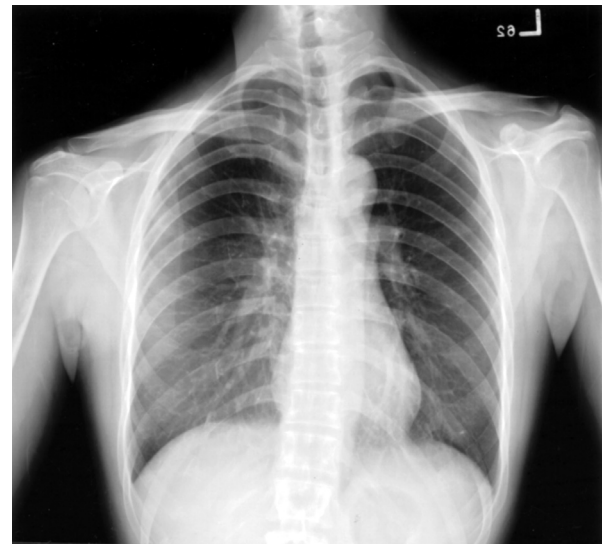

Fig. 3. Follow-up chest radiograph reveals nearly complete resolution 4 days later.

Shanahan in 1908 in 11 patients with epilepsy [2]. The pathogenesis of NPE is not completely understood, and some animal studies reported high interstitial or alveolar protein concentrations, suggesting increased permeability as a mechanism for NPE [3-6]. The increased permeability may be caused by damage to capillary endothelium or by direct neural influences on capillary permeability [7]. Other studies revealed that a dramatic increase of intracranial pressure might stimulate the hypothalamus and medulla, which in turn activate the sympathetic system, resulting in pulmonary vasoconstriction and a subsequent increase in pulmonary capillary hydrostatic pressure and pulmonary edema [8-10]. One study, which was also the largest single series of NPE, performed pulmonary edema fluid analysis and concluded that NPE was commonly related to hydrostatic mechanisms [11]. It seems that both the elevation of pressure in the pulmonary vasculature and the increase of endothelial permeability play important roles in the development of NPE.

The incidence is difficult to estimate due to the difficulty of diagnosing NPE definitely. Some studies reported it as an unusual complication [12-13], but in Weir's review, 31% of 78 fatal subarachnoid hemorrhages had a clinical diagnosis of NPE [14]. Fontes reviewed 14 reports of 21 cases of NPE since 1990: the most frequent underlying factor in NPE was subarachnoid hemorrhage (42.9%), and only 1 case was due to epilepsy (4.8%) [1]. NPE occurred more commonly among females (61.9%) in this review, and the mean age of the 21 patients was 31.6 years [1].

Diagnosis of NPE is based on clinical presentation, and should be considered in patients presenting with signs of respiratory distress after an acute neurological event; however, other causes of respiratory distress, including gastric content aspiration, pneumonia, and heart failure should be excluded first. The clinical presentations of NPE are nonspecific and include difficulties in breathing, cough, chest pain, and bloody expectoration. Physical examination usually reveals tachypnea, tachycardia and rales above the lung without signs of cardiac insufficiency [15-16]. While thoracic radiography frequently discloses bilateral diffuse alveolar infiltrates, unilateral pulmonary edema has been reported [17]. However, with the improved sensitivity of radiographic studies, which was demonstrated in the present case, we consider uneven distribution rather than true unilateral involvement to be the case, if chest tomography is used instead of plain film. One possible explanation for the uneven distribution of pulmonary edema is that positioning of an unconscious patient may result in the edema fluid and transmural pressure of the dependent side being subject to the preferential effects of gravitational force [17]. NPE usually resolves rapidly, within 24-48 hours [15]. In Fontes' review, the NPE in 52.4% of patients resolved within 72 hours, and only 1 case (4.8%) lasted over 7 days [1]. The prognosis is generally good; however, acute respiratory failure and death have been reported [15]. Fontes found that the overall mortality rate was 19%, but only 2 deaths (9.5%) of the 21 patients were directly related to NPE [1].

The treatment is generally supportive, including oxygen supplement and mechanical ventilation, if needed. Animal studies suggest that an alpha-adrenergic blocking agent may be useful in the management of NPE, but no human study is available.

We presented herein a patient who suffered from a seizure attack and had radiographic evidence of pulmonary edema when she was sent to hospital. Cardiogenic pulmonary edema was

ruled out by electrocardiogram, laboratory study and clinical course. Our patient had no pulmonary symptoms at presentation, and therefore, only supportive treatment was given. The chest radiograph and chest computed tomography demonstrated bilateral perihilar involvement, predominantly on the right side. Although the possibility of gastric content aspiration could not be completely ruled out, NPE was the preferred diagnosis due to the lack of signs of systemic inflammation, and rapid and spontaneous clearance of pulmonary infiltrates on the follow-up chest radiograph.

In conclusion, NPE should be in the list of differential diagnoses in patients with bilateral alveolar infiltration after a neurological event. Aggressive respiratory support is indicated for severe cases; however, general supportive care is adequate for most patients, and the infiltration usually resolves rapidly and spontaneously.

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癲癇後的神經性肺水腫—病例報告

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神經性肺水腫是一種中樞神經傷害後少見且不易診斷的肺部併發症。存活者的預後很好；只要神經傷害獲得控制，肺水腫通常在 72 小時內復原。我們報告一個在癲癇發作後，無任何呼吸道症狀但影像學卻意外發現神經性肺水腫的病例。病人未經任何治療而在 96 小時內自行復原。因此，在中樞神經傷害後，若病人產生雙側肺浸潤變化，應將神經性肺水腫列為鑑別診斷之一。嚴重的神經性肺水腫病人要給予積極的呼吸支持；然而，大部分的病人只要給予支持性治療即可，肺部浸潤性變化通常會自行復原。*(胸腔醫學* ***2006; 21: 439-443)***

關鍵詞：神經性肺水腫，癲癇

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Serial Pulmonary Function Tests in a Patient with Cryptogenic Organizing Pneumonia — A Case Report

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Cryptogenic organizing pneumonia (COP) is a rare disorder involving the small airways. Polypoid granulation tissues that occupy the lumen of the small airways, alveolar ducts, and alveoli, and foamy macrophages are commonly present in the airspaces.

We report an 83-year-old male who had a nonproductive cough for 2 months, after which exertional dyspnea developed. A chest radiograph revealed an infiltration with an irregular reticular pattern with air bronchograms in both lower lungs. Empiric antibiotics failed to improve his dyspnea and hypoxia. Chest computed tomography (CT) revealed peribronchial infiltrates with ground glass opacities in both posterior basal lungs. Wedge lung biopsy resulted in a diagnosis of bronchiolitis obliterans organizing pneumonia. As no etiology could be found, the applicable diagnosis was COP. Oral prednisolone, 1 mg/kg/day resulted in dramatic clinical and radiographic improvement. Even after the prednisolone was tapered to 10 mg/day, the patient remained asymptomatic with normal daily activity. ***(Thorac Med 2006; 21: 444-451)***

Key words: cryptogenic organizing pneumonia, bronchiolitis obliterans organizing pneumonia, pulmonary function test

Introduction

Diffuse parenchymal lung disease (DPLD) is increasingly the preferred term to describe a range of disorders previously described as interstitial or diffuse lung disease. The DPLDs are important, accounting for about 15% of cases in respiratory practice [1]. Many of these diseases are refractory to treatment, but cryptogenic organizing pneumonia (COP) responds well to corticosteroids, with two-thirds or more of adequately treated patients having a good outcome.

COP was first described in 1983 by Davison *et al.* [2]. In 1985 Epler *et al.* [3] recommended the term bronchiolitis obliterans with organizing pneumonia, by which they intended to distinguish the disorder from irreversible pulmonary fibrosis. In 2002, the American Thoracic Society/European Respiratory Society International Consensus Panel for the Classification of Idiopathic Interstitial Pneumonia recommended that the term COP be used to describe diseases in which no

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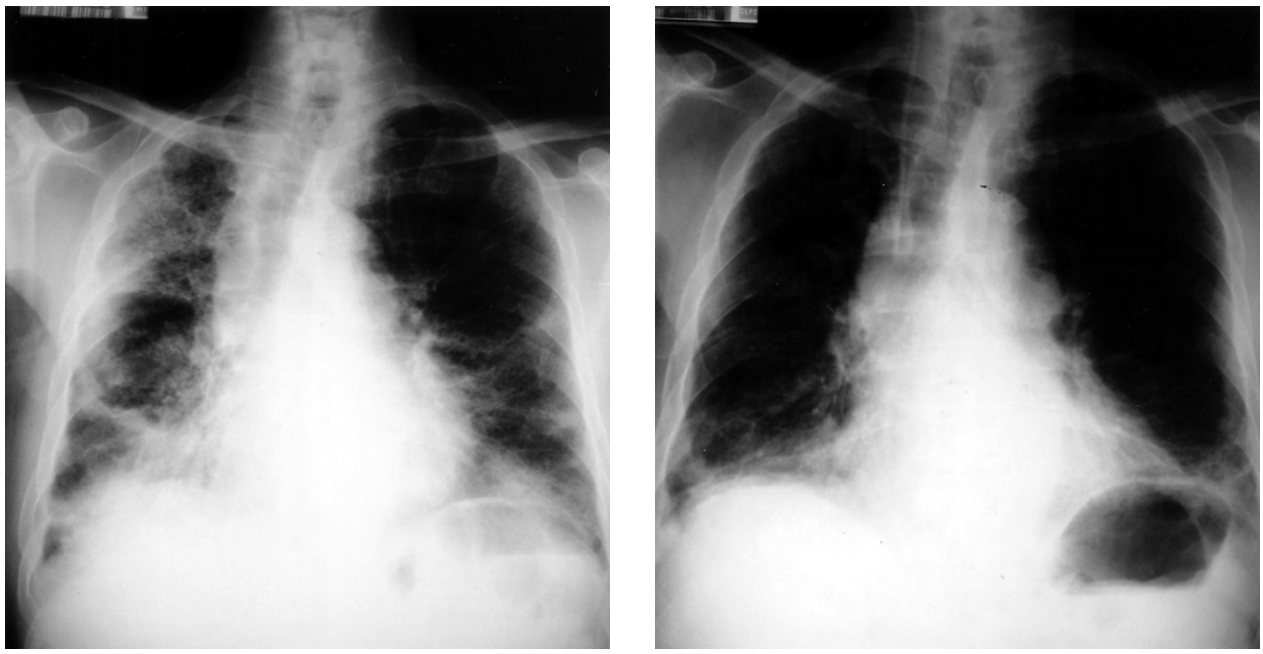
definite etiology can be found. The panel also recommended that pathologists report an 'organizing pneumonia pattern,' as etiologic information may not be available to the pathologist [4].

While COP often responds well to steroids, there is little information available on the objective changes in pulmonary function with treatment. We report a patient with COP for whom we were able to perform serial pulmonary function testing.

Case Report

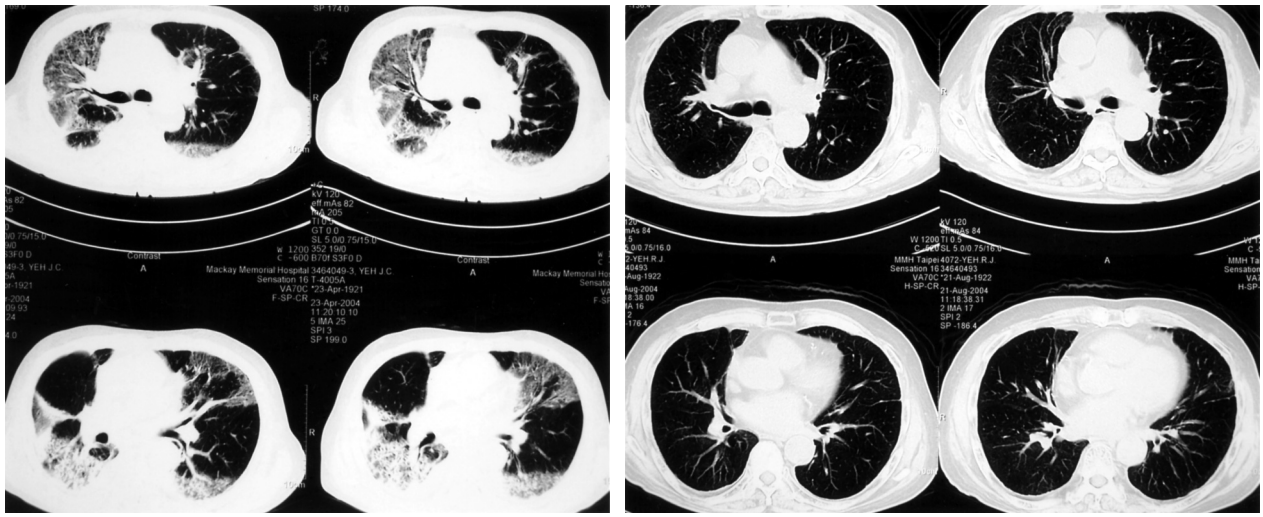
An 83-year-old man had smoked 1 pack of cigarettes per day for 40 years prior to quitting 10 years ago. He had been in excellent health, with no history of underlying heart or lung disease. He had walked a mile daily for years with no extraordinary dyspnea. However, he came to our chest outpatient department complaining of a nonproductive cough lasting for 2 months and new-onset exertional dyspnea of several days' duration. He also noted night fever and weight loss, as well as chest tightness. He denied a sore throat, hemoptysis, inhalation of toxic fumes, radiation exposure, a recent travel history, history of tuberculosis, or aspiration.

On initial examination, his respiratory rate was 24/min with a shallow respiratory pattern. On auscultation, bibasilar inspiratory and expiratory crackles were heard. The remainder of the physical examination was unremarkable. There was no evidence of heart failure, and no cervical or axillary lymphadenopathy, hepatosplenomegaly, or ankle edema. A chest radiograph (Figure 1) revealed infiltration with an irregular reticular pattern and air bronchograms in both lower lungs. There was fibrosis in the right upper lobe and volume loss on the right side, with rightward deviation of the trachea. The admitting dif-



(A) (B)

Fig. 1. Chest radiographs: (A) initial and (B) after 1 month of treatment with prednisolone.



(A) (B)

Fig. 2. Chest CT: (A) initial, showing bilateral lower air-space consolidation, ground-glass opacities, and bronchial wall thickening and dilatation and (B) after 4 months of treatment with prednisolone.

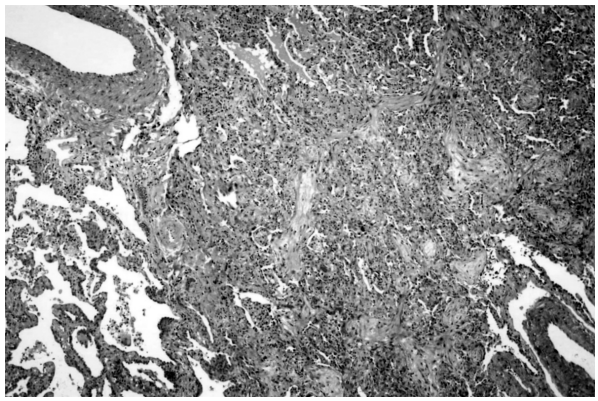
ferential diagnosis included atypical pneumonia and pulmonary tuberculosis.

His blood level of hemoglobin, hematocrit, white cell and differential count, and platelet count were all within the normal range. The results of blood tests for liver function (aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, prothrombin time and albumin) and renal function (blood urea nitrogen and creatinine) were also normal. Tests for anti-nuclear antigen, C3, C4, and rheumatoid factor were negative or within the normal range. On nasal cannula of oxygen at 2 liters per minute, the patient's arterial blood pH was 7.465, PCO_2 32.4 mmHg, PO_2 60.7 mmHg, HCO_3 22.8 mmol/liter, and O_2 saturation 87%. He was given intravenous levofloxacin 500 mg daily to treat possible atypical pneumonia, but his dyspnea persisted for nearly 2 weeks. Isoniazid 300 mg/day, ethambutol 900 mg/day, and rifampicin 450 mg/day were given as a therapeutic trial for possible tuberculosis. However, acid-fast stains of his sputum were negative.

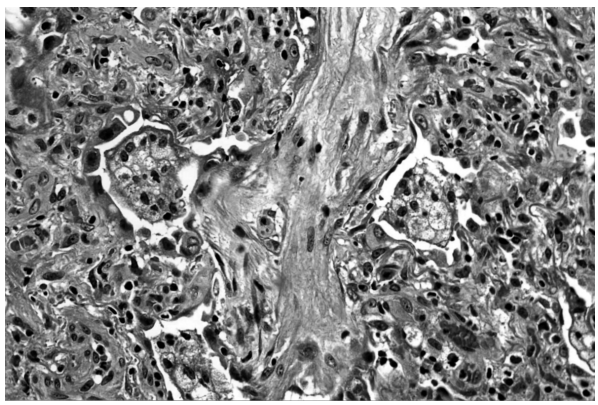
A repeat chest radiograph showed no resolution of the bilateral basal infiltrates. Therefore, a chest CT (Figure 2) was performed and demonstrated peribronchial infiltrates associated with ground glass opacities in the posterior basal lung fields bilaterally. There was also ground glass attenuation in the right upper lobe and the anterior segment of the left upper lobe. These findings were most consistent with DPLD, although the exact diagnosis could not be made from the CT appearance alone.

A video-assisted thoracoscopic lung biopsy of the left lingula was therefore performed. Pathology findings included fibroblast plugs occluding the distal bronchioles, alveolar ducts, and adjacent alveolar spaces. The alveolar walls were thickened with inflammatory infiltrates. These findings were interpreted by the pathologist as bronchiolitis obliterans organizing pneumonia (Figure 3).

The patient was treated with oral predniso-



(A)



(B)

Fig. 3. Lung biopsy: (A) Low-magnification photomicrograph showing lightly stained, elongated fibrous plugs filling the air spaces. Note the clear demarcation between the uninvolved lung parenchyma in the bottom left corner of the picture and the diseased tissue (Hematoxylin and eosin, ×40). (B) Higher-magnification view of air-space plugs with fibroblasts arranged in parallel and embedded in a pale-staining, myxoid matrix. The plugs are covered by a lining of alveolar epithelial cells, and there are foamy macrophages within the air spaces (Hematoxylin and eosin, ×200).

lone, 1 mg/kg/day, leading to a marked improvement in his symptoms. He was able to tolerate normal daily activities, such as walking to the toilet and changing his clothes. After discharge, the prednisolone was tapered to 0.5 mg/kg/day with no return of the dyspnea. His chest radiograph after 1 month of treatment with prednisolone (Figure 1) demonstrated resolution of the bibasilar infiltrates. The patient could walk for a distance of about 400 meters without dyspnea, a quarter of the distance he walked every day before the onset of this disease. A chest CT performed 4 months after initial steroid therapy (Figure 2) revealed only minimal fibrosis in both upper lungs. Since right upper lobe fibrosis was seen on the initial chest film, we could not determine whether the residual fibrosis on the CT was a result of this episode of COP or indicated previous pulmonary tuberculosis.

When first seen, the patient was too dyspneic to tolerate pulmonary function testing, so the earliest study we were able to do was performed 1 week after prednisolone therapy was started. The testing was repeated again at 7 weeks, 6 months, and 1 year after therapy was begun (Table 1). On pulmonary function testing, the patient's vital capacity (VC) improved from 1.99 to 2.85 L (from 68% to 100% of predicted value) and carbon monoxide diffusion capacity (DL_{CO}) from 10.5 to 12.4 ml/mmHg/min (77% to 84% of predicted value). The patient initially had a mild restrictive defect and a decreased carbon monoxide diffusion capacity. These improved substantially with treatment, although he was subsequently found to have an obstructive lung defect.

Discussion

Our patient had COP, an organizing pneumonia for which a careful search did not yield a cause. His clinical findings of an insidious onset, a nonproductive cough, and dyspnea were typical, as was the lack of specific abnormalities on routine laboratory studies [5]. Organizing pneumonia may be idiopathic, when it should be called COP, or secondary to infection (virus, mycoplasma, legionella), drugs (bleomycin, amiodarone), aspi-

Table 1. Pulmonary Function Tests after Prednisolone Treatment

Parameters	Initial: 1 week after treatment started	7 weeks after treatment started	6 months after treatment started	1 year after treatment started
FEV1/FVC %	80	63	61	55
FEV1 (L)	1.59	1.54	1.47	1.45
% of Predicted	71	64	70	67
FEF 25-75% (L)	1.68	0.75	0.59	0.34
% of Predicted	76	31	28	16
TLC (L)	3.31	4.4	4.29	4.05
% of Predicted	62	78	84	76
VC (L)	1.99	2.52	2.58	2.85
% of Predicted	68	81	93	100
DL_{CO} ml/mmHg/min	10.5	10.1	15.1	12.4
% of Predicted	77	72	86	84
FVC (L)	1.98	2.44	2.41	2.65
% of Predicted	68	78	87	93
RV/TLC %	40	63	40	30

FEF: Forced mid-expiratory flow, TLC: total lung capacity, RV: residual volume

ration, irradiation, bone marrow transplantation, lung and heart-lung transplantation, collagen vascular diseases (rheumatoid arthritis, systemic lupus erythematosus), or inflammatory disorders (ulcerative colitis, Crohn's disease) [6]. Our patient had been exposed to none of the drugs implicated in organizing pneumonia, including minocycline, nitrofurantoin, bleomycin, amiodarone, cabamazepine, interferon-α, L-tryptophan, and cocaine [7]. He had no gastrointestinal symptoms, and there was no evidence of collagen vascular disease.

The radiographic patterns in COP (or secondary organizing pneumonia) may include scattered, patchy, bilateral alveolar opacities with a peripheral distribution or diffuse bilateral infiltrates with interstitial opacities [8]. Masuo *et al.* described a perilobular pattern on thin-section CT, which was present in 12 of 21 patients with organizing pneumonia. In addition, 20 had consolidation, which was predominantly subpleural or peribronchial or both in 17 patients, and 18 patients had ground-glass opacification. The perilobular pattern occurred in all lung zones, although it was more common in the middle and lower zones [9]. Our patient did not have this typical perilobular pattern, but he did have ground-glass opacification, mostly in the lower lung zones.

Even though findings on CT may be suggestive of a particular entity, biopsy is usually required for a definitive diagnosis, as in our patient. Transbronchial lung biopsy has been used, but the American Thoracic Society and European Respiratory Society consensus statements recommended wedge lung biopsy, either by video-assisted thoracoscopy or by thoracotomy, as providing the best tissue specimens to distinguish between usual interstitial pneumonia, non-specific interstitial pneumonia, COP, and idiopathic interstitial pneumonia. An adequate tissue specimen is also necessary to exclude other entities

with clinical and radiologic features that mimic idiopathic pulmonary fibrosis [10].

The pathologic diagnosis of organizing pneumonia first requires finding characteristic buds of granulation tissue in the alveoli. This tissue may extend from 1 alveolus to the next through the pores of Kohn in a butterfly pattern. In some cases, different stages of organization, from fibrinoid inflammatory cell clusters to mature fibrotic buds, may appear in the same specimen. The lesions are centered in the small airways and structures distal to them. Foamy macrophages are commonly present in the airspaces [11]. The major histopathologic feature of organizing pneumonia is alveolar space organization (Masson bodies), but the pathology also involves alveolar ducts and respiratory bronchioles, where there is a characteristic polypoid and fibromyxoid appearance [12]. Our patient had the characteristic airspace plugs with fibroblasts arranged in parallel and embedded in a pale-staining, myxoid matrix, as well foamy macrophages within the air-spaces (Figure 3).

The clinical and imaging response of COP to corticosteroids is rapid. Clinical manifestations may abate within 48 hours, and chest radiographs show a complete resolution of the pulmonary opacities within a few weeks, without significant imaging sequelae. Although the efficacy of steroids has been recognized for almost 20 years, the optimal dose and duration of treatment have not been established. Even with an excellent response to steroids, a proportion of patients, reportedly ranging from 13% to 58%, have a relapse of COP. Relapse is rare on doses of more than 20 mg of prednisone per day, so if it occurs in someone taking that high a dose, the diagnosis of COP should be reconsidered, especially if it was not established histologically in the first place [8].

At 1 year after diagnosis, our patient's chest radiograph remained unchanged from that taken after 1 month of treatment. As of this writing, he was maintained on 10 mg of prednisolone a day, and was able to carry on his usual activities without dyspnea. We are monitoring him for any adverse effects of treatment.

What is particularly interesting about this patient's case is that we were able to follow his pulmonary function serially after treatment. Pulmonary function test results in patients with COP may range form normal to severely abnormal. A mild or moderate restrictive defect is the most common finding. The ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC) is generally normal in patients who do not smoke. However, the DL_{CO} is commonly reduced [6]. The initial results with our patient, when he was able to tolerate the testing after 1 week of treatment, revealed a normal FEV1/FVC, but a reduced total lung capacity, vital capacity, and DL_{CO}. Seven weeks later, the restrictive defect and diffusing capacity improved, but an obstructive defect was then found to be present (Table 1). One possible explanation for this unexpected finding of an obstructive lung defect relates to the effects of a concurrent restrictive defect on airway dynamics. In patients with a restrictive lung defect, the elastic recoil pressure increases [13], which might result in enough improvement in air flow that an underlying obstructive defect is obscured. Once the restrictive defect resolves, the obstructive lung defect may then become apparent. Furthermore, a gradual increase in FVC after treatment would necessarily reduce the FEV1/FVC ratio unless there is also a substantial decrease in FEV1 at the same time. The fact that the patient was previously asymptomatic, however, suggests that he had a relatively mild decrease in FEV1. We presume therefore that prior to developing COP, he had mild subcli-

nical airway obstruction, probably related to his 40-year pack-a-day smoking history. The obstructive defect came to light only because we followed his pulmonary function as he recovered from COP. Regardless of how we explain the obstructive defect, the marked improvement in the restrictive defect and diffusing capacity paralleled the clinical and radiographic resolution of his COP.

Conclusion

This case illustrates once more the response of COP to steroids, shown in particular by the improvement in pulmonary function. While symptom resolution is of course often the greatest concern for both patient and clinician, it is reassuring to know that measures such as pulmonary function testing as well as radiography can confirm the improvement objectively.

Acknowledgments

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原因不明器質化肺炎的病人的一系列肺功能變化—病例報告

沈聲燁　林清基　陳碧芳*

原因不明器質化肺炎 (cryptogenic organizing pneumonia) 是一種影響小型氣道的罕見疾病。息肉狀的肉芽組織阻塞了小型氣道，肺泡管及肺泡的管徑，而且泡沫狀的巨噬細胞通常會存在於空腔中。原因不明器質化肺炎，顧名思義，無法找到發生原因或是與以下原因相關：感染，藥物，肺內吸入，放射線，骨髓移植，肺臟或心肺移植，膠原血管疾病或是發炎疾病。

我們報告一個病例：83 歲老先生咳嗽無痰已經有兩個月，之後發現活動性氣促。胸部 X 光顯示雙側下肺野不規則網狀變化及 air bronchogram 。經驗性抗生素治療並不能改善他的氣促及缺氧。胸部電腦斷層可看出兩邊後下側肺部支氣管旁肺浸潤及毛玻璃顯像。開胸活體肺部切片診斷為阻塞性細支氣管炎合併器質化肺炎。

經給予劑量為每公斤每天 1 毫克的口服 prednisolone ，病人的臨床症狀及影像有明顯進步。之後 prednisolone 減量至每日 10 毫克，而病人仍然維持正常活動量而沒有不適症狀。*(胸腔醫學* ***2006; 21: 444-451)***

關鍵詞：原因不明器質化肺炎 (cryptogenic organizing pneumonia)，阻塞性細支氣管炎合併器質化肺炎 (bronchiolitis obliterans organizing pneumonia)，肺功能

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索取抽印本請聯絡：林清基醫師，台北馬偕紀念醫院　胸腔內科，台北市 104 中山區中山北路二段 92 號

Delayed Diagnosis of Endobronchial Foreign Body in Pregnant Women — A Case Report

Li-Pang Chuang, Chih-Hung Chen, Chih-Liang Wang, Yen-Li Chou, Meng-Jer Hsieh

Flexible fiberoptic bronchoscopy is a valuable procedure in pulmonology. Because of the risks to the mother and the fetus related to the procedure and sedation, procedures such as bronchoscopy are usually avoided during pregnancy, which might be the cause of delayed diagnosis of the underlying diseases. We report the case of a pregnant woman with repeated pneumonia, in whom an endobronchial foreign body was finally found and removed by fiberoptic bronchoscope. There have been only a few case reports that have mentioned the utility and safety of bronchoscopy during pregnancy. This patient reminds us to look out for the proper indications of flexible bronchoscopy in pregnancy, and to act with caution, with full consideration of the health and safety of both the mother and the fetus. ***(Thorac Med 2006; 21: 452-456)***

Key words: pregnancy, bronchoscopy, foreign bodies

Introduction

Bronchoscopy is a common procedure in diagnosis and therapy in pulmonology. The indications, contraindications, risks and complications were already well understood. Due to risks to the mother and the fetus related to the procedure and sedation, medical procedures such as flexible bronchoscopy are generally avoided in pregnant women. However, there are still some situations in which flexible bronchoscopy might be indicated. Delayed bronchoscopy might result in delayed diagnosis.

Here we present a case of pregnant woman, suffering from repeat pneumonia, and an endobronchial foreign body was finally found and removed by flexible bronchosopy.

Case Report

A four months' pregnant, 31 year-old female was admitted to our chest ward with the presentations of 6 months' cough with purulent sputum, dyspnea, intermittent fever with chills, and general weakness. She denied obvious body weight loss, nor any experience of choking. Right lung pneumonia was diagnosed in a local hospital and she was treated with oral moxifloxacin, and then amoxycillin-Clavulanic acid with improvement of symptoms and clinical condition. The similar symptoms recurred after oral antibiotics were discontinued. Then she was referred to our hospital

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for further management. On physical examination, she was not febrile at presentation, the body temperature was 37.3°C centigrade, pulse rate 125 beats per minutes, respiratory rate 20 times per minutes, and blood pressure 127/69 mmHg. The breath sound was decreased in the right lower lung field without inspiratory crackles. The hemogram showed white blood cell count at 8900/uL with 80.5% segment. Serum level of C-reactive protein was elevated at 163.27 mg/L. No chest radiograph had been taken due to the pregnancy. Under the suspicion of pneumonia, she was admitted to our chest ward.

Emperic antibiotics with Cefuroxime 750 mg intravenously three times a day were prescribed after admission. Chest sonography showed consolidation change over the posterior aspect of right lower lung (figure 1). Sputum culture grew of two kinds of bacteria, *Klebsiella pneumoniae* and *Haemophilus parainfluenzae*; both were susceptible to Cefuroxime *in vitro*. After 7 days' antibiotic treatment, the clinical symptoms improved and lung consolidation also improved in a subsequent chest echography. She was discharged with one more week's oral Cefuroxime.

However, intermittent cough was still noted

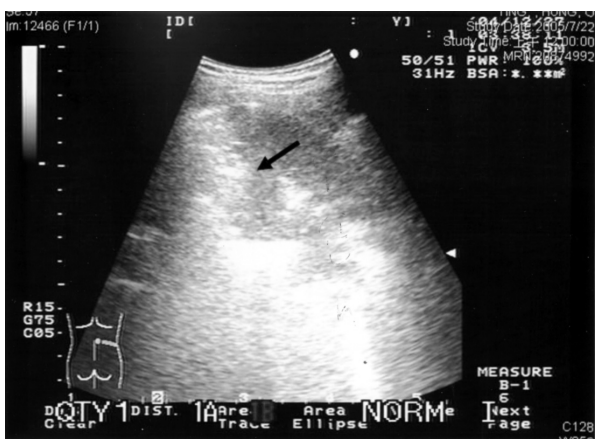

Fig. 1. Chest sonography showing consolidation change in right lower lung field. (Arrow)

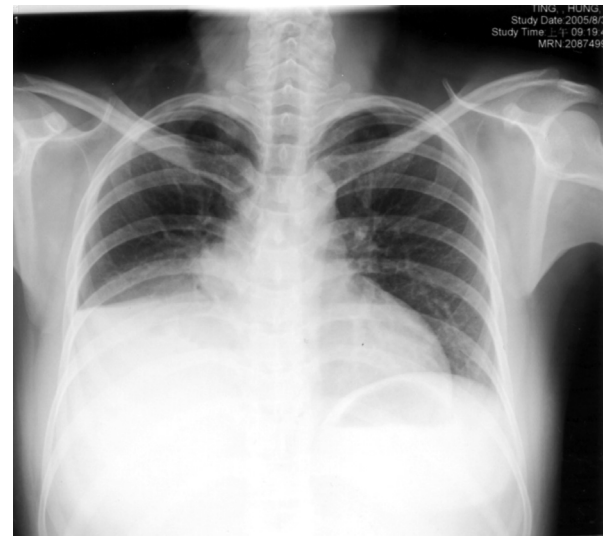

Fig. 2. Chest radiography revealing right lower lung and right middle lung collapse with increasing hilum density.

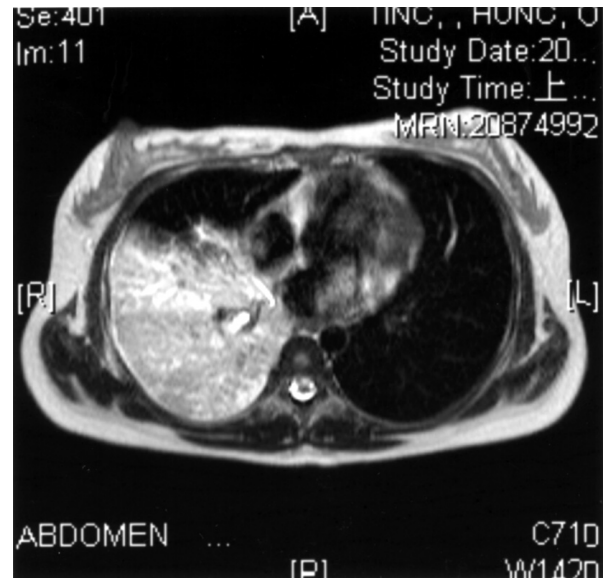

Fig. 3. MRI revealing a soft tissue tumor (2.6x1.9x1.8 cm) in the posterior aspect of right hilar region, resulting compression to the lower bronchus of the right lung. High signal intense parenchyma of right middle and lower lung, pneumonia are considered.

after discharge. Fever with dyspnea recurred after ceasing oral antibiotics. She went back to our emergency room with fever at 38.3°C, tachycardia, and elevated C-reactive protein at 176.73

mg/L.

Emperic antibiotics with Cefuroxime were prescribed initially according to previous sputum culture data. Due to repeated pneumonia episodes, image study was strongly considered. Chest radiograph was taken with shield protection to the fetus. It revealed a right lower lobe and right middle lung consolidation (figure 2). Magnetic Resonance Imaging (MRI), instead of computer tomography (CT) scan, was carried out and showed a soft tissue mass (2.6x1.9x1.8 cm) in the posterior aspect of right hilum with obstructive pneumonia in the right lower lobe due to compression of the right lower bronchus (figure 3). Flexible bronchoscopy was performed for the endobronchial obstruction. One 1.2x2.3 cm nutlet, resulting in total occlusion of the right lower lobar bronchus, was removed by bronchoscopy. Some pus-like and blood tinged secretion was expectorated out thereafter. She was discharged after 10 more days' antibiotic treatment without recurrence of symptoms.

Discussion

Radiation exposure is potentially teratogenic [1]. Ionizing radiation (x-ray), composed of high-energy photons, is capable of damaging DNA and generating free radicals. These effects may lead to fetal malformation, induce malignancy and alteration of germ-line genes. The most common fetal malformations are central nervous system changes, and most cases followed exposure during weeks 10 to 17 of gestation [2]. According to a previous study, exposure amount to the fetus from a two-view chest x-ray of the mother is only 0.00007 rad, and the accepted cumulative dose of ionizing radiation during pregnancy is 5 rad [3]. In this pregnant woman, chest roentgenogram was not been taken initially. Chest ultrasonography is an alternative tool for detecting consolidation of lung parenchyma in patients with pneumonia. However, this may lead to delayed diagnosis of endobronchial lesion owing to the limitation of chest ultrasonography for detecting deep pulmonary lesions [4]. The recurrent symptoms reminded us of the possibility of endobronchial lesions resulting in delayed resolution of pneumonia. The gestational age of this case when chest radiograph was taken was about 22 weeks, and the dose she was exposed to was far from a harmful level (0.00007 rad versus 5 rad).

For avoidance of excessive radiation exposure, MRI instead of CT scan was performed and revealed an obstructive lesion in the right lower lung bronchus. Bronchoscopy is the tool for direst visualization and management of this lesion.

Risks of bronchoscopy during pregnancy are related to the procedure itself and medications used during the procedure [5]. Risks associated with the procedure itself generally include pneumothorax, hypoxemia, airway hyperreactivity, pulmonary hemorrhage, and systemic hypotension or hypertension [6]. Risks associated with the medication including those related to conscious sedation and those contributing to mother-fetus unhealthiness, are teratogenesis, premature labor, maternal cardiac arrhythmias, and depressed mental status with resultant hypoventilation, etc. [7]

During pregnancy, respiratory drive increases due to changing homeostatic set points in respiratory centers, which may be the result of increased pregesterone level [8]. Functional residual capacity decreases approximately 18% during pregnancy, which is caused by diaphragmatic elevation due to increased intraabdominal pressure. It may result in rapid oxygen desaturation during hypopnea, as a result of the loss of oxygen reservoir function of end-expiratory lung volume

[9]. To meet the increased metabolic demands of placenta and fetus, oxygen consumption increases by almost 20% during pregnancy. All the above issues contribute to the increasing risk of hypoxia during bronchoscopy. Besides this, due to the potential risks of hemodynamic changes in the mother that can affect the fetus, medications used during flexible bronchoscopy should be considered carefully [10]. In our case, a finger pulse oximeter monitor was used throughout the whole procedure of bronchoscopy. We used only inhaled lidocaine for local anaethesia. The total amount of inhaled lidocaine was 400mg, which has been shown to be well-tolerated and safe [11].

In summary, the published literature about the safety of flexible bronchoscopy in pregnancy is limited. Only a few case reports have tested the utility and safety of bronchoscopy during pregnancy. We report the case of a pregnant woman, presenting with repeated pneumonia, and an endobronchial nutlet was found and removed by flexible bronchoscope. This may remind us to look out for the appropriate indication of flexible bronchoscopy in pregnant women, to review the potential side effects of the medication to the mother and to the fetus, and to perform it cautiously, including careful monitoring during this procedure.

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延遲診斷支氣管內病兆在一孕婦身上：病歷報告

莊立邦　陳志弘　王智亮　周晏立　謝孟哲

在胸腔科領域中，軟式支氣管鏡是一個很常見且廣被應用的一項檢查。雖然懷孕並不是軟式支氣管鏡檢的一項禁忌症，但是著眼在檢查本身和其相關藥物對母親和胎兒的影響，大多數侵入性的檢查包括軟式支氣管鏡，都會盡量避免。然而這卻會造成某些延遲診斷，尤其是在軟式支氣管鏡檢可能有必要實施的情況下。我們報告了一個懷孕的病人，因為重複性的肺炎而住院治療，最後經由軟式支氣管鏡診斷且取出支氣管內的異物。除了一些少數的病歷報告之外，目前還沒有比較大規模的研究報告去探討軟式支氣管鏡檢在懷孕病人身上的應用和其安全性。這個案例也許可以提供我們一個機會去仔細思考軟式支氣管鏡檢在懷孕病人身上的適應症，並且更小心謹慎的去執行。*(胸腔醫學* ***2006; 21: 452-456)***

關鍵詞：支氣管內異物，軟式支氣管鏡檢，懷孕

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Pulmonary Infection due to *M. Flavescen* — A Case Report and Review of the Literature

Li-Kuo Kuo, Rong-Luh Lin, Chien-Liang Wu

M. flavescens is a member of Runyon group II, the scotochromogens. Although the isolation of *M. flavescens* from human specimens is not uncommon,only in extremely rare cases has this organism been considered to be responsible for disease.We report the case of a 74-year-old male presenting with persistent fever and dyspnea which were unresponsive to empiric antibiotics. Chest X-ray revealed fibrocystic change in the left lower lung field with bilateral apical pleural thickening and decreased left lung volume. Repeated growth of *M. flavescens* was found in the sputum culture. Fever subsided after the use of sensitive anti-mycobacteria agents. These findings suggest the pulmonary infection was caused by *M. flavescens.* ***(Thorac Med 2006; 21: 457-461)***

Key words: non-tuberculous mycobacteria, pulmonary infection, *M. flavescens*

Introduction

Nontuberculous mycobacteria (NTM) have long been considered saprophytes or culture contaminants. The genus Mycobacterium contains more than 80 recognized or proposed species. These species can be divided into 2 groups based upon their growth rate in culture [1]. The slow-growing species requires more than 7 days to form visible colonies on solid media, whereas the rapid-growing species requires less than 7 days. Although there are important exceptions, the slow-growing species are often pathogenic in humans, particularly in immunosuppressed patients or those with chronic lung diseases, whereas the rapid-growing species are usually considered nonpathogenic [2]. Pulmonary infections caused by *M. flavescens* have rarely been reported and they usually occurred in immunocompromised patients [7-12]. The case reported herein is of a rare instance of *M. flavescens* respiratory infection in a patient with chronic lung disease. This should alert clinicians to the possibility that unusual NTM pulmonary infections can occur in immunocompetent hosts.

Case Report

A 74- year-old-male, who had been a 1- pack-per-day smoker for more than 30 years, presented to our institute on 28 June 2005 with fever, productive cough, and dyspnea lasting for 3 days.

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Body weight loss, from 76 kg to 56 kg, had also been also noted in the most recent 10 months. He had had an old pulmonary TB condition and chronic lung disease for many years. The pulmonary function test performed in March, 2004 revealed mild restrictive lung disease. On presentation, his temperature was 38.5°C, pulse rate was 120 beats/minute, and respiratory rate was 24 times/minutes. His blood pressure was 144/79 mmHg. Physical examination revealed respiratory distress with retraction of intercostals and supraclavicular areas. Diffuse crackles and wheezing were heard in bilateral lung fields, especially the basal areas. Laboratory data were as follows: Hb:10 g/dl, WBC: 11800/CMM, glucose:244 mg/dl, BUN:14 mg/dl, Cr:1.3 mg/dl, and Na:130 meq/l. Chest radiography showed fibrocystic change in the left lower lung field, with bilateral apical pleural thickening and decreased left lung volume.(Figure 1).Bacterial infection was considered, but none of the bacteria cultures showed a definite etiology. Serology tests for mycoplasma and chlamydia were negative. Cold agglutinins were nonreactive at 1:16 titer. Urinary legionella antigen was also negative. Empiric antibiotics were prescribed, but fever persisted until the seventh day. At the same time, the 4 sets of sputum culture for acid-fast bacteria done over the past 2 months were identified as *M. flavescens*, using the conventional biochemistry method, and were sensitive to isoniazid and ethambutol, but resistant to rifampin and streptomycin. Two sets of sputum smears for acid- fast bacteria performed after admission were also positive, and were proved later to be *M. flavescens* . Six sets of positive culture results were identified as *M. flavescens* within 3 months. (Table 1) Based on the sensitivity test, isoniazid, ethambutol and clarithromycin were given to the patient. Fever subsided after 3 days, and dyspnea improved greatly, so the patient was discharged without event. Sputum smears and culture for AFB all were converted to negative after 2 months of treatment.

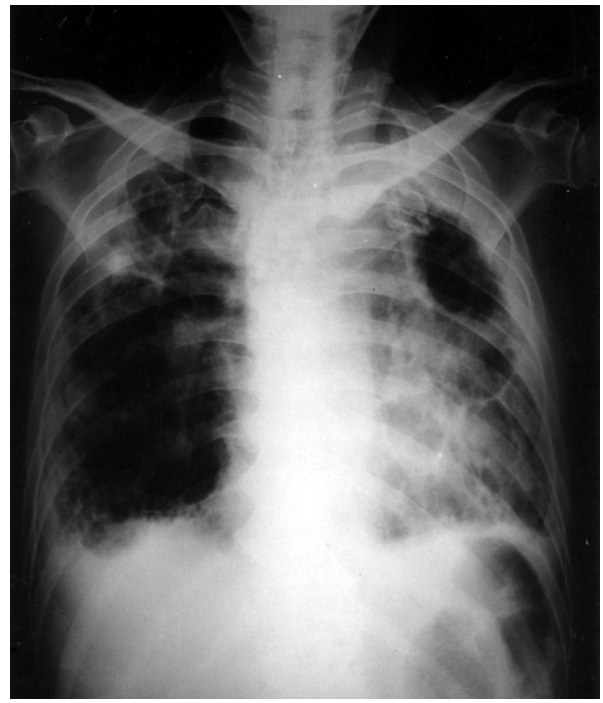

Fig. 1. CXR on admission showing fibrocystic change in the left lower lung field, with bilateral apical pleural thickening and decreased left lung volume.

Discussion

Runyon [4] proposed classifying nontuberculous mycobacteria into 4 groups: group 1, composed of the photochromogens that produce a yellow pigment when exposed to light; group 2, the scotochromogens that develop a yellow pigment when grown in the dark; group 3, the nonchromogens; and group 4, the rapid growers that form colonies in culture at room temperature within 3 to 5 days, instead of the 2 to 3 weeks required by the other mycobacteria. *M. flavescens,* a member of Runyon group II, the scotochromogens, is characterized by a slow

Table 1. Summary of isolation and treatment results

Period	Positive smears*	Positive cultures+	Identification	Drugs	Treatment initiation	Duration
Apr 2005	2/3	2/3	*M. flavescens*			
May 2005	2/3	2/3	*M. flavescens*			
June 2005	2/3	2/3	*M. flavescens*	HEK	June 2005	2 months
Aug 2005	0/3	0/3				

*: positive smears/smears done; +: positive cultures/cultures done ; H: isoniazid; E: ethambutol; K: clarithromycin

growth rate, and was initially described in 1962, following isolation from a drug-treated tuberculous guinea-pig [6]. Although the isolation of *M. flavescens* from human specimens is not uncommon, only in extremely rare cases has this organism been considered to be responsible for disease [5]. The mycobacterial isolate was identified as *M. flavescens* by cultural features such as an intermediate growth rate at 25-37°C, the scotochromogenic pigmentation of the smooth colonies, tolerance to NaCl 5% w/v, and positive tests for nitrate [7].

Pulmonary diseases account for 3 of the 8 reported cases [7-12] of *M.flavescens* infections; other localizations included: 2 skin infections; 1 keratitis; 1 arthritis (AIDS patient); and 1 surgical wound. The 3 patients suffering from lung disease presented with cavitary pneumonia, pleuritis and left upper lobe infiltrates (combined with disseminated infection) [7-8, 11]. The underlying conditions for *M flavescens* infections include metastatic melanoma, chronic granulomatous disease, DM, AIDS, and wound infection (intramuscular injection and corneal ulcer). Two strains showed resistance to isoniazid, but were sensitive to rifampicin, ethambutol, and streptomycin. The medical treatment regimens essentially contained first-line drugs based on the results of the sensitivity tests [7-8].

Our patient had been a heavy smoker for more than 30 years, and suffered from pulmonary TB and alcoholism, which were recognized as risk factors for nontuberculous mycobacteria infection [13]. Frequent exacerbations developed and *M. flavescens* were repeatedly found in the sputum specimens, with sensitivity to isoniazid and ethambutol, and resistance to rifampin and streptomycin. The signs of infection (fever and dyspnea), coupled with a response to specific anti-mycobacterial treatment, suggested that the isolated *M. flavescens* was the causative agent of the infection.

Diagnosis of disease caused by NTM is difficult because these organisms are frequently isolated from the sputum of patients with chronic lung disease. In 1997, the American Thoracic Society (ATS) published diagnostic criteria for NTM pulmonary disease, which include a combinations of clinical presentation, positive culture and a compatible radiographic picture [14]. Our patient met the ATS diagnostic criteria for NTM pulmonary disease. We selected effective drugs (INH and ethambutol) and added clarithromycin (500 mg per day), based on the drug sensitivity test results. Sputum conversion was achieved after treatment for 2 months. Similar to the reported phenomenon that patients infected with *M. xenopi* usually succumbed to underlying structural lung disease rather than the Mycobacterium itself [2]. This patient died 3 months later, due to

respiratory failure resulting from secondary infection from the chronic lung disease.

In conclusion, *M. flavescens* is an opportunistic environmental nontuberculous Mycobacterium, and rarely causes human disease under normal conditions. Immunocompromised status, malignancy and a wound are the risk factors for human infection. This is a rare case of pulmonary infection due to *M. flavescens* in a patient with preexisting chronic lung disease.

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Mycobacterium flavescens 引起之肺部感染—病例報告和文獻回顧

郭立國　林榮祿　吳健樑

Mycobacterium flavescens 在人類常被視為非病原菌,至目前為止只有非常少數的病例報告。其中包括皮膚、眼角膜、關節腔和肺部感染。這些病人大多有癌症、糖尿病或免疫力不全。我們在此報告一位七十歲男性病人，有陳舊性肺結核和長期抽菸史，住院期間一直發燒不退，呼吸困難，經多種抗生素治療無效。痰液中反覆培養出 *mycobacterium flavescens* ，藥物敏感試驗顯示部分抗結核藥有效，經投藥後燒退，呼吸困難改善而出院。最後我們回顧了此一非結核分枝桿菌之特性及相關文獻報告。*(胸腔醫學* ***2006; 21: 457-461)***

關鍵詞：非結核分枝桿菌，肺部感染， *mycobacterium flavescens*

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Pulmonary Large Cell Neuroendocrine Carcinoma Presenting with Metastatic Brain Tumor of Unknown Origin

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Large cell neuroendocrine carcinoma (LCNEC) is a poorly differentiated high-grade neuroendocrine tumor with very aggressive behavior. Herein, we report a 74-year-old male smoker who initially presented with a symptomatic metastatic brain tumor of unknown origin (MBUO). Primary pulmonary LCNEC was not diagnosed until 3 years later. Both the metastatic brain tumor and the primary lung cancer were successfully treated by surgical intervention, and the patient had a very favorable outcome. Management of MBUO should be aggressive if patients have only isolated brain metastasis. Periodic re-evaluation after treatment of the brain tumor may help to detect an earlier stage of primary cancer and may result in a better outcome, even in highly aggressive malignancies like LCNEC. ***(Thorac Med 2006; 21: 462-467)***

Key words: large cell neuroendocrine carcinoma, metastatic brain tumor, malignancy of unknown origin

Introduction

Pulmonary large cell neuroendocrine carcinoma (LCNEC), which accounts for around 3% of lung cancer, is a poorly differentiated high-grade neuroendocrine tumor with very aggressive behavior [1-2]. To the best of our knowledge, LCNEC presenting initially with a metastatic brain tumor of unknown origin (MBUO) has never been reported, although some cases of malignancy of unknown origin (MUO) with pathology of neuroendocrine carcinoma had been mentioned [3]. Herein we report the case of a patient presenting with MBUO which was diagnosed 3 years prior to primary pulmonary LCNEC; the patient had a good prognosis after operating for the solitary brain metastasis and subsequent resection of the primary lung cancer.

Case Report

A 74-year-old man was admitted to Taipei Veterans General Hospital because of abnormal findings on the chest radiograph during regular postoperative follow-up. He denied any subjective discomfort at presentation. He had undergone

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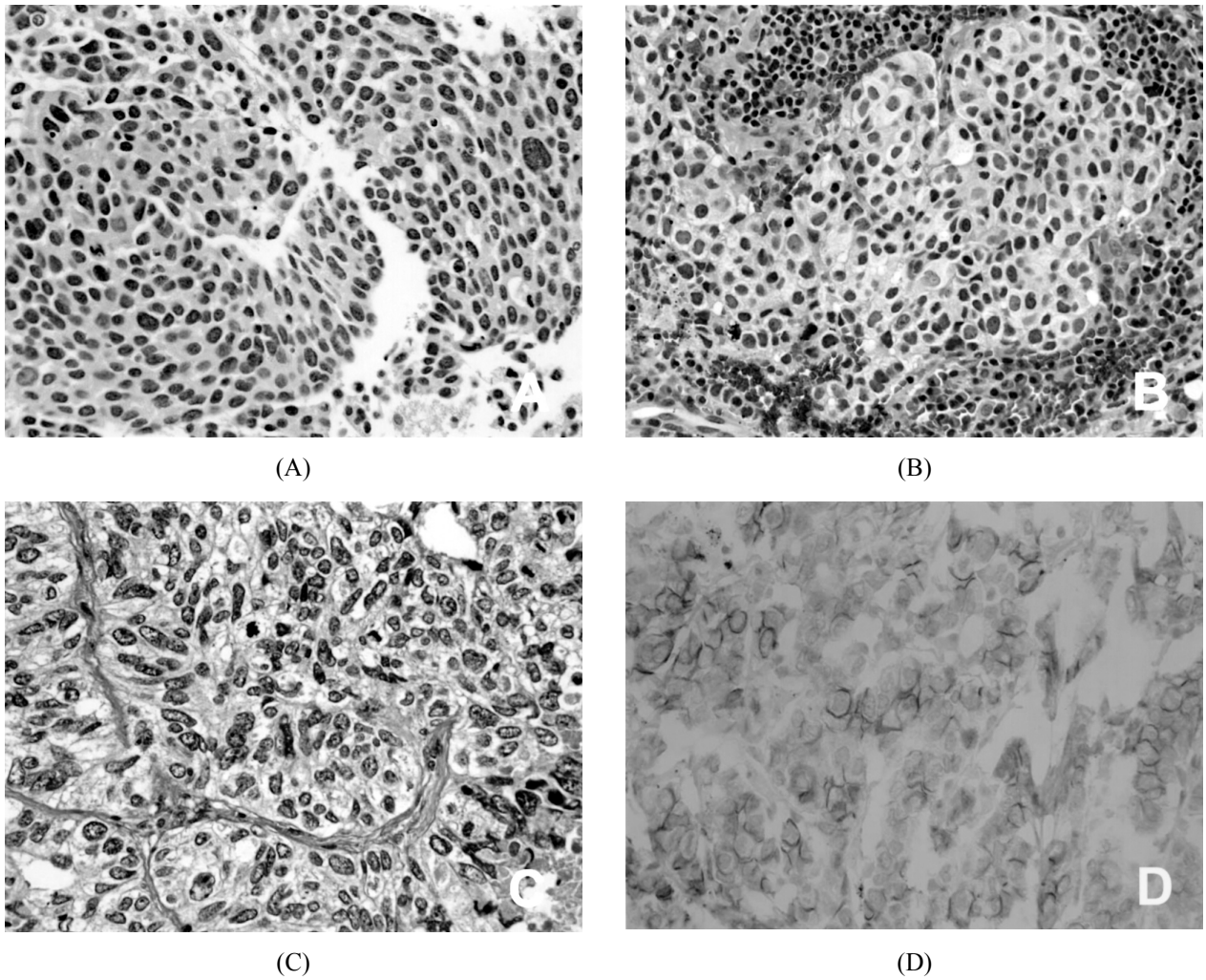

(A) (B)

(C) (D)

Fig. 1. Large cell neuroendocrine carcinoma. Pathology of (A) metastatic brain tumor, (B) bronchoscopic biopsies and (C) resected lung tumor showing similar characteristics: poor differentiation with organoid nesting, and trabecular and palisading patterns. (D) CD56 immunostaining showing a typical membrane pattern.

operation for benign prostate hypertrophy and had hypertension which was under medical control. He had had a 2-pack-per-day smoking habit for 50 years, but quit 10 years ago.

Three years prior to this admission, he had suffered from an acute onset of ataxia, unsteady gait, and nausea. At that time, brain MRI revealed a right cerebellar tumor. After thorough tumor survey without a positive finding, he underwent sub-occipital craniotomy with tumor resection. Pathology of the removed tumor showed a poorly differentiated carcinoma (Figure 1A) that was focally immunoreactive for cytokeratin and non-reactive for glial fibrillary acidic protein. Because there was no clinically evident primary tumor, the tentative diagnosis at that time was MBUO. The patient underwent postoperative whole brain radiotherapy with 30 Gy divided by 15 fractions. In the following 3 years, the patient had regular follow-ups, and neither local tumor recurrence nor primary tumor was found until this admission.

This time, a pulmonary nodule in the right

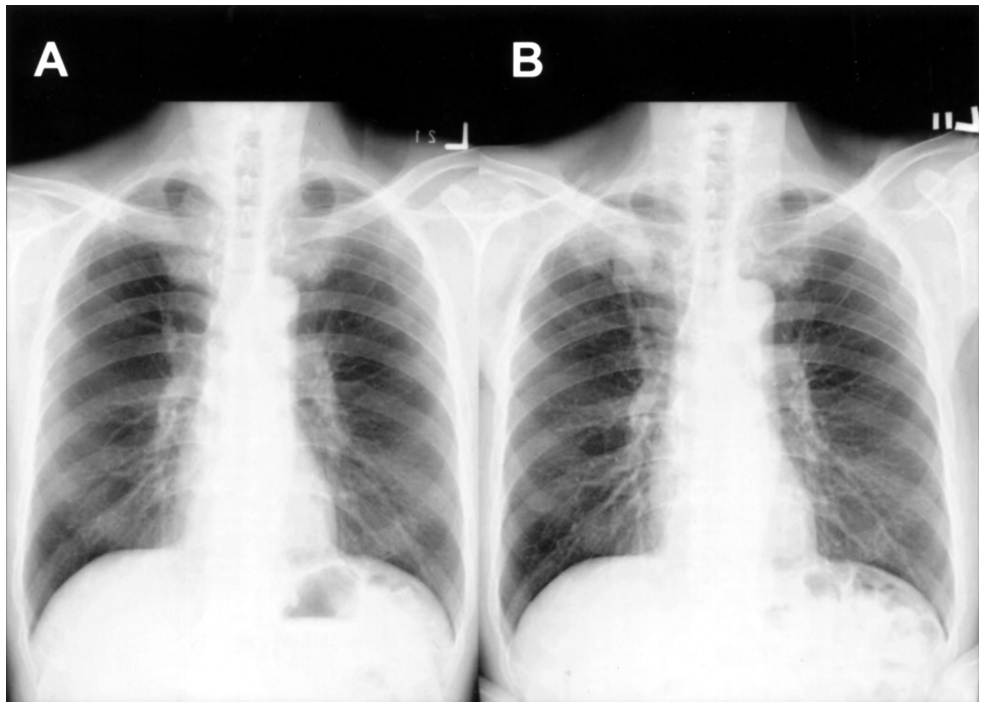

Fig. 2. (A) Chest radiograph taken when the brain tumor was diagnosed, showing only some fibronodular scarring on the right upper lobe. (B) Three years later, the chest radiograph reveals a lobulated mass on the right apex; the fibronodular scarring did not change significantly.

upper lobe of the lung was detected incidentally in an annual chest radiograph follow-up (Figure 2). Chest CT revealed a lobulated mass measuring about 4 cm in diameter at the apical segment of the right upper lobe, but no enlarged mediastinal lymph node was found. Bronchoscopy showed no endobronchial lesion. Biopsy and brushing were performed under fluoroscopic guidance and the cytology disclosed poorly differentiated carcinoma. Pre-operative staging was cT2N0M0 in a thorough evaluation with a whole body bone scan, brain CT, and abdominal sonography. The patient underwent a right upper lobe lobectomy with radical lymph node dissection. The pathology of the resected tumor showed carcinoma with neuroendocrine morphology (Figure 1B), and the tumor cells were immunoreactive for cytokeratin and CD56, while non-reactive for chromogranin A and synaptophysin. The character of the tumor was very similar to that of the brain tumor resected 3 years ago. A total of 26 mediastinal lymph nodes were removed and none showed a metastatic tumor. Given the history of cerebellum metastasis, the patient underwent postoperative chemotherapy with 4 cycles of docetaxel and cisplatin, and so far has had no evidence of tumor relapse for near 2 years.

Discussion

Pulmonary LCNEC, representing around 3% of lung malignancies [4-5], is a poorly differentiated high-grade neuroendocrine tumor with very aggressive behavior [1-2]. According to the 1999 World Health Organization histological typing of the lung, LCNEC is 1 of the 5 variants of large cell carcinoma and is characterized by a neuroendocrine morphology, including organoid nesting,

trabecular, rosette-like and palisading patterns, and neuroendocrine differentiation, which is best demonstrated by immunohistochemistry or electron microscopy [6]. The diagnosis of LCNEC can be difficult because neuroendocrine differentiation has to be recognized initially by light microscopy. Histological criteria for diagnosis of LCNEC include: (1) neuroendocrine morphology using light microscopy, (2) mitotic rate ≥11 events/2 mm^2), (3) the presence of necrosis, (4) the presence of a large cell size, low nuclear to cytoplasmic ratio, vesicular chromatin, and frequent prominent nuclei, and (5) positive immunohistochemical staining for 1 or more neuroendocrine markers [6]. In this case, the pathology of the original brain tumor was not recognized for its neuroendocrine morphology, and therefore no further specific immunohistochemical staining was arranged. The pathology of the follow-up lung tumor showed typical neuroendocrine morphology (Figure 4), and positive CD56 (N-CAM) staining confirmed its neuroendocrine differentiation.

Symptomatic brain metastases in patients without a previously diagnosed malignancy are infrequent (5%) in clinical series [7], and the majority of cases are poorly differentiated adenocarcinomas [8]. Because neuroendocrine tumors account for less than 5% of all cases of MUO [9], theoretically the incidence of LCNEC presenting with MBUO wound be extremely rare. In fact, to the best of our knowledge, this phenomenon has never been reported in the English literature.

It is generally believed that high-grade neuroendocrine carcinoma, especially in the advanced stage, has a very poor prognosis. One study, consisting of 87 cases of pulmonary neuroendocrine carcinoma, showed 5-year survival rates of 67%, 75%, 45% and 0% for stages I, II, III and IV, respectively [1]. Being stage IV disease, however, the present case had a favorable outcome. It has been reported that patients with brain metastases as the only manifestation of an undetected primary tumor had a better prognosis than those whose primary tumor and brain metastasis were diagnosed simultaneously [8]. Although the researchers did not provide an explanation, this phenomenon may be attributed to the limited space within the skull, therefore, neurological symptoms developed while the primary tumor was still clinically undetectable and there were no other metastatic foci. Sometimes, as in the present case, isolated brain metastasis may contribute to the early diagnosis of a primary tumor, and long-term survival is possible.

Eventually, the primary sites of malignancy will be found in about half of the patients with MBUO [10], with the lung being the most frequent (51%) [11]. Although some investigators have suggested spiral CT or positron emission tomography for earlier detection of the occult primary tumor [12], this practice has been criticized for the low yield and lack of impact on patient prognosis [13]. Initiating early management of the brain lesion, without wasting valuable time on a thorough investigation, is of primary importance [14].

In conclusion, although advanced pulmonary LCNEC has a very poor prognosis, patients may benefit from aggressive surgical intervention if they have a resectable primary lung tumor, isolated and treatable brain metastasis, and a good performance status; long-term survival is possible. For patients presenting with MBUO, clinical investigation should not delay the management of metastatic brain tumor, and surgery or radiosurgery in combination with whole brain irradiation may provide the curative therapy for these brain metastases. In addition, periodic re-

evaluation for a primary tumor after treatment of the brain tumor may help in detecting an earlier stage of the primary cancer, even in highly aggressive malignancy like LCNEC.

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以不明原因腦轉移癌爲起始表現的肺大細胞神經分泌性癌

陳俊偉 *,** 邱昭華 **,***** 周德盈 ***,***** 許文虎 ****,*****
彭瑞鵬 **,*****

大細胞神經分泌性癌是一種分化不良、高度的神經內分泌癌且癌性相當惡性。我們報告一位 74 歲的抽煙男性以有症狀的不明原因腦轉移癌為起始表現，直到三年後才診斷原發的肺大細胞神經分泌性癌。腦轉移瘤以及肺腫瘤皆成功的以手術切除，病患因此有相當不錯的預後。如果只有單純的腦轉移，不明原因腦轉移癌的病患應該積極的治療，定期的術後追蹤有助於早期診斷原發癌，即使是像我們在此所報告的高惡性度肺大細胞神經分泌性癌，也可能因此有較佳的預後。*(胸腔醫學 **2006; 21: 462-467**)*

關鍵詞：大細胞神經分泌性癌，腦轉移癌，原發腫瘤未明癌

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Sildenafil Decreases Pulmonary Hypertension in a Mechanically Ventilated Patient with Idiopathic Pulmonary Fibrosis — A Case Report

Chi-Yen Liang, Chang-Wen Chen, Tzuen-Ren Hsiue

Sildenafil (Viagra), a phosphodiesterase-5 (PDE-5) inhibitor, has been shown to reduce pulmonary arterial pressure in patients with either primary or secondary pulmonary hypertension. However, to our knowledge, the use of sildenafil in mechanically ventilated patients with pulmonary hypertension has never been reported. Herein, we described the case of a patient with idiopathic pulmonary fibrosis and secondary pulmonary hypertension, who was intubated due to acute respiratory failure. Oral sildenafil was given for persistent hypoxemia and pulmonary hypertension. The patient's pulmonary artery pressure decreased after sildenafil (from 60/27 mmHg to 36/19 mmHg, half an hour post-sildenafil intake), but the aim of improving oxygenation was not reached during treatment. He ultimately died of refractory hypoxemia. ***(Thorac Med 2006; 21: 468-472)***

Key words: sildenafil, pulmonary hypertension, idiopathic pulmonary fibrosis

Introduction

Idiopathic pulmonary fibrosis (IPF) is a form of chronic interstitial lung disease for which there is no effective treatment, as yet [1]. The prognosis of patients with IPF is extremely poor once they are admitted to the intensive care unit [2-3] because end-stage IPF is characterized by severe pulmonary hypertension which is often unresponsive to oxygen therapy [1]. Traditional therapy aimed at diuresis or afterload reduction is unlikely to be beneficial, and may even jeopardize the preload-dependent right heart function [4].

Three main pathways (endothelin, nitric oxide, and prostacyclin) are involved in the control of vascular tones in patients with pulmonary hypertension [4-5]. The endothelin pathway leads to pulmonary vasoconstriction, while the nitric oxide or prostacyclin pathway produces pulmonary vasodilatation [4]. Both endothelin receptor antagonist and prostacyclin analogues are approved in the management of primary pulmonary hypertension [4]. In addition, available data indicate that patients with secondary pulmonary hypertension may also benefit from these agents [4].

Drugs targeting the nitric oxide pathway have been gaining attention in recent years. Nitric oxide (NO), an endothelium-derived vasodilator, produces vasorelaxation through the stimulation of soluble guanylate cyclase and the increased

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production of intracellular cyclic guanosine monophosphate (cGMP) [4]. Inhalation of NO is already known to produce pulmonary vasodilatation, but it is very cumbersome to apply [5]. Another strategy to enhance the activity of NO in pulmonary hypertension is to inhibit the phosphodiesterase (PDE) enzyme, because this enzyme is responsible for the degradation of cGMP, the key secondary messenger in NO-induced vasodilatation.

Several studies have shown that an inhibitor of 1 isoform of PDE (PDE-5, the most abundant isoform in the pulmonary vasculature), can alleviate primary and secondary pulmonary arterial hypertension [6-8]. In a recent randomized controlled trial, sildenafil, a PDE-5 inhibitor, caused preferential pulmonary vasodilatation and improved gas exchange in patients with pulmonary fibrosis [9]. These findings indicate that sildenafil may be worthy of a trial in patients with end-stage IPF. Herein, we describe the hemodynamics and gas exchange response to orally given sildenafil in a mechanically ventilated IPF patient with secondary pulmonary hypertension.

Case Report

A 57-year-old diabetic man, diagnosed with idiopathic pulmonary fibrosis for several years, was intubated in another hospital due to progressive dyspnea and fever for 3 days. He was transferred to our hospital 1 day later for convenience of care.

Initial arterial blood gas under 100% oxygen and 8 cmH_2O positive end-expiratory pressure (PEEP) showed PaO_2 55mmHg, $PaCO_2$ 76 mmHg, pH 7.32, and bicarbonate 39.2 $meq.liter^{-1}$; blood chemistry revealed no other organ failure except hyperglycemia. A diffuse bilateral interstitial pattern was found on chest X-ray (Figure 1). Following analgesic and sedative administration, he was immediately paralyzed to facilitate oxygen and ventilator adjustment. Blood culture taken before arrival at our hospital grew *H. influenzae*.

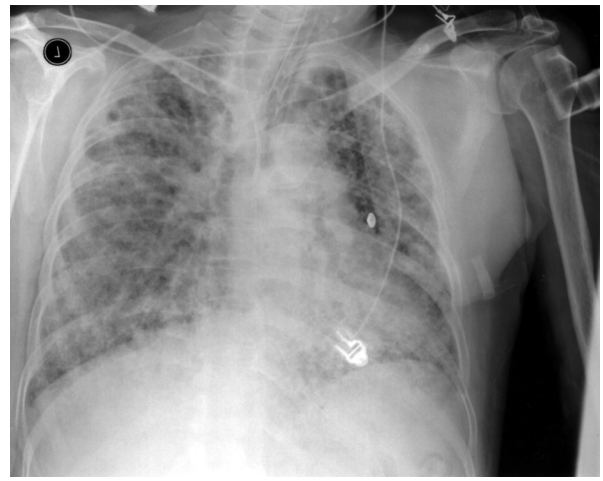

Fig. 1. Initial chest X-ray reveals a bilateral diffuse interstitial pattern which is compatible with the diagnosis of IPF

The patient's body temperature normalized 1 week after treatment with broad spectrum antibiotics (Cefepime) and low-dose steroid, but the PEEP level could only be lowered to 10 cmH_2O and inspired fractional of oxygen was never below 0.4. He was thus tracheostomized 10 days after admission. Weaning was not feasible even after tracheostomy, because of the persistent need of high FiO_2 and the PEEP level. Pulmonary hypertension was suspected at this stage, following cardiac echo examination. The patient agreed to Swan-Ganz catheterization, and pulmonary hypertension was thereby confirmed. Pulmonary arterial pressure (PAP) was 50/26 mmHg (mean 35 mmHg), pulmonary capillary wedge pressure (PCWP) 13 mmHg, and cardiac index 4.35 l/min/m^2.

After further discussion with the family, they consented to the use of sildenafil. The patient was sedated and paralyzed again for his first dose of

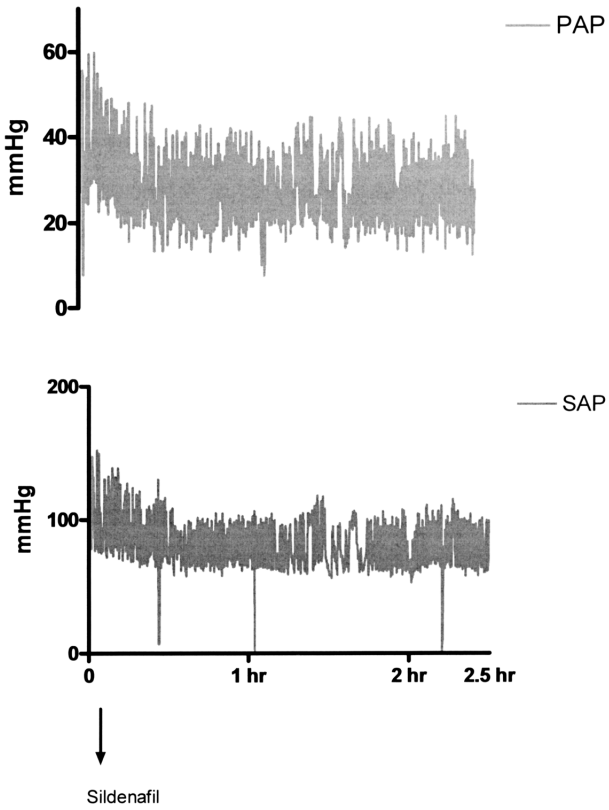

Fig. 2. Systemic and pulmonary arterial pressure tracing following oral intake of sildenafil

sildenafil, in order to reach an objective assessment of his response. Both systemic arterial pressure (SAP) and PAP decreased at the same time, following sildenafil intake, and reached a plateau in about half an hour (Figure 2). The cardiac index and PCWP were similar during the recorded period. The pulmonary vascular resistance index (PVRI) was 425 dyne.sec.m^2.cm^{-5} initially, and decreased to 144 dyne.sec.m^2.cm^{-5} 1 hour after medication. The systemic vascular resistance index (SVRI) was 1421 dyne.sec.m^2.cm^{-5} in the beginning, and declined to 1020 dyne.sec.m^2.cm^{-5} 1 hour after medication. The ratio of PVRI to SVRI decreased from 29.91% to 14.12% 1 hour after sildenafil intake. The hemodynamic benefit persisted for more than 3 hours following intake of sildenafil. However, the arterial blood gas followed-up revealed no improvement in oxygenation after sildenafil intake, despite the beneficial pulmonary hemodynamic response (FiO_2: 0.6, PEEP: 10 cmH_2O, pH 7.296, PaO_2 112.4 mmHg, $PaCO_2$: 90.3 mmHg before sildenafil; pH 7.441, PaO_2 70.6 mmHg, $PaCO_2$: 74.5 mmHg 4 hours after sildenafil).

The patient received 5 days' treatment of sildenafil (50 mg po q6h), and was finally discontinued for lack of oxygenation response. He ultimately died of refractory hypoxemia.

Discussion

This case report demonstrates that sildenafil may be an effective pulmonary vasodilator in end-stage IPF patients with mechanical ventilation. We believe this is the first description of oral sildenafil therapy in an end-stage IPF patient requiring mechanical ventilator support.

IPF is a progressive illness which is characterized by progressive pulmonary fibrosis and decreased lung compliance [10]. For patients with newly diagnosed IPF, the median survival is less than 3 years [1]. Although respiratory failure is a major cause of death in IPF patients, a variety of concomitant diseases, e.g., coronary artery disease or sepsis may occur in IPF.

Obviously, the cause of acute exacerbation of IPF in this case was *H. influenzae* septicemia. However, under appropriate antibiotic therapy, septicemia was apparently under control, but hypoxemia was persistent. The ultimate grave outcome in this group of patients prompted us to use a trial medication which may have been of benefit to the patient. Sildenafil was chosen after pulmonary hypertension was confirmed by pulmonary arterial catheterization. There are several reasons for the selection of sildenafil. First, cGMP-dependent pulmonary vasodilatation is

attenuated in pulmonary hypertension of chronic hypoxia as a result of increased cGMP degradation by PDE-5 [11] and sildenafil is a highly selective PDE-5 inhibitor. Second, sildenafil was shown to improve exercise capacity, functional status, arterial blood gas, and hemodynamics in patients with primary or secondary pulmonary hypertension [8]. Third, there are limited adverse effects in the use of sildenafil [6].

Although both pulmonary and systemic arterial pressure decreased after the administration of sildenafil in this case, the significant decrease in the pulmonary to systemic vascular resistance ratio suggests orally given sildenafil had selectivity over the pulmonary vasculature in our patient. Oral absorption must have been optimal in this case, as the effect of pulmonary vasodilatation lasted for more than 3 hours following intake. However, the partial arterial oxygen pressure was not improved in the meantime. It is likely that ventilation/perfusion matching in the fibrotic lung was not improved via pulmonary vasodilatation in this case. This may be 1 of the reasons for the grave outcome in this patient.

Although our intention of improving in oxygenation in our patient was not achieved with sildenafil, the beneficial hemodynamic response may warrant a future trial in this group of patients who are known to have a poor prognosis once admitted to the ICU.

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口服威而剛有效降低一位原發性肺纖維化併動脈高壓既使用呼吸器病人之肺動脈壓—病例報告

梁啟彥　陳昌文　薛尊仁

肺動脈高壓是一個預後不佳的疾病，若已合併有右心衰竭的情況，則預估存活期不超過一年。對於這類的病患，擴張肺動脈血管，抑制血管內皮增生以及預防血栓形成是主要的治療目標。吸入 NO 藉由增加細胞內的 cGMP 濃度，可選擇性使肺動脈血管的平滑肌放鬆，達到降低肺動脈阻力，降低肺動脈壓，提高運動耐受性 (exercise capacity)，甚至在某些病人可使血氧濃度上升的效果。然而 NO 氣體的攜帶與使用不易限制了其在臨床上的應用。 Sildenafil (威而剛) 可抑制體內分解 NO 的酶 (phosphodiesterase ， PDE)，且對此酶在肺內含量最高的 PDE-5 有選擇性的抑制作用，因此可在較不影響全身血壓的情況下達到降低肺動脈壓的效果。文獻已證實 sildenafil 對於原發性及次發性肺動脈高壓皆有療效。我們將其使用在一位因肺纖維化引起肺動脈高壓，敗血症併呼吸衰竭的病人，希望病人的血氧濃度能有所改善。病人的肺動脈壓與肺血管阻力在使用 sildenafil 後明顯降低，但血氧濃度並無明顯的改善，而病人終究病逝於呼吸衰竭。*(胸腔醫學* ***2006; 21: 468-472)***

關鍵詞：威而剛（Sildenafil），肺動脈高壓，原發性肺纖維化

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Organo-axial Rotation of the Stomach Caused by Rolling up of the Greater Omentum in a Patient with Morgagni Hernia, Sliding Hiatal Hernia and Umbilical Hernia — A Case Report

Ming-Ching Lee *, Chung-Ping Hsu *,**

Morgagni hernias are uncommon diaphragmatic hernias, which usually present late in adult life with minimal symptoms. They are always associated with a true hernia sac and are often contained within the omentum and stomach. Herein we report the case of a 71-year-old female with Morgagni hernia, sliding hiatal hernia and umbilical hernia, which revealed a rolling up of the greater omentum into the chest cavity through a right-side anterior diaphragmatic defect, causing an organo-axial rotation of the stomach, and presenting the symptoms of gastric inlet obstruction. She underwent transabdominal reduction of the greater omentum and repair of the hernia by primary closure, the patient had a rapid and uneventful recovery. ***(Thorac Med 2006; 21: 473-477)***

Key words: morgagni hernia, organo-axial rotation of stomach, diaphragmatic hernia

Introduction

Morgagni hernias are uncommon, and account for only 3% of all diaphragmatic hernias [1]. The diaphragmatic defect described by both Morgagni and Larrey is a triangular space between the diaphragmatic muscle fibers that originates from the xiphisternum and the costal margin and is inserted into the central tendon of the diaphragm. The defect allows herniation of the peritoneal sac and abdominal viscera.

The patient with Morgagni hernia is usually asymptomatic, but may complain of respiratory or gastrointestinal symptoms. While uncommon, the possibility of incarceration and strangulation of the viscera remains and, therefore, surgical repair is recommended for all patients.

Case Report

A 71-year-old obese woman who had had chronic epigastric pain and postprandial vomiting for 6 months was admitted to our hospital. Physical examination revealed obesity (BMI=28) and umbilical hernia. Chest X-ray (CXR) revealed a round mass in the right anterior cardiophrenic

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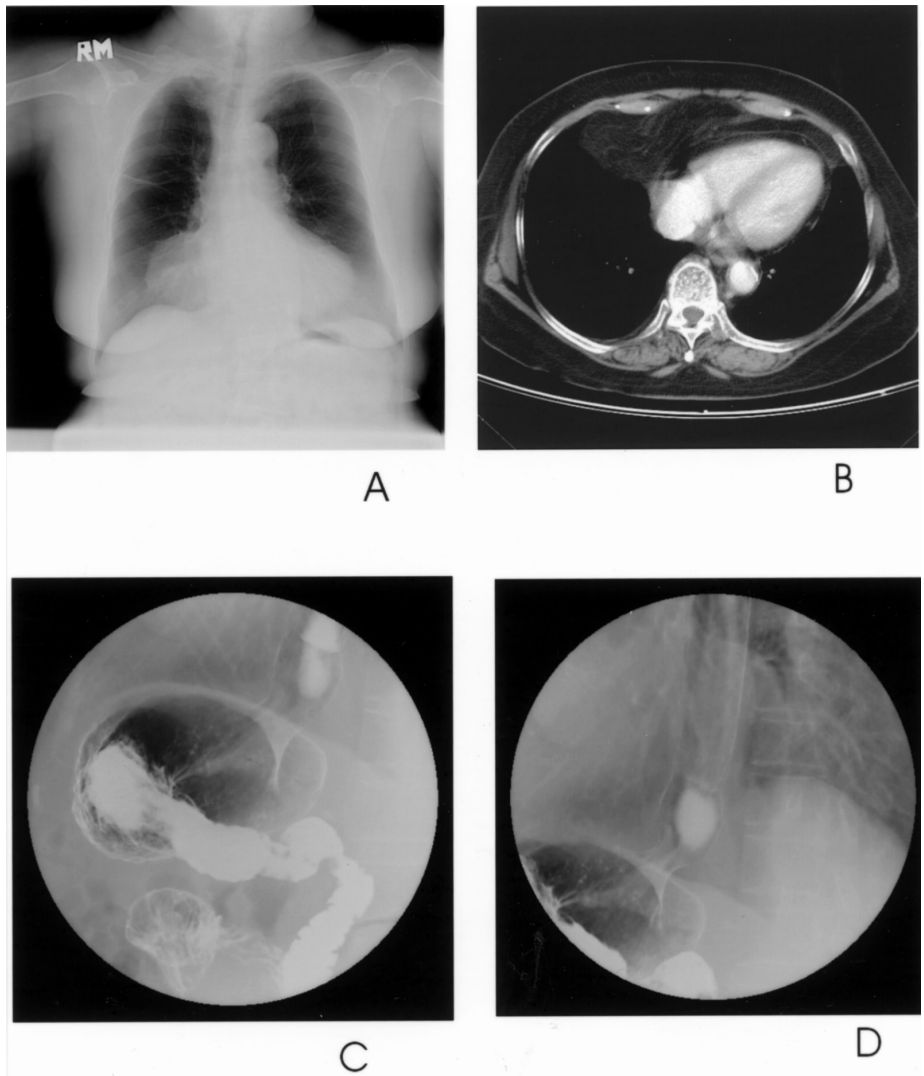

Fig. 1. (A) Posterior-anterior (P-A) chest X-ray reveals soft tissue density at the right cardiophrenic angle. (B) Chest computed tomography shows the Morgagni hernia containing omental fat with a curvilinear density, which is consistent with omental blood vessels. (C) The barium gastro-intestinal series reveals an organo-axial rotation of the stomach. (D) The barium gastro-intestinal series shows a small sliding hiatal hernia.

angle (Figure A). Chest computerized tomography (CT) revealed a right anterior mediastinal fatty mass that originated from the intra-abdominal compartment and showed characteristic curvilinear density, which is consistent with the omental blood vessels (Figure B). A barium gastro-intestinal series revealed organo-axial rotation of the stomach (Figure C) and herniation of a small part of the gastric cardia into the chest cavity (Figure D). Her pre-operative diagnosis was Morgagni hernia combined with sliding hiatal hernia and umbilical hernia.

She underwent a trans-abdominal approach to repair the Morgagni hernia and umbilical hernia. An upper midline incision was made which disclosed a 10x6 cm retrosternal defect

with the greater omentum herniated into the right-side pleural space and covered by the hernia sac. In addition, the rolling up of the greater omentum also caused an organo-axial rotation of the stomach. After manual reduction of the herniated greater omentum into the peritoneal cavity, the margin of the hernia sac was clearly identified. After hernia sac resection, the defect was closed primarily by interrupted, nonabsorbable mattress sutures. The umbilical hernia was then repaired by interrupted sutures from the peritoneal side.

The postoperative course was uneventful. The patient began oral intake on the day after surgery. She was discharged on the third postoperative day and did well thereafter without any recurrence of symptoms.

Discussion

In 1769, Morgagni first described the substernal herniating of abdominal contents into the thoracic cavity after his observation of a gangrenous colon during an autopsy. In 1828, Larrey described a surgical approach to the pericardial sac through an anterior diaphragmatic defect. Previous reports have shown that most patients are female. More than 90% of the Morgagni hernias are on the right side and most hernias have a true hernia sac. The most commonly observed contents of the hernia sac are the omentum (92%), followed by the colon (58%) and stomach (25%) [1-2]. Herniation of the abdominal viscus is typically caused by an increase in intra-abdominal pressure, secondary to trauma, pregnancy, or obesity [3-4]. Beradi *et al*. reported that two-thirds of patients are symptomatic. The most frequently encountered symptoms include upper abdominal discomfort, fullness, bloating, vomiting and bouts of large bowel obstruction [5]. In our case, the patient had had chronic epigastric pain and occasional postprandial vomiting for 6 months.

Diagnosis is usually made by CXR and CT. The usual posteroanterior CXR finding is a rounded opacity at the right cardiophrenic angle. The lateral CXR localizes this opacity to the anterior retrosternal space. The opacification is generally due to the omentum rising through the hernia defect. The radiographic diagnosis of a Morgagni hernia, using a CT scan, is defined by a paracardiac fatty mass with characteristic curvilinear density consistent with the omental blood vessels [6]. The CT scan in our case also revealed these specific findings.

Contrast studies of the upper gastrointestinal tract confirm the diagnosis in patients with visceral herniation. The barium gastro-intestinal series in this case revealed anterior displacement with organo-axial rotation of the stomach and herniation of a small part of the gastric cardia into the chest cavity. During the operation, we found part of the greater omentum incarcerated in the chest cavity through the diaphragmatic defect, which caused its normally anterior surface to face posteriorly. This rolling-up mechanism also caused the stomach to rotate along an axis from the gastroesophageal junction to the duodenum, and resulted in the symptoms of gastric inlet and/or outlet obstruction.

The repair of a Morgagni hernia includes herniated contents reduction, hernia sac resection, and a tension-free closure of the diaphragmatic defect by interrupted heavy suture or mesh repair [7]. The procedure can be accomplished by either the transabdominal or transthoracic approach [1, 8]. The conventional transabdominal approach via an upper midline incision provides excellent visualization of the hernia sac. In this case, we chose the transabdominal approach for concomitant repair of the Morgagni and umbilical

hernias. The small sliding hiatal hernia was not corrected.

In summary, we report an obese patient with Morgagni hernia accompanied with a small sliding hiatal hernia and umbilical hernia. This patient presented with symptoms caused by an organo-axial rotation of the stomach due to herniation of the greater omentum through the diaphragmatic defect, resulting in gastric inlet and/or outlet obstruction. The conventional transabdominal approach provided excellent exposure, easy repair, and satisfactory results in this particular case of Morgagni hernia.

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Morgagni 橫膈疝氣合併滑動性裂孔疝及臍疝氣所引起之大網膜移位及胃部水平扭轉—病例報告

李明璟 *　徐中平 *,**

Morgagni 橫膈疝氣是一個少見的先天性橫膈疝氣。它通常好發在中年肥胖女性且很少伴隨著臨床的症狀。本篇報告所提出的是一位 71 歲女性因 Morgagni 橫膈疝氣引起之上消化道阻塞症狀的病例。經由上消化道鋇劑攝影檢查後發現這是因為大網膜經由 Morgagni 橫膈裂孔往上嵌入胸腔之後，牽扯胃部，而造成胃部向前之水平扭轉，並在臨床上進一步造成上消化道的入口阻塞症狀。經由開腹手術將大網膜及胃部復位並 修補橫膈缺損之後，症狀改善並順利出院。*(胸腔醫學 **2006; 21: 473-477**)*

關鍵詞：Morgagni 橫膈疝氣，胃部水平扭轉

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