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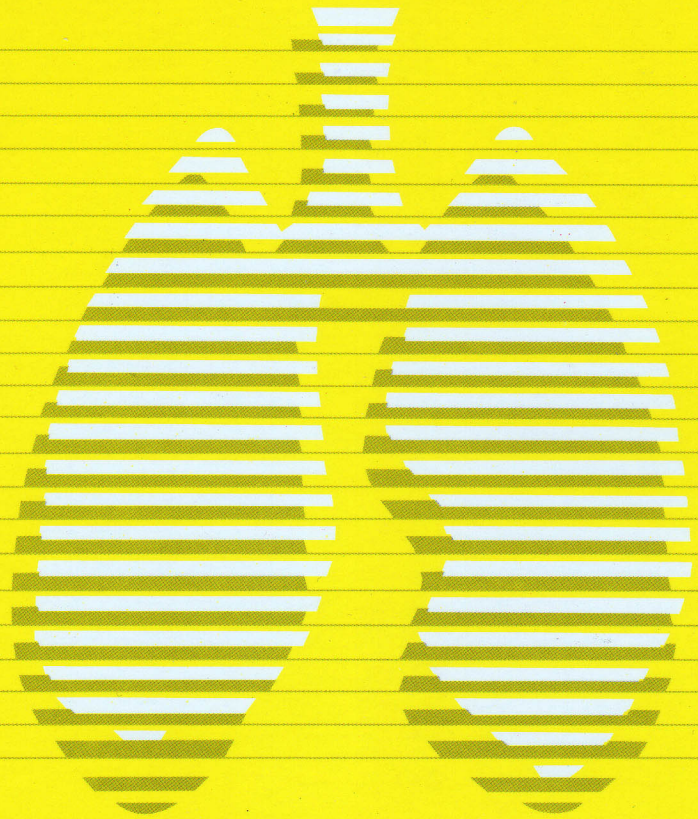

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原著

病例報告

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Orginial Articles

Case Reports

Effects of Repeated Acupuncture on Peak Expiratory Flow Variation and Serum Eosinophil Cationic Protein Concentration in Asthmatic Patients

Sheng-Che Lin*, Kuo-An Chu*,**, Chien-Wei Hsu*,**, Min-Hsi Lin*,**, Yi-Ching Wu*, Hong-Chung Wang*,**, Yao-Ming Ting*,**, Ruay-Sheng Lai*,**

Background: The mechanism involved in acupuncture's immediate bronchodilating effects remains unclear. This prospective randomized crossover controlled study aimed to determine the possible anti-inflammatory effects and clinical and physiologic benefits of repeated acupuncture using serum eosinophil cationic protein (ECP), an indicator of asthmatic inflammation.

Methods: Thirty asthmatic patients were randomly assigned to initially receive real acupuncture (RA) or sham acupuncture (SA) for 3 weeks in a blinded manner. Each patient was then crossed-over with a 3-week wash-out period. The ECP, spirometry, variation of peak expiratory flow rate (PEFR) and frequency of rescue bronchodilator use of each patient were recorded before and after RA and SA.

Result: The 27 patients who completed the trial showed significant improvements in post-RA forced expiratory volume in 1 second, serum ECP concentration, variation of PEFR, and frequency of rescue bronchodilator use compared to post-SA (p<0.05).

Conclusion: Asthmatic patients who received repeated acupuncture had improvements in ECP and better clinical and physiologic responses. ***(Thorac Med 2013; 28: 138-146)***

Key words: acupuncture, asthma, inflammation, spirometry

Introduction

Acupuncture has been used to treat many chronic conditions, including asthma, for thousands of years [1-4]. Previously published literature has reported that acupuncture can improve spirometry [5] and provide symptom relief in patients with asthma [6]. Although there are also reports showing that acupuncture has immuno-modulatory effects on inflammatory cells and cytokines in some asthma patients [7], a solid explanation of the possible mechanism of the clinical and physiologic improvements is still lacking.

Eosinophil cationic protein (ECP) has long been used in asthma management as a good

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clinical indicator of the inflammatory activity of asthma [8-9]. It has also been an objective laboratory indicator of asthmatic control, and an efficient guide for chronic asthma therapy [10-11]. However, the relationship between the clinical effect of acupuncture and ECP response in asthmatic treatment remains unclear. It has been posited that repeated acupuncture may have some anti-inflammatory effect on asthmatic patients, which results in their clinical and physiologic improvement. Hence, this study aimed to evaluate the possible anti-inflammatory and clinical effects of repeated acupuncture on asthmatic patients.

Materials and Methods

Study design

This prospective, randomized, crossover study was conducted in a medical center. The hospital's institutional review board approved the study and the study participants provided informed consent.

Subjects

Asthmatic patients aged 20-75 years consulting at the outpatient clinic of Kaohsiung-Veterans General Hospital were screened for the study. The inclusion criteria were typical chronic recurrent asthma symptoms, use of inhaled rapid-onset bronchodilator as required only, forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <70%, pre-bronchodilator FEV1 35-80% of the predicted value (as calculated with respect to age and height), and at least 12% improvement in FEV1 after the administration of beta-2 agonist medication within 1 month before the study in any pulmonary physiology laboratory. Patients also had to be interested in acupuncture as alternative therapy for asthma and have an initial baseline ECP concentration >12 μg/l.

The exclusion criteria were current smoker, bleeding tendency, severe heart disease, asthma treatment in an emergency department within 1 month before the study, hospitalization for asthma within 2 months before the study, recent upper respiratory tract infection within 2 weeks before the study, and recent history of systemic corticosteroid use within 3 months prior to the study. However, fixed-dose inhalation of corticosteroid or combined inhaled corticosteroid and long-acting beta-agonist and previous experience with acupuncture treatment were allowed.

The study began with a 2-week screening period. Of the 126 asthmatic patients evaluated, 105 received the ECP test; 35 had an ECP concentration >12 μg/l, 30 were enrolled after signing informed consent, and 27 completed the study.

Randomization and intervention

After informed consent, the patients were randomly assigned to initially receive real acupuncture (RA) or sham acupuncture (SA) via random numbers generated by software with simple randomization without blocking. The peak expiratory flow rate (PEFR) and frequency of rescue use of a bronchodilator within 7 days before randomization were recorded. The patients were randomly assigned to receive 3 weeks of either RA or SA (9 sessions, 3 sessions a week) using a single-blinded method (i.e., the patients were blinded). A washout period of 21 days was designed into the study to avoid the lasting effect of previous acupuncture treatment. After the washout period, acupuncture was crossed-over and patients who received RA first then received SA, and vice versa.

Acupuncture

Acupuncture was performed by a single certified and experienced doctor. Single-use, sterile acupuncture needles were used, and acupoints were selected on limbs related to asthma treatment to increase patient compliance in this long-term study. The acupoints used were lung 7, large intestine 4, pericardium 6, stomach 40, large intestine 11, and pericardium 3. "De Qi", defined by the typical sensations of soreness, numbness, fullness, and pain for effective acupuncture, was achieved at all acupoints during the RA sessions. In contrast, SA was applied on 2 non-meridian points on the extremities and treatment was directed to the subcutaneous tissue with the same depth and stimulation as RA. However, a typical sensation of "De Qi" was not necessary during SA. Each acupuncture manipulation lasted for 10-15 minutes and the needles were manipulated twice during each session to intensify the effect. All treatments were completed within 30 minutes.

Patients were withdrawn from the study if they missed 3 sessions or 2 consecutive sessions of acupuncture, in the event of worsening asthma that required treatment with systemic corticosteroids or admission for therapy, or anytime they requested to withdraw from the study for any reason. Inhaled corticosteroid or combined inhaled long-acting beta-agonist, if used, was limited to a fixed-dose during the entire course of the study.

Data collection

Spirometry was performed and blood sampling for ECP was collected at both the beginning and the end of each course of RA or SA. Each patient was supplied with a peak flow meter and instructed in its use. The patients were asked to measure their PEFR twice per day at home, in the morning and in the evening before taking any medication, and to record the best 1 of 3 attempts within 7 days before the 1st day of acupuncture. The patients were taught and requested to record the frequency of use of rescue beta-2 agonist inhalers at home.

Outcomes

Primary outcome: FEV1

Patients underwent spirometry using a single KoKo spirometer (Louisville Co, USA) in the same laboratory by the same technician. Patients were encouraged to perform at least 3 maneuvers during each measurement to meet the criteria of the American Thoracic Society for acceptability and reproducibility. The highest FEV1 value from each set of measurements was used for analysis.

Primary outcome: Serum ECP (μ/L)

The ECP in serum was measured by machine (Pharmacia & Upjohns). Blood serum was separated from the blood sample and frozen at -40^{o}C within a maximum period of 2 hours post-extraction.

Secondary outcome

Daily PEFR and the frequency of rescue inhaled beta-2 agonist were recorded throughout the study period.

Definitions

The following formulae were used:

(i) ΔECP = ECP at the beginning of the 3-week period – ECP at the end of the 3-week period

(ii) ΔFEV1 (%) = 100*(FEV1 at the end of the period – FEV1 at the beginning of the period)/FEV1 at the beginning of the period

(iii) Daily PEFR variation (DPEFRV) (%) = 100*(maximum PEFR – minimum PEFR) / (Evening PEFR + Morning PEFR)*(1/2)

(iv) ΔPEFR variation (%) = (mean DPEFRV during the week before the first day of the 3-week period – mean DPEFRV during the last week of the 3-week period) / mean DPEFRV during the week before the first day of the 3-week period

(v) ΔRBD/W (mean change of weekly rescue bronchodilator) = mean weekly number of times of rescue bronchodilator use during the week before the first day of the period – mean weekly number of times of rescue bronchodilator use during the last week of the period

Statistical analyses

All data were analyzed by statistical software. Data were presented as mean ± standard deviation (SD) or number and percentage. The *t*-test was used to compare continuous variables. All *p* values were 2-tailed.

Results

Twenty-seven of the 30 patients completed the study and were available for analysis. Three patients discontinued the study due to acute exacerbation (1 patient) and inability to fulfill the study requirements (2 patients). Fourteen patients received RA treatment first before SA and 13 patients received SA first. Their demographic data are presented in Table 1. The results of changes in ECP, FEV1, PEFR, and rescue bronchodilator use frequency between RA and SA that were statistically significant are summarized in Table 2. Differences in parameters before and after each session between RA and SA in patients who received RA first are summarized in Table 3, while those of patients who received SA first are summarized in Table 4.

Change in FEV1 percentage

The mean change in FEV1 values during RA was better than that during SA (0.10 ± 0.08 vs. 0.02 ± 0.11 L) and the mean post-acupuncture ΔFEV1 (%) measured during RA and SA were 5.9 ± 5.2% and 2.3 ± 6.9%, respectively (both $p<0.05$). FEV1 improved in both patient groups.

Change in ECP (μ/L)

The ΔECP was 2.8 ± 3.5 μ/L during RA sessions and 1.0 ± 3.0 μ/L during SA sessions (n=27, $p<0.05$). ECP showed improvement in both patient groups.

Data recorded at home

The post-acupuncture changes in PEFR variation during the RA and SA sessions were 5.6 ± 4.2% and 0.5 ± 3.9%, respectively. (n=27, $p<0.05$) The change in RBD/W during RA was better than that during SA (2.2 ± 1.6 vs. 0.4 ± 1.5, n=27, $p<0.05$). There was improvement in the data of both patient groups.

Discussion

Acupuncture has been used to treat many kinds of diseases for more than 2,500 years and has attracted considerable attention in research related to various chronic conditions. Traditional Chinese medicine (TCM) is considered when restoring the balance between 2 forces (yin and yang) and acupuncture is considered effective as treatment for many chronic diseases, including asthma. Many studies have examined the effect of short-term acupuncture on asthma and reported clinical improvements in how the patients feel [6]. Yu and Lee e*t al*. demonstrated the effect of short-term acupuncture on bronchial asthma in 1976 [4] and Virik *et al*. performed

Table 1. Baseline characteristics of the study population

Patient number	n=27
Sex	M: 15, F: 12
Age (years)	57.0 ± 15.6 (20-75)
Baseline average ICS dosage (budesonide equivalent dosage)	499.26 ± 254.53
Baseline ACT score	21.00 ± 2.06
Baseline FEV1 % of predicted (%)	57.3 ± 8.8
Baseline FEV1/FVC (%)	58.2 ± 12.0
Baseline ECP before RA (μg/L)	21.5 ± 13.2
Baseline ECP before SA (μg/L)	18.0 ± 9.3
PEFR variation (%) within 1 week	17.8 ± 8.2
Frequency of rescue bronchodilator use within 1 week	4.4 ± 1.6

Abbreviations: ACT, asthma control test; ECP, eosinophil cationic protein; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; PEFR, peak expiratory flow rate

Note: PEFR variation (%) = 100*(maximum PEFR – minimum PEFR)/(Evening PEFR + Morning PEFR)*(1/2)

Table 2. Changes in FEV1 (%), ECP, PEFR variation (%) and RBD/W before and after each 3-week session of RA and SA

	RA	SA	*p*-value
	Mean ± SD	Mean ± SD	
ΔFEV1 (%)	5.9 ± 5.2	2.3 ± 6.9	<0.05
ΔECP (μg/L)	2.8 ± 3.5	1.0 ± 3.0	<0.05
ΔPEFR variation (%)	5.6 ± 4.2	0.5 ± 3.9	<0.05
ΔRBD/W	2.2 ± 1.6	0.4 ± 1.5	<0.05

Abbreviations: RA, real acupuncture; SA, sham acupuncture

Note:

ΔFEV1 (%) = 100*(FEV1 after acupuncture – FEV1 before acupuncture)/FEV1 before acupuncture

ΔECP = ECP at the beginning of the period – ECP at the end of the period

Daily PEFR variation (DPEFRV) (%) = 100*(maximum PEFR – minimum PEFR)/(Evening PEFR + Morning PEFR)*(1/2)

ΔPEFR variation (%) = (mean DPEFRV within 1 week before the first day of the period – mean DPEFRV during the last week of the period)/mean DPEFRV within 1 week before the first day of the period

ΔRBD/W = Mean change in weekly rescue bronchodilator use

similar studies in 1980 [12]. Takishima *et al*. revealed that acupuncture caused a short-term reduction in airway resistance in 1982 [13]. In a crossover study with 23 asthmatic patients in 2002, Shapira *et al*. reported that a short course of acupuncture treatment did not result in any change in lung functions or patient symptoms [14], whereas Chu *et al*. reported an immediate bronchodilating effect in asthmatic patients, with significantly increased FEV1 after short-term acupuncture stimulation in 2007 [5].

However, the sustained or long-lasting effects of acupuncture as asthma treatment have not been demonstrated up to now. In this study, the subjects had chronic recurrent asthmatic symptoms associated with a positive bronchodilator test before the acupuncture treatment. Spirometry, measurement of ECP concentration,

and data recording were performed before and after each 3-week acupuncture treatment period to evaluate the lasting effect of acupuncture.

The lack of standard acupuncture stimulation and standard acupoints for asthmatic treatment may be 1 of the important reasons why it is clinically challenging to prove the role of acupuncture in asthmatic management. In the present study, the choices of acupoints were based mainly on previous clinical experience with asthma. The acupoints selected were located on the patients' extremities in order to increase patient compliance when acupuncture is performed easily and repeatedly. Different results may be achieved if a greater combination of acupoints is used. Moreover, there was an uncertainty as to which population of asthmatic patients (based on factors such as age, severity classified by spirometry, acute or chronic, and medication differences) would achieve a significant bronchodilating effect from acupuncture. More than half of the study patients had previous experience with acupuncture for treatment of their medical conditions and most had a good clinical experience. These patients may then have a better clinical and physiologic response to acupuncture, no matter the chronic condition, than those without acupuncture experience.

There are still many other limitations regarding the design of a good controlled study on acupuncture treatment. First, should a single acupoint or a combination of several acupoints be used? Many clinical trials choose a single acupoint to evaluate the therapeutic effect. However, when only 1 acupoint is selected, it is highly possible that the therapeutic effect would not be the same as in TCM. At the same time, if a combination of points is used, more variables will make the study more complicated. Second, it is difficult to design a well-controlled acupuncture study. There have been many different kinds of control groups. SA was initially designed with needling at non-meridian points with needle depth, stimulation intensity, and manipulation methods identical to those used in RA. Although most sham points are believed to be inactive, they have been found to have certain therapeutic effects and cannot always be considered to be a valid placebo. As an alternative, minimal acupuncture (very light stimulation at superficial non-meridian points) has been assumed to minimize the therapeutic effect. Placebo acupuncture has been designed to examine the psychological impact of needling while minimizing both the therapeutic and nonspecific effects of needling.

Third, it is very difficult to perform a double-blinded study of acupuncture if non-meridian points are chosen as control points. Since all acupuncturists are familiar with all of the traditional meridian acupoints, it is quite difficult to ask them to consider non-meridian points as therapeutic points. Fourth, the somato-sensation of acupuncture on the meridian acupoints is usually different from that of non-meridian points. There is usually the sensation of "De Qi" when applying RA, but not during SA. Thus, the sensation of "De Qi" is not necessary during SA stimulation. Last, since the diagnosis and treatment system in TCM is very different from that of Western science-based medicine, are there any characteristic differences that can be ascertained, like age, disease duration, disease severity, and grade of bronchodilator response, between the responders and non-responders in the patient groups? All of these factors produce many limitations in the design of a clinical trial of acupuncture.

In a randomized controlled study, Joos *et al*. found that repeated acupuncture could change

Table 3. Changes in FEV1 (%), ECP, PEFR variation (%) and RBD/W before and after each 3-week session of RA and SA in patients who received RA before SA (n=14)

n=14	RA (first)	SA
	Mean ± SD	Mean ± SD
ΔFEV1 (%)	3.8 ± 4.5	1.4 ± 5.8
ΔECP (μg/L)	2.7 ± 4.4	0.7 ± 2.6
ΔPEFR variation (%)	3.7 ± 3.4	0.1 ± 3.0
ΔRBD/W	2.0 ± 1.8	0.1 ± 1.5

Table 4. FEV1 (%), ECP, PEFR variation (%) and RBD/W before and after each 3-week session of RA and SA in patients who received SA before RA (n=13)

n=13	SA (first)	RA
	Mean ± SD	Mean ± SD
ΔFEV1 (%)	3.3 ± 7.9	8.3 ± 5.1
ΔECP (μg/L)	1.3 ± 3.5	3.0 ± 2.4
ΔPEFR variation (%)	0.9 ± 4.8	7.8 ± 4.1
ΔRBD/W	0.6 ± 1.4	2.5 ± 1.3

blood lymphocyte sub-population cytokines and *in vitro* lymphocyte proliferation in asthmatic patients [7]. They concluded that acupuncture has some kind of immuno-modulatory effect on inflammatory cells and cytokines in certain asthma patients. Unfortunately, to date, there have been very limited basic and clinical studies on the topic. Serum ECP as a measure in asthmatic management is useful, as the serum ECP concentration may decrease and correlate with asthma activity after proper anti-inflammatory treatment [8-9]; ECP is known to be a good potential marker of successful long-term management of chronic asthma [11].

There is uncertainty as to whether there are some psychological effects related to the improvement of clinical symptoms and the decrease in the use of rescue inhalation medication due to the "prolonged" subjectively different somatic sensation between RA and SA. Acupuncture has been previously reported to improve the patient's clinical feelings, but there is a paucity of solid evidence on the objective improvement of physiologic and inflammatory markers. The present study was designed to focus only on objective findings based on the primary outcome of FEV1 and ECP change in asthma patients. Clinical scores, such as the parameters recorded in the asthma control test, were not recorded for the study patients.

An older population participated in the current study because the hospital is a veteran's hospital and elderly patients have more free time to fulfill the thrice-weekly visits to complete the study. These older patients seldom like to regularly record their subjective symptom scores, like the asthma control test score, at home. Thus, they were not asked to do so. Furthermore, there is no standard length of washout period after traditional acupuncture. It has

been hypothesized that a 3-week period may be long enough to wash out the effects of either RA or SA, as in a previous study [14]. Despite the limited patient numbers, the final results here show a better response from patients who received RA first (n=14, Table 3) than those who received SA first (n=13, Table 4). Because the patient population was composed of many persistently asthmatic patients, the patients were allowed to keep their fixed low-doses of inhaled steroid if they had been using them before the study.

In this prolonged acupuncture study, 27 study patients demonstrated statistically significant improvement in FEV1 and ECP concentrations post-RA and had significant clinical improvement, including decreased use of the bronchodilator for rescue inhalation and decreased daily PEFR variability. Sustained acupuncture may have an anti-inflammatory effect on asthma. Well-controlled large-population studies with different acupoints and different levels of stimulation are needed to further corroborate the findings here.

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References

1. Eisenberg DM, Davis RB, Ettner SL, *et al*. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA 1998; 280: 1569-75.
2. Chou P, Lai MY, Chung C, *et al*. Acupuncture utilization in Taiwan. Chin Med J 1998; 61: 151-8.
3. Lewith GT, Watkins AD. Unconventional therapies in asthma: an overview. Allergy 1996; 51: 761-9.
4. Yu DY, Lee SP. Effect of acupuncture on bronchial asthma. Clin Sci Mol Med 1976; 51: 503-9.
5. Chu KA, Wu YC, Ting YM, *et al*. Acupuncture therapy results in immediate bronchodilating effect in asthma patients. J Chin Med Assoc 2007; 70: 265-8.
6. Biernacki W, Peake MD. Acupuncture in treatment of stable asthma. Respir Med 1998; 92: 1143-5.
7. Joos S, Schott C, Zou H, *et al*. Immuno-modulatory effects of acupuncture in the treatment of allergic asthma: a randomized controlled study. J Altern Complement Med 2000; 6: 519-25.
8. Bartoli ML, Bacci E, Carnevali S, *et al*. Clinical assessment of asthma severity partially corresponds to sputum eosinophilic airway inflammation. Respir Med 2004; 98: 184-93.
9. Kovacevic S, Bogic M, Peric-Popadic A, *et al*. The influence of atopic constitution, the severity and exacerbation of the disease on the serum eosinophil cationic protein (ECP) concentration in patients with bronchial asthma. Allergy 2003; 58: 1079-81.
10. Baba K, Hattori T, Koishikawa I, *et al*. Serum eosinophil cationic protein for predicting the prognosis of a step-down in inhaled corticosteroid therapy in adult chronic asthmatics. J Asthma 2000; 37: 399-408.
11. Sorkness C, McGill K, Busse WW. Evaluation of serum eosinophil cationic protein as a predictive marker for asthma exacerbation in patients with persistent disease. Clin Exp Allergy 2002; 32: 1355-9.
12. Virsik K, Kristufek D, Bangha O, *et al*. The effect of acupuncture on pulmonary function in bronchial asthma. Progr Respir Res 1980; 14: 271-5.
13. Takishima T, Mue S, Tamura G, *et al*. The bronchodilating effect of acupuncture in patients with acute asthma. Ann Allergy 1982; 48: 44-9.
14. Shapira MY, Berkman N, Ben-David G, *et al*. Short-term acupuncture therapy is of no benefit in patients with moderate persistent asthma. Chest 2002; 121: 1396-400.

重複針灸刺激對氣喘病患尖峰吐氣流速變異性的改變與嗜伊紅性球陽離子蛋白濃度的影響評估

林聖哲 * 朱國安 *,** 許健威 *,** 林旻希 *,** 吳宜瑾 * 王鴻昌 *,**
丁燿明 *,** 賴瑞生 *,**

背景：針刺引起的支氣管擴張的機轉過去並不是很清楚。這個前瞻性隨機交叉研究旨在藉由應用嗜伊紅性球陽離子蛋白，一種氣喘的發炎因子，來確認重複針刺所造成的可能抗發炎效果及臨床和生理上的好處。

方法：30 個病人於 3 週內以隨機單盲方式安排接受實際針刺及假針刺。所有病人在經過 3 週的廓清期後交叉。我們記錄了實際針刺及假針刺前後的嗜伊紅性球陽離子蛋白濃度、肺計量、尖峰吐氣流速變異性的改變、及支氣管擴張劑的使用頻率。

結果：27 個病患完成試驗。實際針刺後，第 1 秒用力吐氣量、血清嗜伊紅性球陽離子蛋白濃度、尖峰吐氣流速變異性的改變及支氣管擴張劑的使用頻率皆有顯著改善。(p<0.05)。

結論：氣喘病患接受重複針刺後有較佳的血清嗜伊紅性球陽離子蛋白濃度改變與臨床生理反應。***(胸腔醫學 2013; 28: 138-146)***

關鍵詞：針刺，氣喘，發炎，肺量計

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First Successful Resuscitation of Mother and Delivery of Baby in a Patient with Severe H1N1 Complicated with ARDS in Taiwan: Experience with ECMO

Kuang-Hui Chiu, Ping-Tsun Lai

H1N1 infection can be very severe and even fatal in high-risk patients including pregnant mothers and females during the peri-partum period. We report the 1st case of mother and fetus that were saved during the 2009 H1N1 pandemic in Taiwan. A 25-year-old G2P1 woman at 34 weeks gestation was infected with H1N1 and progressed to ARDS refractory to ventilatory support with 100% O_2. Emergent caesarian delivery was performed and the baby had an uneventful recovery. The mother was treated aggressively with ECMO and unfortunately developed right-side pneumothorax despite early ECMO use and lung protective ventilation because of tension bullae, which were either acquired or congenital. She was successfully weaned from ECMO within 1 week with subsequent extubation of the endotracheal tube. Her chest tube was removed after 2 weeks in the chest medicine ward. We also reviewed the related literature on severe H1N1 infection among pregnant women, the relationship of various outcomes at different gestational ages, differences in duration from infection to treatment, and also the effect of ECMO use. ***(Thorac Med 2013; 28: 147-153)***

Key words: pregnancy, H1N1, acute respiratory distress syndrome, extracorporeal membrane oxygenation

Introduction

H1N1 infection became a pandemic problem during 2009, and high-risk groups, including pregnant women developed very severe complications. The clinical course was more severe among pregnant women requiring intensive care unit (ICU) admission.

We report a 25-year-old G2P1 pregnant woman at 34 weeks gestation with H1N1 infection that developed severe acute respiratory distress syndrome (ARDS) refractory to mechanical ventilator support. After aggressive treatment with extracorporeal membrane oxygenation (ECMO) and emergent caesarean delivery, both mother and child survived and had an uneventful recovery. We share our experience with this 1st case of Taiwanese pregnant mother

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and baby that survived, along with data and recommendations from the literature around the world to provide a picture of the clinical impact of severe H1N1 on pregnant mothers and also management trends.

Case Report

A 25-year-old G2P1 pregnant woman at 34 weeks gestation had cough for 1 week. Her husband and elder son had upper airway infection several days before her onset of cough. There was no fever initially and the small amount of sputum was whitish without accompanying sore throat or generalized aches. She later had fever for 3 days and shortness of breath for 5 days after onset of cough. She went to a nearby medical center for severe shortness of breath. Her initial H1N1 screening test was negative. She was treated with Unasyn, but progressed to respiratory failure and endotracheal tube insertion was suggested. She was transferred to our hospital by family request on 11/16. The H1N1 screening test at our hospital was also negative. Oseltamivir (150 mg twice daily for 6 days followed by 75 mg twice daily for 6 days) was given after her throat-swab was sent for a H1N1 polymerase chain reaction (PCR) test. The Taiwan Centers for Disease Control (CDC) real-time PCR (rRT-PCR) test confirmed positive for H1N1. Chest computed tomography (CT) (Figure 1) showed bilateral lower lobe pneumonia with right pleural effusion and a right lower lung bullous lesion before endotracheal tube intubation. Respiratory failure (PaO_2: 58.9 mmHg on 100% O_2) developed and endotracheal intubation with mechanical ventilator support was given immediately. Because of her right lower lung bullae, we tried to maintain peak inspiratory pressure (PIP) below 30 mmHg, positive end-expiratory pressure (PEEP) below 8 mmHg and a low tidal volume (350-400 cc). Emergent caesarian section delivery of the baby, as adviced by the gynecologist, was arranged shortly after admission due to fetal distress, to save the life of the baby. The baby fortunately had an uneventful recovery.

ARDS refractory to mechanical ventilation then developed. ECMO was needed to improve her oxygenation and we maintain PEEP around

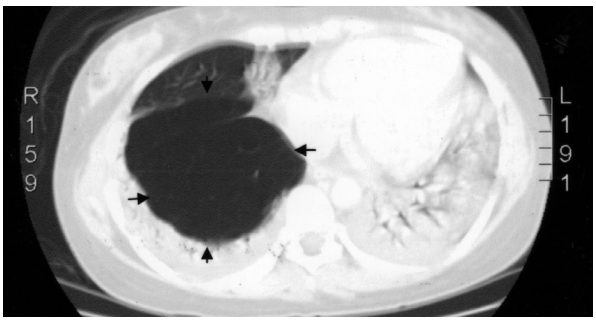

Fig. 1. Chest CT taken on day 1 showing bilateral consolidation with a right lower lobe hypertranslucent lesion suggestive of bullae.

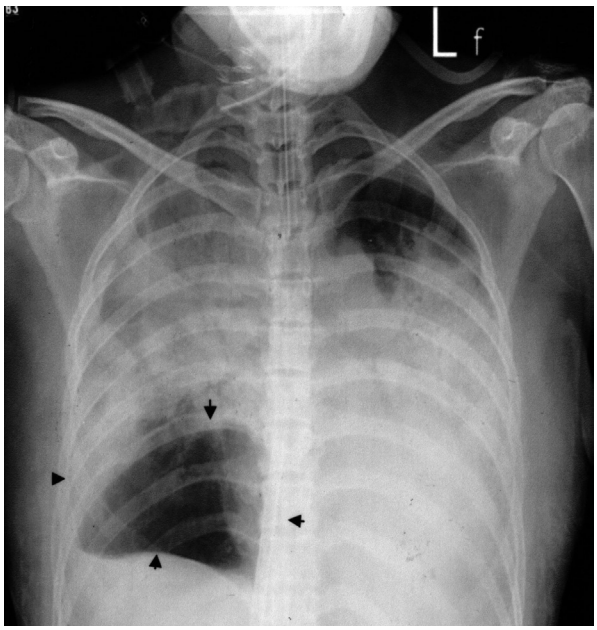

Fig. 2. CXR taken after ECMO use showing persistent bilateral pneumonia with air-bronchogram and a right lower lung hypertranslucent leision suggestive of bullae.

3 mmHg to avoid ventilator-induced lung injury. Follow-up chest X-ray (CXR) (Figure 2) immediately after ECMO support was begun showed extensive bilateral consolidation. We used femoral VV ECMO with blood flow 0.7-3.5 L/min and air flow 2-4 L/min to maintain PaO_2 55-60 mmHg with SpO_2 around 88-92% initially. We used heparin (400-800 U/hr) and adjusted the dosage with activated clotting time (ACT) monitoring every 6 hours to keep ACT at 160 to 80 seconds. Monitored aPTT was around 50 seconds. She developed tension pneumothorax in the right-side chest on hospital day 3, despite early use of ECMO with lung protective ventilation. Immediate chest tube insertion was performed to relieve the tension pneumothorax (Figure 3), which related to the right lower lobe tension bullae. The bullae were not caused by barotrauma because they were present before mechanical ventilation. We gave her proper sedation with Dormicum 5 mg IV PRN, cough control and very gentle chest tube wound care without unnecessary movements to avoid traumatic bleeding. She was weaned from ECMO within 1 week after ARDS had improved and the endotracheal tube was removed 2 days after discontinuing ECMO. However, continuing air leakage from the chest tube required 2 more weeks of hospital stay. She was discharged on 12/19 with chest OPD follow-up and was asymptomatic with no sequela of pulmonary function impairment. CXR (Figure 4) performed 1 year later still revealed bullae in the right lower chest.

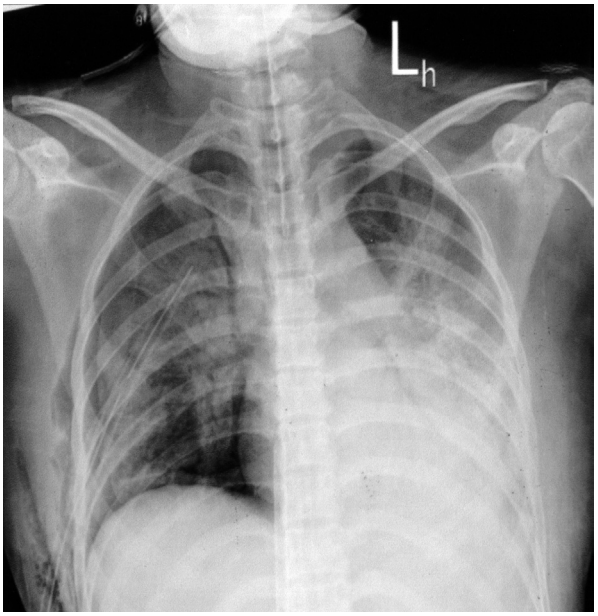

Fig. 3. CXR taken after chest-tube insertion for right-side pneumothorax.

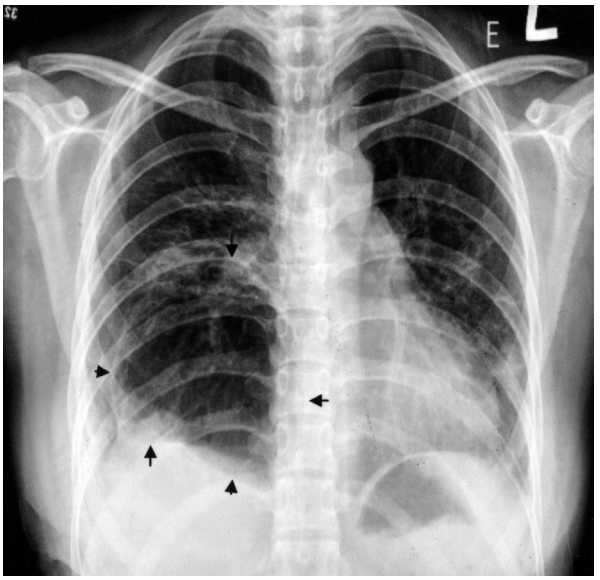

Fig. 4. CXR taken before discharge from the hospital still revealed the existence of right lower lung bullae.

Discussion

During the 2009 H1N1 pandemic, pregnant women were found to have a disproportionately high risk of serious complications associated with high maternal and fetal mortality. A study [1] from Canada indicated that 45.9% of childbearing-age women infected with H1N1 dur-

ing the 2009 pandemic were pregnant and had higher incidence of hospital admission.

Observational analysis of 18 gravid patients revealed that nearly half of pregnant women presented with non-respiratory, gastrointestinal and abdominal complaints during the 2009 pandemic [2]. The California Pandemic (H1N1) Working Group [3] also reported that rapid antigen tests were falsely negative in 38% of patients tested and suggested anti-viral agents should be given on clinical suspicion regardless of screening test results, as in our case.

Oluyomi-Obi *et al*. [4] reported that autopsy of neonatal deaths confirmed multiorgan hypoxic injury consistent with reduced delivery of oxygen to the fetus, revealing that severe maternal hypoxemia was the reason for the poor outcomes. Maternal hypoxia should be aggressively corrected as in our case to improve survival.

Alicia *et al*. [5] reported an association between the severity of illness and the timing of antiviral treatment and pregnancy trimester at symptom onset. Of the 592 women hospitalized due to H1N1, 11.3% were in the 1st trimester, 42.2% were in the 2nd trimester and 46.5% were in the 3rd trimester of pregnancy. Women treated more than 4 days after symptom onset were more likely to require ICU admission than those treated within 2 days: 56.9% versus 9.4%, relative risk 6.0. Among those admitted to the ICU, 20% expired including 7.1% in the 1st trimester, 26.8% in 2nd trimester and 64.3% in the 3rd trimester [5]. In our case, the patient had cough for about 1 week before she came to our hospital. There was some delay in anti-viral treatment because she was transferred to our hospital 1 week after symptoms appeared. Her clinical course was very severe due to her being in the 3rd trimester with delayed anti-viral treatment.

In a study of 64 pregnant women with H1N1 admitted to the ICU, women at more than 20 weeks gestation and infected with H1N1 had a 13-fold greater risk of ICU admission; 69% were mechanically ventilated and 14% were treated with ECMO [6]. In ANZ ECMO [7] data, 16% of ECMO supported patients were pregnant or postpartum women.

Dubar *et al*. [8] compared the characteristics of critically ill and non-severe pregnant women. They found a strong association between the development of a severe outcome and both co-existing illness and a delay in oseltamivir treatment [8]. Compared to observations from the USA, Canada, Australia and New Zealand, their study had a lower maternal & neonatal mortality rate due to a lower incidence of co-existing illness in their population, as well as early diagnosis and a shorter delay to anti-viral treatment [1,4-8]. They also found that caesarean section did not seem to worsen the maternal condition. Aggressive treatment for maternal hypoxia, including ECMO, also led to better than expected outcomes compared to the usual 30% to 35% mortality rate reported for ARDS [8].

Details of the outcomes of 12 pregnant and post-partum women from Australia and New Zealand with H1N1 and ARDS that were treated with ECMO during the 2009 H1N1 pandemic were analyzed [9] to determine the safety and efficacy of ECMO during pregnancy. The survival rates for the mother was 66%, and infant survival was 71%. Complications of ECMO were bleeding (67%) and nosocomial infection (58%). All patients received heparin with aPTT 54-152 sec; massive bleeding was the main cause of death for 3 of 4 mortalities. All patients required PRBC transfusion with vasoactive drug use. Early use of ECMO proved

to be beneficial, with careful precautions taken for any bleeding tendency. ECMO support limited the duration of maternal hypoxia, hypercarbia and acidosis, and also prevented ventilator-associated lung injury. The median duration for ECMO use was 14 days. There were 5 caesarean sections (3 patients after ECMO therapy was completed, 1 just after ECMO was commenced and 1 prior to the commencement of ECMO therapy). Five of the 7 (71%) infants delivered after commencement of ECMO were live births.

In our case, we gave early aggressive treatment with ECMO to avoid maternal hypoxia. Oseltamivir was initiated at admission despite the negative results for the initial H1N1 screening test. The mother was not known to have diabetes mellitus, pregestational obesity or any cardiovascular diseases. She had pneumothorax correlated to her right lung bullae but we used lung protective ventilation to avoid further damage. We also performed an emergent caesarian delivery to save the baby's life. Placing the patient in the prone position to improve oxygenation was not an option since she had undergone a caesarian section. ECMO was the only effective way to improve oxygenation and we avoided massive hemorrhage by careful monitoring with ACT to adjust the heparin dose. Since our patient had undergone caesarean section before ECMO, we did not have to worry about bleeding due to ECMO during the surgery. Most of the massive bleeding cases in Nair *et al's* report [9] were not due to the caesarean section wound.

Even though H1N1 ARDS in some patients is severe and refractory to ventilator support, there is still a good chance of survival by maintaining good maternal oxygenation. Regarding the use of ECMO, most of the complications in Nair *et al's* study were due to massive bleeding and the ECMO flow in their cases was higher than in ours. Careful heparin use very is important to avoid massive bleeding.

Conclusion

H1N1 infection must be treated early and aggressively in high-risk patients, especially in pregnant women. Clinical suspicion is very important, especially during epidemic or pandemic periods, since the clinical presentation might not be typical. Initial false negative H1N1 screening test results could delay treatment and may lead to mortality. The clinical course is more severe among pregnant women in the 2nd half of pregnancy peroid. Early oseltamivir treatment within 2 days after onset of symptoms should be given in suspected cases while waiting for confirmatory test results. Early ECMO use in those patients with ARDS refractory to ventilator support can lead to better clinical outcomes. Care must be taken to avoid major bleeding while using ECMO, so as to reduce mortality. Aggressive management of delivery, including emergent caesarean section if needed, can also save both mother and fetus.

Reference

1. Campbell A, Rodin R, Kropp R, *et al*. Risk of severe outcomes among patients admitted to hospital with pandemic (H1N1) influenza. CMAJ 2010; 182: 349-55.
2. Miller AC, Safi F, Hussain S, *et al*. Novel influenza A (H1N1) virus among gravid admissions. Arch Intern Med 2010; 170: 868-73.
3. Louie JK, Acosta M, Jamieson DJ, *et al*. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. N Engl J Med 2010; 362: 27-35.
4. Oluyomi-Obi T, Avery L, *et al*. Perinatal and maternal outcomes in critically ill obstetrics patients with pandemic

H1N1 Influenza A. J Obstet Gynaecol Canada 2010; 32: 443-7.

5. Siston AM, Rasmussen SA, Honein MA, *et al*. Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States. JAMA 2010; 303: 1517-25.
6. Seppelt I. Critical illness due to 2009 A/H1N1 influenza in pregnancy and postpartum women: population-based cohort study. BMJ 210; 340: c1279.
7. (ANZ ECMO) Davies A, Jones D, Bailey M, *et al*. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. JAMA 2009; 302: 1888-95.
8. Dubar G, Azria E, Tesniere A, *et al*. French experience of 2009 A/H1N1v influenza in pregnant women. PLoS ONE 2010; 5: e13112.
9. Nair P, Davies AR, Beca J, *et al*. Extracorporeal membrane oxygenation for severe ARDS in pregnant and postpartum women during the 2009 H1N1 pandemic. Intensive Care Med 2011 Apr; 37: 648-54.

台灣首例成功急救母親及嬰兒在嚴重甲型 H1N1 流感病毒肺炎造成急性呼吸窘迫症侯群之懷孕病人：體外膜氧合器使用經驗

邱光輝　賴炳村

H1N1 流感感染在高危險群病患，包括孕婦和女性產後期，可能非常嚴重，可能會致命。我們報告一個 25 歲懷孕 34 週 G2P1 婦女感染 H1N1，咳嗽一個星期，發燒 3 天和呼吸窘迫 5 天。她到醫院時已呼吸衰竭，建議要插支氣管內管使用呼吸器時她轉院到我們醫院。住加護病房後插支氣管內管使用呼吸器治療，為了救小孩，緊急剖腹產成功，新生兒無嚴重併發症。她的肺炎進展到呼吸器無法有效治療之急性呼吸窘迫症侯群。我們使用體外膜氧合器和呼吸器的支持。雖然我們早期使用體外膜氧合器並給予肺保護性呼吸器補助，不幸的住院第 3 天後發生右側氣胸，需插胸管。但在一周內成功脫離體外膜氧合器。氣管內管在體外膜氧合器停止使用 2 天後拔管。拔管成功二天後轉到病房，2 週後在病房拔出胸管。我們還回顧了相關文獻中關於嚴重 H1N1 病毒感染的孕婦，比各種輕重度，不同懷孕期，不同從感染到治療的時間對疾病的治療效果。*(胸腔醫學 **2013; 28: 147-153**)*

關鍵詞：懷孕，甲型 H1N1 流感病毒，急性呼吸窘迫症侯群，體外膜氧合器

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Pulmonary Infection with *Pseudallescheria boydii* in an Immunocompetent Patient: A Case Report

Ying-Chun Chien, Yen-Lin Chen, Jih-Shuin Jerng, Chong-Jen Yu

Pseudallescheria boydii is an opportunistic pathogen of immunocompromised patients. While it is still rare in immunocompetent patients, the number of reports of *P. boydii* colonization (mycetoma) or infection of the pulmonary cavity by this pathogen have increased due to improved detection methods and increased numbers of immunocompromised hosts. The optimum treatment for this infection remains unclear. Herein, we present a case with disease progression from mycetoma to peri-cavity lung abscess. In this case, *P. boydii* was isolated from a mixture of pathogens. The infection was successfully treated with voriconazole and adjunct percutaneous drainage and lavage. ***(Thorac Med 2013; 28: 154-159)***

Key words: pulmonary fungal infection, mycetoma, Pseudallescheria

Introduction

The term pulmonary cavity refers to an air-containing lesion with a relatively thick (>4 mm) wall or an air-containing lesion within an area of a surrounding infiltrate or mass [1]. Irrespective of the etiologies of the cavities, the prevalence of intracavitary colonization and infection has increased due to the greater number of immunocompromised hosts. Intervention for pulmonary mycetoma, even when diagnosed early, remains controversial because the clinical course is variable [2]. If mycetoma progresses to infection, the lesion may respond poorly to antimicrobials alone, necessitating additional intervention to reduce the fungal load. Resection of the localized infection remains the treatment of choice, but in patients with a poor pulmonary reserve, alternative measures have been suggested. These measures include drainage and lavage of cavities with potassium iodide or antifungal agents, for which various outcomes have been reported. However, these non-surgical interventions might require repeated sessions because of poor intracavitary retention of the therapeutic agents [3]. Aspergillus is the best recognized and most well-studied mold [4], and reports have indicated that percutaneous intracavitary treatment has been successful in cases of aspergilloma or chronic pulmonary aspergillosis [3,5]. In contrast, treatment for intracavitary infection by Pseudallescheria, which shares some characteristics with Aspergillus, is rarely reported [6]. Herein, we describe a case

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of Pseudallescheria, an uncommon pathogen, in which intracavitary treatment led to a favorable outcome.

Case Report

A 51-year-old man with a history of cryptococcal meningitis presented with hemoptysis and fever for 1 day. He had a 20-pack-year history of smoking and had worked as a cutter and polisher of jade and diamonds for 30 years. Pneumoconiosis was diagnosed 8 years earlier. Serial chest radiographs were obtained during the year prior to admission, and showed an enlarging cavitary lesion at the left upper lobe (LUL) with a newly developed ball-in-hole appearance. Chest computed tomography (CT) analysis led to the suspicion of a fungal mass within the cavity (Figure 1B). Sputum studies did not show evidence of mycobacterial infection, and bronchoscopic biopsy of the cavity wall did not show evidence of granulomatous inflammation or malignancy. However, sputum cultures and bronchial washes revealed the presence of *Pseudallescheria boydii* and *Klebsiella pneumoniae*.

On admission, the patient's temperature was 38.9°C, pulse rate was 138 beats per minute, respiratory rate was 22 breaths per minute, blood pressure was 121/86 mmHg and SpO_2 was 96% under ambient air. Auscultation revealed coarse breathing sounds bilaterally and wheezes in the left upper chest. Chest radiograph showed a ball-in-hole lesion in the LUL. Repeated sputum and bronchial wash cultures showed *K. pneumoniae* and *P. boydii* growth. The patient received intravenous piperacillin/tazobactam plus oral azithromycin followed by ceftriaxone for a total of 3 weeks, but fever persisted. Chest radiograph showed an increased air-fluid level

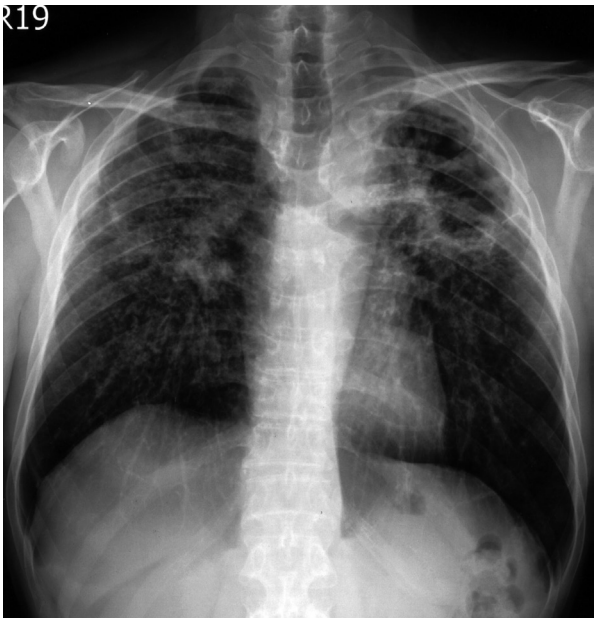

Fig. 1A. Chest radiograph (PA view) showing baseline LUL cavity with pneumoconiosis background, taken 3 months before the patient visited our outpatient clinic.

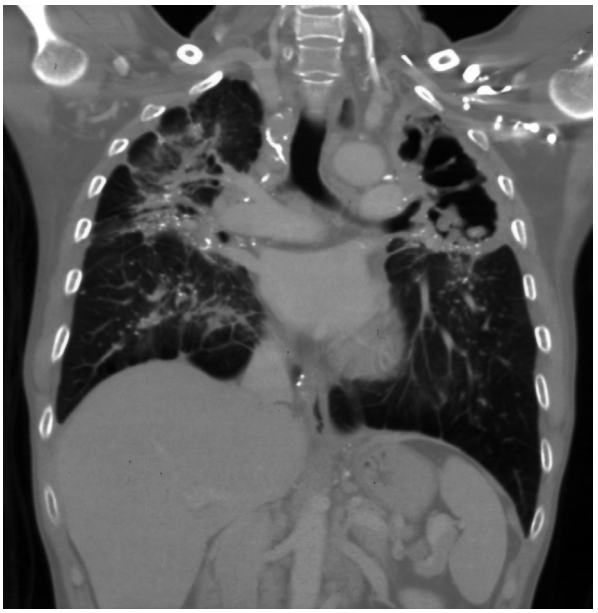

Fig. 1B. Chest CT scan showing LUL ball-in-hole with coronal section.

in the cavity (Figure 2A). A subsequent chest CT revealed left upper and lower lobe involvement. The patient responded poorly to the ad-

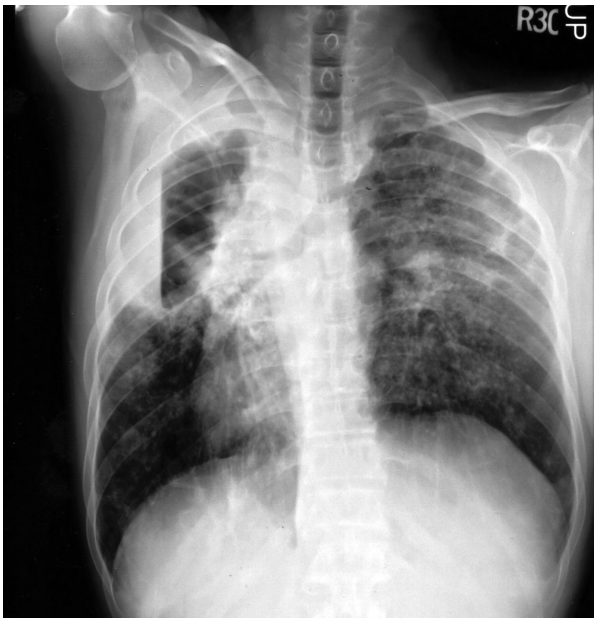

Fig. 2A. Chest radiograph (left decubitus view) showing intracavitary air-fluid level.

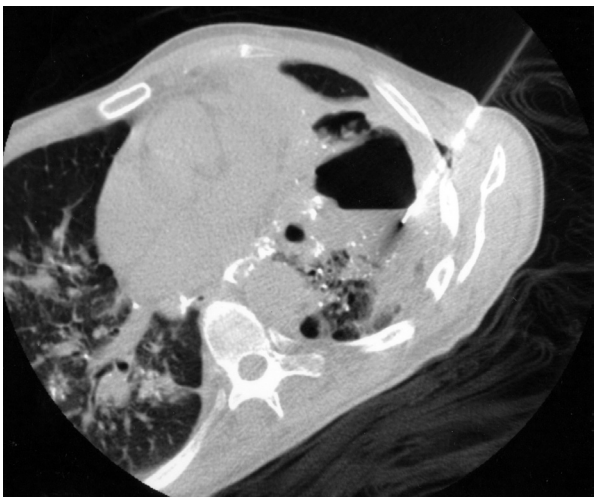

Fig. 2B. Chest CT scan showing CT-guided percutaneous puncture for pigtail catheter insertion.

dition of intravenous voriconazole and ceftazidime. Surgical intervention was not feasible because the patient had poor lung reserves-forced expiratory volume in 1 second (FEV1) was 1.42 L (51.12% of predicted FEV1). Thus, CT-guided percutaneous drainage and lavage with sterile saline were performed using a pigtail catheter (Figure 2B). Lavage was performed 3 times a day for 12 days. During the lavage sessions, the patient would easily cough out some lavage fluid, but he could hold his breath and tolerate a 30 ml bolus lavage without coughing. The patient's fever subsided gradually. Radiographs showed no air-fluid level several days after intervention. Culture of the drainage fluid yielded *P. boydii* and unclassified anaerobes; therefore, ceftazidime treatment was replaced with metronidazole treatment. The effluent of the lavage gradually became lighter, the pigtail catheter was removed without subsequent fever, and the patient was discharged from the hospital. During follow-up, his condition remained stable without fever. Chest radiography revealed no air-fluid level or ball-in-hole lesion in the cavity, although he reported occasional hemoptysis. Compared with the baseline chest radiograph (Figure 1A), the LUL cavity appeared slightly enlarged with wall thickening and a new dense opacity between the cavity and mediastinum. Repeated sputum culture revealed the presence of only *K. pneumoniae*.

Discussion

P. boydii, the teleomorph or sexual state of *Scedosporium apiospermum*, is a ubiquitous filamentous fungus present in soil, sewage, and polluted waters [7]. However, *P. boydii* is isolated in less than 1% of dwellings and does not appear to be a frequent colonizer of humans [8]. Since 1984, a number of cases of colonization or infection of various organs with *P. boydii* has been reported. *P. boydii* is currently recognized as a medically important opportunistic fungus that causes life-threatening infections in immunosuppressed patients. Like Aspergillus,

the range of diseases caused by this fungus is broad, ranging from transient colonization of the respiratory tract to saprophytic involvement of abnormal airways, allergic bronchopulmonary reaction, invasive localized disease, and disseminated disease. Thus, *P. boydii* is emerging as 1 of the most important molds following Aspergillus. During the past year, amphotericin B was the drug of choice when invasive fungal infection was suspected in immunosuppressed patients. Recent evidence has shown that initial use of voriconazole was associated with improved survival and better treatment response to Aspergillus infection [9]. Since amphotericin B is ineffective against *P. boydii*, current practice guidelines provide better coverage when invasive mold infection is suspected. However, diagnosis of *P. boydii* might be delayed among immunocompetent patients due to the supposed low infection risk.

P. boydii resembles Aspergillus in its tendency to invade the vessels, but there are substantial differences between these pathogens in terms of drug susceptibilities [7]. High-dose voriconazole or posaconazole might be effective *in vitro*, if strains with low MIC_{50} are isolated. The drainage culture in the current report yielded both unclassified anaerobes and *P. boydii*, and therefore, voriconazole was the antifungal agent of choice. Treatment designed to decrease the pathogen load must take into account the avascular nature of fungal masses. Intravenous antimicrobials, therefore, are of little therapeutic benefit in these cases. The patient's low pulmonary function excluded surgery as a treatment option. Instead, we used percutaneous pigtail catheter-mediated drainage. Amphotericin B has been used in lavage fluid for chronic cavitary aspergillosis [3,5], but we did not add voriconazole to the lavage fluid because we found no evidence to support this kind of treatment. A saline lavage might be adequate, regardless of the nature of the pathogen, especially in grave circumstances. Intracavitary treatment is especially important when risk of treatment failure is compounded by the presence of possibly resistant strains.

P. boydii is distinctively difficult to treat since it is inherently resistant to most available antifungal agents. Immediate and proper isolation, identification, and susceptibility testing of fungal pathogens are critical for the development of optimal treatment. Advances in antifungal agents and surgical debridement techniques remain essential elements in the battle against these organisms.

Pre-existing cavities are attractive targets for pathogen colonization in immunocompetent patients. *P. boydii* might participate directly in infection, or may be a bystander in the process. The unclassified anaerobe isolated in our case may have been the primary pathogen. Nevertheless, we could not ignore the role of *P. boydii* in our patient, especially after minimal improvement was observed following a course of usually effective antibiotics.

In conclusion, voriconazole is effective *in vitro* against *P. boydii* with low MIC_{50}. In cases of uncontrolled infection, percutaneous pigtail drainage plus lavage with saline might be an effective alternative method. Whether *P. boydii* is a bystander or participant, our experience with the successful treatment of pulmonary *P. boydii* infection mixed with other bacteria highlights the need for clinicians to be aware of possible *P. boydii* infection in low-risk patients.

References

1. Ryu JH, Swensen SJ. Cystic and cavitary lung diseases:

focal and diffuse. Mayo Clin Proc 2003; 78(6): 744-52.
2. Lee JG, Lee CY, Park IK, *et al*. Pulmonary aspergilloma: analysis of prognosis in relation to symptoms and treatment. J Thorac Cardiovasc Surg 2009; 138(4): 820-5.
3. Munk PL, Vellet AD, Rankin RN, *et al*. Intracavitary aspergilloma: transthoracic percutaneous injection of amphotericin gelatin solution. Radiology 1993; 188(3): 821-3.
4. Mason RJ, Broaddus VC, Martin T, *et al*. Murray and Nadel's Textbook of Respiratory Medicine, 5th ed; 2010; Chapter 36: 836-40 & 842-43.
5. Lee KS, Kim HT, Kim YH, *et al*. Treatment of hemoptysis in patients with cavitary aspergilloma of the lung: value of percutaneous instillation of amphotericin B. AJR Am J Roentgenol 1993; 161(4): 727-31.
6. Soman R, Mahashur A, Naphade D, *et al*. *Pseudallescheria boydii* lung infection in an immunocompetent adult, difficulties in diagnosis and management. J Assoc Physicians of India 2010; 58: 633-34.
7. Cortez KJ, Roilides E, Quiroz-Telles F, *et al*. Infections caused by Scedosporium spp. Clin Microbiol Rev 2008; 21(1): 157-97.
8. Beguin H, Nolard N. Mould biodiversity in homes. Air and surface analysis of 130 dwellings. Aerobiologia 1994; 10: 157-66.
9. Karthaus M. Treatment of aspergillosis. Clin Infect Dis 2008; 47(3): 427; author reply 27-8.

免疫健全者之波氏假性黴樣菌之肺部感染—個案報告

錢穎群　陳彥霖　鄭之勛　余忠仁

波氏假性黴樣菌為一已知免疫低下患者之伺機性感染菌。隨著黴菌鑑定的進步以及免疫不全患者的增加，黴菌於肺內空腔的寄生與感染個案增加，然寄生或感染於免疫健全者仍屬少見，而最佳之治療方式仍無定論。本個案完整地呈現黴菌由肺內空腔寄生進展為肺內空腔感染併周遭肺膿瘍。藥物輔以將豬尾巴經由表皮放置於空腔內引流及灌洗，此黴菌與細菌之混和感染因而成功治療，無明顯後遺症。*(胸腔醫學 **2013; 28: 154-159**)*

關鍵詞：肺內黴菌感染，肺內空腔內黴菌寄生，波氏假性黴樣菌

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Late Pulmonary Metastasis of Renal Cell Carcinoma – 13 Years after Radical Nephrectomy: A Case Report

Chih-Hsiang Chien, Yuh-Min Chen

Pulmonary nodules larger than 3 cm in the elderly raise the possibility of malignancy. We present a case of pulmonary metastases that occurred 13 years after radical right nephrectomy for renal cell carcinoma. The patient suffered from cough with hemosputum for days. He visited our outpatient department where pulmonary nodules were detected by chest X-ray examination in February 2012. Computed tomography (CT) of the chest revealed a 3.8 x 3.0 cm soft tissue mass at the right lower lobe (RLL) of the lung, and variably-sized nodules at the bilateral lung fields. Lung cancer, RLL, with lung-to-lung metastasis was suspected. CT-guided biopsy was performed for the RLL mass and histopathology disclosed metastatic renal cell carcinoma. Abdominal CT disclosed a normal appearance of the left kidney and no local recurrence of renal cell carcinoma. We present this case and review the literature of late pulmonary recurrence from renal cell carcinoma. ***(Thorac Med 2013; 28: 160-164)***

Key words: renal cell carcinoma, late pulmonary recurrence

Introduction

The differential diagnosis of multiple pulmonary nodules includes primary pulmonary malignancies with pulmonary metastasis, pulmonary metastases from other malignancies, fungal infection, multiple arteriovenous malformations (AVM), septic emboli, pneumoconiosis, etc [1]. The initial approach with these patients includes history-taking, physical examination, and information from available previous chest X-rays or imaging examinations. As patients get older, the possibility of malignancy with a pulmonary nodule or mass is higher [1].

Renal cell carcinoma (RCC) is the most common type of primary renal malignancy [2]. Although pulmonary metastasis constitutes the majority or most common type of RCC recurrence after nephrectomy, late recurrence after 10 years is rarely reported. We present herein the case of a male patient with pulmonary metastasis from RCC post-radical nephrectomy, with a 13-year disease-free interval.

Case Report

An 86-year-old male underwent right radical nephrectomy for RCC in 1999. The postoperative course was smooth and he did not receive postoperative adjuvant radiotherapy

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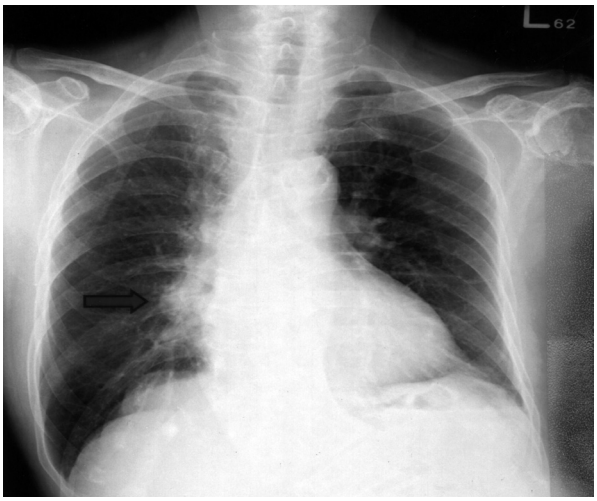

Fig. 1. Chest X-ray (February 2012) revealed a soft-tissue shadow at the right lower lung, near the right hilum (as arrow indicates)

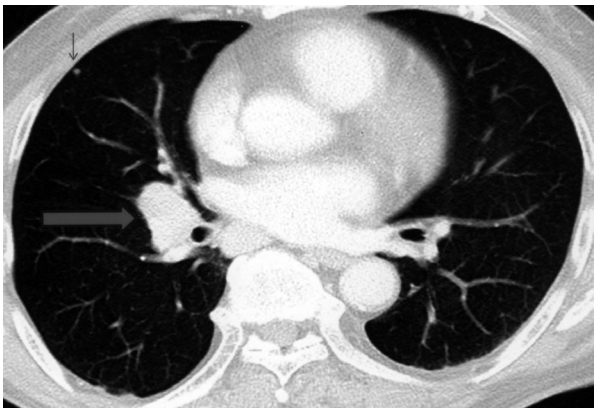

Fig. 2A. Chest CT revealed a soft tissue mass at the right lower lung (big arrow) and a nodule in the right lower lung (small arrow)

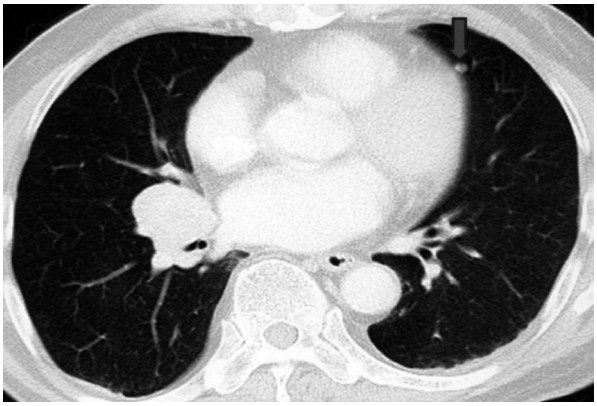

Fig. 2B. Chest CT revealed a nodule at the left lower lung (arrow)

or systemic therapy. No tumor recurrence was found in the next serial follow-up. However, he visited our outpatient clinic in January 2012 due to cough with bloody sputum lasting for days. An abnormal soft-tissue shadow was detected by chest X-ray examination (Figure 1). Chest computed tomography (CT) examination was arranged and the results revealed a 3.8 x 3.0 cm soft tissue mass lesion at the right lower lobe (RLL) of the lung, with variably-sized soft tissue nodules at the bilateral lung fields. Mediastinal lymphadenopathies were also found (Figure 2). Lung cancer, RLL, with lung-to-lung metastasis was suspected.

Bronchoscopy with endobronchial ultrasonography (EBUS) was arranged initially and showed 2 mediastinal LN with hypervascularity at stations 7 and 10R, respectively. Due to the high risk of bleeding, biopsy was not performed. The patient then received CT-guided biopsy of the soft tissue mass in the right lower lung. The histopathology of the RLL tumor disclosed metastatic RCC, clear-cell type, compatible with the pathology findings of the previous radical nephrectomy. The tumor cells were immunoreactive for CD10 and CK, while non-reactive for TTF-1 and RCC stains.

Meanwhile, abdominal CT disclosed the normal appearance of the left kidney and no evidence of local RCC recurrence. Whole body bone scan found no bony metastasis. He was then transferred to the genitourinary outpatient department for further management. After discussion with the patient, he was given small molecule tyrosine kinase (TK) inhibitors (sunitinib) for further treatment. Chest CT in May 2012 revealed that the size of the soft tissue mass lesion at the RLL had decreased (Figure 3).

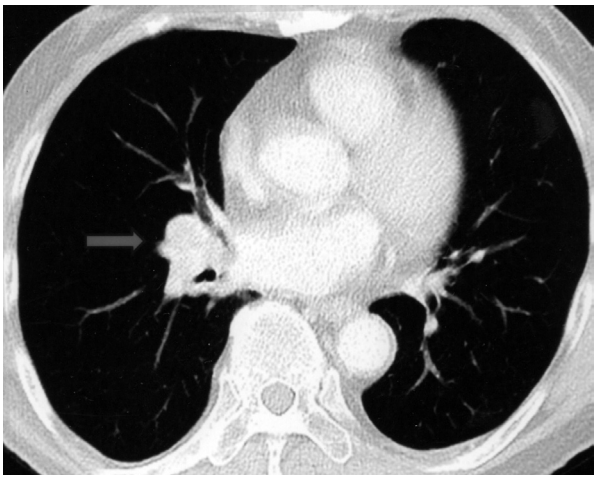

Fig. 3. Chest CT revealed the soft tissue mass at the right lower lung had decreased in size after TK inhibitor treatment for 3 months (arrow)

Discussion

The annual incidence of RCC has increased during the past 2 decades [3]. RCC, which originates within the renal cortex, constitutes 80-85% of primary renal neoplasms. The majority of recurrence or metastases of RCC occurs within the first 5 years after nephrectomy [4]. Recurrence has been reported as 43% in the first year, 70% within the second year, 80% within 3 years, and 93% within 5 years [4-5]. In a series of 2228 patients, the incidence of late renal tumor recurrence after nephrectomy for localized RCC (beyond 5 years) was only 4% [6]. With a median postoperative follow-up of 13.9 years (range 5.1-38.9), 63 patients (4.3%) experienced late renal recurrence at a median of 9.3 years (range 5.1-25.3), and 172 patients (11.8%) developed late distant metastases at a median of 9.6 years (range 5.1-26.6) after surgery [6].

Pulmonary metastasis is the most common presentation of distant metastases of RCC [7]. Lung metastases have been reported in 29-54% of patients with RCC, followed by bone metastases (16-31% of patients) [8-9], liver metastases (8-30% of patients) [8-10] and brain metastases, which occur in 2-10% of patients. Late metastases (>10 years post-nephrectomy) is the specific behavior of RCC and is rare. The longest reported time-to-recurrence after nephrectomy was 45 years [11].

In a previous report of late recurrence or metastases that included 470 RCC patients who had undergone curative treatment and who did not develop recurrence within 10 years of follow-up, the disease-free survival rate at 15 and 20 years was 89.5% and 78.4%, respectively [12]. In the study, multivariate analysis showed that lymph node metastasis was the only factor to predict late recurrence (p=.0334), and age at nephrectomy was the only prognostic factor for overall survival (p<.0001). Thirty of the 470 patients had developed late recurrence in 44 sites, including the lung (36.4%), kidney (25%), and bone (13.6%), followed by the brain, pancreas, adrenal gland, lymph nodes, and liver [12]. Another study reported that late RCC metastases are often combined with rapid disease progression [13]. Patients with untreated metastatic disease have a 5-year survival of 0-18%.

Surgery is curative for the majority of RCC patients without distant metastases, and is therefore the preferred treatment option for stages I, II, and III RCC patients [14]. Neither chemotherapy nor radiotherapy is effective for the treatment of advanced RCC. Immunotherapy with high-dose bolus interleukin-2 (IL-2) can activate an immune response against RCC that results in tumor regression in a minority of patients [15].

Molecularly-targeted therapy with small molecule TK inhibitors (sunitinib, sorafenib, pazopanib) to block the intracellular domain of

the vascular endothelial growth factor (VEGF) receptor may regress the growth of the tumor [16]. As for the treatment of pulmonary metastases, a study of 64 patients with pulmonary metastasectomy reported a 5-year survival of 39.9% and a median survival of 46.6 months [17].

Conclusion

Late recurrence (>10 years) is a rare and specific behavior of RCC. A history of malignant disease (such as RCC) is important when making the differential diagnosis. Lifelong follow-up is necessary for RCC patients who have undergone radical nephrectomy.

References

1. Viggiano RW, Clin Chest Med. Evaluation and management of solitary and multiple pulmonary nodules. Clin Chest Med 1992 Mar; 13(1): 83-95.
2. Curti BD: Renal cell carcinoma. JAMA 2004; 292: 97-100.
3. Nguyen MM, Gill IS, Ellison LM, *et al*. The evolving presentation of renal carcinoma in the United States: trends from the Surveillance, Epidemiology, and End Results program. J Urol 2006; 176 (6 Pt 1): 2397.
4. McNichols DW, Segura JW, DeWeerd JH, *et al*. Renal cell carcinoma: long-term survival and late recurrence. J Urol 1981; 126: 17-23.
5. Ljungberg B, Alamdari FI, Rasmuson T, *et al*. Follow-up guidelines for nonmetastatic renal cell carcinoma based on the occurrence of metastases after radical nephrectomy. BJU Int 1999; 84: 405-11.
6. Kim SP, Weight CJ, Leibovich BC, *et al*. Outcomes and clinicopathologic variables associated with late recurrence after nephrectomy for localized renal cell carcinoma. Urology 2011; 78(5): 1101.
7. AULjungberg B, Alamdari FI, Rasmuson T, *et al*. Follow-up guidelines for nonmetastatic renal cell carcinoma based on the occurrence of metastases after radical nephrectomy. Int 1999; 84(4): 405.
8. Ljungberg B, Alamdari FI, Rasmuson T, *et al.* Follow-up guidelines for nonmetastatic renal cell carcinoma based on the occurrence of metastases after radical nephrectomy. BJU Int 1999; 84(4): 405.
9. Levy DA, Slaton JW, Swanson DA, *et al*. Stage specific guidelines for surveillance after radical nephrectomy for local renal cell carcinoma. J Urol 1998; 159(4): 1163.
10. Frank I, Blute ML, Cheville JC, *et al*. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. J Urol 2002; 168(6): 2395.
11. Tapper H, Klein H, Rubenstein W, *et al*. Recurrent renal cell carcinoma after 45 years. Clinical Imaging 1997; 21: 273-5.
12. Sengaj Y, Horiek S, Kanayamal H, *et al*. Late recurrence of renal cell carcinoma: retrospective and collaborative study of the Japanese Society of Renal Cancer. Urology 2011; 77: 379-84.
13. McNichols DW, Segura JW, DeWeerd JH, *et al*. Renal cell carcinoma: long-term survival and late recurrence. J Urol 1981; 126: 17-23.
14. Pantuck AJ, Zisman A, Belldegrun AS, *et al*. The changing natural history of renal cell carcinoma. J Urology 2001; 166: 1611.
15. Klapper JA, Downey SG, Smith FO, *et al*. High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma: a retrospective analysis of response and survival in patients treated in the surgery branch at the National Cancer Institute between 1986 and 2006. Cancer 2008; 113(2): 293.
16. Atkins MB, Management of advanced renal cancer. Kidney Int 2005; 67(5): 2069.
17. Hofmann HS. Prognostic factors and survival after pulmonary resection of metastatic renal cell carcinoma. European Urology 2005; 48: 77-82.

病歷報告：腎細胞癌的晚發型肺轉移－全腎切除 13 年後復發

簡志翔　陳育民

在老年病患中發現的肺部腫瘤若是大於三公分，該腫瘤為惡性的可能性大為增加，我們報告一個腎細胞癌的病患，十三年前接受右全腎切除後，才在肺部發現轉移的病例。

這位病患的症狀主要是因為咳血數天，於 2012/2 胸部 X 光片檢查發現肺部腫瘤。肺部電腦斷層發現右下肺有 3.8 x 3 cm 的腫塊，同時兩側下肺葉有數個大小不一的結節。最初的影像診斷是肺癌合併肺部轉移。我們安排電腦斷層引導下右下肺腫瘤切片，病理報告是腎細胞癌肺部轉移。腹部電腦斷層顯示左側腎臟正常，右側也沒有腎細胞癌的局部復發。

我們報告這個十三年後的腎細胞癌肺部轉移復發，同時也回顧一些過去的文獻報告。*(胸腔醫學* ***2013; 28: 160-164)***

關鍵詞：腎細胞癌，晚期肺部復發轉移

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Pulmonary Metastasis of Pleomorphic Liposarcoma Presenting as a "Ball-in-Hole" Lesion on Chest Radiograph – A Case Report

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A 54-year-old man with a history of hepatocellular carcinoma and chest wall pleomorphic liposarcoma post-surgical excision presented with 1 month of hemoptysis. CXR revealed a "ball-in-hole" lesion in the right upper lobe. CT scan of the chest revealed a 2.5 cm enhancing nodule at the anti-dependent portion of a 3.7 cm cavity within ground-glass opacity at the apical segment of the right upper lobe. Aspergilloma was suspected. Bronchoscopic examination failed to identify the lesion, so surgical excision was scheduled. Right upper lobectomy with mediastinal lymph nodes dissection was performed utilizing video-assisted thoracic surgery. The lesion was identified as a metastatic pleomorphic liposarcoma in the pathological study. The postoperative course was uneventful, and no recurrence was found 8 months after the surgery. This case illustrates a rare type of liposarcoma with metastasis to the lung, presenting with an unusual pattern on the CXR. ***(Thorac Med 2013; 28: 165-170)***

Key words: "ball-in-hole" lesion, pleomorphic liposarcoma, lung metastasis

Introduction

Liposarcoma is 1 of the most common sarcomas of adulthood. Most liposarcomas arise in the deep soft tissues of the limbs, trunk, or retroperitoneum. Pleomorphic liposarcoma (PL) is the rarest of the different forms of liposarcoma [1]. PL tends to have a progressive clinical course with a high potential for metastasis. "Ball-in-hole" lesions or air-crescent signs on chest radiographs are frequently caused by aspergilloma, and less common factors including malignancy. Lung metastases rarely manifest as "ball-in-hole" lesions on chest X-ray (CXR), regardless of the origin of the primary tumor. Herein, we present the case of a 54-year-old man with metastatic PL of the lung presenting as a "ball-in-hole" lesion.

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Case Report

A 54-year-old man presented with hemoptysis of 1 month's duration in June 2011. No cough, shortness of breath, or chest pain was reported. His past medical history included left lower chest wall PL excised in 2009 at a local hospital, and hepatocellular carcinoma (HCC). He had follow-up for his chest wall PL at the local hospital where the surgery took place. At the same time, he had regular follow-up for his HCC in the gastroenterology outpatient clinic in Kaohsiung Chang Gung Memorial Hospital. Due to the symptom of hemoptysis, the gastroenterologist arranged a CXR examination, which revealed a "ball-in-hole" lesion in the right upper lung (Figure 1) that had not been seen in CXRs in the most recent 2 years (Figure 2). Computed tomography (CT) scan of the chest was then arranged (Figure 3), and revealed a 2.5 cm enhancing nodule at the anti-dependent portion of a 3.7 cm cavity within a ground-glass opacity at the apical segment of the right upper lobe. Differential diagnoses included aspergilloma, pulmonary tuberculosis, tumor and other rare causes, though aspergilloma seemed more likely. Bronchoscopy examination was then performed in July 2011, and found no endobronchial lesion. At the same time, fungus, *Mycobacterium tuberculosis*, and bacterial cultures

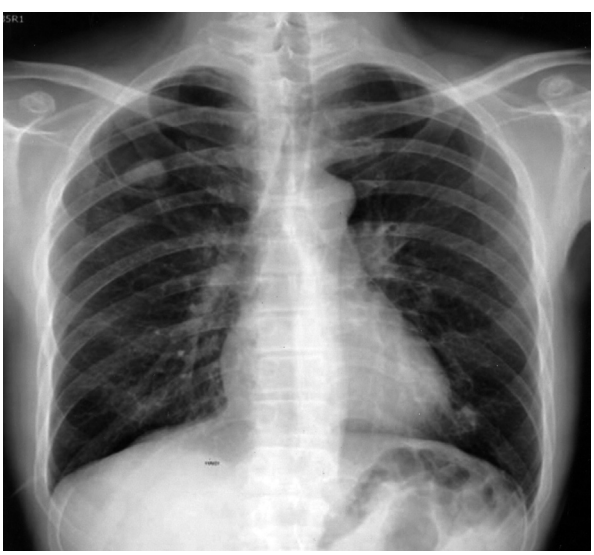

Fig. 1. Patient's CXR in June 2011

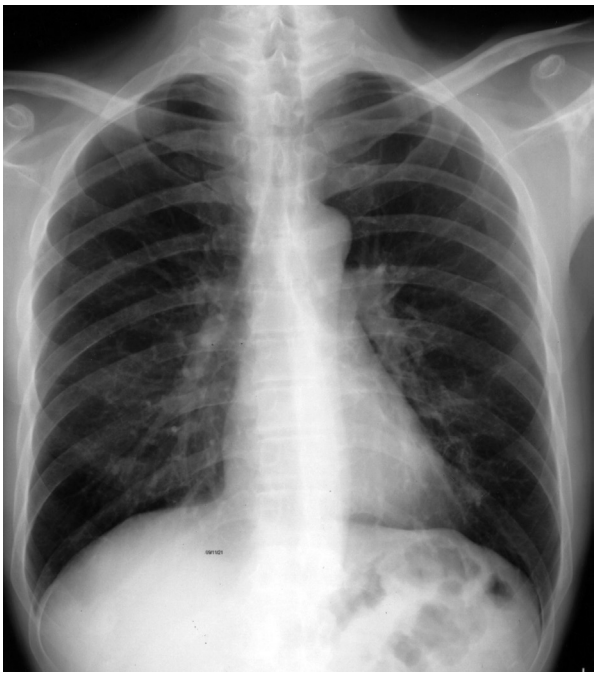

Fig. 2. Patient's CXR in November 2009 taken a few months after his left chest wall surgery

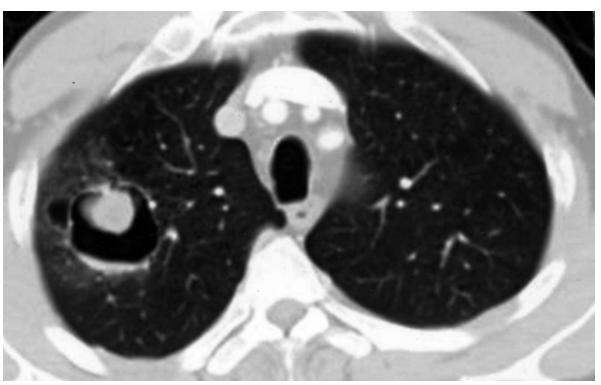

Fig. 3. CT scan of the chest revealed a 2.5 cm enhancing nodule at the anti-dependent portion of a 3.7 cm cavity within ground-glass opacity at the apical segment of the right upper lobe

from bronchial wash fluid failed to cultivate. The patient was then admitted on 13 August 2011 for surgical intervention.

On admission, the patient's physical examination was normal. Routine blood test results were normal. Repeated CXR (Figure 4) on admission still showed a "ball-in-hole" lesion, but this time with an increased ball size compared to the lesion in June. Surgical excision utilizing a video-assisted thoracic surgery (VATS) modality was performed on 15 August 2011. An ill-defined mass about 5 cm in size in the right upper lobe of the lung was indentified intra-operatively. Right upper lung lobectomy with mediastinal lymph nodes dissection was performed and tissue samples were sent for pathological study. The resected samples showed lung tissue with an ill-defined tumor mass composed of sheets of spindle, plump and oval cells featuring scattered bizarre and multinucleated giant cells, frequent mitoses, and areas of hemorrhage and necrosis. The lymph nodes were free of tumor involvement. Immunohistochemical (IHC) staining was then performed with the tissue sample. The IHC results identified the lesion as a metastatic PL (Figure 5). Tracing his medical history, the left chest wall PL excised 2 years ago was highly suspected to be the primary lesion. The postoperative course was uneventful and the patient was discharged 2 weeks after the surgery. Eight months after surgery, there was no recurrence of PL.

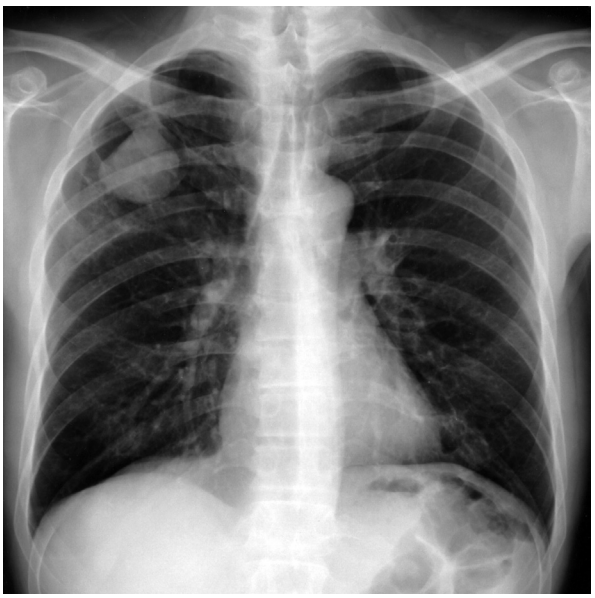

Fig. 4. Patient's CXR in August 2011 prior to surgery, showing the increased size of the lesion compared with the lesion in June 2011

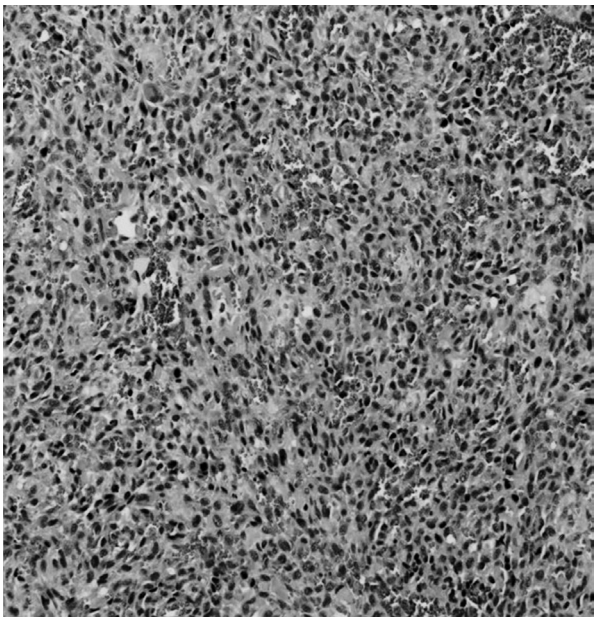

Fig. 5. Specimen of excised lung lesion revealed an ill-defined tumor mass composed of sheets of spindle, and plump and oval cells featuring scattered bizarre and multinucleated giant cells with frequent mitoses. IHC stain proved metastatic pleomorphic liposarcoma

Discussion

The air-crescent sign ("ball-in-hole") seen in the CXR or chest CT scan is most often associated with an inflammatory process such as mycetoma, a hydatid cyst, lung abscess, pulmonary tuberculosis, or a Rasmussen aneurysm in a tuberculous cavity [2-3]. It is less commonly

seen in primary lung malignancy, and even less often in metastatic lung lesions. An estimated 4% of metastatic tumors have been noted to cavitate, as detected by plain radiography [4].

Upon encountering an air-crescent sign or a "ball-in-hole" lesion in the CXR, it is imperative to differentiate malignant from benign lesions, such as mycetoma, but this can be difficult. However, certain radiographic features may provide helpful clues in the diagnostic evaluation of a patient with cavitary lung lesions, if biopsy is not immediately available. Features of chest imaging that supported the diagnosis of a malignant lesion in our patient included an enhanced nodule at the antidependent portion of the cavity on CT scan, and an absence of adjacent bronchiectasis [5]. However, the wall of the cavitary lesion in our case (less than 5 mm) was thinner than what would be expected in a cavitating lung cancer. According to the study by Woodring *et al*. [6] on the diagnostic implications of the cavity wall thickness of solitary cavities of the lung, lesions in which the thickest part of the cavity wall was 1 mm were benign; 92% of lesions with a wall thickness 4 mm or less were benign; lesions 5 to 15 mm were equally divided between benign and malignant; and 95% of lesions with a cavity wall thickness greater than 15 mm were malignant. PL is the rarest subtype of liposarcoma, and accounts for about 5% of all cases [1]. It is more common in middle-aged and older populations, with a similar sex distribution. Most liposarcomas arise in the deep soft tissues of the limbs, trunk, or retroperitoneum. Although the pathology report in our case indicated the lung lesion was a metastatic PL, there was a brief moment when the lesion was suspected to be a primary lung PL, since the patient had no active primary PL in other parts of the body when the lung lesion appeared. However, the suspicion was short-lived, and the diagnosis of metastatic PL originating from the chest wall PL excised 2 years ago was thought to be more likely for several reasons. First, the incidence of primary lung PL is rare. To date, there have been less than 10 cases of primary lung PL reported [7]. Second, PLs have a very high incidence of metastases and tumor-related mortality [8], even in patients who received surgical excision and adjuvant therapy. Isolated lung metastases will develop in about 20% of patients with extremity soft tissue sarcoma during the disease course [9]. Third, although in our case there was a considerable time span between the diagnosis of primary chest wall PL (diagnosed in 2009) and lung metastasis (diagnosed in 2011), studies have shown it is not unusual for PLs to have late metastasis despite the excision of the primary tumor. In one case series [10], the time span between diagnosis of the primary extremity PL and lung metastasis ranged from 0 to 107 months, with a mean of 23 months, which is similar to that of our patient (24 months). This explains why the diagnosis of solitary metastatic PL to the lung, rather than primary lung PL, was more likely for our patient.

In conclusion, an air-crescent sign or "ball-in-hole" lesion in a CXR is more commonly caused by aspergilloma or mycetoma, but malignant causes should not be overlooked, especially in high-risk patients. CT imaging may provide useful clues to differentiate aspergilloma from malignant lesions. Despite excision of the primary and metastatic disease and adjuvant treatment, tumor progression with metastasis is the usual clinical course for PL. This case thus illustrates late metastasis of chest wall PL to the lung with a rare presentation as a "ball-in-hole" lesion on CXR.

References

1. Azumi N, Curtis J, Kempson RL, *et al*. Atypical and malignant neoplasms showing lipomatous differentiation: A study of 111 cases. Am J Surg Pathol 1987; 11: 161-83.
2. Abramson S. The air crescent sign. Radiology 2001; 218: 230-2.
3. Gadkowski LB, Stout JE. Cavitary pulmonary disease. Clin Microbiol Rev 2008; 21(2): 305.
4. Dodd GD, Boyle JJ. Excavating pulmonary metastases. Am J Roentgenol 1961; 85: 277-93.
5. Park Y, Kim TS, Yi CA, *et al*. Pulmonary cavitary mass containing a mural nodule: Differential diagnosis between intracavitary aspergilloma and cavitating lung cancer on contrast-enhanced computed tomography. Clin Radiol 2007; 62: 227-32.
6. Woodring JH, Fried AM, Chuang VP. Solitary cavities of the lung: Diagnostic implications of cavity wall thickness. AJR Am J Roentgenol 1980; 135: 1269-71.
7. Achir A, Ouadnouni Y, Smahi M, *et al*. Primary pulmonary liposarcoma – A case report. Thorac Cardiov Surg 2009; 57: 119-24.
8. Wu JM, Montgomery E. Classification and pathology. Surg Clin N Am 2008; 88: 483-520.
9. Stefan W, Florian G, Sebastian B, *et al*. Growth patterns of lung metastases from sarcomas. Virchows Arch 2011; 459: 213-9.
10. Marlo N, Cesar AM, Saul S. Pulmonary metastasis from liposarcoma: A clinicopathologic and immunohistochemical study of 24 cases. Am J Clin Pathol 2005; 123: 265-75.

多形性型脂肪肉瘤之肺轉移以“Ball-in-hole”之病變呈現於胸部照影

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一位 54 歲男性，有肝癌及胸壁多形性型脂肪肉瘤而接受手術切除之病史，主述咳血一個月。胸部 X 光片發現右上肺部有一 “ball-in-hole lesion”。胸部斷層掃瞄顯示於右上肺葉頂端有毛玻璃樣陰影，而在此毛玻璃樣陰影中有一 3.7 公分空洞，而此空洞中另有一個 2.5 公分的顯影結節。此病變被懷疑是麴菌瘤。因支氣管鏡檢查並未發現異常之病灶，因此安排外科手術切除。病人接受胸腔內視鏡輔助手術以施行右上肺葉及縱膈淋巴結切除。切除之病理組織化驗之後證實為肺轉移之多形性型脂肪肉瘤。病人術後復原良好，在接受手術 8 個月後尚無腫瘤復發跡象。因此，此病例報告描述了一個罕見類型脂肪肉瘤之肺轉移，並於胸部 X 光片上以少見之形式來呈現。*(胸腔醫學 **2013; 28: 165-170**)*

關鍵詞：ball-in-hole 病變，多形性型脂肪肉瘤，肺轉移

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Diaphragmatic Hernia after Percutaneous Radiofrequency Ablation for Hepatocellular Carcinoma – A Case Report and Literature Review

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Radiofrequency ablation (RFA) is now regarded as the first-line therapy for unresectable small-sized or recurrent hepatocellular carcinoma (HCC). The thoracic complications of RFA require our attention, especially when we treat HCC adjacent to the diaphragm. The case we report is that of a patient with an unusual presentation, who was diagnosed with diaphragmatic hernia 14 months after RFA for HCC. We reviewed the medical literature written in English and found that the mean value of time from culprit RFA till hernia diagnosis in 5 cases was 13.8 months. HCC near or adjacent to the diaphragm is a risk factor. One reasonable explanation for this delayed complication is that an initial thermal injury could then lead to progression of the diaphragm defect under the influence of a peritoneopleural pressure gradient, increased intra-abdominal pressure, or focal tumor infiltration. Therefore, newly developed adjuvant maneuvers for RFA, such as subphrenic water or artificial ascites, may be a reasonable choice for specifically selected patients with HCC near the diaphragm. ***(Thorac Med 2013; 28: 171-178)***

Key words: diaphragmatic hernia, radiofrequency ablation, hepatocellular carcinoma

Introduction

Liver cirrhosis and hepatocellular carcinoma (HCC) are leading causes of death in several countries, especially Taiwan. Surgical resection has been considered the first-line treatment for solitary HCC. However, impaired liver function, comorbidity and patients' preference all make surgical intervention impossible. Radiofrequency ablation (RFA) is now widely accepted as a good choice for unresectable small-sized or recurrent HCC. The thoracic complications of RFA require our attention, especially when treating HCC near the diaphragm. We herein report a case with an unusually late complication -- the patient developed diaphragmatic hernia 14 months after RFA for HCC.

Case Report

A 56-year-old man was diagnosed 4 years ago as having chronic hepatitis B and alcohol-

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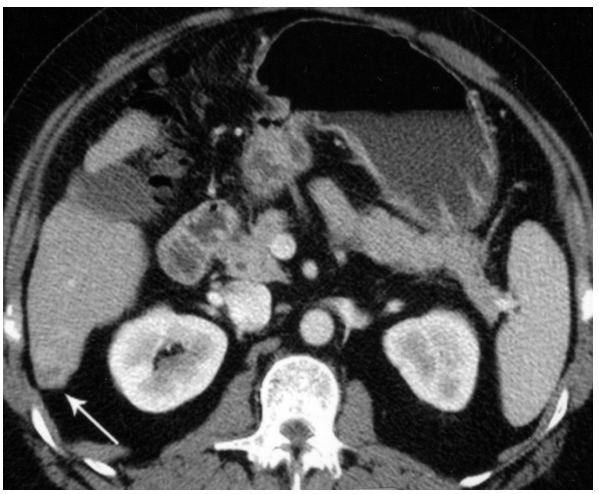
related liver cirrhosis (Grade A, Child-Pugh classification criteria). He received regular follow-up. Six months after the diagnosis of liver cirrhosis, abdominal ultrasonography revealed a hypoechoic nodule in segment VII of the liver, 2.1 cm at its largest diameter. The initial level of alpha-fetoprotein was 6.4 ng/mL and close follow-up was suggested. Six months later, the alpha-fetoprotein level was elevated and the size of the lesion had increased. Ultrasound-guided liver biopsy confirmed the diagnosis of HCC. The findings of subsequently performed dynamic computed tomography (CT) imaging were compatible with HCC. For fear of the possible surgical risks, the patient chose transcatheter hepatic arterial chemoembolization (TACE) and RFA instead of surgical resection. TACE was carried out by the radiologist and RFA was performed 6 weeks later.

RFA was performed percutaneously and the RF needle was advanced to the lesion under ultrasonographic guidance by experienced interventional hepatologists. The RFA equipment consisted of a 200-watt cool-tip RF ablation generator (model CTRF-117) and a single cool-tip electrode 17-gauge needle (model ACT-2030; Valleylab, Boulder, CO). The tip of the RF needle was exposed 3.0 cm for ablation. The ablation size was dependent upon tissue type, vascularization, impedance and temperature. Abdominal ultrasonography was used for follow-up after RFA. If needed, repeated RFA would be considered, based on the treatment result, tumor size and number, location and clinical judgment of the hepatologists.

After RFA, this patient received regular follow-up for 40 months, and no definite recurrence was found. However, TACE was performed in the 17th month for 3 low density lesions under the suspicion of recurrent HCC. Forty months after the first RFA, the abdominal CT revealed a recurrent lesion with the largest diameter of 2.0 cm in the liver tip of segment VI (Figure 1A). He underwent RFA again for the tumor, for a total of 3 times within 1 week. There was no particular abnormality in the



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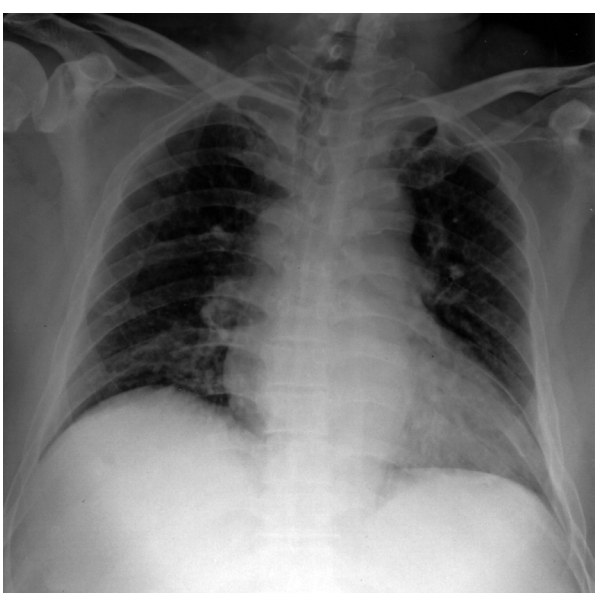


(B)

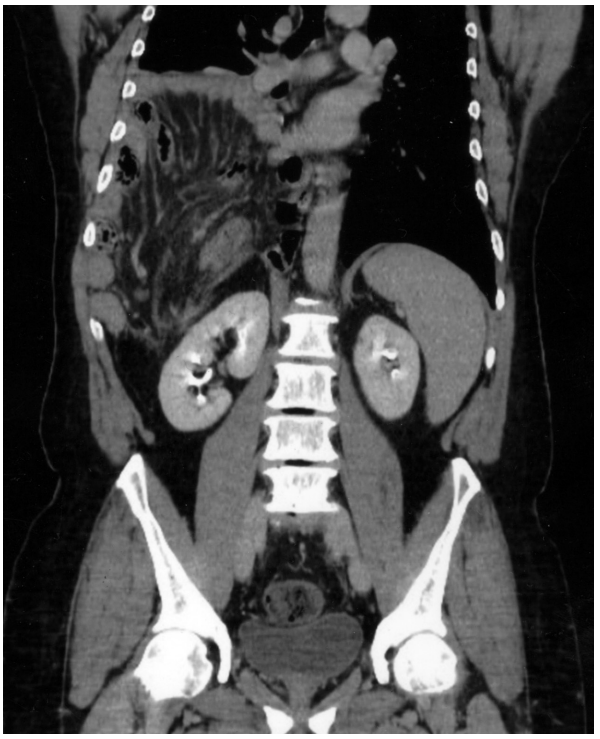
Fig. 1. (A) Abdominal CT reveals a recurrent hepatocellular carcinoma with the largest diameter of 2.0 cm in the liver tip of segment VI. (B) The initial chest roentgenography shows no particular abnormality.

follow-up chest roentgenography (Figure 1B).

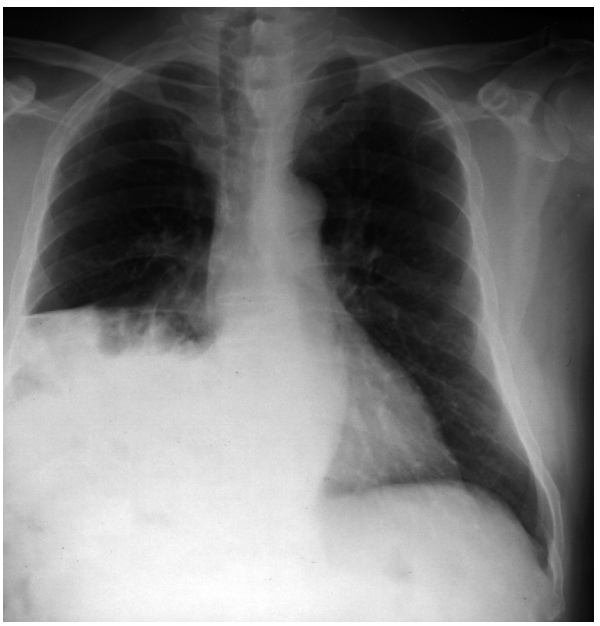
After this intervention, he received regular imaging follow-up, including ultrasonography and CT. There was no recurrence until 11 months later. Multiple enhancing lesions were noted and TACE was carried out. The most unusual finding was the right diaphragmatic hernia (Figures 2A & 2B) which was detected in the follow-up imaging studies 3 months after the TACE.

There was no other discomfort except for mild exertional dyspnea, nor was there a sign or symptom related to bowel incarceration. Four months after the findings of diaphragmatic hernia, he came to our chest medicine outpatient clinic due to progressively deteriorating dyspnea, and was further referred to the chest surgeon for surgical repair.

The diaphragmatic hernia was considered to be closely related to the RFA rather than the TACE, especially the RFA for the lesion in the liver tip of segment VI. TACE was performed via selecting a blood vessel supplying the tumor and then injecting embolic particles or particles containing a chemotoxic agent through the catheter. RFA was performed by advancing a particular kind of needle percutaneously into the tumor under ultrasonographic guidance. Since RFA has the characteristic of local thermal injury, there was the possibility of diaphragmatic injury. But the most extraordinary aspect of this was that the diaphragmatic hernia occurred 14 months after the previous RFA.



(A)



(B)

Fig. 2. (A) Abdominal CT shows right diaphragmatic hernia with intra-thoracic herniation of the small bowel and parts of the hepatic flexure colon associated with lung collapse and pleural effusion. (B) The chest roentgenography shows opacification in the right lower field with pleural effusion.

Discussion

HCC is the most common presentation of malignant liver disease. Most of the cases, approximately 80%, are related to chronic hepatitis B and hepatitis C [1]. For solitary or localized

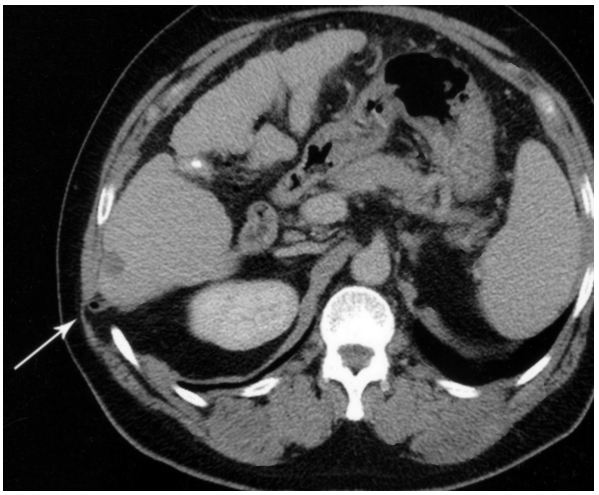


Fig. 3. CT shows a small diaphragmatic defect after the culprit RFA.

HCC, partial hepatic resection has been considered the "gold standard". However, when other factors are considered (such as the size of the tumors, number of lesions, poor liver function reserve, comorbidity and anatomic location), only about 1/5 of HCC cases are resectable [2].

RFA has been developed in the past 2 decades to treat unresectable HCC. The technique generates temperature ablation via the use of a high frequency alternating current electrode and is able to bring about tumor coagulative necrosis. Because of the better clinical outcome with RFA compared to other local ablative therapies, such as percutaneous ethanol injection and percutaneous microwave coagulation [3-7], RFA is now widely accepted as the first-line treatment for unresectable small-sized HCC and as a promising therapy for recurrent and unresectable HCC [8].

Despite the safety and the clinical effectiveness, the complications related to RFA cannot be overlooked. Whether major or minor, the overall complication rate was reported to be from 6.9% to 9.5% in different studies, depending on how complications were defined [9-11]. The most frequent major complications in descending order are tumor seeding, intraperitoneal hemorrhage and liver abscess. Even though relatively rare, thoracic complications, such as pleural effusion requiring treatment, pneumothorax, hemothorax and diaphragmatic injury, were also found [12-13]. Diaphragmatic thickening detected in CT is the most common finding related to diaphragmatic injury due to RFA [14]. This is a kind of thermal injury associated with RFA for the treatment of lesions near the dome of the liver. Most diaphragmatic injuries are self-limiting and need only conservative management [13,15]. The case we presented herein involved a diaphragmatic hernia after RFA, a very rare thoracic complication related to the intervention. The most extraordinary aspect of this case is that this adverse event occurred 14 months after RFA. In addition, the patient did not undergo surgical repair till 4 months later, on account of progressively deteriorating dyspnea.

We reviewed the medical literature written in English, and found only 5 cases of diaphragmatic hernia (including our patient) reported to be related to RFA for HCC [16-19]. Of the 5 illustrated cases, 4 were clearly identified as having HCC adjacent to the diaphragm. The mean value of time from RFA till hernia diagnosis in these 5 cases was 13.8 months (Table 1). We might easily disregard the association between diaphragmatic hernia and RFA because the occurrence of the hernia was obviously delayed in time.

An increasing number of ideas or techniques have been proposed to minimize the thoracic complications of RFA for HCC adjacent to the diaphragm [20-22], for example, subphrenic water injection or artificial ascites. There are at least 2 advantages to this maneuver. First, by

Table 1. Characteristics of diaphragmatic hernia following RFA found in the literature review

	Masahiko Koda *et al*.	Akitaka Shubuya *et al*.	Fabrizio Di Francesco *et al*.	Takuji Yamagami *et al*.	Our case
Patient age and gender	61, Female	72, Male	49, Male	71, Female	56, Male
Diagnosis	Hepatitis B-related cirrhosis, HCC	Alcoholic-related cirrhosis, HCC	Alcoholic and Hepatitis C-related cirrhosis, HCC	Hepatitis C-related cirrhosis, HCC	Alcoholic and Hepatitis B-related cirrhosis, HCC
Tumors size and location	2.1 cm in segment VIII 1.0 cm in segment VIII, adjacent to the diaphragm 1.5 cm in segment VI	1.5 cm on the border of segment IV and VIII, adjacent to the diaphragm	5.2 × 5.2 × 5.4 cm3 right liver dome lesion	2.4 cm in segment VII	2.0 cm in the tip of segment VI, adjacent to the diaphragm
Treatment	Percutaneous RFA	Percutaneous RFA	Percutaneous RFA	Percutaneous RFA	Percutaneous RFA
Number of treatment sessions	2	1	7	1	3
Time from culprit RFA till hernia diagnosed	13 months	18 months	15 months	9 months	14 months
Symptoms	Dyspnea	Dypnea and right upper abdominal pain	Encephalopathy, nausea, vomiting	Dyspnea	Dyspnea
Time from hernia till surgical repair	3 months	Immediately	Immediately for bowel incarceration	No surgical repair. Under observation	3 months

using an adequate amount of 5% dextrose water injection into the area beneath the diaphragm, we are able to separate the liver and diaphragm. Second, we can diminish the acoustic window formed by the air in the lung and enhance the visibility of HCC just beneath the diaphragm.

Since the survival time of patients with HCC may lengthen with improvements in therapeutic modalities, we believe that thoracic complications, as in our case, will gradually increase in frequency. Therefore, newly developed adjuvant maneuvers for RFA, such as subphrenic water or artificial ascites, may be a reasonable choice for specifically selected patients with HCC near the diaphragm.

Why the duration from RFA to the diagnosis of diaphragmatic hernia was so long is another interesting issue. We propose the most probable mechanism here. Most diaphragmatic injury related to RFA is self-limiting. However, if the thermal injury is so severe that it exceeds the self-healing ability of the wound, it will

lead to a small diaphragm defect. In cirrhotic patients with HCC, a peritoneopleural pressure gradient, increased intra-abdominal pressure (when coughing or with increased ascites) and focal tumor infiltration will all result in the progression of the diaphragm defect. Several months later, the small defect will become a larger "hole", leading to symptomatic diaphragmatic hernia. This may be why diaphragmatic hernias related to RFA are diagnosed so late in the clinical process.

After careful review of our patient's CT images, we found that the diaphragmatic defect (Figure 3) after the culprit RFA was quite small. The clinical presentations of this patient were compatible with our reasoning above.

Finally, we would like to recommend that routine chest roentgenography and CT scan are essential for patients receiving RFA for HCC adjacent to the diaphragm. Close observation could be considered for diaphragmatic hernias without signs of bowel strangulation or incarceration. However, surgical repair is still strongly suggested to prevent possibly worsened or lethal complications.

References

1. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012; 142: 1264-73 e1.
2. Lau WY, Lai EC. Hepatocellular carcinoma: current management and recent advances. Hepatobiliary Pancreat Dis Int 2008; 7: 237-57.
3. Shibata T, Iimuro Y, Yamamoto Y, *et al*. Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. Radiology 2002; 223: 331-7.
4. Lencioni RA, Allgaier HP, Cioni D, *et al*. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 2003; 228: 235-40.
5. Lin SM, Lin CJ, Lin CC, *et al*. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. Gut 2005; 54: 1151-6.
6. Lin SM, Lin CJ, Lin CC, *et al*. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or = 4 cm. Gastroenterology 2004; 127: 1714-23.
7. Shiina S, Teratani T, Obi S, *et al*. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology 2005; 129: 122-30.
8. Lau WY, Lai EC. The current role of radiofrequency ablation in the management of hepatocellular carcinoma: a systematic review. Ann Surg 2009; 249: 20-5.
9. Wood TF, Rose DM, Chung M, *et al*. Radiofrequency ablation of 231 unresectable hepatic tumors: indications, limitations, and complications. Ann Surg Oncol 2000; 7: 593-600.
10. Livraghi T, Solbiati L, Meloni MF, *et al*. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. Radiology 2003; 226: 441-51.
11. Curley SA, Marra P, Beaty K, *et al*. Early and late complications after radiofrequency ablation of malignant liver tumors in 608 patients. Ann Surg 2004; 239: 450-8.
12. Bertot LC, Sato M, Tateishi R, *et al*. Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. Eur Radiol 2011; 21: 2584-96.
13. Rhim H, Yoon KH, Lee JM, *et al*. Major complications after radio-frequency thermal ablation of hepatic tumors: spectrum of imaging findings. Radiographics 2003; 23: 123-34; discussion 34-6.
14. Head HW, Dodd GD, 3rd, Dalrymple NC, *et al*. Percutaneous radiofrequency ablation of hepatic tumors against the diaphragm: frequency of diaphragmatic injury. Radiology 2007; 243: 877-84.
15. Kang TW, Rhim H, Lee MW, *et al*. Radiofrequency ablation for hepatocellular carcinoma abutting the diaphragm: comparison of effects of thermal protection and therapeutic efficacy. AJR Am J Roentgenol 2011; 196: 907-13.
16. Koda M, Ueki M, Maeda N, *et al*. Diaphragmatic perfo-

ration and hernia after hepatic radiofrequency ablation. AJR Am J Roentgenol 2003; 180: 1561-2.
17. Shibuya A, Nakazawa T, Saigenji K, *et al*. Diaphragmatic hernia after radiofrequency ablation therapy for hepatocellular carcinoma. AJR Am J Roentgenol 2006; 186: S241-3.
18. di Francesco F, di Sandro S, Doria C, *et al*. Diaphragmatic hernia occurring 15 months after percutaneous radiofrequency ablation of a hepatocellular cancer. Am Surg 2008; 74: 129-32.
19. Yamagami T, Yoshimatsu R, Matsushima S, *et al*. Diaphragmatic hernia after radiofrequency ablation for hepatocellular carcinoma. Cardiovasc Intervent Radiol 2011; 34 Suppl 2: S175-7.
20. Kapoor BS, Hunter DW. Injection of subphrenic saline during radiofrequency ablation to minimize diaphragmatic injury. Cardiovasc Intervent Radiol 2003; 26: 302-4.
21. Rhim H, Lim HK. Radiofrequency ablation for hepatocellular carcinoma abutting the diaphragm: the value of artificial ascites. Abdom Imaging 2009; 34: 371-80.
22. Song I, Rhim H, Lim HK, *et al*. Percutaneous radiofrequency ablation of hepatocellular carcinoma abutting the diaphragm and gastrointestinal tracts with the use of artificial ascites: safety and technical efficacy in 143 patients. Eur Radiol 2009; 19: 2630-40.

以射頻燒灼術（RFA）治療惡性肝腫瘤後所引發的橫膈膜疝氣：病例報告以及文獻回顧

陳皇吉　鄭清源 *　紀炳銓　林慶雄

射頻燒灼術（RFA）目前被認為是針對無法切除的小型惡性肝腫瘤，或是再復發患者的第一線治療。因射頻燒灼術所引發的胸腔併發症，特別引起我們的注意。我們所報導的病例是一個少見的個案，他在接受惡性肝腫瘤的射頻燒灼術 14 個月後才出現橫膈膜疝氣。我們做了文獻回顧，發現用英文撰寫的 5 個病例中，導致問題的射頻燒灼術到出現橫膈膜疝氣的時間平均為 13.8 個月。我們發現肝腫瘤靠近橫膈膜是一個危險因子。之所以射頻燒灼術到橫膈膜疝氣出現的時間會這麼久，我們認為合理的解釋是：一剛開始只是熱燒灼的損傷，接著在腹腔與胸腔間的壓力差、腹內壓上升、或是局部腫瘤浸潤等多種因素影響下，小缺損逐漸進展到橫膈膜疝氣。因此如果要做射頻燒灼術，一些新發展出的輔助方法，比方說像在橫膈下注水或是造成一個人工的腹水，對於特定有橫膈附近惡性肝腫瘤的患者而言，可能是一個合理的選擇。*(胸腔醫學* ***2013; 28: 171-178)***

關鍵詞：橫膈膜疝氣，射頻燒灼術，惡性肝腫瘤

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Multiple Disseminated Sclerosing Hemangiomas of the Lungs

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Hsian-He Hsu*, Wann-Cherng Perng

Sclerosing hemangioma (SH) is a relatively rare, benign neoplasm of the lung. The characteristic features of SH include asymptomatic, peripheral, solitary, well-circumscribed nodules in women aged around 40 years. The pattern of multiple nodules is rare, with an incidence of 4-5% in pulmonary SH. We present the case of a 44-year-old asymptomatic woman who had undergone chest roentgenography that revealed numerous small nodular opacities with slight thickening along the interstitial lines in both the lungs during a regular examination; her chest computed tomography scan revealed innumerable diffuse nodules that mimicked disseminated malignant lesions in all lobes of both the lungs. In this case,s in which no primary lesion was detected, we performed wedge resection of the right upper lobe to establish a definitive diagnosis; histological analysis of the resected tissue confirmed SH. Follow-up data of 4 years suggested that SH in this case wasis indolent without treatment. A review of previously reported cases with multiple nodules suggested that fewerless than 3 nodules of around 1 cm to 3 cm were observed in a limited number of lobes. However, we report, for the first time, a case with innumerable diffuse nodules less than 1 cm in diameter, spreading in all lobes of both the lungs. Although the incidence of multiple SH is very low, itthese should be considered when evaluating any patient with multiple diffuse miliary-like nodules. HoweverFurther, these findings do not indicate an unfavorable outcome. ***(Thorac Med 2013; 28: 179-185)***

Key words: sclerosing hemangioma, disseminated nodules

Introduction

Sclerosing hemangioma (SH) is a relatively rare, benign neoplasm of the lung. The characteristic features of SH include asymptomatic, peripheral, solitary, well-circumscribed nodules in women with a mean age of 40 years at diagnosis. The pattern of multiple nodules is rarely observed, with an incidence of 4%-5%, and most nodules are present in small numbers in a limited number of lobes [1-2]. We present a case of SH with diffuse and innumerable nodules that mimicked disseminated malignancy in all lobes of both lungs. Follow-up data of 4

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years suggested that the SH in this case was indolent without therapy.

Case Report

A 44-year-old asymptomatic woman underwent chest roentgenography that showed numerous small nodular opacities with slight thickening along the interstitial lines in both lungs (Figure 1) during a regular examination in June 2007. She was then referred to our hospital for further examinations. A computed tomography (CT) scan of the chest showed innumerable diffuse small nodules of various sizes, less than 1 cm in diameter (up to 0.8 cm in maximum diameter in the right upper lobe), in all lobes of both lungs (Figure 2A, 2C). Each lesion was a round-shaped nodule with a distinct margin and homogeneous density. Lymphadenopathy was not observed. Her clinical status was unremarkable. She had never smoked and rarely consumed alcohol. Her family history was negative. Physical examination revealed no remarkable signs. Repeated examination of the sputum showed no acid-fast bacilli or malignant cells. Peripheral blood count and biochemical examination results were within normal limits. Cryptococcus antigen was not detected in the serum. The levels of serum tumor markers, including carcinoembryonic antigen (CEA), squamous cell carcinoma (SCC)-associated antigen, cancer antigen 19-9 (CA19-9), cancer antigen 15-3 (CA153), and alpha-fetoprotein (AFP), were all within normal range; the exception was cancer antigen 125 (CA-125; 64.75 units/mL; normal range, 0.00-35.00 units/mL). However, pelvic ultrasonography and contrast-enhanced abdominal CT scans both showed no remarkable finding. Radiological examination revealed multiple well-defined nodules; hence, the lesions were suspected to be metastatic lung tumors. However, gastroduodenoscopy and fiberoptic colonoscopy revealed no apparent tumors. To obtain a definitive diagnosis of metastatic lung tumors, we performed wedge resection of the right upper lobe. On microscopic examination, the resected sections showed 3 well-circumscribed pulmonary nodules (up to 0.6 cm in maximum diameter) with a mixed solid cellular area, papillary structures composed of surface epithelial cells and internal round tumor cells, small vascular proliferation, and blood-filled spaces, which were consistent with the features of SH (Figure 3). Based on the histological findings and the observation of multiple lesions in all lobes of both lungs, further examination of these lesions was not performed. After surgery, the residual lesions were carefully followed by serial radiographs at every outpatient department visit. CT scan of the chest in November 2011 revealed that the sizes of the pulmonary nodules had not changed during the 4 years,

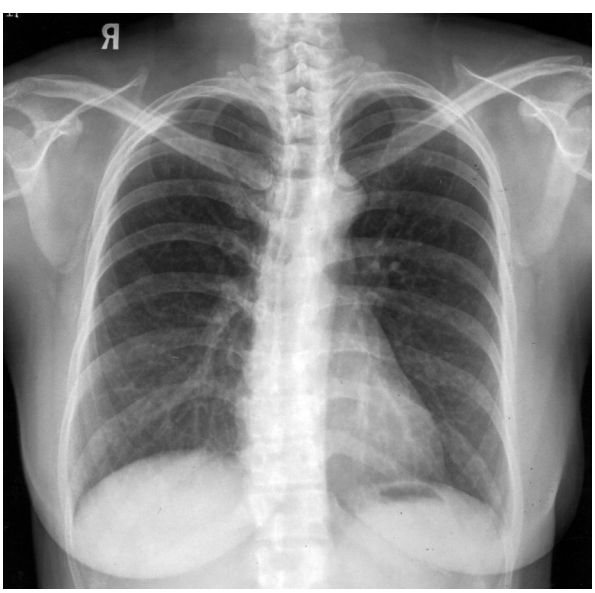

Fig. 1. Numerous small nodular opacities with mild interstitial line thickening in both lungs.

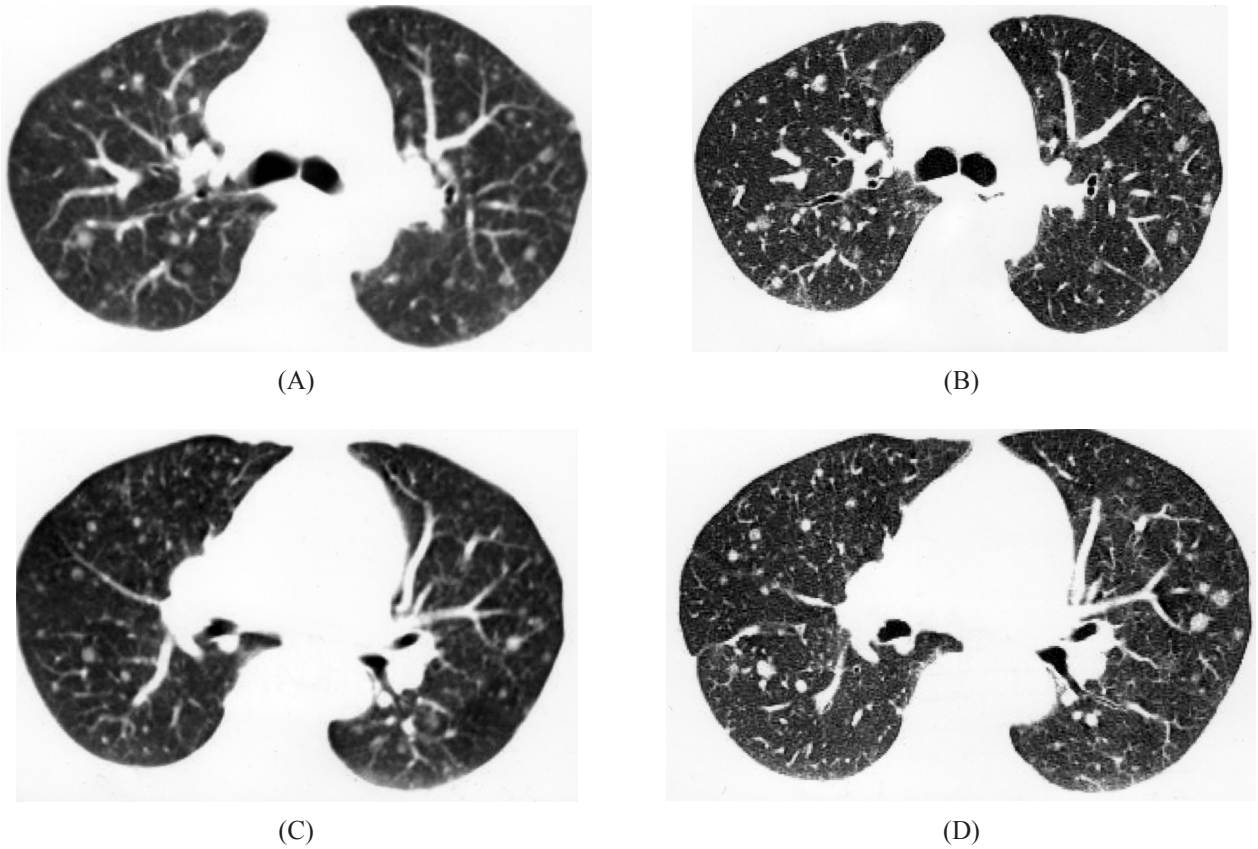

Fig. 2. (A) Multiple small pulmonary nodules in both upper and lower lobes; (B) the number of nodules was unchanged after 4 years. (C) Multiple small pulmonary nodules in the right middle lobe, left lingular lobe, and bilateral lower lobes; (D) the number of nodules was unchanged after 4 years. There was no change in the size of the pulmonary nodules over the course of 4 years, and no new lesion had developed.

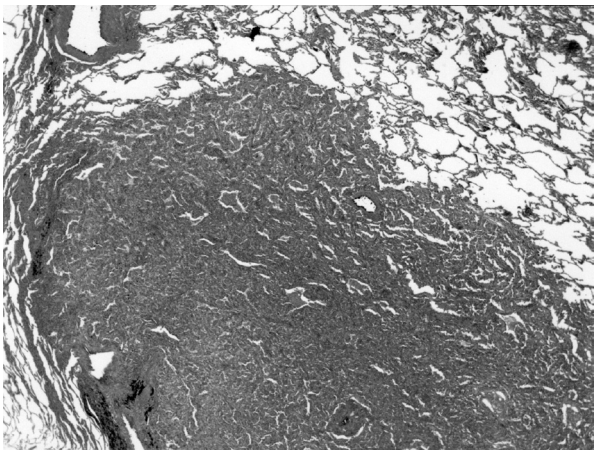

Fig. 3. Papillary structures composed of surface epithelial cells and internal round tumor cells, small vascular proliferation, and blood-filled spaces.

and no new lesion was noted (Figure 2B, 2D). Her postoperative course was uneventful and she showed good recovery without any sign of recurrence.

Discussion

Pulmonary SH, which was first described by Liebow and Hubbell in 1956 [3], is a relatively rare benign pulmonary tumor with an incidence of about 1% of all lung tumors [4]. A high incidence of pulmonary SH has been reported in Asia [5]. According to the new 1999 World Health Organization (WHO)/Interna-

tional Association for the Study of Lung Cancer (IASLC) criteria, pulmonary SH is now included in the category of miscellaneous tumors in the WHO classification of lung tumors. Immunohistochemical and ultrastructural studies of this tumor have suggested an epithelial (type II pneumocyte) origin [6]. In addition to pulmonary SH, other terms such as pneumocytoma, sclerosing pneumocytoma, and papillary pneumocytoma have been used to describe this condition [7].

Histological examination revealed that SH is composed of 4 main components, namely, papillary, sclerotic, solid, and hemorrhagic architectural patterns in different proportions. Almost 56% of tumors are composed of all 4 patterns. Further, 39% of tumors exhibit 3 patterns, with papillary, sclerotic, and solid being the most frequent. All tumors contain more than 2 histological patterns and no tumor exhibits a single pattern. The papillary pattern is observed in 95% of tumors [1]. In the papillary pattern, the tumors mainly exhibit proliferation of 2 types of epithelial cells: round or polygonal or stromal cells and cuboidal or surface cells. Cuboidal surface cells that line papillary structures or form tubules and polygonal round cells with pale cytoplasm constitute the interstitium of the lesion.

In 1989, Maezato *et al*. reviewed the clinical features of 255 Japanese patients with pulmonary SH and reported that the ratio of female-to-male patients was 6:1. SH occurred more frequently in middle-aged women with an average age of 47 years (range, 7-77 years) [2]. Most patients are asymptomatic, and the majority of tumors are identified incidentally during chest radiograph screening. In symptomatic patients, the common symptoms include hemoptysis (11% of all SH patients), chronic cough (8.5%), and chest pain (4.9%) [1]. Symptom presentation may result from impingement of a large tumor on adjacent structures of the bronchovascular bundles. Radiological examination revealed that SH typically presents as a peripheral (95%), solitary (96%), well-circumscribed homogeneous nodule (74%) with a diameter of less than 3 cm (range, 0.3 to 7 cm; mean, 2.6 cm). In addition to the classic features of SH, several unusual presentations have been observed, including multifocal lesions (4%), hilar lymph node metastasis (1%), and endobronchial (1%), pleural (4%), and mediastinal (1%) lesions [1]. The rate of tumor occurrence in the right (54%) and left (46%) lobe of the lung is almost equal, whereas the incidences in the upper and lower lobes are 25% and 47%, respectively [1]. Therefore, the tumors are predominantly located in the lower lobes. Calcification is variable but may be present in a small number of tumors; cyst formation is rare but is known to occur, and cavitation does not occur [8-10]. A chest CT scan shows a round to oval-shaped well-defined nodule or mass with marked contrast enhancement [11-12]. Although the lesion on chest CT suggests a benign pulmonary tumor, especially in the absence of adverse clinical events, a further invasive procedure is usually needed for definitive diagnosis.

SH presents predominantly as a solitary pulmonary nodule; multiple lesions are rare, with an incidence of about 4% [1-2,13-19]. A review of previously reported cases with multiple lesions suggests the lesions present in 3 kinds of patterns: a dominant tumor surrounded by multiple satellite lesions, multiple tumors in a single lobe, and solitary tumors in multiple lobes. The patterns are observed mostly when 3 or fewer nodules with sizes of around 1 to 3 cm are present in a limited number of lobes

[4,6,18,20-23]. With this case, we report, for the first time, a patient with diffuse miliary-like nodules of SH of less than 1 cm in diameter, spreading in all lobes of both lungs. However, in this case, we could not verify whether the lesions were multicentric in origin or the result of intrapulmonary metastasis. The small residual lesions did not change in size over a long period; hence, they were thought to be multicentric and indolent.

In a rare case with disseminated multiple nodules in both lungs, it is difficult to distinguish the nodules from metastatic lung tumors, even with an indolent clinical presentation. Further, confirmed results are usually needed for a definitive diagnosis. However, many aspiration cytology or intraoperative frozen section analyses are not conclusive for SH, because the results can vary depending on the tumor pattern in the sampled area [7]. The architectural variation and 2 epithelial cell types may not be readily appreciated for the diagnosis. The histological differential diagnoses might include bronchioloalveolar carcinoma, papillary thyroid carcinoma, papillary renal cell carcinoma, epithelioid hemangioendothelioma, carcinoid carcinoma, and inflammatory pseudotumor [1]. The presence of 2 distinct epithelial cell populations and the mixture of architectural patterns are helpful in differentiating SH from bronchioloalveolar carcinoma with a papillary architecture.

SH of the lung is generally thought to be a benign lesion and surgical excision yields a good clinical outcome without the need for additional therapy [7]. However, further diagnosis or treatment of these lesions was abandoned in our case, because residual multiple nodules were diffusely spread in all lobes of both lungs and they were very similar to resected nodules in the CT findings. Distant organ metastasis from SH has not been previously reported, and mortality has not been attributed to SH. We followed this patient with annual chest radiography for 4 years, and noted that the residual nodules remained unchanged. Chest CT scan after 4 years also showed no change in the residual lesions. The spreading of multiple SH lesions in all lobes of both lungs has rarely been reported, but the condition does not lead to an unfavorable outcome.

Conclusion

In conclusion, this is the first report on stable SH with innumerable diffuse nodules that mimicked disseminated malignancy in all lobes of both lungs observed for a long period. Even though the incidence of multiple SH is low, this condition should be considered when evaluating any patient with multiple diffuse miliary-like nodules.

References

1. Devouassoux-Shisheboran M, Hayashi T, Linnoila RI, *et al*. A clinicopathologic study of 100 cases of pulmonary sclerosing hemangioma with immunohistochemical studies. TTF-1 is expressed in both round and surface cells, suggesting an origin from primitive respiratory epithelium. Am J Surg Pathol 2000; 24: 906-16.
2. Maezato K, Hitomi S, Kuwabara M. A case of multiple sclerosing hemangioma of the lung and a review of the literature in Japan (Eng abstr). Nihon Kyoubu Shikkan Gakkai Zasshi 1989; 27: 230-3.
3. Liebow AA, Hubbell DS. Sclerosing hemangioma (histiocytoma, xanthoma) of the lung. Cancer 1956; 9: 53-75.
4. Hanaoka J, Ohuchi M, Inoue S, *et al*. Bilateral multiple pulmonary sclerosing hemangioma. Jpn J Thorac Cardiovasc Surg 2005; 53: 157-61.
5. Kalhor N, Staerkel GA, Moran CA. So-called sclerosing hemangioma of lung: current concept. Ann Diagn Pathol. 2010; 14: 60-7.

6. Maeda R, Isowa N, Miura H, *et al*. Bilateral multiple sclerosing hemangiomas of the lung. Gen Thorac Cardiovasc Surg 2009; 57: 667-70.
7. Keylock JB, Galvin JR, Franks TJ. Sclerosing hemangioma of the lung. Arch Pathol Lab Med. 2009; 133: 820-5.
8. Sugio K, Yokoyama H, Kaneko S, *et al*. Sclerosing hemangioma of lung: radiographic and pathological study. Ann Thorac Surg 1992; 53: 295-300.
9. Im JG, Kim WH, Han MC, *et al*. Sclerosing hemangiomas of the lung and interlobar fissures: CT findings. J Comput Assist Tomogr 1994; 18: 34-8.
10. Nam JE, Ryu YH, Cho SH, *et al*. Air-trapping surrounding sclerosing hemangioma of the lung. J Comput Assist Tomogr 2002; 26: 358-61.
11. Chung MJ, Lee KS, Han J, *et al*. Pulmonary sclerosing hemangioma presenting as solitary pulmonary nodule: dynamic CT findings and histopathologic comparisons. AJR Am J Roentgenol 2006; 187: 430-7.
12. Cheung YC, Ng SH, Chang JW, *et al*. Histopathological and CT features of pulmonary sclerosing haemangiomas. Clin Radiol 2003; 58: 630-5.
13. Colby TV, Koss MN, Travis WD. Tumors of the lower respiratory system. In Rosai J, Rosai JS, editors, Atlas of tumor pathology, 3rd series, Fascicle 13. Washington, DC: Armed Forces Institute of Pathology 1995; 465-71.
14. Spencer H, Nambu S. Sclerosing haemangiomas of the lung. Histopathology 1986; 10: 477-87.
15. Hayashi A, Takamori S, Mitsuoka M, *et al*. Unilateral progressive multiple sclerosing hemangioma in a young female successfully treated by pneumonectomy: report of a case. Int Surg 2002; 87: 69-72.
16. Joshi K, Shankar SK, Gopinath N, *et al*. Multiple sclerosing haemangiomas of the lung. Postgrad Med J 1980; 56: 50-3.
17. Noguchi M, Kodama T, Morinaga S, *et al*. Multiple sclerosing hemangiomas of the lung. Am J Surg Pathol 1986; 10: 429-35.
18. Lee ST, Lee YC, Hsu CY, *et al*. Bilateral multiple sclerosing hemangiomas of the lung. Chest 1992; 101: 572-3.
19. Chon S-H, Jeon YB, Jung TY, *et al*. Multiple sclerosing hemangiomas of the lung -a case report. Korean J Thorac Cardiovasc Surg 1999; 32: 408-12.
20. Kim GY, Kim J, Choi YS, *et al*. Sixteen cases of sclerosing hemangioma of the lung including unusual presentations. J Korean Med Sci 2004; 19: 352-8.
21. Soumil VJ, Navin B, Sangeeta D, *et al*. Multiple sclerosing hemangiomas of the lung. Asian Cardiovasc Thorac Ann 2004; 12: 357-9.
22. Komatsu T, Fukuse T, Wada H, *et al*. Pulmonary sclerosing hemangioma with pulmonary metastasis. Thorac Cardiov Surg 2006; 54: 348-55.
23. Hishida T, Yoshida J, Nishimura M, *et al*. Multiple sclerosing hemangiomas with a 10-year history. Jpn J Clin Oncol 2005; 35(1): 37-9.

瀰漫性多發肺硬化性血管瘤

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硬化性血管瘤（Sclerosing hemangioma）是肺部相對較少見的良性腫瘤，常見於 40 幾歲無症狀的中年女性，其典型呈現是位於肺部周邊單顆邊緣清楚的結節，而多發性結節表現的硬化性血管瘤是非常少見的，佔所有肺部硬化性血管瘤約 4-5% 的發生率。我們報告一位 44 歲無症狀的女性，於例行的胸部 X 光檢查發現兩側肺部有數顆小結節影合併輕微間質線條增厚；肺部電腦斷層於兩側所有的肺葉呈現多處瀰漫性類似惡性腫瘤散佈的結節，在未知原發病灶的情形下，為了得到更進一步的確切診斷，病患接受了右上肺楔狀切除手術，其病理上的結果診斷為硬化性血管瘤；在術後追蹤的 4 年間雖未接受任何治療，臨床與影像檢查並無新的變化。回顧以多發性結節表現的硬化性血管瘤文獻上，大部分的結節數小於 3 顆、直徑大小介於 1 到 3 公分之間、且侷限於局部的肺葉。而我們報告的個案是以無數小於直徑 1 公分的結節散佈於兩側所有的肺葉來表現，這種表現是至今沒有被報告過的。雖然多發性肺硬化性血管瘤不常見，但臨床影像上遇到多處瀰漫性似粟粒般結節表現時，仍須想到硬化性血管瘤的可能性，且此種發現並不代表預後較差。*(胸腔醫學 **2013; 28: 179-185**)*

關鍵詞：硬化性血管瘤，瀰漫性結節

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Disseminated Cryptococcosis in a HIV-Negative Patient Initially Presenting as Bilaterally Massive Pleural Effusion: A Case Report & Literature Review

Mei-Yin Chen, Chi-Wei Tao

Cryptococcus neoformans is a human fungal pathogen that causes life-threatening infection in immunocompromised hosts, and in some cases, immunocompetent hosts. Inoculation is usually via the inhalation of soil aerosols. Disseminated disease is the most common presentation among immunocompromised persons with malignancy, human immunodeficiency virus infection, corticosteroid use, or organ transplantation, but is rare in immunocompetent hosts. The most common plain radiographic findings are focal infiltrates and pulmonary nodules. Chest computed tomography similarly reveals one or more peripheral nodules with or without cavitation and/or areas of consolidation. We present the case of a 72-year-old, HIV-negative Taiwanese woman with mild type 2 diabetes mellitus under good dietary control who presented with cough and dyspnea. Initial chest plain film showed bilaterally massive pleural effusion. Disseminated cryptococcosis with pleural effusion, meningitis, pericardial effusion, infective endocarditis, peritonitis, and cryptococemia was diagnosed, and despite adequate antifungal treatment the patient developed multiple organ failure and eventually expired. ***(Thorac Med 2013; 28: 186-191)***

Key words: disseminated cryptococcosis, bilaterally massive pleural effusion

Introduction

Cryptococcus neoformans is a ubiquitous encapsulated yeast-like fungus that predominantly infects the lung or central nervous system. The portal of entry is the lung, sometimes followed by hematogenous spread to other organs. The clinical presentation of pulmonary cryptococcosis varies along a spectrum from asymptomatic infection to severe pneumonia and respiratory failure. Disseminated cryptococcal infection is rare in immunocompetent patients, and chest X- ray (CXR) rarely reveals pleural effusion alone [1].

We report herein a non-immunocompromised female patient with disseminated cryptococcosis and an initial CXR presenting bilaterally massive pleural effusion.

Case Report

A 73-year-old female presented to the emer-

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gency department with a 2-week history of dyspnea. She was initially treated for aspiration pneumonia with empiric antibiotics for sputum culture grown with carbapenem-resistant *Pseudomonas aeruginosa*.

The patient denied any history of malignancy or recent travel. She was human immunodeficiency virus-negative and without a history of organ or bone transplantation, immunodeficiency disorder, or immunosuppressive medications. She had taken no medication for chronic illness before the development of a recent left middle cerebral artery infarct with intracerebral hemorrhage, and underwent craniotomy, cranioplasty, and tracheostomy at another tertiary care hospital 2 months prior to this admission. She also had mild type 2 diabetes mellitus under good dietary control for 1 year. Her social history and family history were noncontributory.

CXR on admission showed infiltration in the left lower lobe (LLL) and right lower lobe (RLL) and bilateral minimal pleural effusion. The patient's general condition improved, and CXR revealed no active lung lesion after antibiotic treatment for aspiration pneumonia. On hospital day 9, she developed a hyperkalemic bradyarrhythmic attack, and a massive amount of coffee ground-like material was retrieved using suction via a nasogastric tube. Given her respiratory embarrassment and low blood pressure, she was transferred to the intensive care unit (ICU). The patient was in severe cardiorespiratory distress, and mechanical ventilation was started.

Upper gastrointestinal panendoscopy revealed hemorrhagic gastritis, gastric ulcer, and duodenal ulcers, and proton pump inhibitors were given. A packed red blood cell transfusion was also performed for severe anemia. The patient developed acute renal failure afterwards

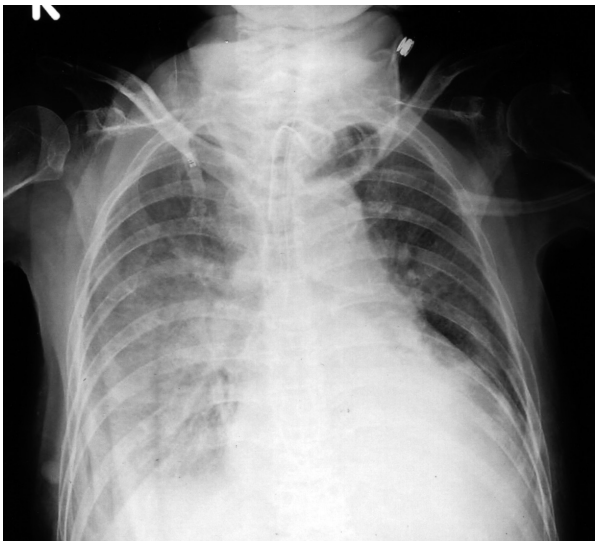

Fig. 1. Chest radiography revealed bilateral pleural effusion.

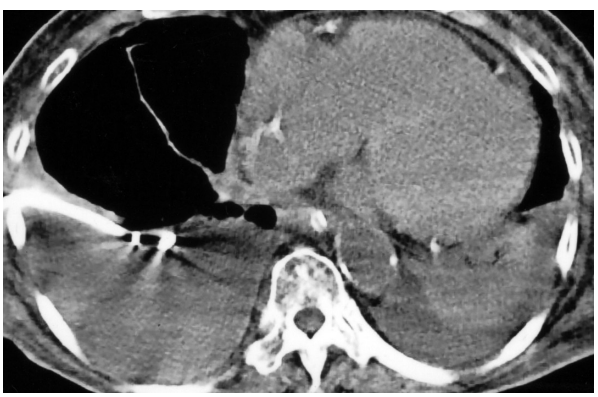

Fig. 2. Chest computed tomography revealed massive pleural effusion with subsegmental atelectasis of the LLL; a pigtail catheter was inserted.

and repeated CXR showed bilaterally massive pleural effusion (Figure 1). Sono-guided thoracentesis was performed on hospital day 14, and pleural fluid revealed evidence of exudate. Pleural effusion grew *Cryptococcus neoformans*, and India ink test revealed encapsulated yeast (Figure 2). Serum cryptococcal antigen was also positive (1: 8192X). Bronchoscopy revealed no evidence of endotracheal lesion. Though initially negative, blood culture also

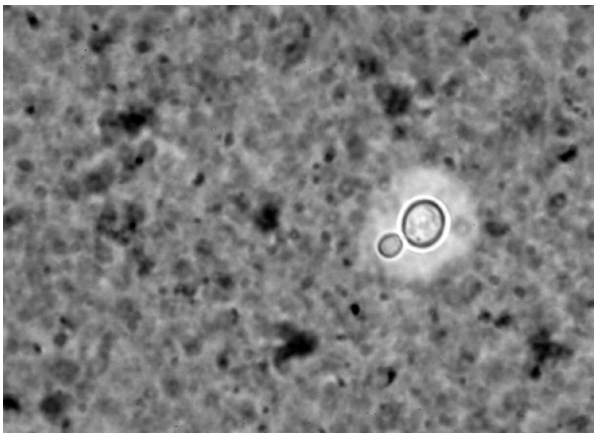

Fig. 3. India ink test of cerebrospinal fluid demonstrates encapsulated yeast.

grew *C. neoformans*. Chest CT scan revealed massive pleural effusion with subsegmental atelectasis of the RLL, and a pigtail was inserted (Figure 3). Lumbar puncture was performed on hospital day 16; cerebrospinal fluid culture grew *C. neoformans*. Amphotericin B was started as induction therapy on hospital day 16 for disseminated cryptococcal infection. Hemodialysis was begun on hospital day 29 due to the development of acute renal failure. Echocardiography showed multiple vegetative growths at the aortic and mitral valve and a small amount of pericardial effusion. Pericardiocentesis was performed, and pericardial fluid culture grew *C. neoformans* later. Abdominal sonography revealed a small amount of ascites, and ascitic fluid culture also grew *C. neoformans*.

Laboratory studies were obtained and revealed a white blood cell (WBC) count of 14.4 $\times$ 10^3 cells/uL, with 88% polymorphonucleated cells (PMNs), and a platelet count of 47 $\times$ 10^3/uL. An extended metabolic and liver panel demonstrated: sodium 149 mmol/L, potassium 3.4 mmol/L, BUN 147 mg/dL, creatinine 4.31 mg/dL, total bilirubin 0.6 mg/dL, AST 80 U/L, ALT 64 U/L, and alkaline phosphatase 200 U/L. HIV antibody and anti-nuclear antibody were found to be negative. The levels of tumor markers (CEA, AFP, CA125, CA19-9, CA153) were within normal limits.

The patient was diagnosed having disseminated cryptococcosis presenting with bilaterally massive pleural effusion, meningitis, pericardial effusion, peritonitis, infective endocarditis, and cryptococemia. She was given 4 weeks of IV amphotericin B (1 mg/kg/day) for induction therapy. Oral fluconazole (6 mg/kg/day) was added as consolidation therapy during the 5th week of medical treatment, and was continued as a single-agent maintenance therapy after 4 weeks of consolidation therapy. The patient was transferred to the respiratory care ward on hospital day 97 due to difficulty weaning, and expired soon thereafter.

Discussion

C. neoformans causes infection following inhalation through the respiratory tract, and disseminates hematogenously. Two *C. neoformans* serotypes are currently recognized: the most common causative agent of cryptococcosis, serotype A (*C. neoformans var. grubii*), and the relatively less virulent serotype D (*C. neoformans var. neoformans*) [2]. Serotype D is ubiquitous, but serotype A occurs mainly in tropical and subtropical climates, probably because of its strong association with certain species of Eucalyptus tree [3-4]. The most commonly infected sites are the central nervous system and lung; pulmonary cryptococcosis is rare in the immunocompetent patient [5]. In a study by Aberg *et al*. [6], only 18 (35%) out of 52 patients with pulmonary cryptococcosis were immunocompetent. Radiographic features of pulmonary cryptococcosis in immunocompe-

tent patients vary. The most common findings are solitary or a few well-defined, non-calcified nodules that are often pleural-based [7] and focal infiltrates. Other features include masses, segmental or lobar consolidation, or reticulonodular opacities [8]. The last is more common in immunocompromised patients. Cavitation may occur within nodules or areas of infiltrate and has been noted in 14-21% of plain chest radiographs and 10-42% of computed tomography scans of immunocompetent patients with cryptococcal infection; a much higher rate has been observed (62.5% vs. 15.4%) [9]. A solitary cryptococcal nodule or mass may simulate lung cancer [1], and pleural effusion is rare.

Disseminated cryptococcosis is defined by 1) a positive culture from at least 2 different sites, or 2) a positive blood culture [10]. The clinical presentation of disseminated cryptococcosis varies and depends on the organ involved. A diffuse maculo-papular rash may be an important diagnostic clue indicating disseminated disease [11], and CNS involvement is the most common manifestation of disseminated cryptococcosis. The diagnostic "gold standard" for *C. neoformans* infection is growth of an organism in culture from an otherwise sterile site [12].

Patients with severe pulmonary disease (eg, diffuse pulmonary infiltrates) or disseminated disease (eg, at least 2 noncontiguous sites or cryptococcal antigen titer ≥ 1:512) should be managed as for CNS disease. The treatment consists of antifungal therapy that includes induction, consolidation, and maintenance phases [13], and reducing immunosuppressive therapy if possible. Induction therapy consists of 2-4 weeks of amphotericin B (0.7-1.0 mg/kg/day IV) plus flucytosine (100 mg/kg/day orally in 4 divided doses). In patients with renal insufficiency, liposomal amphotericin B (5 mg/kg/day) may be substituted for amphotericin B. Consolidation therapy with fluconazole (6-8 mg/kg/day, oral) for 8 weeks followed by maintenance therapy with fluconazole (200-400 mg/day, oral) for 6 to 12 months should be given to the infected patients [13]. Reduction of immunosuppressive therapy may be beneficial for control of cryptococcal infection, but must be balanced with the potential for organ rejection and immune reconstitution.

Disseminated cryptococcosis is associated with a high mortality rate, exceeding 60%, especially in those patients with development of meningitis and acute respiratory failure [10,14-15]. In our case, the patient also presented with infective endocarditis; medical treatment is usually unsuccessful in patients with *Pseudomonas aeruginosa*, Brucella species, *Coxiella burnetii*, Candida species, and other fungal infections [16]. Uncontrolled sepsis due to any pathogen, is usually an indication for surgery. Our patient finally expired due to poor response to the medical treatment.

Conclusion

Cryptococcus is the 4th most common opportunistic infection in AIDS patients [14], and disseminated cryptococcosis is rare in immunocompetent patients. Diagnosis relies mostly on histology, fungal culture, serum cryptococcal antigen, and radiography. Prognosis depends on immunological status and underlying comorbidities.

References

1. McAdams HP, Rosado-de-Christenson ML, Templeton PA, *et al*. Thoracic mycosis from opportunistic fungi: radiologic-pathologic correlation. RadioGraphics 1995;

15: 271-86.
2. Lin X, Heitman J. The biology of Cryptococcus neoformans species complex. Annu Rev Microbiol 2006; 60: 69-105.
3. Kwon-Chung KJ, Bennett JE. Epidemiologic differences between the two varieties of Cryptococcus neoformans. Am J Epidemiol 1984; 120: 123-30.
4. Ellis DH, Pfeiffer TJ. Natural habitat of Cryptococcus neoformans var. gattii. J Clin Microbiol 1990; 28: 1642-44.
5. Kiertiburanakul S, Wirojtanaugon S, Pracharktam, *et al*. Cryptococcosis in human immunodeficiency virus-negative patients. Int J Infect Dis 2006, 10(1): 72-78.
6. Aberg JA, Mundy LM, Powderly WG. Pulmonary cryptococcosis in patients without HIV infection. Chest 1999; 115: 734-40.
7. Yang C J, Hwang JJ, Wang TH, *et al*. Clinical and radiographic presentation of pulmonary cryptococcosis in immunocompetent patients. Scan J Infect Dis 2006; 38: 788.
8. Nadrous HF, Antonios VS, Terrell CL, *et al*. Pulmonary cryptococcosis in nonimmunocompromised patients. Chest 2003; 124: 2143-7.
9. Chang WC, Tzao C, Hsu HH, *et al*. Pulmonary cryptococcosis: comparison of clinical and radiographic characteristics in immunocompetent and immunocompromised patients. Chest 2006; 129; 333-40.
10. Chuang YM, Ho YC, Chang HT, *et al*. Disseminated cryptococcosis in HIV-uninfected patients. Eur J Clin Microbiol Infect Dis 2008, 27(4): 307-10.
11. Licci S, Narciso P. Disseminated cryptococcosis in an HIV-negative patient. Int J infect Dis 2009; 13(3): e139-40.
12. Satishchandra P, Mathew T, Gadre G, *et al*. Cryptococcal meningitis: Clinical, diagnostic and therapeutic overviews. Clin Infect Dis 2000; 30(4): 710-8.
13. Perfect JR, Dismukes WE, Dromer F, *et al*. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious disease society of America. Clin Infect Dis 2010; 50: 291.
14. Sasisopin Kiertiburanakul, Somnuek Sungkanuparph, Benjamas Buabut. Cryptococcuria as a manifestation of disseminated cryptococcosis and isolated urinary tract infection. Jpn J Infect Dis 57; 203-05, 2004.
15. Vilchez RA, Linden P, Lacomis J. Acute respiratory failure associated with pulmonary cryptococcosis in non-AIDS patients. Chest 2001; 119: 1865-9.
16. Mylonakis E, Calderwood SB. Infective endocarditis in adults. N Engl J Med 2001; 345(18): 1318-30.

一位非愛滋病毒感染之病患得到瀰漫性新型隱球菌感染初期以雙側大量肋膜積液表現之病例報告及文獻回顧

陳美音　陶啟偉

新型隱球菌是一種感染人類的黴菌致病菌。通常會對免疫功能不全之病人，有時也對免疫功能正常之病人產生造成生命威脅之感染。感染途徑通常經由吸入土壤氣霧。瀰漫性感染通常發生於免疫力不全之病人，尤其是有惡性腫瘤，愛滋病毒感染，使用類固醇，或器官移植後之病人，但極少見於免疫力正常之病人。常見之胸部 X 光表現為局部浸潤或肺結節。電腦斷層亦呈現一或多個開洞或未開洞之周邊結節或實質病變。

我們在此呈現之病例為一 72 歲台灣女性，無愛滋病，有輕微糖尿病但經由飲食控制良好，主訴咳嗽及呼吸困難。胸部 X 光呈現雙側肋膜積水。後來診斷為瀰漫性新型隱球菌感染，包括肋膜積水，腦膜炎，心包膜積水，感染性心內膜炎，腹膜炎，及新型隱球菌造成的菌血症。即使給予適當治療，病人仍然產生多重器官衰竭，最後死亡。*(胸腔醫學 **2013; 28: 186-191**)*

關鍵詞：瀰漫性新型隱球菌感染，雙側大量肋膜積液

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Successful Weaning from Prolonged Mechanical Ventilation after Inspiratory Muscle Training of a Patient with Duchenne Muscular Dystrophy

Chao-Hsien Chen, Chang-Yi Lin, Ming-Jen Peng, Chien-Liang Wu

Duchenne muscular dystrophy (DMD) is a hereditary, X-linked recessive disease characterized by progressive muscle weakness. Impairment of respiratory muscle function with respiratory failure is the most common cause of death in patients with DMD. These patients have a life expectancy of approximately 20 years if left untreated. Once mechanical ventilation is initiated, respiratory muscle impairment, as a result of disuse atrophy and contractile dysfunction, will increase the difficulty of weaning these patients. Inspiratory muscle training (IMT) is a pulmonary rehabilitation measure thought to primarily improve inspiratory muscle function. Although the use of IMT remains controversial in patients with DMD, there appear to be benefits in the early stage of the disease. The effect of IMT on weaning patients from prolonged mechanical ventilation has been demonstrated. Herein, we report the case of a 20-year-old patient with DMD, admitted with pneumonia complicated with respiratory failure and prolonged mechanical ventilation, who was successfully weaned from ventilatory support after IMT. ***(Thorac Med 2013; 28: 192-199)***

Key words: Duchenne muscular dystrophy, inspiratory muscle training, prolonged mechanical ventilation, pulmonary rehabilitation, respiratory failure, weaning

Introduction

Duchenne muscular dystrophy (DMD) is a common and severe form of muscular dystrophy that occurs almost exclusively in males [1]. Due to mutations of the dystrophin gene and a defective dystrophin protein, patients with DMD develop progressive muscle degeneration that involves the respiratory muscles in advanced stages of the disease. Although pharmacological and multi-disciplinary management of DMD has improved function, maximized quality of life, and delayed disease progression, DMD remains an incurable disease. With the gradual decline in forced vital capacity (FVC) [2], pulmonary recruitment and nocturnal ventilation are initially indicated, and continuous non-invasive/invasive ventilation is indicated in the later stages of the disease [3]. Once mechanical ventilation (MV) is initiated, weaning

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can be challenging.

Patients receiving prolonged MV (PMV) account for 14% of all patients who require MV; these patients have a higher hospital mortality rate compared with other patients [4]. For patients on PMV in Taiwan, successful weaning is commonly defined as the withdrawal of MV for 5 or more days [5]. The successful weaning of patients continues to be a challenging task for critical care teams; effective strategies are still being investigated. One potential method to facilitate pulmonary rehabilitation and successful weaning is inspiratory muscle training (IMT). IMT uses increasing resistance to provide pressure and/or flow loading during inspiration to improve inspiratory muscle function. Methods of IMT include providing nonlinear resistance using an external resistor with a small opening or achieving specified inspiratory pressure levels before each breath using a threshold device. Both methods offer pressure and flow loading, and have been shown to increase maximal inspiratory pressure and flow [6-7]. Another method is decreasing the trigger sensitivity of the ventilator to increase the inspiratory effort [8]. There is a growing body of evidence supporting the benefits of IMT in the successful weaning of patients on PMV [8,12-18]. Herein, we report the case of a patient with DMD who was successfully weaned from PMV after pulmonary rehabilitation with IMT.

Case Report

A 20-year-old man presented with a 1-week history of fever and cough with yellow sticky phlegm. He was brought to our emergency room because of progressive dyspnea.

The patient had a waddling gait at the age of 5 and was unable to run or jump normally. He frequently fell and had difficulty getting up after falling. His limbs weakened progressively, to the point at which he had difficulty feeding himself. After he had been hospitalized several times because of recurrent pneumonia, DMD was diagnosed. His mother and an older sister were confirmed as carriers by genetic testing. Before this episode, he was able to sit on a wheelchair and breathe normally without supplemental oxygen, but required assistance in his activities of daily living.

Upon arrival at the emergency room, his temperature was 38.2°C, pulse, 153 beats/minute, and respiration, 28 breaths/minute. Blood pressure was 105/77 mmHg. The patient was 146 cm in height and 29.5 kg in weight. On auscultation, crackles were detected at the left lower lung field. Decreased muscle power (2~3+/5) with muscle atrophy of all 4 extremities was noted. Arterial blood gas testing indicated respiratory acidosis with partial metabolic compensation (pH: 7.186; pCO_2: 88.2 mmHg; HCO_3: 32.6 mmol/L) and hypoxemia (pO_2: 62 mmHg). Leukocytosis (white blood cells: 30,400 cells/μL; neutrophils: 85%) and elevated C-reactive protein concentrations (14.7 mg/dL) were found. Biochemistry test results were within normal limits, except for creatine kinase (540 IU/L). Chest radiography revealed a pneumonic patch at the lower left lung (Figure 1). Due to pneumonia complicated with respiratory failure, the patient was intubated and MV support was initiated.

After treatment with intravenous antibiotics, the patient's fever subsided and his general condition improved. Chest radiographs on Day 14 showed resolution of the lower left lung pneumonia (Figure 2). A spontaneous breathing trial with a T-piece was attempted on Day 8, but failed because of tachycardia. Several wean-

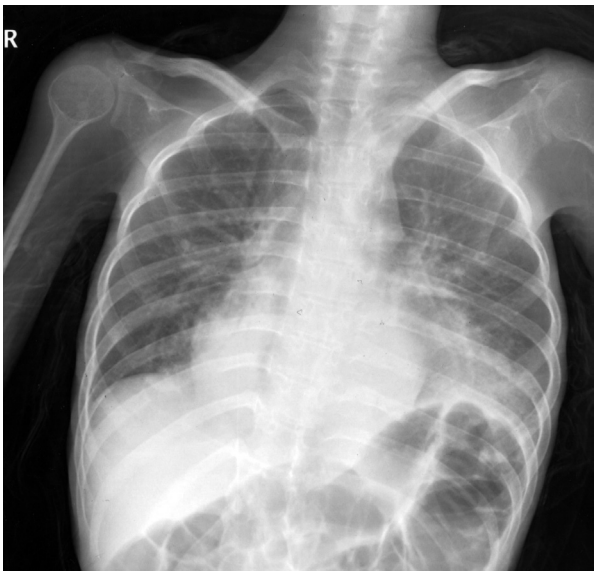

Fig. 1. Chest radiography on Day 1 showed thoracic scoliosis and infiltrates in the lower left lung. A significant amount of air was present in the intestines.

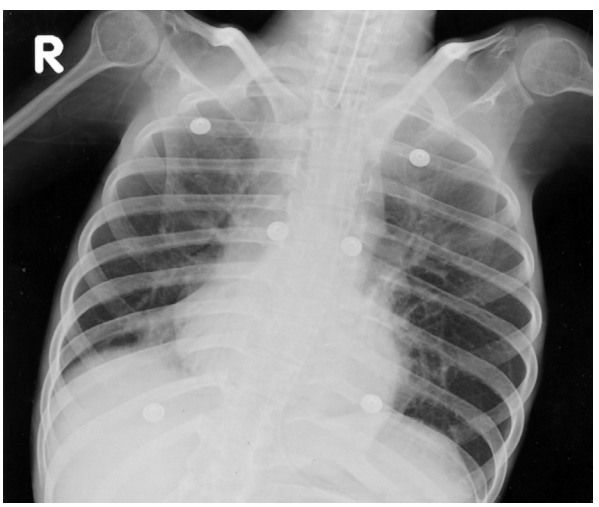

Fig. 2. Chest radiography on Day 14 showed complete resolution of infiltrates in the lower left lung.

ing attempts with gradually decreased pressure support also failed because of the development of dyspnea, tachycardia (heart rate > 140 beats/minute), and respiratory acidosis. The weaning program was changed to an adaptive support ventilation (ASV) mode on Day 18. A daily T-piece was attempted from Day 34, but the patient could tolerate the T-piece for less than 4 hours only.

IMT (30 minutes twice daily) was started on Day 42 using a resistor (Inspiratory Muscle Trainer, DHD Healthcare, Wampsville, NY) attached to the inspiratory arm of a T-piece with a 10% fraction of oxygenation (FiO_2) higher than with the ventilator support. The resistor offered non-linear inspiratory pressure and flow loading. The diameter, starting at 7 mm, was reduced by 1 mm every 2 days to increase loading. After a 30-minute training session, the patient was reconnected to the ventilator and rested in the ASV mode. After 7 days of IMT, the patient's maximal inspiratory pressure (Pi-Max) had decreased from -20 to -28 mmH_2O, tidal volume (V_T) increased from 285 to 320 mL, and the rapid-shallow-breathing index (RSI, f/V_T) improved from 65 to 55 breaths/min/L (Figure 3). The patient was successfully weaned from the ventilator on Day 50 and transferred to the normal ward under spontaneous breathing with a T-piece and tracheostomy. He was discharged on Day 62 after admission.

Discussion

Inspiratory muscle weakness and/or fatigue are significant factors contributing to weaning difficulty [9]. For the patient described in this report, respiratory failure may have been caused by 2 pathological mechanisms. First, weakness of both the inspiratory and expiratory muscles and scoliosis are known to contribute to the restrictive pulmonary defect in patients with DMD [10]. This pulmonary defect is characterized by decreased total lung capacity, vital capacity (VC), maximal inspiratory pressure (MIP), and peak expiratory pressure, and

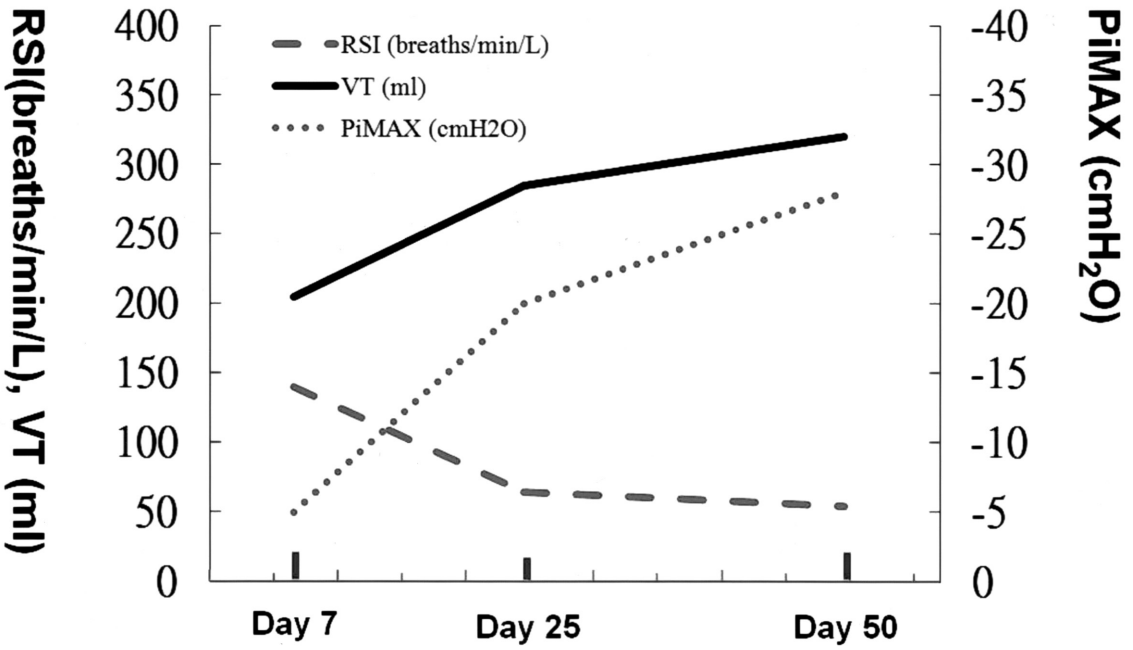

Fig. 3. Representative measurements of pulmonary parameters on Day 7 (before weaning), Day 25 (after the adaptive support ventilation mode), and Day 50 (after inspiratory muscle training). Parameters included maximal inspiratory pressure (PiMax), tidal volume (V_T), and rapid-shallow breathing index (RSI, f/V_T).

increasing residual volume with disease progression. By the age of 20, half of all patients with DMD have less than 20% of the predicted FVC [2]. Hypoventilation initially appears during sleep and leads to respiratory failure and the need for long-term ventilatory support in the later course of DMD. A decreased ability to expectorate is a causative factor in recurrent pneumonia. Second, PMV leads to atrophy and contractile dysfunction of the diaphragm, and consequent inspiratory muscle weakness. Diaphragmatic atrophy can occur as soon as 18 to 96 hours after diaphragmatic inactivity under MV [11]. Therefore, IMT is a logical treatment strategy, for which there is increasing evidence of a benefit in selected ventilator-dependent patients [8,12-18].

Although the use of IMT in the treatment of patients with DMD is still controversial, it seems to offer benefits in the early stage of the disease. In a randomized controlled trial involving 30 patients with DMD, Wanke *et al*. [19] found that 10 of 15 patients had improved MIP and endurance after 1 month of IMT. These positive effects remained 6 months after the training course. Patients with advanced DMD (5/15), who had VC values < 25% predicted and/or $PaCO_2$ values > 45 mmHg, did not exhibit improvements in inspiratory muscle strength. Wanke *et al*. concluded that IMT is useful in patients with DMD, except those with advanced disease. Other reports have described increases in MIP or endurance, but not in VC, and there was no change in respiratory muscle performance in 1 report [6].

The benefit of IMT for the weaning of patients from PMV has been demonstrated in several studies (Table 1). In 1 trial [13], no im-

Table 1. The effects of IMT on pulmonary function and ventilator weaning in patients on prolonged mechanical ventilation

Authors	Type of study	Patient number (n)	Patient group	Method of IMT	PiMax	VC	Endurance	Successfully Weaned
Aldrich [12] (1985)	CS	n=4	CHF/COPD	Resistor	↑	--	↑	3/4
Aldrich [13] (1989)	CS	n=27	7 PNMD & 20 PLD	Resistor	↑	↑	↑	12/27
Martin [14] (2002)	CS	n=10	2 NMD	Threshold	--	--	--	9/10
Sprague [15] (2003)	CS	n=6	Post-operation	Threshold	↑	--	--	6/6
Bissett [16] (2007)	CS	n=1	Post-operation	Threshold	--	--	--	1/1
Caruso [8] (2005)	RCT	n=12/13*	Surgical patients	Insensitive trigger of ventilator	NS	--	--	NS
Cader [17] (2010)	RCT	n=21/20*	Age > 70	Threshold	↑	--	--	14/21 vs. 14/20 ↓weaning time
Martin [18] (2011)	RCT	n=35/34*	Medical and Surgical patients	Threshold	↑	--	--	25/35 vs. 16/34

IMT: inspiratory muscle training; CS: case series; PiMax: maximal inspiratory pressure; VC: vital capacity; RCT: randomized controlled trial; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; PNMD: primary neuromuscular disease; PLD: primary lung disease; NS: non-significant.

* IMT/control.

provement was found after ventilator manipulation with a relatively low intensity of resistance (10-40% of MIP vs. resistance gradually increased to the highest tolerable level in other studies). Among these studies, there were only 9 patients [13-14] with neuromuscular disease; 6 of whom were successfully weaned after IMT. IMT was well tolerated in these patients and no major adverse side effects were reported.

Effective IMT must include periods of fatiguing exercise alternating with sufficient rest periods. Inhalation through an external resistance device can facilitate moderate to severe pressure and flow load [6]. Our IMT protocol involved a gradually increasing inspiratory load, alternating with rest under ventilator support, in 30-minute training sessions twice daily. Previous research has shown that the ventilated patients who benefit the most from IMT are those that are alert and cooperative, medically stable, and able to tolerate a T-Piece for more than 30 minutes [7]. Our patient met all of these criteria when starting IMT.

Our report showed the apparent benefit of IMT in weaning a patient with DMD from PMV. To our knowledge, there has been only 1 other report similar to our own: Aldrich and Uhrlass [20] reported the case of a patient with DMD who had increased VC/V_T and MIP after IMT, and was successfully weaned from MV.

Although Wanke *et al*. [19] have suggested that IMT is ineffective in advanced cases of DMD, our experience leads us to believe that IMT may be beneficial in selected DMD patients on MV. The respiratory failure of our patient was initially caused by pneumonia rather than disease progression. Previous studies [6] have shown no increases in VC in patients with DMD after IMT. However, our patient did exhibit an increase in VC after IMT, suggesting that the etiology of inspiratory muscle weakness may have been a combination of DMD and prolonged ventilator-induced weakness. In addition to the proliferation of muscle fibers as a result of IMT, other mechanisms have been proposed to explain the associated benefits, including alterations in neural pathways, muscle perfusion, and decreased lactate concentrations or sympathetic tone in response to lactate [7]. These changes may have underlain the successful ventilator weaning of our patient after IMT.

In conclusion, our report demonstrates the benefit of IMT in facilitating the successful weaning of a patient with DMD from PMV who did not respond to traditional weaning strategies such as increasing periods of daily T-Piece trials and/or gradual reductions in pressure support. IMT may be an alternative form of pulmonary rehabilitation in these severely disabled patients for whom other forms of pulmonary rehabilitation have failed. Further, IMT might shorten the weaning duration and improve weaning rates after the resolution of predisposing factors. Additional studies are needed to confirm the efficacy of IMT for weaning patients with DMD from PMV. These studies should seek to find the appropriate starting time for IMT, the appropriate intensity of IMT, and the characteristics of patients who are most likely to benefit from this intervention.

References

1. Bushby K, Finkel R, Birnkrant DJ, *et al*. Diagnosis and management of Duchenne muscular dystrophy, part 1: Diagnosis, and pharmacological and psychosocial management. Lancet Neurol 2010; 9: 77-93.
2. Kohler M, Clarenbach CF, Bahler C, *et al*. Disability and survival in Duchenne muscular dystrophy. J Neurol Neurosurg Psychiatry 2009; 80: 320-5.
3. Bushby K, Finkel R, Birnkrant DJ, *et al*. Diagnosis and management of Duchenne muscular dystrophy, part 2: Implementation of multidisciplinary care. Lancet Neurol 2010; 9: 177-89.
4. Funk GC, Anders S, Breyer MK, *et al*. Incidence and outcome of weaning from mechanical ventilation according to new categories. Eur Respir J 2010; 35: 88-94.
5. 中央健康保險局:「全民健康保險呼吸器依賴患者整合性照護前瞻性支付方式」試辦計畫支付標準。呼吸器試辦計畫書 2011.1.27 更新。
6. McCool FD, Tzelepis GE. Inspiratory muscle training in the patient with neuromuscular disease. Phys Ther 1995; 75: 1006-14.
7. Bissett B, Leditschke I, Paratz J, *et al*. Respiratory dysfunction in ventilated patients: Can inspiratory muscle training help? Anaesth Intensive Care 2012; 40: 236-46.
8. Caruso P, Denari SD, Ruiz SA, *et al*. Inspiratory muscle training is ineffective in mechanically ventilated critically ill patients. Clinics (Sao Paulo) 2005; 60: 479-84.
9. Powers SK, Kavazis AN, Levine S. Prolonged mechanical ventilation alters diaphragmatic structure and function. Crit Care Med 2009; 37: S347-53.
10. Gozal D. Pulmonary manifestations of neuromuscular disease with special reference to Duchenne muscular dystrophy and spinal muscular atrophy. Pediatr Pulmonol 2000; 29: 141-50.
11. Levine S, Nguyen T, Taylor N, *et al*. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 2008; 358: 1327-35.
12. Aldrich TK, Karpel JP. Inspiratory muscle resistive training in respiratory failure. Am Rev Respir Dis 1985; 131: 461-2.
13. Aldrich TK, Karpel JP, Uhrlass RM, *et al*. Weaning from mechanical ventilation: Adjunctive use of inspiratory muscle resistive training. Crit Care Med 1989; 17: 143-7.
14. Martin AD, Davenport PD, Franceschi AC, *et al*. Use of

inspiratory muscle strength training to facilitate ventilator weaning: A series of 10 consecutive patients. Chest 2002; 122: 192-6.

15. Sprague SS, Hopkins PD. Use of inspiratory strength training to wean six patients who were ventilator-dependent. Phys Ther 2003; 83: 171-81.
16. Bissett B, Leditschke IA. Inspiratory muscle training to enhance weaning from mechanical ventilation. Anaesth Intensive Care 2007; 35: 776-9.
17. Cader SA, Vale RG, Castro JC, *et al*. Inspiratory muscle training improves maximal inspiratory pressure and may assist weaning in older intubated patients: A randomised trial. J Physiother 2010; 56: 171-7.
18. Martin AD, Smith BK, Davenport PD, *et al*. Inspiratory muscle strength training improves weaning outcome in failure to wean patients: A randomized trial. Crit Care 2011; 15: R84.
19. Wanke T, Toifl K, Merkle M, *et al*. Inspiratory muscle training in patients with Duchenne muscular dystrophy. Chest 1994; 105: 475-82.
20. Aldrich TK, Uhrlass RM. Weaning from mechanical ventilation: Successful use of modified inspiratory resistive training in muscular dystrophy. Crit Care Med 1987; 15: 247-9.

利用吸氣肌肉訓練使一位長期使用呼吸器之裘馨氏肌肉失養症病人成功脫離呼吸器

陳昭賢　林長怡　彭明仁　吳健樑

裘馨氏肌肉失養症是以漸進性肌肉無力為特徵的隱性性染色體遺傳疾病。呼吸肌無力併呼吸衰竭是裘馨氏肌肉失養症病人主要的死因，若沒有適當的治療平均只能活到二十多歲。但是一旦使用呼吸器，呼吸肌肉無力還會因沒有使用而加重，因此脫離呼吸器的過程將會相當的艱辛。吸氣肌肉訓練是一種主要改善吸氣肌群的呼吸復健運動。雖然說吸氣肌肉訓練應用在裘馨氏肌肉失養症的病人上還未有定論，不過似乎在疾病的早期是有所幫助的。此外，吸氣肌肉訓練在協助長期使用呼吸器的病人脫離呼吸器上的好處，已經有很好的證據。在本文中，我們將討論一名 20 歲的裘馨氏肌肉失養症病患，因為肺炎導致呼吸衰竭，在傳統的呼吸氣脫離策略失敗後，藉由吸氣肌肉訓練成功的脫離呼吸器的經驗。*(胸腔醫學 **2013; 28: 192-199**)*

關鍵詞：裘馨氏肌肉失養症，吸氣肌肉訓練，長期使用呼吸器，呼吸復健，呼吸衰竭，脫離呼吸器

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