The Relationship of Exhaled Nitric Oxide Levels with Measures of Disease Control and Disease Severity in Asthma

Hsin-Kuo Kao, Gee-Chen Chang*, Jia-Horng Wang

The current concept of asthma pathogenesis is that a characteristic chronic inflammatory process involving the airway wall causes the development of airflow limitation and increased airway responsiveness. Exhaled NO is significantly greater in asthmatic subjects than in normal subjects. Recently, the measurement of exhaled nitric oxide has been proposed as a noninvasive means for assessing the degree of airway inflammation. We examined the correlation between asthma disease control and disease severity and exhaled NO as a marker of airway inflammation. In this cross-sectional study, we chose the use of rescue medications and the degree of reversibility of airflow obstruction after administration of a bronchodilator as measures of asthma control. We chose irreversible airflow obstruction, and baseline predicted FEV1 as measures of asthma severity. We designed a questionnaire for the 86 patients (ages ranging from 9 to 92 years) with asthma, performed spirometric testing before and after administration of a bronchodilator, and measured exhaled NO levels in all participants. Exhaled NO levels were not correlated with the markers of asthma disease control: daily use of rescue medications (p=0.381) and reversibility of airflow obstruction (p=0.506). Exhaled NO levels were not correlated with the markers of asthma disease severity: fixed airflow obstruction (p=0.842) and severity, according to predicted FEV1 (p=0.820). We conclude that exhaled NO did not correlate with measures of asthma control and severity in this study. A study with a larger sample size may demonstrate statistical significance. A longitudinal assessment of exhaled NO levels may provide a clinical role for NO in monitoring asthma control and severity. ***(Thorac Med 2003; 18: 467-473)***

Key words: asthma, nitric oxide, exhaled nitric oxide, disease control, disease severity

Introduction

Asthma is a chronic inflammatory disorder characterized by the presence of inflammatory cells and the release of several inflammatory mediators in the airway [1]. Exhaled NO is the first noninvasive marker for airway inflammation. Previous studies have demonstrated that exhaled NO was significantly greater in asthmatic subjects than in normal subjects, or in subjects with wheeze but no airway hyperresponsiveness (AHR) [2-3]. The measurement of exhaled nitric oxide has been proposed as a noninvasive, simple test to assess airway inflammation in asthma.

Department of Respiratory Therapy, Taipei Veterans General Hospital, Taipei
*Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung
Address reprint requests to: Dr. Hsin-Kuo Kao, Department of Respiratory Therapy, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Rd, Taipei 112, Taiwan, R.O.C.

The concept of asthma disease control versus severity used in this study follows the NAEPP guideline. We chose the use of rescue medications [4] and degree of reversibility of airflow obstruction after administration of a bronchodilator [5] as measures of asthma control. We chose irreversible airflow obstruction, and baseline predicted FEV1 as measures of asthma severity [6], and examined the correlation between asthma disease control and disease severity and exhaled NO as a marker of airway inflammation.

Material and Methods

We conducted a cross-sectional survey of patients with physician-diagnosed asthma. The patients were followed by chest specialists during the asthma educational program. Inclusion criteria comprised both a history of physician-diagnosed asthma using the ATS criteria [7] and the current use of anti-asthma medications.

Complete identification data were available for 155 patients who were then contacted by phone for an asthma evaluation, but the data for 69 patients were incomplete. The remaining 86 subjects were included in the analysis.

Questinnarie

We developed a Questionnaire focused on all medication use, including inhaled and oral corticosteroids, bronchodilators, theophylline, leukotriene modifiers, cromolyn, and nedocromil. Daily and nocturnal symptoms, best peak expiratory flow rate, and allergy history were also included.

Spirometry

All subjects withheld the use of short-acting bronchodilators for at least 4 hours and long-acting beta-agonists for at least 12 hours before spirometry. Spirometric findings (FEV1 and forced vital capacity [FVC]) were measured by a trained technician using a portable spirometer (Schiller AG Spirovit SP-10), following American Thoracic Society standards.[8] Bronchodilator test results were determined by means of spirometry performed after one puff of berotec (200ug per puff) through a spacer. Pulmonary function tests were repeated 20 minutes after bronchodilator administration. A 12% or greater and 200ml increase in FEV1 or FVC was considered a positive bronchodilator response. Fixed airflow obstruction was defined as a FEV1 percent predicted of less than 70% and the absence of a positive bronchodilator response. High severity was defined as a baseline FEV1 percent predicted of less than 60%. Low severity was defined as a baseline FEV1 percent predicted more than 60%.

Exhaled NO analysis

We measured exhaled NO using a Nitric Oxide Analyzer NOA 280 (Model 280; Sievers Instruments, Inc.) in seated subjects without nose clips. The NO analyzer has a response time of 200ms, repeatability +/- 1ppbv, sensitivity <5ppb, range 5-500000ppb, and sample size 100-300 ml/min. Subjects exhaled from total lung capacity to residual volume while maintaining a mouth pressure of 20cmH_2O, thus maintaining a stable flow rate during exhalation (0.057 L/sec) for at least 6 seconds. A restricted flow exhaled breath technique was used to exclude nasopharygeal NO from the exhaled air. The plateau value of exhaled NO was recorded. Maneuvers not resulting in an exhaled NO plateau, with irregular pressure tracings, or exhalation less than 6 seconds were rejected. Participants repeated the maneuver until 3 acceptable tests were performed. The average of the 3 plateau values was recorded. NO concentration (parts per billion or nanoliters per liter) was converted to NO output (nanoliter per minute) by multiplying the NO concenrtration by the constant flow rate (liter per minute).

Statistical analysis

Statistical analysis was performed using SPSS 11.0 software. All values are reported as mean ± SE. A Mann-Whiney U test was used to compare exhaled NO concentrations between groups, since values for NO were not normally distributed. Probability (p) values were two-sided, and values less than or equal to 0.05 were considered statis-

tically significant.

Results

Of the 86 patients included in this study, 59 were male and 27 were female. The mean age was 65.1 years (Table 1), ranging from 9 to 92 years. The percentage of patients with severe asthma (FEV1<60% predicted value) was 27.9%. The mean value of predicted FEV1 was 82.86%. The mean percentage of the bronchodilator response was 10.1%.

Measures of asthma disease control and exhaled NO

The mean exhaled NO level was 18.53±1.91 ppb in patients with daily rescue medications use and 22.40±1.82 ppb in patients without daily rescue medications use (p= 0.381) (Table 2). This was not statistically significant. The mean exhaled NO level was 21.05±2.33 ppb in patients with a positive bronchodilator response and 21.73±1.78 ppb in patients without a positive bronchodilator response (p= 0.506). this was also not statistically significant. We further analyzed the measures of medication use and exhaled NO concentration. (Table 3 & Figure 1). This was not statistically significant (p=0.095). There was also no correlation between bronchodilator response and exhaled NO concentration (r= 0.005, p=0.965). (Figure 2)

Measures of asthma severity and exhaled NO

Exhaled NO did not correlate with measures of asthma severity (Table 4), including fixed airflow obstruction and severity according to predicted FEV1. There was also no correlation between the baseline predicted FEV1 and exhaled NO concentration (r=0.132, p=0.266). (Figure 3)

Discussion

Exhaled NO levels did not correlate with measures of asthma control and severity in this study. Prior studies support the concept that exhaled NO levels are related to asthma control rather than to asthma severity [9-10]. Several possible explanations exist for this discrepancy, and our results may be interpreted.

Table 1. Baseline characteristics of the study group (n=86)

Variable	
Age, y (mean ± SD)	65.13 ± 15.82
Sex, F (%)	31.4
Age when asthma was diagnosed	38.2 ± 10.2
Medication use	
No medication (%)	19.7%
Occasional bronchodilator (%)	6.9%
Daily bronchodilator and/ or inhaled steroid (< 800ug/day) (%)	47.6%
Bronchodilator on demand and daily inhaled steroid (≥ 800ug/day) or occasional systemic steroid (%)	24.4%
Bronchodilator on demand and daily inhaled steroid (≥ 1000ug/day) and daily systemic steroid (%)	1.2%
Severity	
FEV1 > 80% predicted (%)	51.2
FEV1 60 to 80% predicted (%)	20.9
FEV1 < 60% predicted (%)	27.9
FEV1 % predicted (mean ± SD)	82.86 ± 31.22
Bronchodilator response (%)	10.1 ± 13.6

Table 2. Measures of asthma disease control and exhaled NO concentration (n=86)

	Exhaled NO level (mean ppb ± SE)		
	Yes	No	p value
Daily rescue medications use	18.53±1.91 (n=22)	22.40±1.82 (n=64)	0.381
Positive bronchodilator response	21.05±2.33 (n=41)	21.73±1.78 (n=45)	0.506

Table 3. Measures of medication use and exhaled NO concentration

Group	Medication	Number of patients	Exhaled NO level (ppb±SE)
0	No medication	17	17.4±8.4
1	Occasional bronchodilator	6	32.2±25.2
2	Daily bronchodilator and/ or inhaled steroid (< 800ug/day)	41	20.0±13.4
3	Bronchodilator on demand and daily inhaled steroid (≥ 800ug/day) or occasional systemic steroid	21	16.3±8.3
4	Bronchodilator on demand and daily inhaled steroid (≥ 1000ug/day) and daily systemic steroid	1	13.3

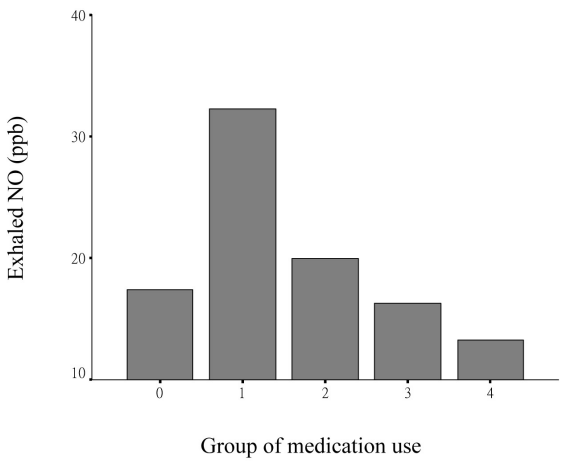


Fig. 1. Measures of medication use and exhaled NO concentration (p=0.095). ppb: parts per billion.

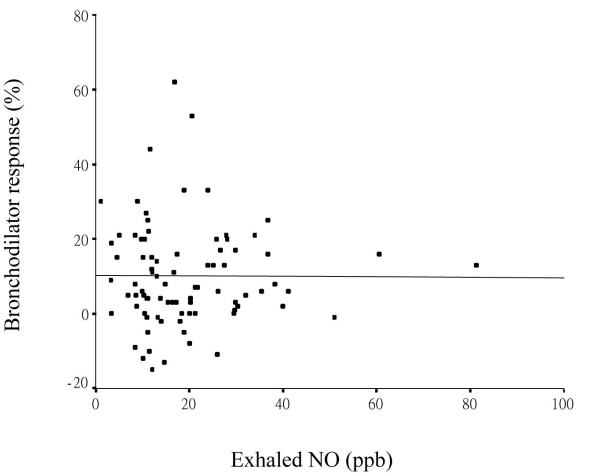


Fig. 2. Correlation between bronchodilator response and exhaled NO concentration (r=0.005, p=0.965). ppb: parts per billion.

First, this study was a cross-sectional study of 86 subjects with mild and stable asthma. The small size should increase the chance of type 2*(B)* error. (e.g., not demonstrate a correlation between exhaled NO levels and measures of asthma control or asthma severity).

Second, there are several major factors which may change NO levels in normal subjects. Some routinely used tests can transiently reduce exhaled NO, for example, repeated spirometry [11], physical exercise [12], and sputum induction [13]. Habitual factors such as smoking [14] and alcohol ingestion [15] reduce exhaled NO. Upper respiratory infection significantly increases exhaled NO [16]. A broad range of exhaled NO levels, from 3.5ppb to 78.4ppb, was seen in this study. Differences in patterns of medication use, patient clinical status at the time of evaluation, and measurement techniques, may ex-

Table 4. Measures of asthma disease severity and exhaled NO concentration

Severity measures	Exhaled NO level (ppb±SE)		p value
	Yes	No	
Fixed airflow obstruction	19.33±2.88(n=12)	21.75±1.62(n=74)	0.842
Severity according to baseline predicted FEV1			
High (predicted FEV1 < 60%)	20.70±2.72(n=22)		0.820
Low (predicted FEV1 ≥ 60%)	21.66±1.71(n=64)		

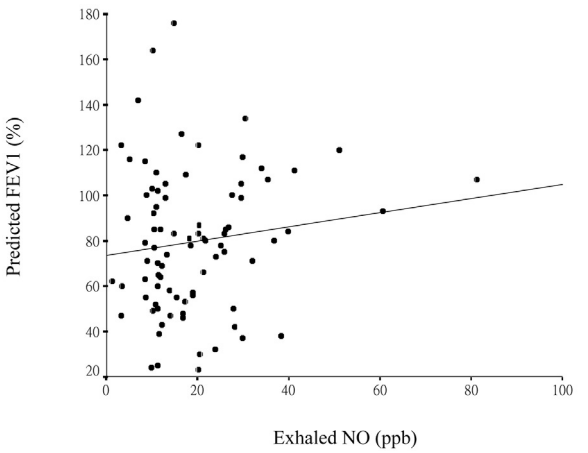


Fig. 3. Correlation between baseline predicted FEV1 and exhaled NO concentration (r=0.132, p=0.266). ppb: parts per billion.

plain a part of the variance observed between studies.

Third, oral or inhaled corticosteroids with asthma are associated with decreased exhaled NO [17]. Exhaled NO behaves as a rapid response marker, which is extremely sensitive to steroid treatment, as it may be significantly reduced even after 6 h following a single treatment with a nebulized corticosteroid [18], or within 2 to 3 days after inhaled corticosteroids [17], reaching maximal effect after 2 to 4 weeks of treatment [19-20]. The different dosage and frequency of rescue glucocorticoids use may change the exhaled NO levels. Treatment with inhaled corticosteroids reduces exhaled NO levels, and therefore exhaled NO cannot be directly related to asthma severity. Neither short-acting nor long-acting β2-agonists reduce exhaled NO [21]. There may even be a short-term increase in exhaled NO after the use of β2-agonists, which may be due to the opening up of airways with higher local NO concentrations [22].

Fourth, exhaled NO in patients occasionally using bronchodilators (group 1) was higher than in other groups (Table 3 and Figure 1). The subclinical airway inflammation reflected by the elevated levels of exhaled NO may be severe, and should be treated with corticosteroids to prevent this continuous risk of exacerbation. Patients with daily inhaled steroid use (groups 2,3,4) are associated with lower exhaled NO levels. In fact, inhaled corticosteroids reduce exhaled NO levels in asthmatic patients [17], and the effect is dose-related [23]. Thus, exhaled NO is elevated in mild asthma, but is near normal in stable moderate asthma adequately treated with corticosteroids.

Fifth, our study was composed of a single measurement of exhaled NO, and was not longitudinal in nature. A single measurement of exhaled NO for clinical use must be interpreted carefully. According to the Stuart study [24], changes in exhaled NO over time in the longitudinal assessment of asthma control had a higher positive predictive value of between 80% and 90%, for predicting and diagnosing loss of control, than single measurements of exhaled NO.

We found no correlation between exhaled NO and disease control or disease severity in asthma. According to the recommendation of Kharitonov and coworkers [25], individual NO values such as individual peak expiratory flows should be established and monitored, and when the levels are above or below a certain reference level, steroids or other treatment should be either reduced or increased.

Conclusion

Exhaled NO did not correlate with measures of asthma control and severity in this study. A study with a larger sample size may demonstrate statistical significance. A longitudinal assessment of exhaled NO levels may provide a clinical role for NO in monitoring asthma control and severity. Further investigations, relating exhaled NO to other putative markers of airway inflammation such as chemokines or cytokines in serum or secretions, may be warranted.

References

1. Djukanovic R, Roche WR, Wilson JW, *et al*. Mucosal inflammation in asthma, Am Rev Respir Dis 1990; 142: 434-57.
2. Kharitonov SA, Yates DH, Tobbins RA, *et al*. Increased nitric oxide in exhaled air of asthmatic patients. Lancet 1994; 343: 133-5.
3. Salome CM, Roberts AM, Brown NJ, *et al*. Exhaled nitric oxide measurements in a population sample of young adults. Am J Respir Crit Care Med 1999; 159: 911-6.
4. NHLBI USPHS. Expert panel report 2. Guidlelines of the diagnosis and management of asthma. Bethesda (MD): National Institutes of Health; 1997. NIH publication No. 97: 4051.
5. Enright PL, Lebowitz MD, Cockroft DW. Physiologic measures: Pulmonary function tests; asthma outcome. Am J Respir Crit Care Med. 1994; 149: S9-18.
6. Osborne ML, Vollmer WM, Pedula KL, *et al*. Lack of correlation of symptoms with specialist-assessed long-term asthma severity. Chest 1999; 115: 85-91.
7. Anonymous. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease and asthma. Am Rev Respir Dis 1987; 136: 225-34.
8. Becklake M, Crapo RO. Lung function testing. Selection of reference values and interpretive strategies. Am Rev Respir Dis 1991; 144: 1202-18.
9. Jeffrey MS, William EH, Stephen AT *et al*. J Exhaled nitric oxide levels correlate with measures of disease control in asthma. Allergy Clin Immunol 2000; 106: 645-50.
10. Kharitonov SA, Barnes PJ. Clinical aspects of exhaled nitric oxide. Eur Respire J 2000; 16: 781-92.
11. Deykin A, Massaro AF, Coulston E, *et al*. Exhaled NO following repeated spirometry or repeated plethysmography in health individuals. Am J Respir Crit Care Med 2000; 161: 1237-40.
12. Phillips CR, Giraud GD, Holden WE. Exhaled nitric oxide during exercise: site of release and modulation by ventilation and blood flow. J Appl Physiol 1996; 80: 1865-71.
13. Piacentini GL, Bodini A, Costella S, *et al*. Pediatr Pulmonol 2000; 29: 430-3.
14. Kharitonov SA, Robbins RA, Yates DH, *et al*. Acute and chronic effects of cigarette smoking on exhaled nitric oxide. Am J Respir Crit Care Med 1995; 152: 609-12.
15. Yates DH, Kharitonov SA, Robbins RA, *et al*. The effect of alcohol ingestion on exhaled nitric oxide. Eur Respir J 1996; 9: 1130-3.
16. Murphy AW, Platt-Mills TA, Lobo M, *et al*. Respiratory nitric oxide levels in experimental human influenza. Chest 1999; 114: 452-6.
17. Kharitonov SA, Rates DH, Barnes PJ. Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients. Am J Respir Crit Care Med 1996; 153: 454-7.
18. Kharitonov SA, Barnes PJ, O'Conor BJ. Reduction in exhaled nitric oxide after a single dose of nebulized budesonide in patients with asthma. Am J Respir Crit Care Med 1996; 153: A799.
19. Kharitonov SA, Yates DH, Chung KF *et al*. Change in the dose of inhaled steroid affect exhaled nitiric oxide levels in asthmatic patients. Eur Respir J 1996; 9: 196-201.
20. van Rensen EL, Straathof KC, Veseli-Charvat MA, *et al*. Effect of inhaled steroids on airway hyperresponsiveness, sputum eosinophils, and exhaled nitric oxide levels n patients with asthma. Thorax 1999; 54: 403-8.
21. Yates DH, Kharitonov SA, Barnes PJ. Effect of short- and long-acting inhaled beta2-agonists on exhaled nitric oxide in asthmatic patients. Eur Respir J 1997; 10: 1483-8.
22. Ho LP, Wood FT, Robson A, *et al*. The current single exhalation method of measuring exhales nitric oxide is affected by airway caliber. Eur Respir J 2000; 15: 1009-13.
23. Jatakanon A, Kharitonov SA, Lim S, *et al*. Effect of differing doses of inhaled budesonide on markers of airway inflammation in patients with mild asthma. Thorax 1999; 54: 108-14.
24. Stuart LJ, John K, Jan OC *et al.* The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. Am J Respir Crit Care Med 2001; 164: 738-43.
25. Kharitonov SA, Peter JB. Exhaled markers of pulmonary disease. Am J Respir Crit Care Med 2001; 163: 1693-1722.

吐氣一氧化氮與氣喘控制及嚴重度之相關性

柯信國　張基晟*　王家弘

前言：氣喘之病理變化為慢性呼吸道發炎，導致氣流阻塞及氣道敏感性增加。吐氣一氧化氮於氣喘患者相較一般正常人為高，所以一氧化氮之測量可作為呼吸道發炎之指標。我們選擇緊急藥物使用及氣流阻塞恢復程度為氣喘控制指標，另選擇氣道阻塞不可恢復性及第一秒吐氣容積為氣喘嚴重度指標。

材料及方法：計有八十六位病患接受問卷調查、支氣管擴張劑使用前後之肺功能檢查及測量吐氣一氧化氮濃度。

結果：吐氣一氧化氮濃度與氣喘控制指標中是否每日緊急藥物使用及是否氣流阻塞可恢復性均未達統計學上意義，吐氣一氧化氮濃度與氣喘嚴重度指標中是否固定氣流阻塞及第一秒吐氣容積高低均未達統計學上意義。

結論：具有較多病患數目之研究可能可顯現出統計上意義，並且長時間多次測量吐氣一氧化氮濃度之變化可能較單次測量更具臨床應用價值。***(胸腔醫學 2003; 18: 467-473)***

關鍵詞：氣喘，一氧化氮，吐氣一氧化氮，疾病控制，疾病嚴重度

台北榮民總醫院　呼吸治療科　台中榮民總醫院　內科部　胸腔內科 *
索取抽印本請聯絡：柯信國醫師，台北榮民總醫院　呼吸治療科，臺北市石牌路二段 201 號

Factors Associated with Asthma Patients Dropping Out from Outpatient Clinic Follow-up

Tsung-Jen Hung*, Cheng-Hung Lee, Chiung-Zuei Chen,
Yuan-Chin Chu, Tzuen-Ren Hsiue

Asthma requires long-term self-management with regular physician support and surveillance. However, most studies of patients who drop out from treatment or follow-up of their condition have focused on psychiatric and pediatric patients, and there have been relatively few studies on patients with asthma. Patients who drop out may not receive adequate medical care, and place themselves at risk of unnecessary morbidity and mortality. The purpose of this study was to determine the percentage of asthma patients who drop out during follow-up, and the reasons and predictive factors for this dropping out. The medical records of 168 patients with asthma, who had attended a chest special clinic from 1989 to 2002 at our hospital, were analyzed. A telephone survey was performed to determine the reasons for dropping out. The overall dropout rate was 58.9% of the 168 patients attending the clinic during the study period, and a high percentage (46.5%) of these drop-outs occurred during the first 6 months. The three most common reasons for dropping out were symptom improvement, inconvenient consultation, and patient decision to use other hospitals. The predictive factors for dropout were female gender and the presence of coexisting chronic diseases. According to the patient-generated complaints, some strategies to ensure patient education, and intervention to ease the inconvenience of follow-up, might be helpful. Early detection and intervention for patients at high risk of dropout might improve the management efficiency of patients with asthma. ***(Thorac Med 2003; 18: 474-480)***

Key words: Asthma, Dropping out, outpatient clinic

Introduction

Patients who do not attend scheduled appointments, commonly called "non-attendance" or "drop-out" patients, represent important problems in many medical outpatient clinics. Previous studies have reported dropout rates in the range of 3 to 42% [1-10]. There is concern that patients who drop out from scheduled follow-up may not receive adequate medical care, and may suffer from unnecessary morbidity and mortality. Missed appointments also reduce the efficiency of medical care. Previous research on dropouts has focused mostly on the problems of psychiatric and pediatric patients [1], and relatively few studies have been carried out with patients with medically chronic diseases, such as hypertension [5-6] and asthma [11].

Asthma, one of the most commonly encoun-

Department of Internal Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
* Department of Intensive Care Medicine, Chi Mei Hospital, Tainan, Taiwan
Address reprint requests to: Dr. Tzen-Ren Hsiue, Professor of Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, No 138, Sheng-Li Rd, Tainan, 704, Taiwan

tered diseases in outpatient clinics, is a chronic inflammatory disorder of the airways with recurrent exacerbation, which requires long-term care. The prevalence of asthma has considerably increased over the last two decades and imposes a substantial burden on patients, their families and society. Surprisingly, a literature review of the past 25 years revealed few studies on the problem of patient dropout during treatment at asthma clinics [11]. Woodward's study at a nurse-run asthma clinic found that the reasons for the high dropout rate of 52.6% were multifactorial. However, no independent factor predictive of dropout was found.

The purpose of this study was to determine the dropout rate of patients with asthma at a special chest clinic, the reason that they were lost to follow-up, and the factors associated with dropping out. Early detection of asthma patients at high risk of dropping out might improve the efficiency of health care by enabling health professionals to provide targeted interventions aimed at the patient-generated complaints.

Patients and Methods

Subjects

From January 1989 to Oct 2002, the appointment records of 175 subjects with asthma, aged at least 15 years old, who had attended a special chest clinic at the National Cheng Kung University Hospital, a tertiary referral medical center in southern Taiwan, were investigated. A total of 168 of these subjects were eventually included in the study, and their appointment records were investigated retrospectively. Six subjects were excluded due to death, and one patient was excluded due to adequate control of asthma, which was defined as no attack during an outpatient clinic follow-up period longer than one year.

Subjects who had not attended scheduled appointments for 6 months or more were defined as the dropout group. Subjects in the dropout group were contacted by telephone survey to investigate the reasons for non-attendance. Subjects were asked to consider 12 possible reasons for dropping out, and were allowed to choose any number of these reasons and given the chance to indicate additional reasons. Attempts were made to contact subjects in the dropout group at different times, and on different days if the initial attempt at contact was unsuccessful. A non-responding subject was defined as a subject who could not be contacted during at least 10 attempts.

The clinical variables recorded at the initial clinic visit included age, gender, pulmonary function test, family history, and the presence of coexisting chronic diseases (hypertension, diabetics, chronic liver disease, and chronic renal insufficiency). The variables recorded at the last clinic visit included the number of oral medications and the number of different inhalation devices (meter-dose-inhaler, turbuhaler and accuhaler) prescribed. Spirometry and lung volumes (helium dilation method) were performed with a rolling seal spirometer, following the standard methods suggested by the American Thoracic Society [12].

Data analysis

The data gathered in this research were analyzed using SPSS 10.0 for Windows. Analytical methods used included descriptive statistics: percentage and average; and inferential statistics: t-test, chi-square test, and linear regression. The significant level was set at a p value less than 0.05.

Results

The 168 subjects recruited for participation in the study included 84 males (50%) and 84 females (50%). The mean age of the subjects at the time of their initial clinic visit was 44.52 years old (44.52± 16.16) (Table 1 and Table 2).

There were 99 subjects who met the criteria for classification as dropouts. Sixty-nine subjects who completed follow-up were included as the attendance group. Therefore, the dropout rate in this series of patients was 58.93%. Among the subjects in the dropout group, 34 could not be reached: 9 subjects had no current telephone number, 2 had unlisted numbers and 15 had incorrect telephone

Table 1. Demographic and clinical data of all subjects (numerical variables) (N=168)

Numerical variables	Mean	SD
Age at first OPD visit (yr)	44.52	16.16
Duration of follow-up (months)	41.29	43.18
Number of times of follow-up	30.22	32.90
FEV_1 (L/sec)	1.93	0.77
FEV_1, % predicted	67.17	20.42
FEV_1/FVC, %	64.38	15.17
Number of oral medications	4.64	2.06

FVC: forced vital capacity

FEV_1: forced expiratory volume in one second

Table 2. Demographic and clinical data of all patients (categorical variables) (N=168)

Categorical variables	N	%
Gender		
Male	84	50
Female	84	50
Coexisting chronic disease		
No	114	67.9
Yes	54	32.1
Number of different inhalation devices		
0	2	1.2
1	30	17.9
2	126	75
3	10	6

numbers on their charts, 7 were non-responders, and one had died. The expired subject had died after a 6-month absence from scheduled appointments, and the family would not reveal the cause of his death, so we still assigned him to the dropout group. Forty-six percent of subjects in the dropout group were lost to follow-up within 6 months of the first visit. The demographic and clinical data of the two groups are shown in Table 3.

Sixty-five of the 99 subjects contacted completed the telephone interview. Thirty-nine subjects (60.0%) indicated one reason, 20 subjects (30.77%) two reasons, and 6 subjects (9.23%) indicated three reasons for dropping out. The most common reason for dropout was symptom improvement (64.6%), followed by inconvenient consultation (33.8%), the decision by the subject to use another hospital (24.6%), and fear of medication side effects (7.7%). The reasons for dropping out are shown in Table 4.

There were significant differences between the dropout group and the attendance group in gender, age at the time of the first OPD visit for treatment of asthma, duration of follow-up, number of times of follow-up, pulmonary function test, and presence of coexisting chronic diseases (Table 5). There were significantly more female ($p < 0.01$) and younger ($p = 0.001$) subjects in the dropout group than in the attendance group. The presence of coexisting chronic diseases was more common in the attendance group ($p < 0.001$). Subjects in the dropout group had better initial pulmonary function test results ($p = 0.023$). Family history, number of different inhalation devices, and number of oral medications were similar in the two groups.

Statistical analysis showed that gender, age, pulmonary function test results, and the presence of coexisting chronic diseases were significantly correlated with dropping out. Using dropout as a dependent variable in linear regression, gender and the presence of coexisting chronic disease explained 11.5% of the variance in the stepwise regression model.

Discussion

The chronicity and increased prevalence of asthma require that patients become active partners with health professionals in the regular follow-up, surveillance, and treatment of their condition. Unfortunately, patients with asthma are prone to lapse in compliance or even drop out when the condition is mild or asymptomatic [13]. Nevertheless, the consequences of stopping treatment may be delayed. This study was designed to determine the dropout rate in asthma clinics, the reasons, and the factors predictive of dropout, in order to improve the management of patients with asthma.

The results showed that 99 out of 168 patients with asthma dropped out of scheduled follow up,

Table 3. Comparison of clinical characteristics of the dropout group and the attendance group

Variables	Dropout group	Attendance group	Statistical value	*P* value
Age at first OPD visit (yr)	41.17±16.08	49.33±15.15	t=-3.31	0.001
Duration of follow-up (months)	21.00±27.06	70.39±45.44	t=-8.08	< 0.001
Number of times of follow-up	16.74±20.45	49.57±37.56	t=-6.61	< 0.001
FEV_1 (L/sec)	2.03±0.79	1.78±0.71	t=2.17	0.032
$FEV_{1,}$ % predicted	70.17±19.61	62.91±20.93	t=2.29	0.023
FEV_1/FVC, %	66.04±14.82	62.01±15.45	t=1.70	0.091
Number of oral medications	4.39±2.04	4.99±2.06	x^2=10.16	0.426
Number of different inhalation devices			x^2=4.888	0.180
0	1(50%)	1(50%)		
1	23(23.2%)	7(10.1%)		
2	70(70.7%)	56(81.2%)		
3	5(50%)	5(50%)		
Gender			x^2=7.11	0.008
Male	41(41.4%)	43(62.3%)		
Female	58(58.6%)	26(37.7%)		
Coexisting chronic diseases			x^2=15.76	0.000
No	79(79.80%)	35(50.72%)		
Yes	20(20.20%)	34(49.28%)		
Family history			x^2=3.345	0.067
Negative	73(73.7%)	59(85.5%)		
Positive	26(26.3%)	10(14.5%)		

FVC: forced vital capacity

FEV_1: forced expiratory volume in one second

Table 4. Reasons for dropping out (n=65)

Reasons	Count	% Of cases
Symptom improvement	42	64.6
Inconvenient consultation		
Hospital factor	8	12.3
Patient factor	14	21.5
Fear of drug side effects	5	7.7
Patient decision to use another clinic	16	24.6
Financial constraints	1	1.5
Control of symptoms with herbs	4	6.2
Poor response to treatment	3	4.6
Medication side effects	3	4.6
Dr/staff problem	1	1.5
Total responses	97	149.2

Multiple answers were allowed

Inconvenient consultation (hospital factor): waiting too long, difficult to register

Inconvenient consultation (patient factor): moved, too busy, too far

Table 5. Stepwise linear regression of the dropout rate (N=168) with gender and coexisting chronic disease

Variables	B value	Beta	R^2	F value
Coexisting chronic disease	.292	.277	.115	10.665*
Gender	-.151	-.153		
Constant	1.545			

* p <0.001

representing a dropout rate of 58.9%. This result is similar to that of a study by Woodward, in which a dropout rate of 52.6% was reported [11]. Studies of other chronic diseases have reported dropout rates between 3 and 42% [1-10], which is much less than in the present study. This suggests that many patients with asthma lack adequate medical care, and deserve more attention from professionals.

In this study, a high percentage of dropouts (46.5%) occurred within 6 months of the first visit. Similar findings have been reported in patients receiving care at diabetic clinics, with dropout rates of 33% and 54.5% within 6 months from the first attendance [14-15]. These findings suggest the need for comprehensive patient education in the first 6 months of clinic attendance for those patients who are at high risk of dropping out.

This study found that the reasons for dropping out were multifactorial. The predominant reason was symptom improvement, followed by inconvenient consultation. This result is somewhat different from the findings of Woodward [11], in which forgetting, difficulty getting time off work, and considering the visits not necessary were reported as the main reasons for dropping out. One possible explanation for this discrepancy is that Asian subjects may have a greater desire to rationalize their behaviors rather than admitting their own forgetfulness.

Because the reasons for dropping out vary widely, successful interventions may need to address a variety of factors and be tailored to the individual patient. Potentially helpful interaction between patients and healthcare providers should include educational efforts regarding the disease and the importance of continuing care. In addition, health professionals could provide alternatives to patients which might increase compliance, such as discussing convenient times for clinical visits, checking that the registration number of the patient who is just visiting the doctor in the clinics on the website before visiting the hospital, or referring some patients to nearby clinics, and discussing potential financial problems.

In this study, we excluded the variables of duration and number of follow-up visits because they are confounding variables to the factors associated with dropping out. There were significant differences between the dropout group and the attendance group in gender, age at the time of the first OPD visit, initial pulmonary function test results, and presence of coexisting chronic diseases. Although these variables may have affected the variance in the assessment of the dropout rate, their statistical significance partly disappeared in the stepwise analysis.

Stepwise analysis indicated that female gender and presence of coexisting chronic disease were the most predictive variables for dropping out. Degoulet et al. similarly had found that there was a lower dropout rate in patients with hypertension if they had a coexisting disease such as asthma or stroke [6]. The effect of gender on the dropout rate has varied among patients with different diseases [1-4, 6-9, 11, 13, 16]. Female gender was significantly associated with dropping out in this study. This result may be explained by the fact that the average age of female subjects in this study was 40 years old. Women of this age in Taiwan are often faced with heavy family responsibilities, which may increase their tendency to drop out from follow-up at asthma clinics.

In conclusion, a high percentage of patients with asthma drop out from follow-up at outpatient clinics, indicating that their asthma management is far from satisfactory. These data suggest the need for strategies to increase the attendance rate. The high percentage (46.5%) of dropouts during the first 6 months in this study indicates the importance of intervention to prevent dropping out during this period. Previous studies have found that intervention aimed toward patient-generated complaints was useful in reducing the dropout rate [5]. This suggests that the reinforcement of comprehensive education programs and strategies to reduce waiting time, such as informing patients about the timing of visits or checking the registration number of patients that has been assessed on the website, may improve the attendance rate. Recognizing patients who are at high risk of dropping out as early as the first visit may have important practical consequences. Awareness of factors affecting the dropout rate should help focus the attention of physicians toward this problem, and help in changing their approach to patients, which might result in improved care. Although not modifiable, female gender and the presence of coexisting chronic diseases were the most predictive factors of dropping out. This

may have been due to the nature of the subjects attending our clinic. Further research is needed in various settings to extend our understanding of the risk factors for dropping out from follow-up among asthma patients treated at outpatient clinics. In addition, more research is needed into the morbidity and mortality levels among the dropout patients.

References

1. Deyo RA, Inui TS. Dropouts and broken appointments. A literature review and agenda for further research. Med Care 1980; 18: 1146-57.
2. Goldman L, Freidin R, Cook EF, *et al*. A multivariate approach to the prediction of no-show behavior in a primary care center. Arch Intern Med 1982; 142: 563-7.
3. Baekeland F, Lundwall L. Dropping out of treatment: a critical review. Psychol Bull 1975; 82 738-83.
4. Hamilton W, Sharp D. Nonattendance at general practices and outpatient clinics. BMJ 2001; 323: 1081-2.
5. Finnerty FA Jr, Mattie EC, Finnerty FA 3d. Hypertension in the inner city. I. Analysis of clinical dropouts. Circulation 1973; 47: 73-5.
6. Degoulet P, Menard J, Vu H. A., *et al*. Factors predictive of attendance at clinic and blood pressure control in hypertensive patients. BMJ 1983; 287: 88-93.
7. Griffin S. Lost to follow-up: the problem of defaulters from diabetes clinics. Diabetic Med 1998; 15 (suppl. 3): S14-24.
8. Narayan V, Sircar AR, Singh JV. Analysis of irregulars and dropouts in a diabetes clinic. Indian J Med Res 1978; 68: 540-5.
9. Hammersley MS, Holland MR, Waiford S, *et al*. What happens to defaulters from a diabetic clinic? BMJ 1985; 291: 1330-2.
10. Scobie IN, Rafferty AB, Frank PC, *et al*. Why patients were lost from follow-up at an urban diabetic clinic? BMJ 1983; 286: 189-90.
11. Woodward V. Non-attendance at a nurse-run asthma clinic. J Clin Nurs 1998; 7: 380-1.
12. American Thoracic Society. Standardization of spirometry 1994 update. Am J Resp Cri Care Med 1995; 152: 1107-36.
13. Blackwell B. Patient compliance. NEJM 1973; 289: 252.
14. Graber AL, Davidsonnn P, Brown AW, *et al*. Dropout and relapse during diabetes care. Diabetes Care 1992; 15: 1477-83.
15. Kawahara R, Amemiya T, Yoshino M, *et al*. Dropout of young non-insulin-dependent diabetics from diabetic care. Diabetes Res Clin Prac 1994; 24: 181-5.
16. Sugarman JR, Bauer MC, Barber EL, *et al*. Factors associated with failure to complete treatment for diabetic retinopathy among Navajo Indians. Diabetes Care 1993; 16 (suppl 1): 326-8.

門診氣喘病人中輟原因之探討

洪崇仁* 李政宏 陳炯睿 朱遠志 薛尊仁

氣喘病人的照顧，需要病人本身的自我照顧以及規則地由醫師追蹤監測。然而，關於病人自行中輟門診追蹤的研究報告，大都集中在精神科及兒科，僅有少數報告針對氣喘病人。這些自行中輟門診追蹤的病人，可能無法接受必須的醫療照顧並承受一些原先可避免的發病以及死亡。這篇研究的目的即是在探討門診氣喘病人的中輟率、原因以及預測因子。所以我們回顧研究 168 位從 1978 至 2002 年間，曾在本院某一固定胸腔科門診治療過的氣喘病人的病歷資料。並對自行中輟之病人以電話訪談的方式，了解其中輟原因。結果顯示中輟率為 58.9%，且有相當高比率 (46.5%) 的病人是在前六個月中輟追蹤。中輟最常見的三個原因分別是症狀改善、看診不便以及轉至其他醫院追蹤。中輟的預測因子為女性及同時有其他慢性病存在。我們相信針對病人所提出的原因，來對應施行的改善方案，如加強衛教及提供一些避免看診不便的方法是有用的。而早期辨識出可能中輟的病人應可以降低中輟率增進對氣喘病人的照護。***(胸腔醫學 2003; 18: 474-480)***

關鍵詞：氣喘，中輟，門診

成大醫學院內科　奇美醫院加護醫學部 *
索取抽印本請聯絡：薛尊仁醫師，成功大學附設醫院　內科部胸腔內科，台南市勝利路 138 號

Adenosquamous Carcinoma of the Lung: Surgical Results at Taichung Veterans General Hospital

Chou-Ming Yeh, Chih-Yi Chen, Chun-Ping Hsu*, Jiun-Yi Hsia, Cheng-Yen Chuang**

Adenosquamous carcinoma of the lung is an uncommon malignancy. All studies have emphasized the poorer prognosis of adenosquamous carcinoma compared to either adenocarcinoma or squamous cell carcinoma of the lung. In this study, we analyzed 60 cases of adenosquamous carcinoma of the lung at our institute, and discuss, in this report, the histogenesis and biologic behavior of the malignancy. ***(Thorac Med 2003; 18: 481-485)***

Key words: adenosquamous carcinoma, lung cancer

Introduction

Adenosquamous carcinoma of the lung is a rare subset of pulmonary cancer, and constitutes 0.4 ~ 4.0% of all lung cancers [1,3,5-6]. The neoplasm is not clearly defined [1-4]. According to the World Health Organization's histological classification, adenosquamous carcinoma harbors both squamous cell carcinoma and adenocarcinoma components [2-3,9], however, the percentage of each component is not well detailed [2,5]. All investigators have mentioned the aggressive biological behavior and poor prognosis of the malignancy [1,3,7], despite the clear differentiation and peripheral location of the tumor lesion [1,5,8]. In this study, we analyzed 60 cases of adenosquamous carcinoma of the lung at our unit, and reviewed the definition, histogenesis, biologic behavior, and prognosis of adenosquamous carcinoma of the lung.

Material and Methods

From November 1982 to March 2003, 1890 patients with lung cancer underwent surgical intervention at our department. Of these patients, 60 were pathologically diagnosed with adenosquamous carcinoma, and were selected for the study. Fifty-eight patients received surgical intervention. The other 2 patients were found to have neck lymph node metastases, proven by excision biopsy, and did not undergo an operation. Of the 58 patients who underwent surgery, 2 expired within one month and were excluded from the study, because neither of the deaths were tumor-related. All the surgical specimens were proved by light microscopy to have both squamous cell and adenocarcinomatous components. The staging of the tumor was based on the Union Internationale Contre le Cancer (UICC) TNM system.

Statistical analyses were performed using the Kaplan-Meier method and the log rank test.

Results

Division of Thoracic Surgery, Department of Surgery, Taichung Veterans General Hospital, *National Yang Ming University, Taipei, Taiwan; Division of Thoracic Surgery, Department of Surgery, Show-Chwan Memorial Hospital** Address reprint requests to: Dr. Chou-Ming Yeh, Division of Thoracic Surgery, Department of Surgery, Taichung Veterans General Hospital, No. 160, Sec. 3, Taichung-Kung Road, Taichung, Taiwan

The study cohort consisted of 42 male and 14 female patients. The mean age was 63.7 years old, ranging from 40 to 79 years. The median follow-up interval was 23.6 months, ranging from 2 to 137 months.

The surgical interventions performed were pneumonectomy (5.4%), bilobectomy (12.5%), sleeve lobectomy (7.1%), lobectomy (69.6%), and wedge resection (3.6%). (Table 1)

The staging of the tumors was done based on the UICC TNM system. Stage III was the most frequent and accounted for 57.1% of the patients. The remaining staging percentages were: stage I (19.6%), stage II (19.6%), and stage IV (3.6%). (Table 2)

For all 56 patients with adenosquamous carcinoma of the lung, the median survival interval was 1.5 years, and the 5-year survival rate was 18.29% (Figure 1). The median survival intervals and 5-year survival rates, based on the staging of the tumors, are calculated individually and shown in Table 3 and Figure 2.

Lymph-node metastases were found in 44 of the 56 patients (78.57%). The median survival time and 5-year survival rate of the patients with lymph node involvement (N1+N2) were 1.33 years and 16.26%. On the other hand, the median survival time and 5-year survival rate of those with no lymph node involvement (N0) were 3.24 years and 31.52%, respectively. (Table 3 and Figure 3)

Table 1. Surgical methods used

Operation	No.	Percentage
Bilobectomy	2	3.6
Lobectomy	39	69.6
Lobectomy+LLL wedge resection	1	1.8
Pneumonectomy	3	5.4
RML+RLL bilobectomy	4	7.1
RUL+RML bilobectomy	1	1.8
Sleeve lobectomy	4	7.1
Wedge resection	1	1.8
Wedge resection + thymectomy	1	1.8
Total	56	100.0

Table 2. Pathological staging of the patients

STAGE	No.	Percentage
I	11	19.6
II	11	19.6
III	32	57.1
IV	2	3.6
Total	56	100.0
STAGE	No.	Percentage
IA	1	1.8
IB	10	17.9
IIA	1	1.8
IIB	10	17.9
IIIA	27	48.2
IIIB	5	8.9
IV	2	3.6
Total	56	100.0

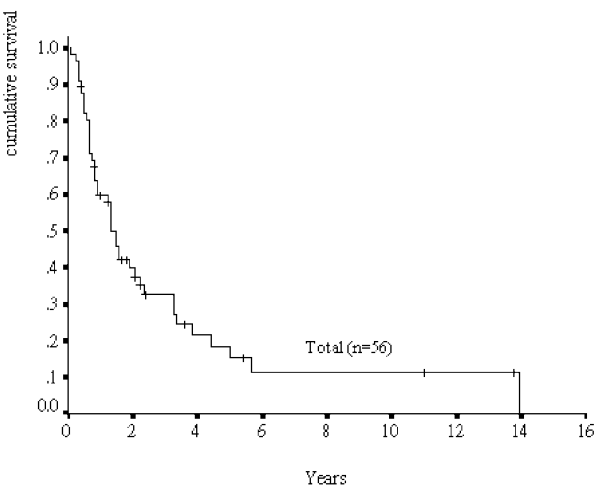


Fig. 1. The overall cumulative survival curve of the 56 patients.

Discussion

Adenosquamous carcinoma of the lung is an uncommon subtype of lung cancer. According to earlier reports, it constitutes 0.4~4.0% of all lung cancers [1,3,5,6]. In this study, 60 out of 1890 lung cancer patients were proven pathologically to have adenosquamous carcinoma (3.17%). Because of the fairly low incidence, the clinicopathological charac-

Table 3. Survival analysis

Variable	Median survival time (years)	5-year survival rate
Stage		
I	3.91	36.65%
II	5.39	67.69%
III	0.97	3.62%
IV	1.00	0.00%
Lymph node status		
N0	3.24	31.52%
N1	1.58	41.81%
N2	1.10	4.91%
N1+N2	1.33	16.26%

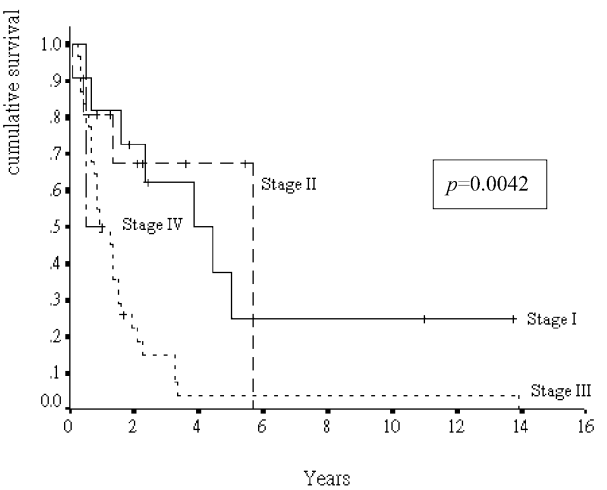


Fig. 2. The cumulative survival curve of the individual stages

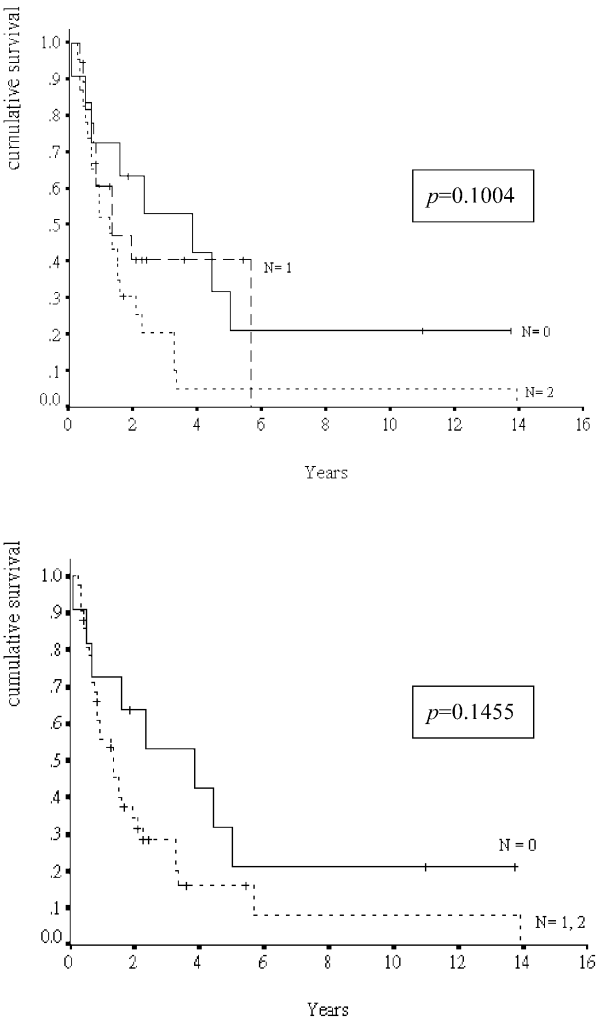


Fig. 3. The cumulative survival curve of individual lymph node statuses

teristics of adenosquamous carcinoma are still unclear [1-3,5].

The diagnostic criteria of adenosquamous carcinoma were established by the Japan Lung Cancer Society, and defined the tumor as one composed of at least 20% each of adenocarcinoma and squamous cell carcinoma [4]. On light microscopic examination, adenosquamous carcinoma shows unequivocal squamous differentiation in the form of intracellular keratinization or intercellular bridges, and unequivocal glandular differentiation in the form of glandular, tubular, or papillary structures [5,9,12].

In previous reports, all investigators have emphasized the poor prognosis of adenosquamous carcinoma of the lung [2-3,7-8], even with a peripheral location and good differentiation [3,8]. In our study, the overall cumulative 5-year survival of patients with adenosquamous carcinoma was 18.29%, in contrast to the adenocarcinoma (24.2%) and squamous cell carcinoma (27.4%) patients in our unit [3].

In our study, lymph-node metastasis was common (78.57%). Other investigators have also suggested that adenosquamous carcinoma has a high rate of early metastasis [1,8], including lymph-node

metastasis [3,8]. Marc Requet reported that five-year survival in patients with lymph node involvement was 30.8%, and that of patients who were lymph node involvement-free was 47% [8]. However, our study revealed respective survivals of 16.26% and 31.52%, with no statistical significance (p=0.1455).

The histogenesis of adenosquamous carcinoma of the lung remains unclear [1,3,5,10-11]. Many hypotheses have been put forth, including those of adenocarcinoma with squamous metaplasia, a collision tumor, high-grade mucoepidermoid carcinoma, and a bipotential undifferentiated cell origin [3,5,10]. Ichinose et al [11], in 67% of their studied adenosquamous lung carcinoma patients, demonstrated similar biological characteristics, in terms of DNA ploidy patterns, between the adenocarcinomatous and squamous carcinomatous components. All of these hypotheses require further investigation.

In conclusion, this study confirms the poor prognosis and aggressive biological behavior of adenosquamous carcinoma of the lung [1,3,5]. Determination of the clinocopathological characteristics of adenosquamous carcinoma of the lung requires further investigation.

References

1. Frizgibbons PL, Kern WH. Adenosquamous carcinoma of the lung: a clinical and pathologic study of seven cases. Human pathology 1985; 16: 463.
2. World Health Organization. The World Health Organization histological typing of lung tumors. 2nd ed. Am J Clin Pathol 1982; 77: 123-36.
3. Hsia JY, Chen CY, Hsu CP, *et al*. Adenosquamous carcinoma of the lung: surgical results compared with squamous cell and adenocarcinoma. Scand-Cardiovasc-J 1999; 33(1): 29-32.
4. The Japan Lung Cancer Society. General Rules for Clinical and Pathological Recording of Lung Cancer. 3rd ed. Tokyo: Kanehara, 1987.
5. Kamiyoshihara M, Hirai T, Kawashima O, *et al*. A clinicopathologic study of resected cases of adenosquamous carcinoma of the lung. Oncol-Rep 1998; 5(4): 861-5.
6. Wu N, Lu N, Chen Y. Adenosquamous carcinoma of the lung: a radiologic pathologic study. Zhonghua-Zhong-Liu-Za-Zhi 1997; 19(6): 434-6.
7. Shimizu J, Oda M, Hayashi Y, *et al*. A clinicopathologic study of resected cases of adenosquamous carcinoma of the lung. Chest 1996; 109(4): 989-94.
8. Riquet M, Perrotin C, Lang-Lazdunski L, *et al*. Do patients with adenosquamous carcinoma of the lung need a more aggressive approach? Inter-Med 2001; 40(11): 1132-5.
9. Kanazawa H, Ebina M, Ino-Oka N, *et al*. Transition from squamous cell carcinoma to adenocarcinoma in adenosquamous carcinoma of the lung. Am-J-Pathol 2000; 156 (4): 1289-98.
10. Steel VE, Netteshelm P. Unstable cellular differentiation in adenosquamous cell carcinoma. J Natl Cancer Inst 1981; 67: 149-54.
11. Ichinose Y, Hara N, Takamori S, *et al*. DNA ploidy pattern of each carcinomatous component in adenosquamous lung carcinoma. Ann Thorac Surg 1993; 55: 593-6.
12. Colby TV, Koss MN, Travis WD. Tumors of the lower respiratory tract. Atlas of Tumor Pathology, Third series, Fascicle 13. Washington, DC. Armed Forces Institute of Pathology 1995; pp 279-86.

肺部腺扁平癌：台中榮總之手術結果

葉周明　陳志毅　徐中平*　夏君毅　莊政諺**

肺部腺扁平癌是少見的肺癌，所有文獻記載皆強調此類肺癌的預後比肺腺癌或肺扁平細胞癌都差；在本文中，我們分析本院20年來肺部腺扁平癌之手術結果，並將討論此類肺癌之特性。*（胸腔醫學 2003; 18: 481-485）*

關鍵詞：腺扁平癌，肺癌

台中榮民總醫院外科部　胸腔外科　國立陽明大學*　彰化秀傳紀念醫院外科部　胸腔外科**
索取抽印本請聯絡：葉周明醫師，台中榮民總醫院外科部　胸腔外科，台中市台中港路三段 160 號

The Experience of Continuous Prone Position Ventilation in Patients with Severe Community—Acquired Pneumonia in Taichung Veterans General Hospital, Taiwan

Ming-Cheng Chan, Chieh-Liang Wu*, Su-Chen Pong**, Hsiu-Hwa Liu**, Li-Yin Chang**, Shiang-Liang King, Chi-Der Chian

Background: Prone position ventilation has been widely used in the treatment of acute lung injury/acute respiratory distress syndrome (ALI/ARDS). However, the time spent in prone position ventilation has varied greatly. We evaluated the safety of continuous prone position ventilation (CPPV) in the treatment of ALI/ARDS caused by severe community-acquired pneumonia.

Methods: We retrospectively reviewed 18 patients at Taichung Veterans General Hospital, Taiwan. They had received CPPV with an ACTION Bed Pad (Action Products, Inc., MD USA). In addition to demographic data, we recorded APACHE-II, lung injury scores (LIS), oxygenation status, and the complications during CPPV.

Results: Eighteen patients (M/F: 15/3) were treated with CPPV for 3.5 ± 1.65 days (range, 1-8). On admission day, the mean APACHE II and LIS were 24.78 ± 8.04, and 3.06 ± 0.53, respectively. The mortality rate was 33.3%, but only 2 patients died within 7 days. The complications included facial swelling (72.2%), shallow pressure sores (38.9%), pneumothorax (11.1%), and one episode of accidental extubation. Facial edema resolved soon after turning the patient back to the supine position. Pressure sores did not lead to major sequela. The peak PaO_2/FiO_2 improvement was on the 2nd day of CPPV. Most of the improvement could be maintained for 72 hours from the beginning of CPPV. Most of the patients could be ventilated with FiO_2 of no more than 60% after they had been turned back to the supine position.

Conclusion: Our experience showed that CPPV improved oxygenation and was a safe method for treating patients with ALI/ARDS due to severe community-acquired pneumonia. Three-day CPPV seemed to be necessary to avoid high FiO_2 after turning the patients back to the supine position. ***(Thorac Med 2003; 18: 486-492)***

Key words: adult respiratory distress syndrome/acute lung injury (ARDS/ALI), continuous prone position ventilation, and severe community-acquired pneumonia.

Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital
*National Yang-Ming University, School of Medicine, Taipei; **Department of Nursing, Taichung Veterans General Hospital
Address reprint requests to: Dr. Chieh-Liang Wu, Department of Internal Medicine, Taichung Veterans General Hospital, 160 Taichung Harbor Road, Section 3, Taichung, Taiwan, 407

Introduction

Acute respiratory distress syndrome and acute lung injury (ARDS/ALI) are two common and devastating complications of patients in the intensive care unit. The condition is defined by an acute onset episode with bilateral infiltrates on chest radiography and severe hypoxemia, but without obvious left-side heart failure [1]. The incidence of ARDS in previous reports ranged from 12.6 to 15.3 per 100,000 population per year [2-4]. The mortality rate was from 40 to 50 percent. The etiology of ARDS can be divided into direct and indirect lung injury. Pneumonia is the most common cause among these patients [5]. In addition to managing the underlying disease, intensive supportive care is necessary to improve oxygenation. Traditionally, ventilator support and a high concentration of inspired oxygen were employed. A protected strategy using a ventilator setting with low tidal volume and high positive end expiratory pressure has been proven beneficial [6]. However, the mortality rate is still high, and the survivors have even had some functional disabilities [7].

Prone position ventilation can improve oxygenation and respiratory mechanics in patients with ARDS/ALI, especially in the early stage [8]. The response of an improvement of oxygenation in prone position ventilation is poorer in patients with pulmonary causes of adult respiratory distress syndrom [9], but Gattinoni et al reported that the prone position improved the 10-day mortality in patients with lower PaO_2/FiO_2 [10]. However, there is no clinical guideline as to when and how prone position ventilation should be applied.

Adverse events in prone position ventilation, such as facial swelling, tubal disconnection, accidental extubation, and enteral feeding intolerance, are major concerns. The patients have been placed in the prone position from 2 to 12 hours in most of the studies [11-12]. In a previous report, 12-hour prone position ventilation was regarded as a safe procedure without significant adverse events. However, there is limited data regarding the placing of patients in the prone position continuously for more than 24 hours. In order to evaluate the efficacy and safety of CPPV, we reviewed 18 patients who had been admitted to the intensive care unit due to severe community-acquired pneumonia with acute respiratory failure. All of these patients were placed in the prone position continuously due to refractory hypoexmia.

Methods

Patient Eligibility

We retrospectively reviewed all the patients who had been admitted to the intensive care unit of Taichung Veterans General Hospital due to respiratory failure, and who had undergone mechanical ventilation from January 2000 to December 2002. All of these patients had severe community-acquired pneumonia with acute respiratory failure, and met the criteria for ALI/ARDS, using the American-European Consensus Conference definition. They had also been treated with CPPV for more than 24 hours. Their medical records were reviewed.

Treatment protocol

According to our ARDS/ALI treatment protocol, most of these patients had a Swan-Ganz catheter emplacement for hemodynamic monitoring, and an arterial line was set for blood pressure monitoring and blood sampling. All of them received oxygen saturation monitoring continuously by pulse oximeter .The choice of antibiotics was based on the guidelines of the American Thoracic Society for community-acquired pneumonia [13-14] and the clinical condition, as judged by the in-charge physicians. During the period of CPPV, all patients were sedated with a continuous infusion of midazolam, and received a neuromuscular blockade with atracurium besylate. The patients were kept at level 6 on the Ramsay scale.

Placing Patients in the Prone Position

The patients were turned into the prone position by three nursing staff personnel and a physician, using a standardized protocol. All the tubes and catheters were kept from dislodging by one nurse

during the procedure. The patients were placed on a silicon pad (Action Products, Inc., MD USA), and the dependent parts, including the hip and face, were placed on a silicon cushion. The position was changed every two hours, from side to side, to avoid pressure sore formation. A nasogastric tube was inserted and a pump was used for continuous feeding. The sputum was removed with a closed system suction tube (PHASCO Inc. Taiwan). The patients were turned in the supine position when the SpO_2>90% with FiO_2 <60% for more than 24 hours.

Statistical analysis

The data are expressed as mean ± standard deviation (range). The analysis of the changes in PaO_2/FiO_2 and FiO_2 were carried out using one-way ANOVA with a Friedman test. A *p* value less than 0.05 was considered statistically significant.

Results

Patient characteristics (Table 1)

Fifteen male and 3 female patients were included in this study. The mean APACHE-II and LIS scores on admission were 24.78 ± 8.04 and 3.06 ± 0.53, respectively. The mean PaO_2/FiO_2 ratio was 100.97 ± 32.15. The duration of CPPV was 3.5 ± 1.65 days (range, 1-8).

Complications of continuous prone positioning

The most common complications were facial swelling, gastrointestinal intolerance, and catheter dislodgement. One of the two episodes of pneumothorax occurred after turning the patient to the supine position. One episode of accidental extubation happened while turning the patient to the prone position. All of the complications are listed in Table 2.

Improvement of oxygenation

We also observed the serial change of oxygenation in each patient. The increase in PaO_2/FiO_2 ratios after prone positioning were 84%, 119%, and 98%, on three subsequent days. The peak PaO_2/FiO_2 improvement was on the second day after prone

Table 1. Demographic data of 18 patients with ARDS due to severe community-acquired pneumonia

Characteristic		Precentage
Mean age		58.5 (20-91)
Gender	Male	15 (83.3)
	Female	3 (16.7)
Comorbidity	Diabetes	4 (26.7)
	Chronic lung disease	1 (6.7)
	Cerebral vascular disease	2 (13.3)
	Chronic renal failure	0 (0)
	Cardiovascular disease	1 (6.7)
	Liver disease	3 (13.3)
APACHE II score		24.78
LIS before the prone position		3.06
PaO_2: FiO_2 before the prone position		100.97
14-day mortality		4 (22.2%)
28-day mortality		5 (27.8%)
Overall mortality		6 (33.3%)
Average duration of the prone position		3.56 (1-8)
Mean FiO_2 after turning to the supine position		61.54%
Positive end expiratory pressure		13

Table 2. Complications of continuous prone positioning in 18 patients with ARDS due to severe community-acquired pneumonia

Complication	Rate
Facial swelling	13 (72.2%)
Eye swelling	2 (11.1%)
Lip swelling	9 (50%)
Nipple swelling	2 (11.1%)
Pressure sores	7 (38.9%)
Vomiting	2 (11.1%)
Catheter dislodgement	1 (5.6%)
Accidental extubation	1 (5.6%)
Pneumothorax	2 (11.1%)

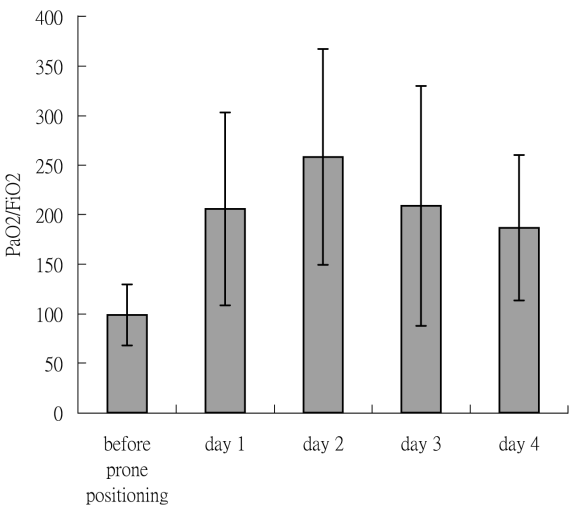


Fig. 1. PaO_2/FiO_2 is shown on the day before and after prone positioning. The peak improvement of oxygenation is on the 2nd day of prone positioning, and the effect is maintained for more than 3 to 4 days (84%, 119%, and 98% on 3 subsequent days after turning to the prone position, p=0.127).

positioning (Figure 1). A mild elevation of FiO_2 was seen after turning the patient to the supine position. Most of the patients could be kept in a good oxygenation status with FiO_2 no more than 60% in the supine position, after a 3-day prone position ventilation (Figure 2).

Discussion

Our results showed that CPPV improved oxygenation. The effect of prone positioning improving oxygenation started immediately on the 1st day after this maneuver, and could last for more than 3 days. However, the effect of improving oxygenation began to decrease on the 3rd day of turning the patient into the prone position. Most important of all, we found that the complications related to CPPV were no more than those reported by Gattinoni el al. [10].

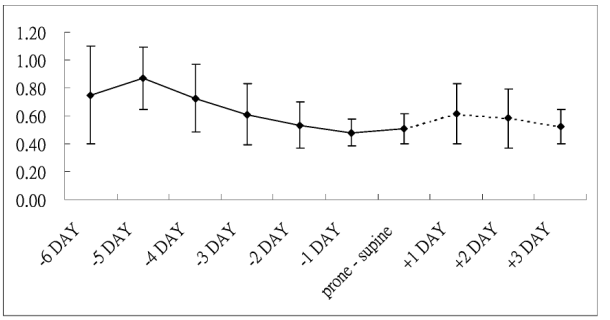


Fig. 2. In the ventilator setting, FiO_2 can be decreased to around 50% gradually after prone positioning. When the patients were turned back to the supine position, they needed around a 20% increase in FiO_2, but most of them could be maintained with FiO_2 less than 60%.

Placing patients in the prone position has been used with those with acute lung injury or acute respiratory distress syndrome for about thirty years [15-16]. The pathophysiological mechanisms of adult respiratory distress syndrome are severe inflammatory reaction in the alveoli, endothelial and epithelial injury, pulmonary infiltrates, and eventually severe hypoxemia and shock. Several mechanisms have been proposed to account for the improvement of oxygenation in the prone position, including better ventilation-perfusion matching, an increase in lung volume and alveoli recruitment, and regional changes in ventilation associated with alterations in compliance. The response rate of improved oxygenation in patients with ARDS, using the prone position, ranged from 57% to 100% [17-18]. Those with a larger shunt and more compliant chest wall will have a more significant improvement in oxygenation [19]. In our study of severe community-acquired pneumonia with refractory hypoxemia, most of the patients had an improvement in oxygenation after CPPV.

There is no universal agreement on how long

this maneuver should be employed and when it should be discontinued. Most investigators have kept patients in the prone position for 4 to 6 hours a day. Oxygenation usually worsened as the patients were turned into the supine position, and there was a significant fluctuation of oxygenation using such intermittent position-changing maneuvers. Some patients even had to be turned back to the prone position immediately, due to severe hypoxemia. It has been shown that there is a continuous improvement in oxygenation for 18 hours in the period of prone positioning, and the effect does not appear to reach a plateau [20]. Oxygenation deteriorates one hour after turning to the supine position, but there is no increase in the frequency of adverse events with such a long duration of prone positioning. In our study, the patients were kept in the prone position continuously for at least 24 hours. In most of the patients, oxygenation improved for 72 to 96 hours. Then, most of our patients were turned to the supine position. Oxygenation deteriorated only a little, as represented by a slight elevation of FiO_2 (Figure 2). The mean FiO_2 on the day of turning to the supine position was 50.77%, then 61.54% on the subsequent day. Five patients needed FiO_2 of more than 60%. One patient had pneumothorax and the FiO_2 was elevated to 100%. The condition of the other patients deteriorated later, and another three patients needed FiO_2 of more than 60% transiently. This amount of FiO_2 could be reduced later. This indicated that the mechanisms for improving oxygenation would disappear when ARDS developed into a fibroproliferative stage.

The etiology of ARDS can be divided into pulmonary and extrapulmonary events. The prognosis is usually poorer in the former group of the patients. It has been reported that the short-term survival rate of patients at high risk might improve with this maneuver, but the overall mortality did not change. Community-acquired pneumonia is the most common cause of adult respiratory distress syndrome. The mortality of patients with severe community-acquired pneumonia is related to the requirement of mechanical ventilation, the utilization of an oxygen supplement of more than 60%, and the coexistence of ARDS [21]. In our study, the overall mortality was 33%, and most of the mortality occurred within fourteen days after admission to the intensive care unit. For those patients with ARDS/ALI due to severe pneumonia, the outcome was promising. The setting up of a future prospective study in this area would be worthwhile.

Complications are a major concern when using this maneuver with patients. In our study, the prolongation of prone position ventilation did not result in additional significant complications associated with the maneuver. The most frequent complications were facial swelling, cutaneous bed sores, and enteral feeding intolerance. We used the ACTION Bed Pad to prevent pressure sores. This technique did work well during continuous prone positioning, even for as long as 8 days. Most of these complications were self-limiting and resolved themselves as the patients were turned to the supine position. Two major complications were observed in the study, and included two pneumothoraces and one accidental extubation. One episode of pneumothorax, which occured 3 days after turning the patient to the supine position, might be related to a ventilator setting with a high PEEP and the underlying pathological change. The accidental extubation occurred while turning the patient to the supine position, and was probably caused by an overextension of the neck. The more frequent of changing of position might create more such adverse events. As for enteral feeding intolerance, the use of a feeding pump could alleviate this problem. Feeding tolerance usually improved after turning the patient to the supine position.

In conclusion, CPPV for 24 hours a day was able to improve oxygenation in patients with community-acquired pneumonia with acute respiratory failure. We could see a trend toward an improvement in oxygenation for 72 to 96 hours after prone positioning. With the improvement in oxygenation, physicians have more time to correct the underlying medical problems, and the adverse effects caused by high inspired oxygen concentrations could thus be minimized. Most of the complications were minor or self-limiting. This protocol can also reduce

the nursing staff workload required for changing position, and decrease the incidence of some adverse events that occur during this maneuver. Further randomized prospective studies are needed to verify this protocol.

References

1. Bernard GR, Artigas A, Brigham KL *et al*. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149 (3 Pt 1): 818-24.
2. Arroliga AC, Ghamra ZW, Perez TA *et al*. Incidence of ARDS in an adult population of northeast Ohio. Chest 2002; 121(6): 1972-6.
3. Hudson LD, Steinberg KP. Epidemiology of acute lung injury and ARDS. Chest 1999; 116(1 Suppl): 74S-82S.
4. Antonsen K, Wetterslev J, Bonde J. [Incidence, severity and mortality of acute respiratory failure in Denmark]. Ugeskr Laeger 2000; 162(20): 2876-81.
5. Jerng JS, Yu CJ, Liaw YS *et al*. Clinical spectrum of acute respiratory distress syndrome in a tertiary referral hospital: etiology, severity, clinical course, and hospital outcome. J Formos Med Assoc 2000; 99(7): 538-43.
6. The Acute Respiratory Distress Syndrome Network Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342(18): 1301-8.
7. Herridge MS, Cheung AM, Tansey CM *et al*. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003; 348(8): 683-93.
8. Lee DL, Chiang HT, Lin SL *et al*. Prone-position ventilation induces sustained improvement in oxygenation in patients with acute respiratory distress syndrome who have a large shunt. Crit Care Med 2002; 30(7): 1446-52.
9. Lim CM, Kim EK, Lee JS *et al*. Comparison of the response to the prone position between pulmonary and extrapulmonary acute respiratory distress syndrome. Intensive Care Med 2001; 27(3): 477-85.
10. Gattinoni L, Tognoni G, Pesenti A *et al*. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 2001; 345(8): 568-73.
11. L'Her E, Renault A, Oger E *et al*. A prospective survey of early 12-h prone positioning effects in patients with acute respiratory distress syndrome. Intensive Care Med 2002; 28(5): 570-5.
12. McAuley DF, Giles S, Fichter H *et al*. What is the optimal duration of ventilation in the prone position in acute lung injury and acute respiratory distress syndrome? Intensive Care Med 2002; 28(4): 414-8.
13. Niederman MS, Mandell LA, Anzueto A *et al*. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001; 163(7): 1730-54.
14. Niederman MS, Bass JB, Jr., Campbell GD *et al*. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. American Thoracic Society. Medical Section of the American Lung Association. Am Rev Respir Dis 1993; 148(5): 1418-26.
15. Piehl MA, Brown RS. Use of extreme position changes in acute respiratory failure. Crit Care Med 1976; 4(1): 13-4.
16. Douglas WW, Rehder K, Beynen FM *et al*. Improved oxygenation in patients with acute respiratory failure: the prone position. Am Rev Respir Dis 1977; 115(4): 559-66.
17. Jolliet P, Bulpa P, Chevrolet JC. Effects of the prone position on gas exchange and hemodynamics in severe acute respiratory distress syndrome. Crit Care Med 1998; 26(12): 1977-85.
18. Stocker R, Neff T, Stein S *et al*. Prone postioning and low-volume pressure-limited ventilation improve survival in patients with severe ARDS. Chest 1997; 111(4): 1008-17.
19. Lee DL, Chiang HT, Lin SL *et al*. Prone-position ventilation induces sustained improvement in oxygenation in patients with acute respiratory distress syndrome who have a large shunt. Crit Care Med 2002; 30(7): 1446-52.
20. McAuley DF, Giles S, Fichter H *et al*. What is the optimal duration of ventilation in the prone position in acute lung injury and acute respiratory distress syndrome? Intensive Care Med 2002; 28(4): 414-8.
21. Torres A, el Ebiary M. [Severe community-acquired pneumonia]. Med Clin (Barc) 1999; 112(10): 378-9.

持續性俯臥姿使用於嚴重社區行肺炎病患—台中榮總之經驗

詹明澄　吳杰亮*　彭素貞**　劉秀華**　張麗銀**　金湘玲　江自得

背景：俯臥姿已經被廣泛的使用在急性肺損傷與急性呼吸窘迫症候群之病患，但使用俯臥姿的時間卻有很大的差異。本研究旨在評估持續性俯臥姿使用於嚴重社區型肺炎的安全性。

方法：這是一個回溯性的研究，收集的資料包括 APACHE-II score 、 LIS score 、氧氣濃度狀態及俯臥姿期間所產生的併發症等。

結果：我們共收集了 18 個嚴重社區型肺炎接受俯臥姿治療的病人。平均俯臥時間為 3.5 ± 1.65 天，入院時 APACHE-II 和 LIS 平均分別為 24.78 ± 8.04 及 3.06 ± 0.53 。死亡率為 33.3％ ，有兩名於 7 天內死亡。俯臥姿期間主要合併症為臉部水腫（72.2%），表淺型壓瘡（38.9%），氣胸（11.1%）及一次氣管內管滑脫。臉部水腫於仰臥時很快即消失，而壓瘡都不嚴重。於俯臥第二天 PaO_2/FiO_2 可達最大之改善，大部分病人於第四天回復仰臥，多能使 FiO_2 使用小於 60%。

結論：我們的經驗顯示持續性俯臥姿對嚴重社區型肺炎合併急性呼吸窘迫症候群的病患可改善血氧狀態，而且安全。三天持續性俯臥對於避免因回復仰臥而提高 FiO_2 是必要的。***（胸腔醫學 2003; 18: 486-492）***

關鍵詞：急性肺損傷與急性呼吸窘迫症候群，持續性俯臥姿，嚴重社區型肺炎

台中榮民總醫院　胸腔內科　國立陽明大學醫學院 *　台中榮民總醫院　護理部 **
索取抽印本請聯絡：吳杰亮醫師，台中榮民總醫院　胸腔內科，台中市中港路三段 160 號

Hyperbaric Oxygen Therapy for Carbon Monoxide Intoxication in a Case of Thermal Inhalation Injury

Kun-Lun Huang*,**, Ching-Pying Wu*, Wann-Cherng Perng*, Show-Yan Chen**

Severe carbon monoxide (CO) intoxication accounts for a major part of the fatal poisonings in developed countries. CO intoxication is nevertheless treatable if proper interventions are undertaken in time. Hyperbaric oxygen is the treatment of choice for CO intoxication. However, concurrent lethal conditions other than this treatable problem should be identified when the CO intoxication is a complication of fire victims. We report a case of acute CO intoxication, who recovered well from CO poisoning after hyperbaric oxygen therapy, but deteriorated into acute respiratory failure on the next day due to deterioration of the inhalation injury to the lungs. ***(Thorac Med 2003; 18: 493-499)***

Key words: hyperbaric oxygen therapy, carbon monoxide intoxication, inhalation lung injury

Introduction

Carbon monoxide (CO) intoxication is a serious health problem that accounts for about half of the fatal poisonings in the developed countries [1-2]. CO poisons tissues through severe cellular hypoxia, resulting in acute symptoms of headache, loss of consciousness, and death, as well as chronically unfavorable cognitive sequelae. Hyperbaric oxygen (HBO_2) therapy is often recommended for patients with acute CO intoxication. Advantages of treatment with hyperbaric oxygen include the enhancement of oxygen dissolving in the plasma [3-4] and the acceleration of CO elimination [5-6]. It has been shown that HBO_2 reduced not only the morbidity and mortality rates, but also the risk of cognitive sequelae [7-8].

Carbon monoxide is produced in a variety of conditions coexisting with an incomplete combustion of carbon-containing materials and a decrease in available oxygen. CO buildup in a fire environment is the most dangerous because it may complicate the management of patients with burn injury, smoke inhalation, and aspiration pneumonitis [9-10]. However, since most physicians accept HBO_2 as the treatment of choice for CO intoxication, patients with a high level of carboxyhemoglobin (COHb) will be immediately subjected to HBO_2 therapy, no matter how he (she) sustained this intoxication. The coexisting pulmonary complications may not be unmasked until the patient recovers from the CO poisoning. As the patient's condition deteriorates inside the hyperbaric chamber, it is almost impossible for a hyperbaricist to differentiate these symptomatic lung injuries from tension pneumothorax, which is the most serious pulmonary complication of HBO_2 therapy. We report herein a case of acute CO intoxication deterio-

* Division of Chest Medicine, Department of Internal Medicine, Tri-Service General Hospital, Taipei, Taiwan, R.O.C.
** Institute of Undersea and Hyperbaric Medicine, National Defense Medical Center, Taipei, Taiwan, R.O.C.
Address reprint requests to: Dr. Kun-Lun Huang, National Defense Medical Center, Institute of Undersea and Hyperbaric Medicine, 161 Ming-Chuan E. Road, Sec. 6, Taipei 114, Taiwan, R.O.C.

rating into acute respiratory failure due to inhalation injury to the lungs.

Case Report

A 66-year-old female was rescued from a fire environment and was sent to our emergency room in a coma. There was no burn injury to the skin or hair, only ash on her face. A high level of blood COHb proved the diagnosis of acute carbon monoxide intoxication (Table 1). The patient underwent HBO_2 therapy immediately after the diagnosis. Her consciousness recovered completely after one course of HBO_2 with 2.5 atmospheres absolute (ATA) for 90 minutes. The routine chest radiography taken in the MICU did not identify any significant abnormal lesion in the lung (Figure 1). After observation for 24 hours, the endotracheal tube was removed and she was transferred to the ward where she awaited for the second course of HBO_2 therapy.

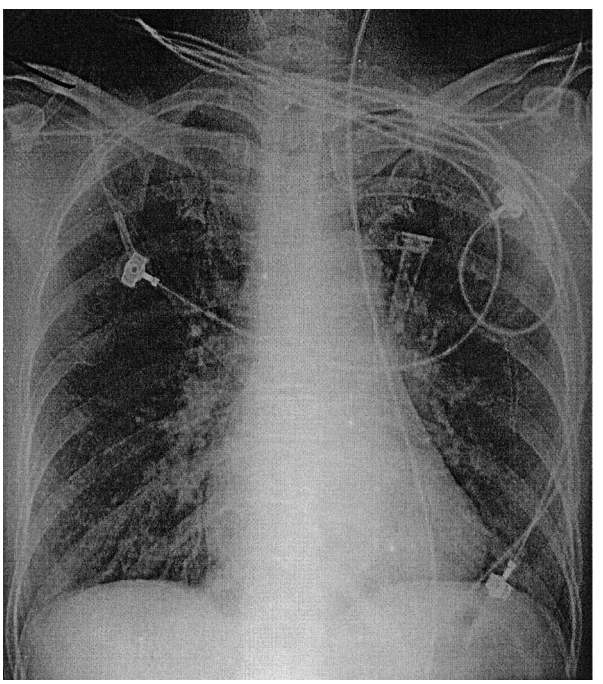


Fig. 1. The chest radiograph taken after completion of the first course of HBO_2 therapy and removal of the endotracheal tube on the second day of admission shows minimal infiltrations in the right lower lung.

The patient underwent another course of HBO_2 therapy in a relatively good condition on the next day. She did not have pulmonary complaints until the end of the HBO_2 treatment, when she suffered dyspnea and restlessness in the hyperbaric chamber. The physical examination revealed diffuse wheezing in both lung fields. The blood gas analysis identified severe hypoxemia with an arterial saturation of 80% (Table 1), and the chest radiography showed a collapse of the left upper lobe (Figure 2). As consciousness progressed into delirium, the patient was re-intubated and was transferred to the MCIU again for respiratory care and diagnostic procedures.

Bronchoscopy was done to identify the etiology of the lung collapse in the left upper lobe. It revealed diffuse ulcers of the mucosa from the lower trachea to the main bronchus on both sides. A thin layer of casts were coated on the right main bronchus extending to the bifurcation of the trancus intermediate. Since the casts were dry, the bronchial lumens were still patent. In the left lung, however, sticky gray sputum mixed with carbonaceous materials flooded into the lumen and plugged the upper lobe bronchus totally. The airways were so firmly obstructed that the sputum clots could not be removed simply by negative pressure suction. The sputum clots were chopped up by the biopsy

Table 1. The arterial blood analysis.

	On arrival (0 hr)	After intubation (1 hr)	After HBO_2 (6 hr)	Before reintubation (40 hr)
pH	7.097	7.315	7.413	7.193
$PaCO_2$, mmHg	53.6	33.6	42.0	69.1
HCO_3^-, mEq/L	16.2	17.1	25.8	26.0
PaO_2, mmHg	16.2	22.6	186.1	64.5
COHb, %	61.0	23.9	0.2	0.1

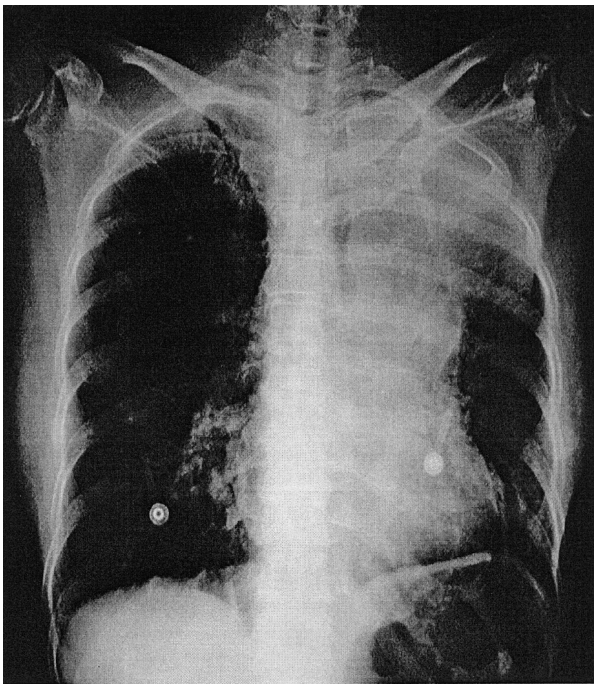


Fig. 2. The chest radiograph shows a collapse of the left upper lobe on the 3rd day of admission, when patient's condition deteriorated again into respiratory failure.

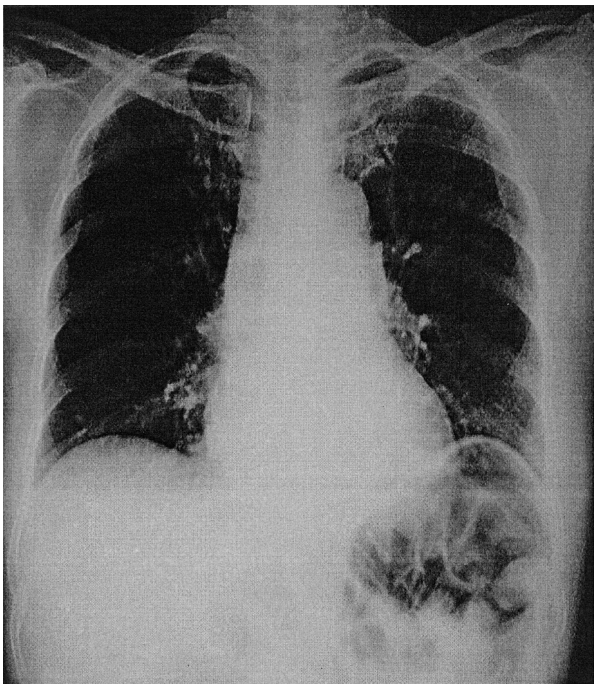


Fig. 3. The chest radiograph taken before discharge from the hospital shows full recovery of the pulmonary condition.

forceps and then removed piece by piece. The hypoxemia then reverted quickly. A repeated bronchoscopy was done on the next day, and revealed only erythema and swelling of the mucosa in the bronchial trees. The patient was weaned off the ventilator, the endotracheal tube was removed in a week, and the patient was discharged from the hospital after another week. The follow-up chest radiograph showed nearly full recovery of the lung atelectasis (Figure 3).

Discussion

Hyperbaric oxygen is the treatment of choice for CO intoxication. The advantages of this treatment include high oxygen delivery in the blood and rapid CO elimination from the tissues. The quick reversal of tissue hypoxia is life-saving. HBO_2 therapy also decreases the frequency and severity of delayed neurological sequelae in patients who have suffered CO poisoning. Disadvantages of HBO_2 therapy, on the other hand, include a potential oxygen toxicity, barotraumas such as tension pneumothorax, and the risks associated with waiting and transportation to a treatment center. Hyperbaricists are all able to accurately identify and to readily deal with these potential complications. However, it is important to realize that CO intoxication may be complicated with preexisting or combined conditions, a situation which is potentially as fatal as the CO poisoning itself.

Carbon monoxide is a colorless and odorless gas which passes rapidly through the air-blood barrier of the alveolar membrane and is extremely soluble in blood. CO binds avidly to hemoglobin in the blood. The affinity of hemoglobin for CO is 200 to 250 times as great as that for oxygen [11]. The consequence of this competitive binding is a left shift of the oxygen-hemoglobin dissociation curve and an alternation of this curve to a more hyperbolic shape, resulting in the impaired release of oxygen at the tissue level [12]. CO also binds the cytochrome system [9,13] in the mitochondria, causing severe cellular hypoxia, lipid peroxidation

[14], and organ damage. These mechanisms of intoxication are responsible for the acute multiple organ failure after CO intoxication, as well as for delayed neurologic injury and myocardial dysfunction, if not treated appropriately.

Hyperbaric oxygen increases blood oxygen delivery by elevating the physical dissolution of oxygen in the plasma. In the hyperbaric environment of 2.5 ATA, the plasma oxygen content is 2.5 times as great as that breathing oxygen at an ambient pressure of 1 atmosphere, and 12.5 time greater than breathing room air [3]. The oxygen content in plasma (6 vol%) is sufficient for tissue survival without oxygen supplied by hemoglobin. Hyperbaric oxygen also accelerates CO elimination. The half-life of carboxyhemoglobin is 4 to 6 hours when the patient is breathing room air, 40 to 80 minutes breathing oxygen, and 15 to 30 minutes in HBO_2 therapy [5,15]. The rationale of using HBO_2 therapy as the primary treatment for CO intoxication is clear, and updated data suggest the beneficial effects of hyperbaric oxygen in reducing mortality and morbidity due to CO intoxication [1,2,7]. In a randomized, controlled clinical trial, Ducasse et al. [16] demonstrated that HBO_2 reduces the time to improvement of the patient's clinical and biological conditions after CO poisoning. Tham et al. [7], in a randomized prospective study, reported that 23% of patients with CO intoxication managed with only oxygen breathing developed subtle delayed neuropsychiatric symptoms, whereas none of the other 30 patients treated with hyperbaric oxygen did. In a recent double-blind, randomized trial, Weaver et al. [8] further demonstrated the advantages of HBO_2 therapy in reducing the risk of cognitive sequelae after acute CO intoxication.

As most therapies do, hyperbaric oxygen carries risks during and after treatment. Acute complications of HBO_2 include barotraumas to the nasal sinus and the tympanic membrane of the ears, oxygen toxicity to the central nervous system, and tension pneumothorax [3]. The manifestations include pain in the ear and nasal sinus or epistaxis in barotrauma, convulsion or vomiting in O_2 toxicity, and dyspnea and cardiovascular collapse in pneumothorax. Although these complications may cause serious injury to the patient, they are all reversible with proper management. The symptoms seen in our case when she completed the second course of HBO_2 therapy resemble those of the most serious complication of the treatment, i.e., tension pneumothorax. However, this possibility was excluded simply by taking a chest radiograph, which showed no pneumothorax, but a collapsed left lung (Figure 2). Since atelectasis of the lung has never been reported as a complication of HBO_2 therapy, other causes should be evaluated to manage the problem of dyspnea.

The adverse effects of smoke inhalation and thermal injury are the leading causes of respiratory morbidity and mortality in fire victims. Certainly, toxic gases such as CO and hydrogen cyanide produced in the fire environment play important roles in causing cellular hypoxia during smoke inhalation. In addition, toxic chemicals such as hydrogen chloride and aldehydes present in smoke are mucosa irritants resulting in serious damage to the bronchial mucosal, pulmonary edema, and death. Furthermore, thermal injury to respiratory mucosa due to high temperatures in heat and flames may also cause respiratory complications in fire victims [6]. The pathogeneses of thermal and chemical injuries include the impairment of the mucociliary function, mucus hypersecretion, epithelial sloughing, surfactant inactivation, increased vascular permeability, and bronchoconstriction [17-18]. Unlike the manifestations of gas intoxication occurring immediately after exposure in the fire environment, the symptoms of airway and mucosal injuries are usually acute, occurring within the first 24 to 48 hours of exposure, or subacute, occurring 3 to 4 days after the original injury [19]. Our patient suffered dyspnea and disturbance of consciousness 40 hours after exposure to the fire environment. Thermal or chemical injury to the airway should be differentiated from the complications of hyperbaric treatment because the symptoms also occurred on completion of second course of HBO_2 therapy.

Early diagnosis of inhalation injury to the lung is difficult until it becomes clinically symptomatic.

Fire victims may remain completely asymptomatic for more than 72 hours and then quickly develop acute respiratory distress syndrome [20]. The chest X-ray examination and arterial blood gas analysis may have little value in disease prediction [21-22]. Although bronchoscopy may be useful in predicting the development of lung injury in patients exposed to a fire environment [20], it is invasive and is usually not a routine examination. However, identifying thermal inhalation injury of the lung in a fire victim presenting pulmonary symptoms is important because of the different treatment outcome. In a study of 2297 burn patients, Thompson et al. [23] reported an overall mortality rate of 56% in patients with inhalation injury, in contrast to 4.1% in those without pulmonary involvement. In addition, the management of inhalation injury is frustrating because there is no specifically effective treatment. In a case presenting acute respiratory failure for any etiology, the bronchoscopy should be done before the endotracheal tube is removed, and the ventilator weaning and extubation may be postponed if thermal injury to the airway is identified. This may avoid a delayed respiratory failure and reduce the risk of re-intubation.

In summary, fire victims may come to medical attention with a variety of presentations, including acute and subacute/chronic manifestations. Carbon monoxide intoxication is the most treatable complication of the smoke inhalation injury, and hyperbaric oxygen is the treatment of choice. As patients survive the acute respiratory injury, it is important to identify the risk of subacute/chronic complications, because they contribute to the high mortality rate of fire victims, and because the treatments are mostly supportive.

References

1. Ernst A, Zibrak JD. Carbon monoxide poisoning. N Engl J Med 1998; 339: 1603-8.
2. Weaver LK, Hopkins RO, Elliott G. Carbon monoxide poisoning. N Engl J Med 1999; 340: 1290-2.
3. Kindwall EP. A history of hyperbaric medicine. In: Kindwall EP, ed. Hyperbaric Medicine Practice. Flagstaff; Best Publishing Co., 1994: 1-16.
4. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. N Engl J Med 1996; 334: 1642-8.
5. Pace N, Strajman E, Walker EL. Acceleration of carbon monoxide elimination in man by high pressure oxygen. Science 1950; 111: 652-4.
6. Thom SR, Keim LW. Carbon monoxide poisoning: a review epidemiology, pathophysiology, clinical findings, and treatment options including hyperbaric oxygen therapy. J Toxicol Clin Toxicol 1989; 27: 141-56.
7. Thom SR, Taber RL, Mendiguren II, *et al*. Delayed neuropsychologic sequelae after carbon monoxide poisoning: prevention by treatment with hyperbaric oxygen. Ann Emerg Med 1995; 25: 474-80.
8. Weaver LK, Hopkins RO, Chan KJ, *et al*. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 2002; 347: 1057-67.
9. Thom SR. Smoke inhalation. Emerg Med Clin N Am 1989; 7: 371-87.
10. Ely EW, Moorehead B, Haponik EF. Warehouse workers' headache: emergency evaluation and management of 30 patients with carbon monoxide poisoning. Am J Med 1995; 98: 145-55.
11. Rodkey FL, O'Neal JD, Collison HA, *et al*. Relative affinity of hemoglobin S and hemoglobin A for carbon monoxide and oxygen. Clin Chem 1974; 20: 83-4.
12. Roughton FJW, Darling RC. The effect of carbon monoxide on oxyhemoglobin dissociation curve. Am J Physiol 1994; 141: 17-31.
13. Zhang J, Piantadosi CA. Mitochondrial oxidative stress after carbon monoxide hypoxia in the rat brain. J Clin Invest 1992; 90: 1193-9.
14. Thom SR. Carbon monoxide-mediated brain lipid peroxidation in the rat. J Appl Physiol 1990; 68: 997-1003.
15. Smith G. The treatment of carbon monoxide poisoning with oxygen at two atmosphere absolute. Ann Occup Hyg 1962; 5: 259-63.
16. Ducasse JL, Celsis P, Marc-Vergnes JP. Non-comatose patients with acute carbon monoxide poisoning: hyperbaric or normobaric oxygenation? Undersea Hyperb Med 1995; 22: 9-15.
17. Fein A, Grossman RF, Jones JG, *et al*. Carbon monoxide effect on alveolar epithelial permeability. Chest 1980; 78: 726-31.
18. Clark WR, Nieman G, Hakim TS. Distribution of extra-

vascular lung water after acute smoke inhalation. J Appl Physiol 1990; 68: 2394-402.
19. Loke J, Paul E, Virgulto JA, *et al*. Rabbit lung after acute smoke inhalation. Cellular responses and scanning electron microscopy. Arch Surg 1984; 119: 956-9.
20. Masanes MJ, Legendre C, Lioret N, *et al*. Using bronchoscopy and biopsy to diagnose early inhalation injury. Macroscopic and histologic findings. Chest 1995; 107: 1365-9.
21. Robinson TJ, Bubna-Kasteliz B, Stranc MF. Alterations in pulmonary ventilation and blood gases in acute burns. Br J Plast Surg 1972; 25: 520-60.
22. Moylan JA, Adib K, Birnbaum M. Fiberoptic bronchoscopy following thermal injury. Surg Gyn Obs 1975; 140: 541-3.
23. Thompson PB, Herndon DN, Traber DL, *et al*. Effect on mortality of inhalation injury. J Trauma Inj Inf Crit Care 1986; 26: 163-5.

熱吸入性肺損傷合併一氧化碳中毒之高壓氧治療—病例報告

黃坤崙*,** 吳清平* 彭萬誠* 陳紹原**

一氧化碳中毒雖然是已開發國家中最常見的致命性中毒事件，只要及時處理得當通常是可以治癒的。高壓氧治療是一氧化碳中毒之首選治療方式。在火災生還病人合併的問題中，一氧化碳中毒常常不是單獨存在；相反的，許多足以致命的呼吸道傷害應及時予以診斷。我們在此報告一火災生還者，初步診斷為急性一氧化碳中毒而接受高壓氧氣治療。病人雖然在治療後迅速恢復意識，並成功拔除氣管內管，卻在隔日又發生急性呼吸衰竭。 最後診斷是濃煙嗆傷合併熱吸入肺損傷及急性一氧化碳中毒。*(胸腔醫學 2003; 18: 493-499)*

關鍵詞：高壓氧治療，一氧化碳中毒，熱吸入性肺損傷

三軍總醫院 胸腔內科* 國防醫學院 海底醫學研究所**
索取抽印本請聯絡：黃坤崙醫師，三軍總醫院 胸腔內科，臺北市內湖區民權東路六段 161 號

Pleural Effusion as the Initial Clinical Presentation in Pulmonary Cryptococcosis — A Report of a Case with Unusual Manifestation, and a Literature Review

Chia-Loung Hsieh, Chi-Huei Chiang, Reury-Perng Perng

The diagnosis of the pulmonary cryptococcosis is relatively difficult. This is due to its non-specific symptoms and usually negative culture results, the low sensitivity of the serum cryptococcal antigen test, and the wide variety of radiological appearances. Although immunocompromised patients are at the highest risk, it may occur in patients with normal immunity. In immunocompetent patients with pulmonary cryptococcosis, several radiographic patterns are exhibited, including pulmonary nodules, interstitial infiltrations, and consolidation. Pleural effusion rarely occurs in immunocompetent patients.

This patient was a victim of pulmonary tuberculosis (TB) complicated with pleural effusion and chest wall involvement. After complete anti-TB treatment, the pleural effusion disappeared. Unfortunately, 2 years later, right-side pleural effusion recurred and a loss of body weight was also noted. The initial impressions were 1, pulmonary TB reactivation complicated with pleural effusion; and 2, adenocarcinoma of the lung with pleural effusion. Sono-guided thoracocentesis was performed. Cytology examinations of the pleural fluid showed highly suspected cryptococcus infection, but the cryptococcal antigen test showed negative. He underwent a video-assisted thoracoscopic decortication for further diagnosis, and treatment for fibrothorax. The pathology of the tissue from decortication showed yeast-like microorganisms. Due to the renal impairment after amphotericin B treatment, he received fluconazole therapy, and regularly followed up in the outpatient department. After antifungus treatment, he gained weight and felt better than before. Based on this unusual presentation of cryptococcosis, physicians should consider the possibility of cryptococcosis of the lung complicated with pleural effusion in the differential diagnosis of chronic pleural effusion in Taiwan. ***(Thorac Med 2003; 18: 500-506)***

Key words: cryptococcosis, pleural effusion

Introduction

Cryptococcosis is an uncommon infection of the lung. Since 1980, the occurrence of fungal infection has been rising rapidly worldwide [1]. This increase in the rate of fungal infections has been attributed mainly to the advent of the acquired immune deficiency syndrome, the increasing use of broad-spectrum antibiotics, widespread use of immunosuppressive agents in transplantation and

Chest Department, Taipei Veterans General Hospital
Address reprint requests to: Dr. Chi-Huei Chiang, Chest Department, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan

cancer treatment, intravascular devices, and the increasing number of critically ill patients [1-4]. Cryptococcal infection has followed the same pattern. However, the diagnosis of this disease is relatively difficult. This is mainly due to its non-specific symptoms and usually negative sputum culture results [5], the low sensitivity of the serum cryptococcal antigen test [6,7], and the wide variety of patterns on chest radiographs [2,5,8-11]. Radiographic findings of pulmonary cryptococcosis are as follows: nodule(s) or mass(es), interstitial infiltrates, consolidation, hilar or mediastinal lymphadenopathy, cavitary lesions, and pleural effusions [2,5,8,9]. Pleural effusion occasionally occurs in immunocompromised patients with cryptococcosis and suggested disseminated disease. In normal hosts with cryptococcosis, pleural effusion is rarely seen [10].

Herein, we report a case of cryptococcosis in a non-immunosuppressed patient, who presented with the unusual initial manifestation of right-side pleural effusion.

Case Report

Mr. Chang, a 91-year-old male, had been quite well in the past until 2 years ago, when chronic dyspnea for 7-8 months was noted. He visited a local clinic, but in vain. A mass lesion on the right lower chest wall then developed. Body weight loss and general weakness were also noted. He visited the same clinic again. Because of an abnormal chest film, he was then transferred to our hospital. Chest X-ray and computed tomography (CT) revealed a massive amount of right-side pleural effusion with some air in it. Chest sonography with thoracocentesis was done. Pleural fluid was exudates. Cytology and acid-fast staining of the pleural fluid were all negative. Needle aspiration from the right lower chest mass was performed. Acid-fast staining of the aspirate of the mass showed TB bacilli (1+). Under the impression of right chest wall skin TB infection and TB pleurisy, he was given anti-TB treatment for 9 months. The mass on the right lower chest wall improved after the treatment. Follow-up chest films were taken months after the termination of the anti-TB treatment and showed only right-side destroyed lung. No pleural effusion was found.

Unfortunately, intermittent cough developed 2 months previous to this admission. He received examinations at a local clinic and pleural effusion was noted. He was then transferred to our hospital where the chest X-ray (Figure 1) and CT scan (Figure 2) revealed right-side pleural effusion and a thickening of the right pleura. Chest sonography was done and showed a small amount of complex pleural effusion. Thoracocentesis was performed and turbid yellowish fluid was aspirated out. The pH value of the pleural fluid was 7.183. The white blood cell count of the pleural fluid was 22/mm^3 with lymphocytes predominating (neutrophils : lymphocytes = 0:22). Initial impressions were: 1. pulmonary TB reactivation complicated with pleural effusion; and 2. adenocarcinoma of the lung

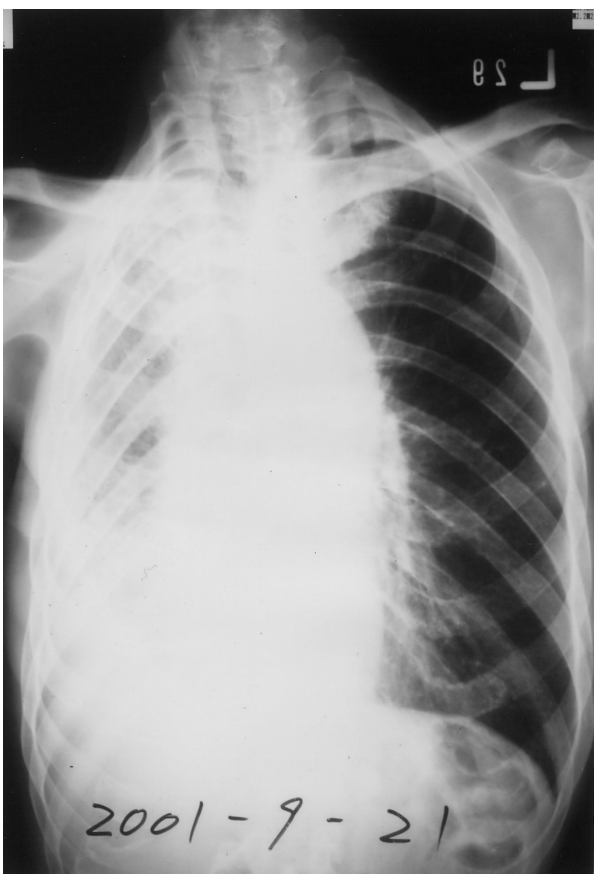


Fig. 1. Chest X-ray on presentation shows volume reduction of the right lung. Right-side pleural effusion and pleural thickness are noted.

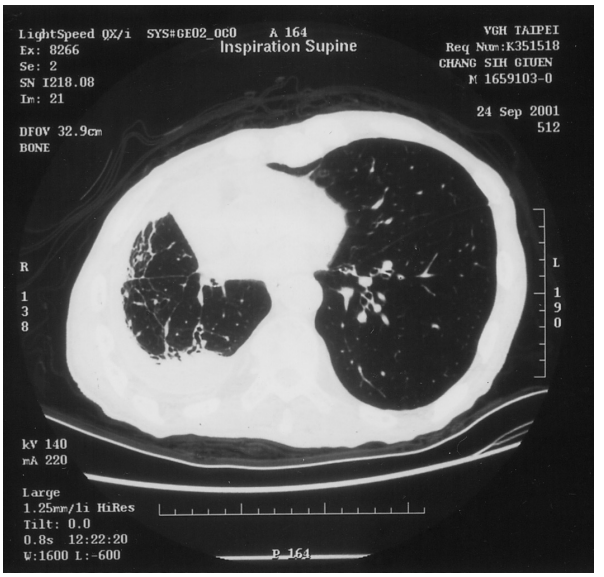


Fig. 2. Chest CT scan shows volume reduction of the right lung. Right side pleural effusion and pleural thickness are noted. An increased reticular shadow with interstitial fibrosis in the right lung are also noted.

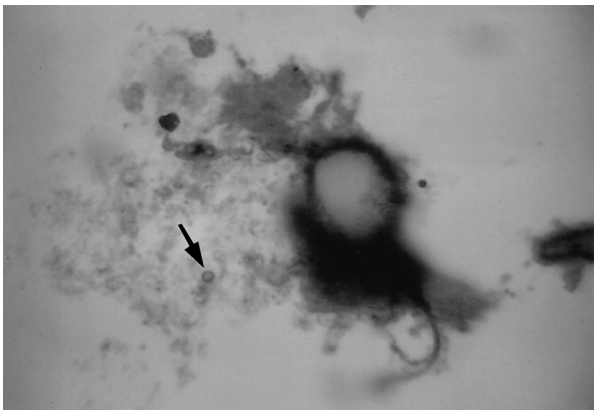


Fig. 3. Pleural effusion cytology shows thin-walled yeast-like micro-organisms (arrow), highly suspicious of Cryptococcus. (Papanicolaou stain, x400)

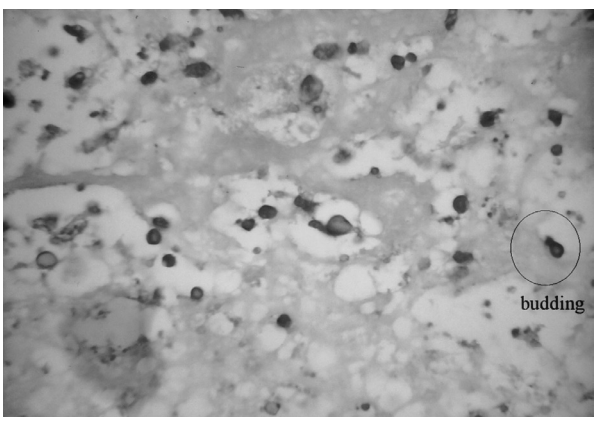


Fig. 4. Pathological exam reveals thin-walled yeast-like micro-organisms with budding, positive for PAS stain (x400)

with pleural effusion. However, acid-fast staining of the pleural fluid showed negative. Cytology of the fluid was highly suspicious for cryptococcosis (Figure 3). He was then admitted. After admission, he was in a cachectic status and was bed-ridden all day. No fever was noted. Laboratory data revealed WBC 6200 /mm³ (neutrophils:lymphocytes=61.3: 23.4). Serum IgG, IgA, IgM, C3, C4, CRP, RF, and ANA were checked to rule out the possibility of collagen vascular diseases-induced pleural effusion, but all were within normal limits. A repeated sonographic thoracocentesis was performed. Acid-fast staining of the pleural fluid showed negative. Pleural effusion cytology was highly suspicious of cryptococcosis again. Pleural biopsy was also performed, but showed only fibrin materials with no evidence of inflammatory reaction, tissue necrosis, or granuloma formation. Under the suspicion of cryptococcal infection, amphotericin B was used and was later shifted to fluconazole due to amphotericin B-induced acute renal deterioration. However, a fungus culture of the pleural fluid was negative, and the latex test-cryptococcal antigen showed negative, too. An anti-HIV EIA test was performed to rule out the possibility of immunodeficiency status, but the report was also negative. For further diagnosis and management of the fibrothorax, he underwent video-assisted thoracoscopic decortication. Right-side pleural thickening with much necrotic tissue and fibrin tissue coating on the whole right pleura were noted. The pathology of the tissues obtained from decortication showed a picture of necrotic tissue admixed with organizing fibrin material in which yeast-like micro-organisms were noted (Figure 4). He then received fluconazole treatment, the symptoms subsided, and the general condition improved markedly. He was discharged and regularly followed up at outpatient department.

Discussion

Cryptococcosis is caused by *Cryptococcus neoformans*, a thin-walled, non-mycelial, budding yeast, 2 to 20 μm in diameter, that is characterized by a thick polysaccharide capsule best seen on India ink stains [9]. Three genetically distinct varieties of *C. neoformans* have been recognized: *C. neoformans var grubii* (serotype A), *C. neoformans var. neoformans* (serotype D), and *C. neoformans gattii* (serotype B and C). The majority of infections world-wide are caused by isolates of *C. neoformans var. grubii*, serotype A, which is ubiquitous in nature, and associated with soil, avian habitats, and decaying wood. Isolations of *C. neoformans var. gattii* are largely restricted to tropical and subtropical regions, where they are found in association with decaying wood and the almond trees in Colombia. *C. neoformans var grutii* and *C. neoformans var neoformans* predominantly affect immunocompromised hosts, while the variety *gattii* nearly always infects immunocompetent hosts [3].

Cryptococcosis usually occurs in males. In the study by Ronald Rozenbaum et al, non-immunosuppressed patients with cryptococcosis were predominantly male (3:2). Cryptococcosis usually occurs in the third to fifth decades. However, the mycosis has also developed in children and the elderly [11].

Pulmonary infection with *C. neoformans* has been known since Sheppe's report in 1924 [12]. In Taiwan, Lee et al first reported two cases of cryptococcosis at National Taiwan University Hospital in 1957 [13]. In the following years, cryptococcosis has been reported only rarely. With the advent of the acquired immune deficiency syndrome epidemic from the early 1980s to the early 1990s, the incidence of cryptococcosis has risen dramatically. The frequency of cryptococcosis has been declining since the mid-1990s in Europe and America due to the development of more effective antiretroviral therapy and prophylactic treatment regimens designed to prevent fungal infections. However, this disease is still recognized as one of the most common life-threatening opportunistic infections of immunocompromised patients [1].

Although the respiratory tract is thought to be the normal portal of entry for *C. neoformans*, the most favorable site for *C. neoformans* is the central nervous system. The respiratory tract was the second most favorable site for cryptococcus infection, in one report [11]. The majority of nonimmunosuppressed patients with pulmonary cryptococcosis do not have respiratory symptoms at the time of admission. Cough and chest pain were the most frequent clinical manifestations [11]. Other pulmonary symptoms include dyspnea, fever, weight loss, purulent sputum, and hemoptysis [2,9,11]. Due to its clinically "silent" characteristics, the incidence of pulmonary cryptococcosis may be underestimated.

Radiographically, pulmonary cryptococcosis exhibits a wide variety of patterns. In 1968, Winston [8] analyzed seventeen cases with pulmonary cryptococcosis, and seven radiographic features were identified: pulmonary infiltrates (nine patients), nodule(s) (two patients), consolidation (one patient), pulmonary infiltrates with pleural effusion (one patient), infiltrates with a pulmonary mass (one patient), infiltrates with a hilar mass (one patient), an enlarged left hilum (one patient), and pleural effusion alone (one patient).

Ronaldo [11] analyzed 52 patients with cryptococcal pulmonary involvment (34 patients were nonimmunosuppressed, seven patients were victims of AIDS, and eleven patients were patients with other diseases or with immunosuppressive drug usage). In the nonimmunosuppressed group, seven types of radiographic findings were identified: nodules (70.6%), alveolar infiltrates (20.6%), mixed (alveolar and interstitial) infiltrates (5.9%), cavitation (5.8%), pleural effusion (2.9%), and normal (2.9%). In the AIDS group, five types of radiographic findings were noted: interstitial infiltrates (28.6%), mixed (alveolar and interstitial) infiltrates (42.9%), cavitation (14.3%), pleural effusion (28.6%), and normal (14.3%). In the group of patients with other diseases or with immunosuppressive drug usage, seven types of radiographic findings were noted: nodules (63.6%), alveolar

infiltrates (18.2%), interstitial infiltrates (9.1%), cavitation (9.1%), pleural effusion (9.1%), mediastinal lymph nodes involvement (9.1%), and normal (9.1%).

Judith [9] studied the radiographic patterns of pulmonary cryptococcosis patients without HIV infection. In the disseminated cryptococcosis group (six patients), three patients presented with interstitial infiltrates, one solely with pleural effusion, one with nodule and interstitial infiltrates, and one with nodular lesions. In the definite cryptococcosis group (seven patients), two patients presented with consolidation, two with interstitial infiltrates, one with interstitial infiltrates and pleural effusion, and one with nodular infiltrates with pleural effusion. Among the 13 patients, only three presented with pleural effusion.

In Taiwan, according to a review by Chao-Chuang Chou (14 patients) [2], the characteristic radiographic findings of pulmonary cryptococcosis were as follows: single or multiple nodule(s) or mass (es) (64.3%); infiltration (21.4%), and consolidation (7.1%). Cavitation occurred in seven cases (50%). Pleural effusion presented in only one patient (7.1%).

Pleural effusion is an uncommon presentation of pulmonary cryptococcosis, occasionally occurring in immunocompromised patients, and usually accompanied by nodular lesions or interstitial infiltrates. However, it rarely occurs in immunocompetent patients. Our case was an immunocompetent patient with pulmonary cryptococcosis presenting with pleural effusion. Based on a review of the literature, this is quite uncommon.

In our case, the latex test-cryptococcal antigen showed negative. Serum tests for cryptococcal antigen are specific [14], however, the sensitivity of this test is low. Edson and coworkers at the Mayo Clinic found cryptococcal antigen in the serum of only 1 of 13 patients with cryptococcosis (unpublished observations) [6]. In the study by Duperval [7], latex cryptococcal antigen was positive in three of eight patients (37%). Therefore, the failure to detect cryptococcal antigen in the serum of a patient with pneumonia does not exclude the possibility of cryptococcal pulmonary infection. Núñez [15] postulated that a positive serum cryptococcal antigen might reflect an increased risk for more severe local disease or for dissemination in patients with isolated pulmonary cryptococcosis, and may serve as a marker of disease activity or overall organism burden. In febrile patients with advanced HIV disease, a screening serum cryptococcal antigen is useful, and a high titer is suggestive of invasive disease [16]. However, this serum test for cryptococcal disease is less sensitive to diagnosing cryptococcal patients without AIDS [9].

Firm guidelines for the treatment of cryptococcosis are still unavailable. Kerkering concluded that immunocompetent hosts with isolated pulmonary cryptococcosis do not require anti-fungal therapy [17]. Judith concurred in this opinion for asymptomatic patients, but he thought patients who are symptomatic, who have a positive serum cryptococcal antigen, and who have underlying immunological disorders, should be treated [18]. Administration of amphotericin B, alone or in combination with 5-fluorocytosine was the standard regimen until the late 1980s. Due to its relatively high failure rate, high incidence of adverse reactions, and the inconvenience of prolonged intravenous treatment, new anti-fungal drugs such as fluconazole have been tested. Dromer found that the treatment efficacy did not differ in groups treated with combination or single-use amphotericin B- and fluconazole [18]. Therefore, the best treatment regimen and duration are still controversial. We propose that the dose, duration, and combination therapy should be based on the severity of disease and outcome of treatment.

There are many differential diagnoses in patients with exudative pleural effusion. In the case reported herein, pleural effusion cytology was negative for malignant cells, and no neoplastic lesion was identified, so neoplastic disease was less likely. Acid-fast staining of the pleural fluid and pathology of the pleural biopsy were performed for the possibility of TB pleurisy, but all showed negative. Serum IgG, IgA, IgM, C3, C4, RF, and ANA were checked to rule out the possibility of collagen vascular diseases, but all were within

normal limits. The only positive finding was highly suspected cryptococcosis. However, pulmonary cryptococcosis presenting with only pleural effusion is quite uncommon, and the serum cryptococcal antigen test showed negative. For further diagnosis, a surgical intervention was performed, yielding the final diagnosis and ruling out the possibility of TB reactivation complicated with pleural effusion. Although pleural effusion as a clinical presentation in pulmonary cryptococcosis is rare, in the future, it should be taken it into consideration for the differential diagnosis of chronic pleural effusion in Taiwan.

References

1. Kwon-Chung KJ, Sorrell TC, Dromer F, *et al*. Cryptococcosis: clinical and biological aspects. Medical Mycology 2000; 38, suppl 1: 205-13.
2. Chou CC, Chen CR, Lee LN, *et al*. Pulmonary cryptococcosis: clinical analysis and treatment of 14 cases. J Formosan Med Assoc 1987; 86: 459-66.
3. Ellis D, Marriott D, Hajjeh RA, *et al*. Epidemiology: surveillance of fungal infections. Medical Mycology 2000; 38, suppl 1: 173-82.
4. Ko SC, Chen KY, Hsueh PR. Fungal empyema thoracis an emerging clinical entity. Chest 2000; 117: 1672-8.
5. Campbell GD. Primary pulmonary cryptococcosis. Amer. Rev. Resp. Dis. 1966; 94: 236-43.
6. Jensen WA, Rose RM, Hammer SM, *et al*. Serologic diagnosis of focal pneumonia caused by *Cryptococcus neoformans*. Am Rev Respir Dis 1985; 132: 189-91.
7. Duperval R, Hermans PE, Brewer NS, *et al*. Cryptococcosis, with emphasis on the significance of isolation of *Cryptococcus neoformans* from the respiratory tract. Chest 1977; 72: 13-9.
8. Warr W, Bates JH, Stone A, *et al*. The spectrum of pulmonary cryptococcosis. Annals of Internal Medicine 1968; 69(6): 1109-16.
9. Aberg JA, Mundy LM, Powderly WG. Pulmonary cryptococcosis in patients without HIV infection. Chest 1999; 115: 734-40.
10. Woodring JH, Ciporkin G, Lee C, *et al*. Pulmonary cryptococcosis. Seminars in Roentgenology 1996; 31 (1): 67-75.
11. Rozenbaum R, Goncalves AJ. Clinical epidemiological study of 171 Cases of cryptococcosis. Clinical Infectious Diseases 1994; 18: 369-80.
12. Sheppe WM. Torula infection in man. Amer. J. Med. Sci. 1924; 167: 91.
13. Lee TK, Chiu WS, Hsu CJ, *et al*. Cryptococcosis: a review with two case reports. J Formosan Med Assoc 1959; 58: 567-78.
14. Stockman L, Roberts ED. Specificity of the latex test for Cryptococcal antigen: a rapid, simple method for eliminating interference factors. J Clin Microbiol 1983; 17: 945-7.
15. Núñez M, Peacock JE, Chin R. Pulmonary cryptococcosis in the immunocompetent host: therapy with oral fluconazole: a report of four cases and a review of the literature: Chest 2000; 118: 527-34.
16. Chuck SL. Infections with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. N Engl J Med 1989; 321: 794-9.
17. Kerkering TM, Duma RJ, Shadomy S. The evolution of pulmonary cryptococcosis: clinical implications from a study of 41 patients with and without compromising host factors. Annals of Internal Medicine 1981; 94: 611-6.
18. Dromer F, Mathoulin S, Dupont B, *et al*. Comparison of the efficacy of amphotericin B and fluconazole in the treatment of cryptococcosis in human immunodeficiency Virus-negative patients: retrospective analysis of 83 cases. Clinical Infectious Diseases 1996; 22, suppl 2: S154-60.

以肋膜腔積液爲表現之肺部新形隱球菌感染—病例報告及文獻回顧

謝佳龍　江啟輝　彭瑞鵬

肺部新形隱球菌感染是一不常見的黴菌感染症。由於其症狀較不具特異性，病原體不易由肺部分泌物培養出來，且其影像學上會有許多各種不同的表現，因此診斷上相對來說較為困難。雖然免疫功能不全的病患對罹患此病會有較高的危險性，它也會發生在免疫功能正常的病人身上。以免疫功能正常的病患來說，肺部的侵犯主要有三種形式：肺部結節，間質性浸潤，以及肺實質性病變。以肋膜積液來表現者極為罕見。

在此我們報告一個病例：他是一個結核性肋膜炎合併有胸壁結核菌感染的患者，經過完整的抗結核藥物治療，肋膜積液已完全消失。兩年後，肋膜積液再度出現，初步門診臆斷為肺結核復發或是肺腺癌合併肋膜積水。患者住院接受超音波導引肋膜液抽取術。肋膜液細胞學檢查高度懷疑為新形隱球菌感染，但仍不能排除結核性肋膜炎。患者並接受手術。手術取下之組織病理報告為酵母菌狀微生物且排除肺結核。因患者使用 amphotericin-B 後出現副作用，因此以 fluconazole 治療。

台灣疾病型態愈來愈像歐美，隱球菌感染較以前常見，所以今提出此罕見之病例，可讓臨床醫師對於肋膜積液鑑別診斷之參考。***(胸腔醫學 2003; 18: 500-506)***

關鍵詞：新形隱球菌，肋膜腔積液

台北榮民總醫院　胸腔部
索取抽印本請聯絡：江啟輝醫師，台北榮民總醫院　胸腔部，台北市北投區石牌路二段 201 號

Pulmonary Nocardiosis with Brain Abscess — A Case Report and Literature Review

Yen-Kun Ko, Chih-Yu Hsu

Nocardiosis is an uncommon disease in humans, and is considered an opportunistic infection which characteristically develops in immunocompromised persons. We report a patient with chronic obstructive pulmonary disease (COPD) with acute exacerbation, who had been treated with long-term corticosteroids. About seven days after admission, the patient developed high fever and bilateral pneumonia. Unfortunately, acute respiratory failure and multiple brain abscesses developed during hospitalization. Gram's staining of deep-suctioned sputum revealed Nocardia species. Empirical antibiotics were then changed to trimethoprim-sulfamethoxazole (TMP-SMZ) and minocycline for pulmonary nocardiosis, and ceftriaxone for brain abscess. The condition of the central nervous system (CNS) still worsened, despite the fact that the pneumonic patch was resolving under the appropriate antibiotic therapy. Cardiopulmonary resuscitation was performed subsequently, on the 38th hospitalization day, but in vain. The relevant literature is reviewed, including the risk factors, clinical symptoms, diagnosis, and management of nocardiosis. ***(Thorac Med 2003; 18: 507-512)***

Key words: pulmonary nocardiosis, brain abscess

Introduction

Nocardia spp. is ubiquitous in the environment, being found primarily in soil. The species may cause either skin lesions by direct inoculation during trauma or pulmonary diseases through inhalation. There is no absolute evidence for person-to-person transmission [1]. Analysis of underlying diseases and predisposing factors suggests that bronchopulmonary abnormalities may predispose to colonization, but infection is unusual without immunosuppression. A history of prior steroid use and a smear showing *Nocardia spp.* has correlated highly with infection [2].

Beaman and colleagues [3] have reported that nocardiosis appears to affect males more often than females at a ratio of 3:1, and most patients are between the ages of 21 and 50 years.

The respiratory tract is the most common site of involvement. Hematogenous dissemination is the major threat of pulmonary nocardiosis, and the CNS is the most common location [4]. Since the clinical and radiological findings of pulmonary nocardiosis are nonspecific, the diagnosis is difficult and thus frequently delayed [5].

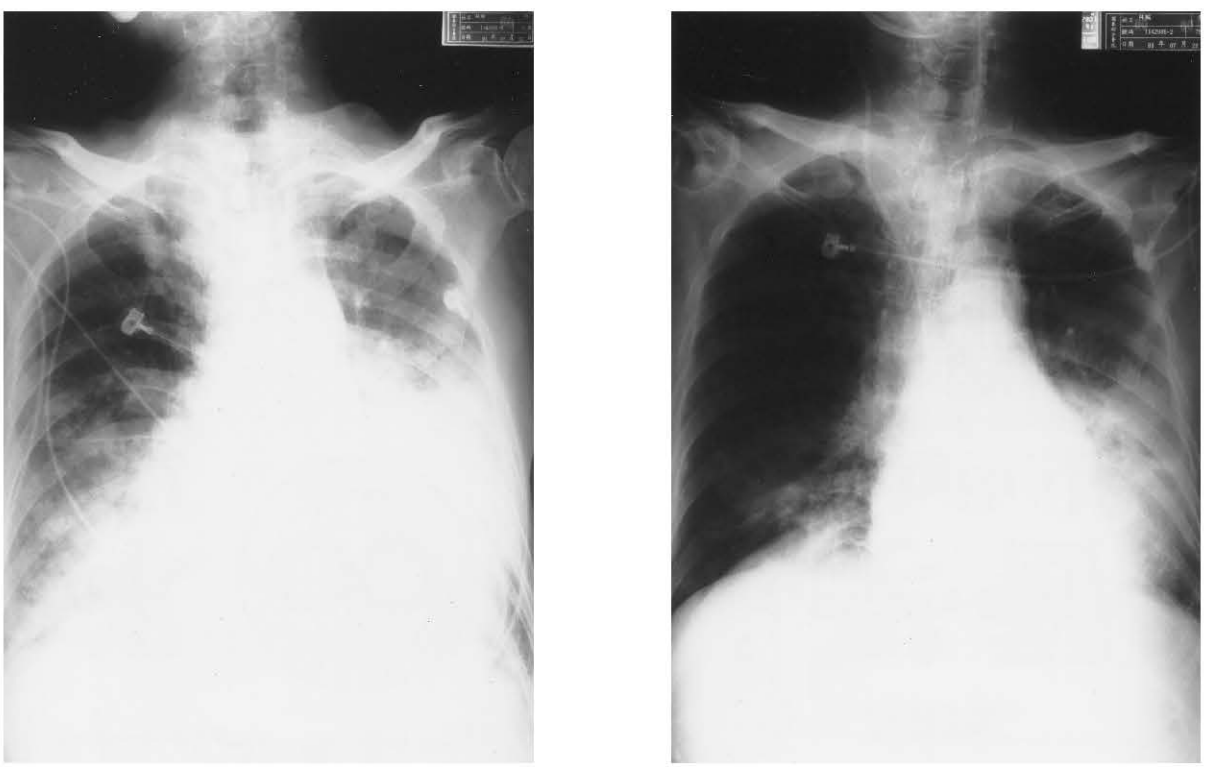
Case Report

A 75-year-old male patient was a victim of COPD, and had been regularly treated with inhaled

Section of Pulmonary Medicine, Department of Internal Medicine, Cathay General Hospital, Taipei, Taiwan, R.O.C.
Address reprint requests to: Dr. Chih-Yu Hsu, Section of Pulmonary Medicine, Department of Internal Medicine, Cathay General Hospital, No. 280, Sec. 4, Jen-Ai Road, Taipei, Taiwan, R.O.C.

bronchodilators and oral or inhaled corticosteroids (prednisolone 15 mg/day or fluticasone inhaler 250 μg twice/day) for 5 years. On July 2, 2002, he was sent to our Emergency Service because of an episode of acute exacerbation of COPD, which showed no parenchymal infiltrates on the chest radiograph. He was admitted and treated with a β_2 agonist agent via a small volume nebulizer, and an intravenous administration of hydrocortisone (100 mg q6h). The respiratory symptoms improved, and the steroid was changed to oral prednisolone (30 mg/day) on July 6. Unfortunately, high fever, leukocytosis, and bilateral pneumonia (Figure 1A) developed on July 12. Penicillin and amikacin were given for empirical therapy initially, then penicillin was changed to vancomycin 2 days later because the sputum culture grew methicillin-resistant *Staphylococcus aureus* (MRSA). The bilateral pneumonic shadows worsened, and he was intubated due to severe hypoxemia. Gram's staining of sputum smears, which were taken through an endotracheal tube, revealed *Nocardia spp.* (Figure 2, left) without other organisms on July 18. The microorganisms also stained with modified acid-fast stain (Figure 2, right). Pulmonary nocardiosis was diagnosed based on the history and sputum smear, so an oral form of TMP-SMZ (TMP 12 mg/kg/day and SMZ 60 mg/kg/day) and minocycline (200 mg/day) were given. The sputum cultures and the Gram's stain of the sputum smears were checked repeatedly, and all revealed *Nocardia spp.* The clinical symptoms, including the fever and dyspnea, improved, as well as the follow-up chest radiograph (Figure 1B). The endotracheal tube was removed on July 28.

Unfortunately, the patient developed a sudden onset of right hemiplegia on July 30. Brain computed tomography (CT) showed multiple brain abscesses (Figure 3). Ceftriaxone (4 gm/day) was added together with the TMP-SMZ and minocycline for its excellent CNS penetration, because the location



(A) (B)

Fig. 1. (A) Chest radiograph (July 12, 2002) shows bilateral diffuse ill-defined basal infiltration, especially on the left side. (B) Chest radiograph (July 28, 2002) reveals multiple cavities in resolution.

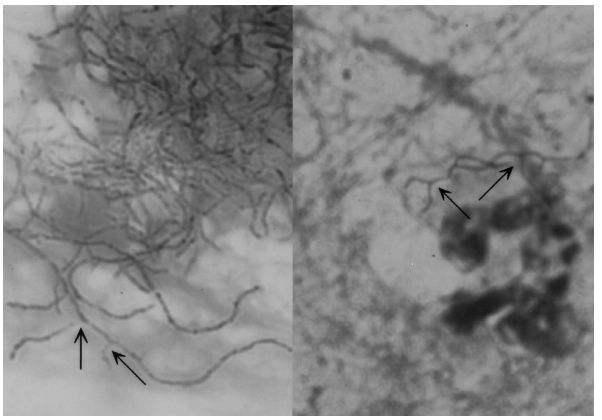


Fig. 2. Gram-positive, beaded, branching filamentous microorganisms. The organisms branch at right angles (arrow). Left: Gram's stain, oil x1000. Right: Modified acid-fast stain, oil x1000.

of the brain abscesses in this patient was not accessible by surgical intervention. The patient fell into a coma due to increased intracranial pressure (IICP), and developed a spiking fever from August 5, without deterioration of oxygenation and chest radiographic findings.

Bradycardia and shallow breathing with severe respiratory acidosis and mild hypoxemia caused by uncal herniation occurred on August 8. Cardiopulmonary resuscitation was performed subsequently, on the 38th hospitalization day, but in vain.

Discussion

Nocardia spp. may be considered opportunistic pathogens. Most victims are associated with a preexisting immunocompromised condition, such as renal or cardiac transplantation, human immunodeficiency virus infection, malignant neoplasm, chronic pulmonary disorders, or immunosuppressive therapy, particularly long-term or high-dose corticosteroid usage [6].

Our patient was a victim of COPD and regularly treated with steroids. Pulmonary nocardiosis should have been highly suspected when he contracted pneumonia one week after admission. The colonization of *Nocardia species* can be found in this type of patient's respiratory tract, and is almost always considered as a late-presenting community-acquired

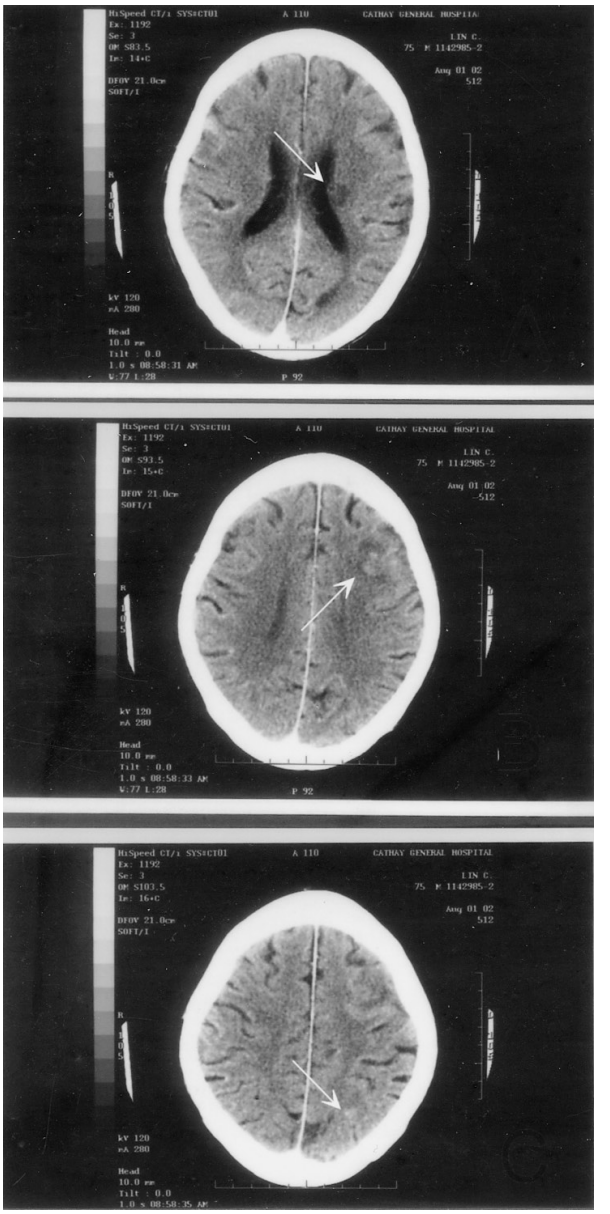


Fig. 3. Brain CT with contrast medium shows three focal brain softenings over the left frontal area with rim hyperdensity (upper: white arrow), left deep subcortical with hypodense shadow (middle: white arrow), and left posterior parietal area with contrast enhancement (lower: white arrow).

infection, or nosocomial outbreak in immunocompromised patients, which can be attributed to airborne transmission [7].

The appearance of pulmonary nocardiosis on the chest radiograph may be varied and nonspecific. The common radiological manifestations include

lobar or multilobar consolidation, solitary mass, reticulonodular infiltrates, and pleural effusion. Otherwise, cavitation and the upper lobes are more commonly involved [8].

The patient developed multiple brain abscesses about 3 weeks after the appearance of pulmonary nocardiosis, because disseminated nocardiosis is often a late-presenting infection with widespread abscess formation [4], and the brain is the most frequent extra-pulmonary site [9]. Secondary cerebral localization and silent destructive infection are sufficiently common, so CT with contrast medium enhancement or magnetic resonance imaging scans should be performed in all cases of pulmonary nocardiosis before the neurologic deficits occur [10].

Tissue diagnosis of a cerebral mass in the setting of proven pulmonary nocardiosis is not always necessary [4], and lumbar puncture is usually contraindicated in a patient with a parenchymal abscess, because the diagnostic yield is poor, and the lumbar puncture increases the risk of herniation [11]. So these invasive diagnostic procedures were not performed with this patient.

Nocardia are slow-growing organisms, so the microbiology laboratory should always be informed when nocardiosis is suspected, because the diagnosis may be missed by routine laboratory methods. The reports of Gram's stained smear and culture of this patient's sputum were all revised after the microbiology laboratory was informed of the probability of nocardiosis. Direct smears from such specimens should always be prepared for Gram's stain and modified acid-fast stain (1% sulfuric acid as a decolorizing agent). Gram's stained smears, typically show gram-positive, beaded, branching, filamentous hyphae, which must branch at right angles [12].

Nocardia spp. will grow slowly over a period of 2 days to 3 weeks on most non-selective media. In specimens of respiratory secretions containing mixed flora, nocardial colonies are easily obscured by those of more rapidly growing bacteria. So the sputum culture of our patient revealed *Staphylococcus aureus* (MRSA) initially, and the culture from deep-suctioned sputum showed *Nocardia spp.* after the culture plates had been preserved for a longer period. This is a pitfall for diagnosis and lead to therapeutic failure. The nocardial colonies may be increased by the use of selective media such as Thayer-Martin agar (containing colistin, nystatin, and vancomycin) or paraffin agar [13].

The early use of appropriate antimicrobial drugs is very important for treatment of nocardiosis because it is associated with frequent dissemination and high mortality. Sulfonamides are the therapy of choice, and the recommended dose of TMP-SMX is 5 to 10 mg/kg TMP and 25 to 50 mg/kg SMX, depending on the extent of disease [14]. Oral alternatives to sulfonamides include minocycline, which may be effective [15]. Third-generation cephalosporins have the advantages of excellent CNS penetration and low toxicity. The use of additional drugs in severely ill patients, for example, amikacin, imipenem, or ceftriaxone, may improve the prognosis, especially in disseminated infection or in an immunocompromised host [4,16].

In a clinically stable, immunocompetent patient with a brain abscess, an empirical trial of sulfa drugs is reasonable. If the condition deteriorates or if the abscess does not decrease in size within 4 weeks, stereotactic aspiration should be performed to confirm the diagnosis and to decompress the lesion [10].

The optimal duration of therapy is uncertain, but long-term therapy is the rule because nocardial infections tend to relapse. Nonimmunosuppressed patients with pulmonary or systemic nocardiosis should be treated for a minimum of 6~12 months; those with CNS infection should be treated for 12 months. All immunosuppressed patients should receive a minimum of 12 months therapy [4].

The mortality is significantly increased in patients with dissemination, especially in those in which the CNS is involved and those receiving corticosteroid or antineoplastic drugs. Cure rates of almost 90% are found in patients with pleuropulmonary disease, as compared with 63% in disseminated infection, and 50% in brain abscess [17].

Learning from this case, the diagnosis of nocardiosis should have been kept in a high index

of suspicion when pneumonia developed in this patient, and the microbiology laboratory should have been informed earlier. With the appropriate antibiotic therapy, the pneumonia resolved and respiratory symptoms improved. But the CNS condition worsened, and ultimately led to cardiopulmonary collapse, which was caused by IICP and uncal herniation. Brain imaging should be performed when pulmonary nocardiosis is diagnosed, and followed more frequently when the condition of the CNS deteriorates. The early use of additional drugs and the stereotactic aspiration of the brain abscess, which can decompress the lesion, may improve the prognosis.

References

1. Provost F, Laurent F, Blanc MV, *et al*. Transmission of nocardiosis and molecular typing of Nocardia species: a short review. Eur J Epidemiol 1997; 13: 235-8.
2. Rosett W, Hodges GR. Recent experiences with nocardial infections. Am J Med Sci 1978; 276: 279-85.
3. Beaman BL, Burnside J, Edwards B, *et al*. Nocardial infections in the United States. J Infect Dis 1976; 134: 286-9.
4. Lerner PI. Nocardiosis. Clin Infect Dis 1996; 22: 891-905.
5. Menendez R, Cordero PJ, Santos M, *et al*. Pulmonary infection with Nocardia species: a report of 10 cases and review. Eur Respir J 1997; 10: 1542-6.
6. McNeil MM, Brown JM. The medically important aerobic actinomycetes: Epidemiology and microbiology. Clin Microbiol Rev 1994; 7: 357-417.
7. Schaal KP. Medical and microbiological problems arising from airborne infection in hospitals. J Hosp Infec 1991; 18 Suppl A: 451-9.
8. Kramer MR, Uttamchandani RB. The radiographic appearance of pulmonary nocardiosis associated with AIDS. Chest 1990; 98: 382-5.
9. Beaman BL, Beaman L. Nocardia species: Host-parasite relationships. Clin Microbiol Rev 1994; 7: 213-64.
10. Mamelak AN, Obana WG, Flaherty JF, *et al*. Nocardial brain abscess: treatment strategies and factors influencing outcome. Neurosurgery 1994; 35: 622-31.
11. Roos KL, Tyler KL. Bacterial meningitis and other suppurative infections. In: Harrison TR. Principles of Internal Medicine. 15th edition. The United States of America. McGraw-Hill 2001; 2462-71.
12. Brown JM, McNeil MM, Desmond EP. Nocardia, Rhodococcus, Gordona, Actinomadura, Streptomyces, and Other Actinomycetes of Medical Importance. In: Murray PR, Baron EJ, Pfaller MA, *et al*. Manual of Clinical Microbiology. 7th edition. Washington DC; American Society for Microbiology 1999; 370-93.
13. Shawar RM, Moore DG, La Rocco MT. Cultivation of Nocardia spp. on chemically defined media for selective recovery of isolates from clinical specimens. J Clin Microbiol 1990; 28: 508-12.
14. Wallace RJ, Septimus EJ, Williams TW, *et al*. Use of trimethoprim-sulfamethoxazole for treatment of infections due to Nocardia. Rev Infect Dis 1982; 4: 315-25.
15. Bach MC, Monaco AP, Finland M. Pulmonary nocardiosis. Therapy with minocycline and with erythromycin plus ampicillin. JAMA 1973; 224: 1378-81.
16. Gombert ME, duBouchet L, Aulicino TM, *et al*. Antimicrobial synergism in the therapy of experimental cerebral nocardiosis. J Antimicrob Chemother 1989; 23: 39-43.
17. Smego RA, Moeller MB, Gallis HA. Trimethoprim-sulfamethoxazole therapy for Nocardia infections. Arch Intern Med 1983; 143: 711-8.

肺部奴卡氏菌感染症併發腦膿瘍—一病例報告和文獻回顧

柯延昆　徐志育

奴卡氏菌感染症在臨床上是較為少見的疾病，一般被認為是一種伺機性感染，通常發生在免疫功能異常的人身上。我們報告一位長期使用類固醇藥物的慢性阻塞性肺病發生急性惡化的患者。在住院 7 天後，開始發高燒並產生了兩側性肺炎。病患不幸在住院期間接著發生急性呼吸衰竭及多發性腦膿瘍。深部痰液的革蘭氏染色發現了典型的奴卡氏菌，於是開始使用 trimethoprim-sulfamethoxazole 及 minocycline 來治療肺部奴卡氏菌感染症，甚至加上 ceftriaxone 來治療腦膿瘍。在合適的抗生素治療下，肺炎逐漸的改善，但是中樞神經症狀卻仍然持續惡化。在住院第 38 天時，病人因病情惡化而接受心肺復甦術急救，卻仍然急救無效。我們回顧一些文獻報告，並且討論奴卡氏菌感染症之危險因子及臨床表現之症狀，此外也討論其診斷方法以及治療。***(胸腔醫學 2003; 18: 507-512)***

關鍵詞：肺部奴卡氏菌感染症，腦膿瘍

國泰綜合醫院　胸腔內科
索取抽印本請聯絡：徐志育醫師，國泰綜合醫院　胸腔內科，台北市仁愛路四段 280 號

Cardiac Tamponade Due to Pneumopericardium — A Case Report

Meng-Hsuan Cheng, Jong-Rung Tsai, Chau-Chyun Sheu, Jen-Yu Hung, Te-Hung Hsu, Ming-Shyan Huang

Cardiac tamponade most commonly results from an accumulation of blood or other fluids within the pericardial sac. However, there is a growing body of clinical evidence showing that pneumopericardium can lead to cardiac tamponade, as well. Although air tamponade can be treated effectively by either needle aspiration or insertion of a pericardial tube, the development of a pneumopericardium is a bad prognostic sign. A review of the literature concerning the various causes of pneumopericardium, the clinical features, and the principles of treatment is included. ***(Thorac Med 2003; 18: 513-518)***

Key words: pneumopericardium, cardiac tamponade, barotrauma

Introduction

Pneumopericardium is a very uncommon disorder and suggests the presence of a communication between the pericardial sac and an adjacent air-containing organ, or infection of the pericardium by gas-forming organisms. It also can result from trauma, fistula, and diagnostic and therapeutic procedures such as positive pressure ventilation, especially in infants [1-3]. However, most cases have occurred in preterm newborn infants treated with positive pressure ventilation for neonatal respiratory distress syndrome [4-5]. Infection of the contiguous organs can also result in pneumopericardium, as is illustrated in the case we present.

Case Report

A 43-year-old man was transferred to our hospital in November 2001 due to a worsening of bilateral pneumonia. He was a case of acute myeloid leukemia (AML), subclass M2, based on the French-American-British (FAB) criteria, with the initial presentation of pancytopenia. He received the first course of chemotherapy in July 2001; however, many blast cells were noted on the bone marrow aspiration exam thereafter. He underwent a second course of chemotherapy in September; unfortunately, prolonged neutropenic fever, then bilateral pneumonia on the chest X-ray films were found.

Intravenous empiric therapy with piperacillin, ceftazidime, vancomycin, and imipenem was administered. However, fever persisted despite broad-spectrum antibiotic treatment, so treatment with amphotericin B was started. Dyspnea was noted whenever amphotericin B was given, so fluconazole was used instead. The patient's condition deteriorated progressively and he was later intubated. He was transferred to our intensive care unit after

Department of Internal Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, R.O.C.
Address reprint requests to: Dr. Ming-Shyan Huang, Department of Internal Medicine, Kaohsiung Medical University, Kaohsiung, 807, Taiwan, R.O.C.

intubation with ventilator support for 15 days. After admission, the patient was found to be dyspneic and diaphoretic, with a blood pressure of 84/57 mmHg and a pulse rate of 146 bpm. Coarse crackles were audible throughout the entire lung field during inspiration and expiration. No subcutaneous emphysema was found. Heart sounds were normal and pulsus paradoxus was absent. The electrocardiogram revealed sinus tachycardia. There was no evidence of pneumopericardium on the previous chest radiograph, as seen in figure 1 (5 days before admission to our hospital and 10 days after intubation). The central venous pressure revealed 36 cm H_2O. The clinical picture was compatible with cardiac tamponade, and the chest radiograph showed a large pneumopericardium (Figure 2). A 16-gauge central venous cannula was introduced into the pericardial sac via the subxiphisternal route, using an aseptic technique. Much air was aspirated, and the cannula was connected to an underwater-sealed drainage system. A rapid response was observed with a slowing down of the heart rate and blood pressure to their former level. The pericardial fluid was taken for microbiological examination, but no growth was reported. In addition, a computed tomographic (CT) examination of the chest was obtained (Figure 3). Due to a malfunctioning of the central venous cannula, he underwent a pericardiectomy and biopsy with a culture of the pericardial tissue (Figure 4). No obvious fistula was found during the procedure. In the microscopic examination of the pericardial wall, only polymorphonuclear leukocytes, histiocytes, and lymphocyte infiltrates without hyphae were found. We also arranged two bronchoscopic exams. However, neither the pericardium exam nor the bronchoalveolar lavage revealed evidence of invasive pulmonary aspergillosis. In the beginning, intravenous empiric therapy with daily amikacin 1g , olfloxacin 400mg every 12h, and daily fluconazole 400mg was administered for about 4 days. After *Acinetobacter baumannii* had been cultured from the sputum and the bronchial

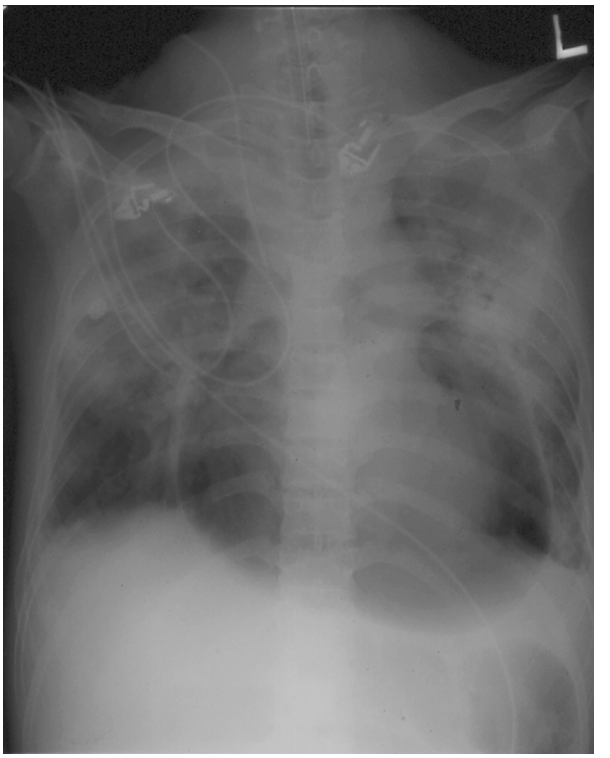


Fig. 2. Chest radiograph shows two radiolucent areas along the lateral borders of the heart suggesting pneumopericardium.

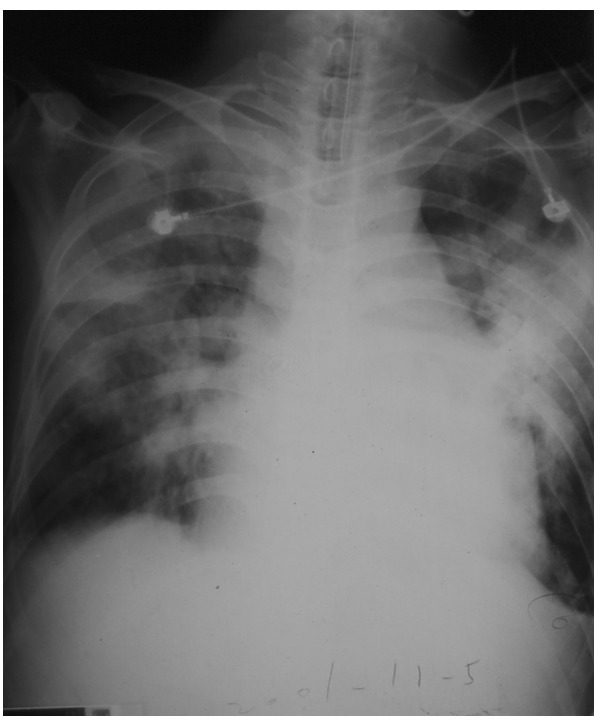


Fig. 1. Chest radiograph taken 10 days after mechanical ventilation reveals bilateral parenchymal infiltrates, but no evidence of pneumopericardium.

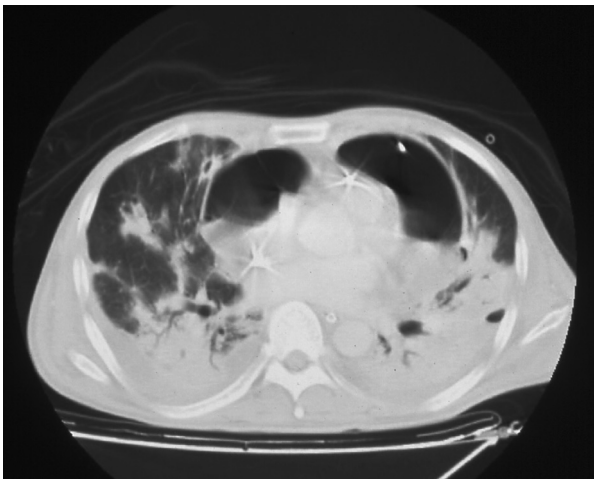


Fig. 3. Chest radiograph shows a tube drain was introduced into the pericardial cavity.

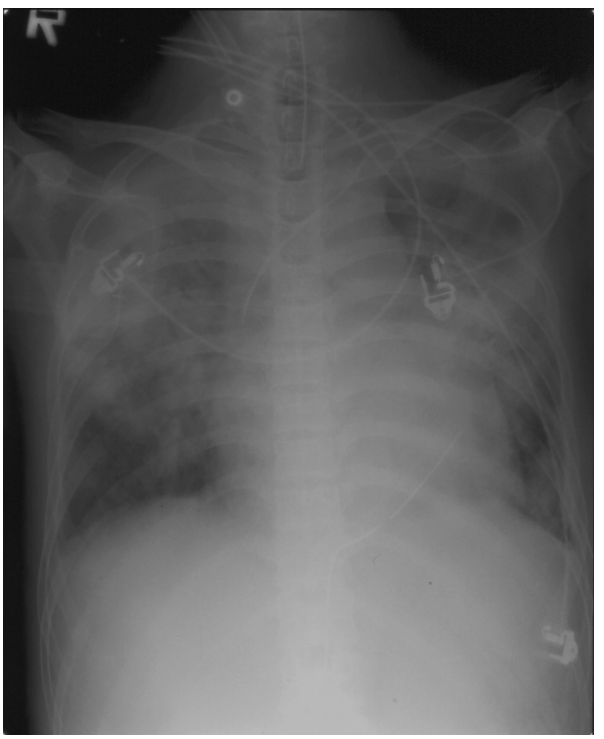


Fig. 4. CT scan of the chest demonstrates pneumopericardium with a flattening of the anterior face of the heart and extensive bilateral air space consolidation.

washing fluid, meropenem 1g every 8h and amphotericin B 500mg daily were given instead. Because of the lack of evidence of fungal pneumonia and the presence of severe side effects, the amphotericin B was stopped 6 days later. He developed a superficial infection, presumed to be due to *Staphylococci*, which was treated with vancomycin 1g every 12h intravenously. After adequate antibiotic treatment, the patient showed improvement clinically and radiologically. A chest film, followed up one year later, showed only residual infiltrates in both lungs (Figure 5).

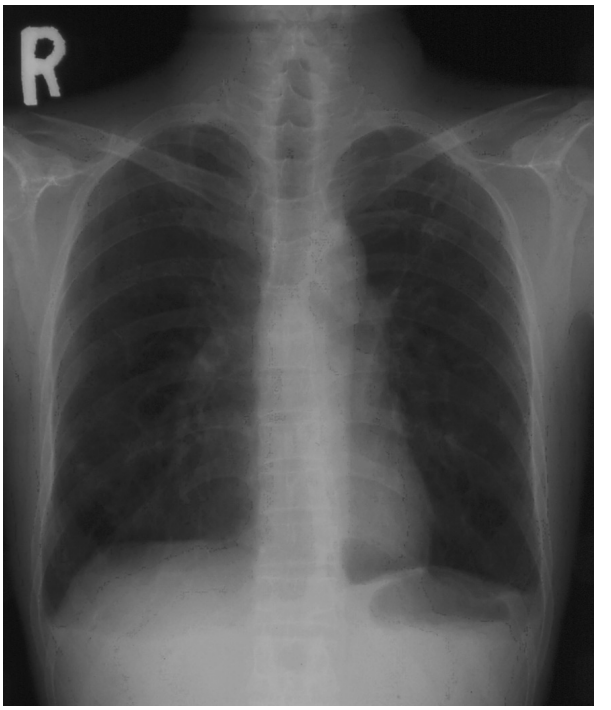


Fig. 5. A chest film, followed up one year later, shows only residual infiltrates in both lungs.

Discussion

Pneumopericardium, a form of barotrauma, refers to the presence of air within the pericardial sac, a condition that is much less common than either pneumothorax or pneumomediastinum [6]. The pathophysiological mechanism causing pneumopericardium in positive pressure ventilation is probably related to a rise in intra-alveolar pressure to that above atmospheric pressure. The end result is a rupture of the alveoli, then air dissecting to the hilar area, mediastinum, and through the pericardial reflection on the pulmonary vessels, into the peri-

cardial cavity [2]. Histological preparations have demonstrated a site of potential weakness where the parietal pericardium is reflected on the visceral pericardium near the ostia of the pulmonary veins [5]. This occurs more frequently in infants than in adults, probably due to the stronger adhesions between the pericardial layers in the adult, precluding communication between the pericardial space and the mediastinum [6]. In mechanically ventilated patients, there is an increased incidence of pulmonary barotrauma, especially when there is an associated underlying pulmonary parenchymal process and high airway pressure [7-8]. The previous ventilator record showed the plateau pressure to be around 33-37 cmH_2O, with a positive end-expiratory pressure setting of 4 cmH_2O in this patient. It is possible that the patient developed alveolar disruption from severe acute lung injury, and high airway pressure contributed to the increase in the pressure gradient between the alveoli and the bronchovascular sheath, leading to pneumopericardium. Radiologic findings in pneumopericardium are characteristic. A single band of gas is usually visible within the pericardial sac outlining the heart. By contrast, pneumomediastinum usually manifests as a multitude of thin streaks of gas, which seldom surround the heart completely and which are rarely confined to the cardiac region only. Isolated pneumopericardium does not extend into the upper mediastinum and neck, a common finding in pneumomediastinum [9].

The occurrence of the physical signs observed in cardiac tamponade are fairly consistent. They include (1) elevation of the jugular pressure, (2) elevation of the pulmonary artery wedge pressure, (3) tachycardia, (4) a pulsus paradoxus greater than 10 mmHg, (5) a pulse pressure less than 30 mmHg, (6) pericardial friction rub, (7) diminished intensity of heart sounds evidenced clinically by the presence of faint heart sounds and the absence of an apical impulse, and (8) electrical alternans [10].

The development of a pneumopericardium is a bad prognostic sign. The presence of air within the pericardial space usually reflects the severity of an underlying disease, and death occurs as a result of this disease process [1]. In adults who have simple pneumopericardium without tension, no active intervention is required. The mainstay of treatment is prompt surgical drainage and adequate antibiotic therapy. If there is evidence of cardiac tamponade immediate surgical aspiration is required to prevent further hemodynamic deterioration.

There have been some reports about pneumopericardium associated with systemic aspergillosis in a child with acute lymphoblastic leukemia [11-14]. The use of immunosuppressive drugs, the presence of severe neutropenia, and prolonged treatment with broad spectrum antibiotics are the basic predisposing factors to opportunistic fungal infection. Aspergillus and candida species are most frequently responsible [15]. The diagnosis of systemic aspergillosis, especially *Aspergillus pericarditis*, is very difficult and frequently reached by the exclusion of other causes, with confirmation being made often only at autopsy. Early diagnosis is very important for successful treatment [16]. Our patient was under high risk of invasive pulmonary aspergillosis and *Aspergillus pericarditis* during prolonged neutropenia, which is known to be a major risk for invasive pulmonary aspergillus in patients with acute leukemia. In a case with an underlying disease of acute myelogenous leukemia and prolonged neutropenic fever, *Aspergillus fumigatus* was cultured from the bronchoalveolar lavage. Unfortunately, the patient died later. At autopsy, on microscopic examination of the pericardial wall, there were no leukemic infiltrates, but the blood vessels had infarcted and hyphae had disseminated [11]. So we arranged two courses of bronchoalveolar lavage and a pericardial wall biopsy during the pericardiectomy; however, no evidence of aspergillus infection was found. Aspergillosis of the lungs may cause bronchopneumonia and hemorrhagic infarction. The fungus may spread by direct invasion or, more commonly, by blood stream dissemination to internal organs, including the intestines, brain, kidneys, liver, esophagus, and heart [17]. Pulmonary aspergillosis can also be complicated by bronchopleural fistula, pericarditis, pneumopericardium or pericardiac tamponade

either by air or effusion [12-13,18]. In particular, patients with a history of severe and prolonged neutropenia are at high risk of developing opportunistic fungal infections, such as invasive aspergillosis. Invasive pulmonary aspergillosis is commonly fatal and the majority of cases have significant pulmonary involvement [19].

Furthermore, tension pneumopericardium is a very unusual cause of hemodynamic compromise in the blunt trauma patient. The patients are often severely injured, and a high index of suspicion is required to make the diagnosis [20].

Air tamponade is especially likely to develop in mechanically- ventilated patients and occurs most frequently in premature infants with respiratory distress syndrome or in adults who have sustained chest trauma. Our case report illustrates an unusual manifestation of cardiac tamponade due to pneumopericardium in an immunosuppressed patient.

References

1. Cummings RG, Wesly RL, Adams, DH, Lowe JE. Pneumopericardium resulting in cardiac tamponade. Ann Thorac Surg 1984; 37: 511-8.
2. Katzir D, Klinovsky E, Kent V, *et al*. Spontaneous pneumopericardium: case report and review of the literature. Cardiology 1989; 76: 305-8.
3. Smith LG, Naqvi T. Images in clinical medicine: Tension pneumopericardium. N Engl J Med. 1995; 332: 1481.
4. Moodie DS, Kleinberg F, Hattery RR, *et al*. Neonatal pneumopericardium. Mayo Clin Proc. 1976; 51: 101-6.
5. Mansfield PB, Graham CB, Beckwith JB, *et al*. Pneumopericardium and pneumomediastinum in infants and children. J Pediat Surg 1973; 8: 691
6. McEachern RC, Patel RG. Pneumopericardium associated with face-mask continuous positive airway pressure. Chest 1997 ;112: 1441-3.
7. Hurd TE, Novak R, Gallagher TJ. Tension pneumopericardium: a complication of mechanical ventilation. Crit Care Med 1984; 12: 200-1.
8. Gammon RB, Shin MS, Groves RH Jr, *et al*. Clinical risk factors for pulmonary barotraumas: a multivariate analysis. Am J Respir Crit Care Med 1995; 152: 1235-40
9. Bejvan SM, Godwin JD. Pneumomediastinum: old signs and new signs. Am J Roentgenol 1996; 166: 1041-8.
10. Adcock JA, Lyons RH, Barnwell JB. The circulatory effects produced in a patient with pneumopericardium by artificially varying the intrapericardial pressure. Am Heart J 1940; 19: 283-91.
11. van Ede AE, Meis JF, Koot RA, *et al*. Pneumopericardium complicating invasive pulmonary aspergillosis: case report and review. Infection 1994; 22: 102-5.
12. Luce JM, Ostenson RC, Springmeyer SC,*et al*. Invasive aspergillosis presenting as pericarditis and cardiac tamponade. Chest 1979; 76: 703-5.
13. Muller NL, Miller RR, Ostrow DN, *et al*. Tension pneumopericardium: an unusual manifestation of invasive pulmonary aspergillosis. Am J Roentgenol. 1987; 148: 678-80.
14. Merino JM, Diaz MA, Ramirez M, *et al*. Complicated pulmonary aspergillosis with pneumothorax and pneumopericardium in a child with acute lymphoblastic leukemia. Pediatr Hematol Oncol. 1995; 12: 195-9.
15. Radaelli F, Cortelezzi A, Zocchi L, *et al*. Diagnosis and treatment of fungal infections in patients with hematologic malignancies. Hematol. Oncol 1986; 4: 129-34.
16. Walsh TJ, Bulkley BH. Aspergillus pericarditis: clinical and pathologic features in the immunocompromised patient. Cancer 1982; 49: 48-54.
17. Young RC, Bennett JE, Vogel CL, *et al*. Aspergillosis. The spectrum of the disease in 98 patients. Medicine 1970; 49: 147-73.
18. Owens CM, Hamon MD, Graham TR, *et al*. Bronchopericardial fistula and pneumopericardium complicating invasive pulmonary aspergillosis. Clin Lab Hematol. 1990; 12: 351-4.
19. Herbert PA, Bayer AS. Fungal pneumonia. Invasive pulmonary aspergillosis. Chest 1981; 80: 220-5.
20. Gould JC, Schurr MA. Tension pneumopericardium after blunt chest trauma. Ann Thorac Surg 2001; 72: 1728-30.

心包膜積氣合併心包填塞—一病例報告

鄭孟軒　蔡忠榮　許超群　洪仁宇　許德宏　黃明賢

因心包膜積氣而引起的心包填塞是一種臨床罕見疾病，大部分發生於新生兒因呼吸窘迫症候群使用呼吸器時，或成人胸部受鈍傷，或與鄰近含氣體的器官產生瘻管時。病人的臨床表現有氣促，血壓降低，心包膜摩擦音，奇脈（pulsus paradoxus），中央靜脈壓上升，但因不一定每種症狀均會出現，且病人出現心包膜積氣時通常背後都有重大疾病，這兩大原因都可能會使臨床醫師疏忽了這種死亡率超過百分之五十的罕見併發症。文獻報告成人因心包膜積氣而引起的心包填塞通常出現於胸部受鈍傷，插管不當或氣喘發作併高氣道壓時，但均屬個案報告，且出現此種併發症通常是非常快速的。這裡提出一位 43 歲男性因急性骨髓性白血病於接受化學治療後併發白血球低下性發燒與雙側肺炎，於使用呼吸器十五天後產生心包膜積氣併心包填塞。在此我們報告這位病人的臨床表現，胸部 X 光發現與治療經過並回顧歷年來與此種病歷相關的文獻報告。 ***（胸腔醫學 2003; 18: 513-518）***

關鍵詞：心包膜積氣，心包填塞，氣壓傷害

高雄醫學大學附設中和紀念醫院　胸腔內科
索取抽印本請聯絡：黃明賢醫師，高雄醫學大學附設中和紀念醫院　胸腔內科，高雄市十全一路 100 號

Huge Pulmonary Cryptococcoma Treated with Pneumonectomy — A Case Report

Wei-Tong Woon, Chao-Chien Wu, Tzu-Cheng Wu, Ming-Jang Shieh*

The pulmonary manifestations of cryptococcosis are diverse but most commonly include single or multiple pulmonary nodules and segmental or lobar consolidation. A large mass-like pattern is an uncommon finding. We report a case of 47-year-old healthy male presenting with a large pulmonary cryptococcoma with poor response to medical treatment alone. The patient was satisfactorily treated with a left pneumonectomy under cover of fluconazole therapy. Thus, thoracic surgery may be indicated in the event of a failure of medical therapy, and pulmonary cryptococcosis should be considered in the differential diagnosis of a mass lesion. Literature concerning the diagnosis and management of pulmonary cryptococcosis is also reviewed. ***(Thorac Med 2003; 18: 519-524)***

Key words: pulmonary cryptococcosis, cryptococcoma, and pneumonectomy

Introduction

Cryptococcosis is caused by *Cryptococcus neoformans*, a thin-walled, nonmycelial budding yeast, 2 to 20 micrometers in diameter, that is characterized by a thick polysaccharide capsule best seen in Indian ink stains [1-2]. Inhalation of the organism from contaminated soil or dust is considered the usual route of infection. The spectrum of pulmonary cryptococcosis depends on host defenses. In the immunocompromised, a cryptococcal infection often causes symptomatic pulmonary infections, and often disseminates to the central nervous system (CNS), skin, and bones. In the immunocompetent, most pulmonary infections are minor and go unnoticed [2-3]. A picture with a large mass on the chest X-ray is an uncommon finding.

Case Report

A 47-year-old man was hospitalized because of a one-month history of intermittent hemoptysis. He had also experienced low-grade fever, anorexia, and a 3-kilogram body weight loss in the previous 2 months. On admission, the patient's vital signs were normal, although he was febril. There was no clubbing of the fingers or enlarged lymph nodes. Chest examination showed decreased breathing sounds and dullness to percussion on the left lower chest, without wheezing or crackles. The hematological studies, including bleeding profiles, were unremarkable. Blood biochemical studies, including electrolytes, hepatic enzymes, and kidney function, were all within normal range. The chest radiograph showed a 12x14 cm mass in the left lingular and lower lung field (Figure 1). Chest computed tomo-

Chest Division, Department of Internal Medicine, Thoracic Surgery*, Department of Surgery, Kaohsiung Chang Gung Memorial Hospital, Taiwan.
Address reprint requests to: Dr. Chao-Chien Wu, Chest Division, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, No.123, Ta-Pei Road, Niao-Sung Hsiang, Kaohsiung Hsien, Taiwan, R.O.C.

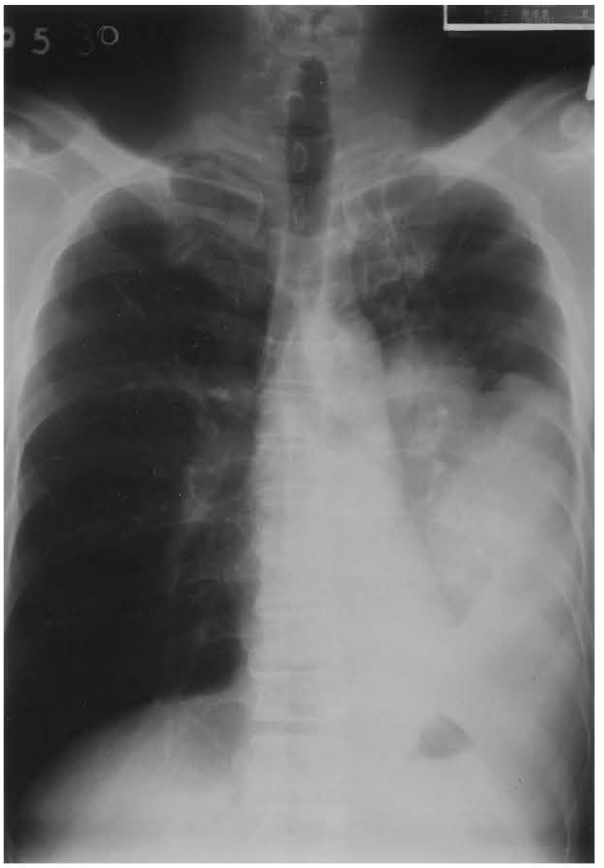


Fig. 1. Chest radiograph showing a huge lobulated mass in the left lingular and lower lobes.

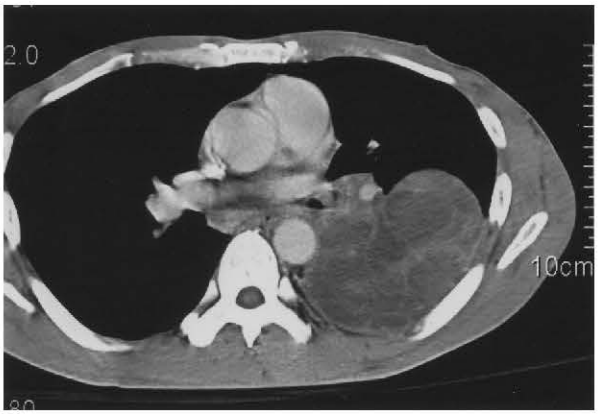


Fig. 2. The post-contrast chest computed tomography reveals a big mass with heterogeneous enhancement in the superior aspect of the left lower lobe.

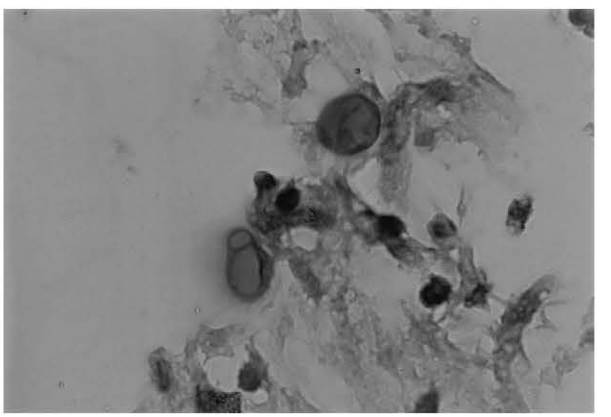


Fig. 3. The pathological examination of the lung mass by ultrasound-guided biopsy shows budding yeasts with thick capsules. (periodic acid-Schiff stain, X400)

graphy was performed and revealed a huge mass with heterogeneous enhancement in the superior aspect of the left lower lobe, with an invasion of the left upper lobe and left hilum (Figure 2). Left hilar lymphadenopathy and mediastinal lymphadenopathy were also noted. The sputum cytology study and acid-fast stain were negative. A bronchoscopy was not undertaken because of the patient's refusal. Chest ultrasound-guided biopsied lung tissue histopathologically revealed numerous budding yeasts with thick capsules (Figure 3). Assay of the serum cryptococcal antigen in the serum was positive, with a very high titer of 1:16384. Pulmonary cryptococcosis was therefore diagnosed. A lumbar puncture was performed, and revealed a negative cerebrospinal fluid study. The serology study was negative for human immunodeficiency virus (HIV) antibody. Intravenous amphotericin B 0.5mg/kg per day was started. Hemoptysis was aggravated despite one month of medical treatment, and the serial chest X-ray did not show any improvement. The patient thus underwent surgery, in addition to treatment with amphotericin B. A huge tumor, 20 cm in diameter, was noted, involving the left upper and left lower lobes (Figure 4). A left pneumonectomy was performed, because the tumor had caused extensive destruction to the left lung. He had an uneventful convalescence and was discharged after 40 days of hospitalization, and after receiving a total 1.5 g amphotericin B infusion. He was then followed up at the outpatient clinic with

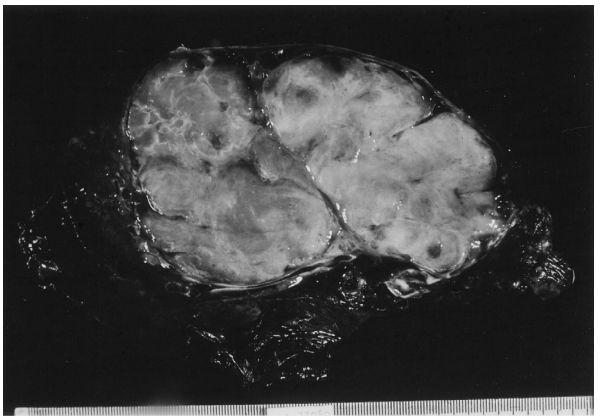


Fig. 4. View of the resected left lung showing the well defined mass occupying the left upper and lower lobes.

oral fluconazole 400 mg daily for a further 6 months.

Discussion

The most common causes of lung masses are bronchogenic carcinoma, metastatic tumors, other malignant tumors, and benign tumors such as hamartoma, abscess, round pneumonia, loculated pleural fluid, cysts, and pulmonary sequestration. Less common causes include fungal disease such as cryptococcosis, nocardiosis, aneurysm, infarction, and hematoma [4].

Cryptococcus neoformans may colonize the airway, thus, sputum cultures and bronchial washings are unreliable in diagnosing cryptococcosis. A positive sputum culture or bronchial washing specimen in an immunocompromised patient, however, should be viewed as highly suspicious of the disease [2-3]. Definitive diagnosis of pulmonary cryptococcosis requires an identification of the organism in tissues from biopsy or surgical specimens [2-3]. The use of ultrasound or fluoroscopy-guided needle aspiration or biopsy has facilitated the diagnosis of pulmonary cryptococcosis. Ultrasound is particularly useful since the pulmonary cryptococcoma tend to be subpleural, and many studies have demonstrated that ultrasound-guided lung aspiration is not only effective and rapid [5], but also a safe method for diagnosis [6].

It is likely that a large segment of immunocompetent hosts have been exposed to *C. neoformans*. One study from the Bronx, New York, showed that the majority of children older than two years had serologic evidence of exposure to *C. neoformans* [7]. We assume that subclinical primary infections are very common, and that the vast majority of these are asymptomatic. Thus, the pulmonary lesions that accompany cryptococcosis are usually clinically and radiographically silent [8].

The most common presentations of symptomatic pulmonary cryptococcosis are cough, chest pain, increased sputum production, fever, and weight loss [3]. Dyspnea, night sweats, and hemoptysis occasionally occur [3]. Up to one third of patients with definitive radiographic abnormalities from *Cryptococcus neoformans* are asymptomatic [2-3].

Excluding the subclinical primary infections, the chest radiographic features of pulmonary cryptococcosis in immunocompetent patients may vary widely. The presentations of pulmonary cryptococcosis on chest radiographs most commonly include single or multiple pulmonary nodules and segmental or lobar consolidation [2,9]. Additional features include interstitial infiltrates, miliary disease, cavitation, hilar and mediastinal adenopathy, and pleural effusion [2,9-10]. A large pulmonary mass in immunocompetent patients is less common.

The immune status of the affected individual appears to be the most important element in determining the subsequent course of the infection (ie, resolution of the pneumonia versus symptomatic dissemination) [8,11]. Hammerman et al, in their study, concluded that the majority of patients with pulmonary cryptococcosis recovered without antifungal therapy. Treatment was given if there was evidence of disease progression or if the lesion failed to resolve over a one-to-two-month period of close radiographic observation [12]. Based on a review of 41 cases seen before 1982, Kerkering et al concluded that immunocompetent hosts with isolated pulmonary cryptococcosis do not require antifungal therapy [13]. However, pulmonary cryptococcosis can eventuate into severe pneumonia

with respiratory failure or into extrapulmonary dissemination, particular to the CNS, even in immunocompetent patients [12-14]. In the retrospective review by Kerkering et al [13], 17% of healthy hosts with untreated pulmonary cryptococcal infection developed CNS dissemination. Thus, the threat of pulmonary cryptococcosis dissemination in immunocompetent patients is very real. Accordingly, Hammerman et al [12] and Kerkering et al [13] strongly asserted that the morbidity and mortality from pulmonary cryptococcosis may be reduced if treatment is initiated before the occurrence of dissemination with meningeal involvement.

Patients presenting with symptomatic pulmonary infection due to *C. neoformans* should be treated with either fluconazole or amphotericin B. Fluconazole (400 mg per day) is preferred for most patients since it can be administered orally and is less toxic than amphotericin B. Amphotericin B plus flucytosine are the preferred drugs for induction therapy in patients with CNS involvement, or extensive multi-organ disease. We would administer the induction therapy in these settings for the first 14 days, after which therapy can be changed to fluconazole, provided there is clinical improvement. The duration of therapy for patients with isolated, symptomatic pulmonary disease is three to six months, depending upon the extent of infection [8].

Patients with asymptomatic pulmonary cryptococcosis with a negative serum cryptococcal antigen may not require any systemic therapy. Asymptomatic patients with detectable serum cryptococcal antigen levels are given fluconazole therapy. In the guidelines from the Infectious Diseases Society of America on the treatment of pulmonary cryptococcosis, the recommended treatments for mild to moderate pulmonary disease are either fluconazole (200 to 400 mg/day for 6 to 12 months), itraconazole (200 to 400 mg/day for 6 to 12 months), or amphotericin B (0.5 to 1.0 mg/kg per day for a total of 1 to 2 g of therapy). Those with severe pulmonary disease or immunocompromised hosts should be treated like CNS disease patients [11].

The indications for surgery are life-threatening pulmonary hemorrhage, definitive management of persistent or refractory pulmonary disease, and for diagnosis, but it is rarely needed [15].

Thus, thoracic surgery may be indicated in the event of a failure of medical therapy, as in this case.

References

1. Haque AK. Pathology of common pulmonary fungal infections. J Thorac Imaging 1992; 7: 1-11.
2. Patz EF Jr, Goodman PC. Pulmonary cryptococcosis. J Thorac Imaging 1992; 7: 51-5.
3. Boyars MC, Zwischenberger JB, Cox CS Jr. Clinical manifestations of pulmonary fungal infections. J Thorac Imaging 1992; 7: 12-22.
4. James C. Reed: Solitary Pulmonary Nodule. Robert A. Hurley. Chest Radiology: Plain film patterns and differential diagnoses, 4th edition. St. Louis: Mosby-Year Book, Inc. 1997; 328-354.
5. Sherman ME, Orr JE, Balogh K, *et al*. Primary diagnosis of disseminated fungal disease by fine needle aspiration of soft tissue lesion. Diagno Cytopathol 1991; 7: 536-9.
6. Lee-LN, Yang-PC, Kuo-SH, *et al*. Diagnosis of pulmonary cryptococcosis by ultrasound guided percutaneous aspiration. Thorax 1993; 48: 75-8.
7. Goldman DL, Khine H, Abadi J, *et al*. Serologic evidence for Cryptococcus neoformans infection in early childhood. Pediatrics 2001; 107: E66.
8. Gary MC, John RP. Cryptococcal pneumonia. In: UpToDate, Rose, BD (Ed), Wellesley, MA: UpToDate. 2002.
9. Khoury MB, Godwin JD, Ravin CE, *et al*. Thoracic cryptococcosis: immunologic competent and radiologic appearance. AJR 1984; 142: 893-6
10. Meyohas MC, Roux P, Bollens D, *et al*. Pulmonary cryptococcosis: localized and disseminated infections in 27 patients with AIDS. Clin Infect Dis 1995; 21: 628-33.
11. Saag MS, Graybill RJ, Larsen RA, *et al*. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. Clin Infect Dis 2000; 30: 710-18.
12. Hammerman KJ, Powell KE, Christianson CS, *et al*. Pulmonary cryptococcosis: clinical forms and treatment. Am Rev Dis 1973; 108: 1116-23.
13. Kerkering TM, Duma RJ, Shadomy S. The evolution of pulmonary cryptococcosis. Ann Intern Med 1981; 94: 611-

6.
14. Robinson GR II. Severe cryptococcal pneumonia. N Engl J Med 1995; 332: 1752.
15. Takaro T. Mycotic infections of interest to thoracic surgeons. Ann Thorac Surg 1967; 3: 71-83.

手術切除巨大肺隱孢球菌瘤：病例報告及文獻回顧

溫偉東　吳沼漧　吳自成　謝敏璋*

隱孢球菌感染在肺部的表現是多樣性的，但大部份是以單獨或多個肺結節、肺小葉或肺大葉肺性肺實質化病變來表現。以巨大腫瘤樣的形態來表現是不常見的。我們報告一位 47 歲的健康男性，其肺部隱孢球菌感染是以肺腫瘤的形態來表現，同時對單獨藥物治療效果不彰。最後病人是以左肺切除併用抗黴菌藥物治療。據此，肺部隱孢球菌感染若對內科治療失敗，可考慮外科手術治療。同時，隱孢球菌感染可能要列入肺腫塊的鑑別診斷。我們並且回顧了隱孢球菌感染的診斷及處置的相關回顧。*（胸腔醫學 2003; 18: 519-524）*

關鍵詞：肺隱孢球菌感染，隱孢球菌瘤，肺切除術

高雄長庚紀念醫院　胸腔內科　胸腔外科 *
索取抽印本請聯絡：吳沼漧醫師，高雄長庚紀念醫院　胸腔內科，高雄縣烏松鄉大埤路 123 號

Invasive Pulmonary Aspergillosis in Immunocompromised Cases with Acute Respiratory Failure — Three Case Reports

Chao-Shin Cheng, Ming-Jhieh Chang, Shiu-Feng Huang*, Chung-Chi Huang

The early diagnosis and prompt aggressive management of invasive pulmonary aspergillosis (IPA) are continuing problems. We herein report 3 cases. The first 2 had leukemia; one of them was diagnosed by necropsy as having IPA and the other was proved to have IPA by open lung biopsy while he was alive. Case 3 had been diagnosed as systemic sclerosis, and was found to have IPA by necropsy. Whenever bacterial cultures are all negative or the clinical condition deteriorates despite adequate antibiotics use in immunocompromised hosts, physicians should suspect this disease. Chest CT films are more sensitive than radiograms. Video-assisted open lung biopsy is also a relatively safe procedure. Pathological diagnosis is often more rapid than culture. ***(Thorac Med 2003; 18: 525-530)***

Key words: invasive aspergillosis, immunocompromised host, video-assisted open lung biopsy

Introduction

The diagnosis of invasive aspergillosis in immunocompromised patients is based on clinical suspicion when these cases have characteristic signs or symptoms, imaging studies, and the pathologic and microbiological examination of affected tissue [1].The prognosis of the disease improves with early diagnosis and the initiation of specific treatment.

Definitive proof of invasive aspergillosis requires demonstrating the hyphal invasion in tissue specimens obtained by invasive diagnostic procedures, together with a positive culture for *Aspergillus spp.* from the same specimen [1,2].

This disease has become a significant problem in the treatment of immunocompromised hosts [3], therefore the need for training in clinical mycology is more and more important.

Case 1

This 31-years-old female patient was diagnosed with acute myeloid leukemia (AML M5a) in Feb. 2001, presenting initially with fever and lymph adenopathy. She initially underwent chemotherapy, which was unsuccessful, and went on to receive a bone marrow transplantation (BMT) in Oct. 2001.

Acute graft-versus-host disease (GVHD) developed in Nov. 2001 with the presentation of a generalized skin rash and bullas formation. She then received high-dose steroids (solu-medrol 250 mg iv q12h) and anti-human lymphocyte immunoglobulin treatment for about 1 month.

Division of Pulmonary and Critical Care Medicine, Department of Pathology*, Chang Gung Memorial Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Chung-Chi Huang, Chang Gung Memorial Hospital, Taipei, Taiwan, 5, Fu-Shin Street, Kweishan, Taoyuan 333, Taiwan

Right-side chest pain and breathlessness later developed, and leukopenic fever occurred on Dec. 14, 2001. The CBC/DC showed Hb 9.7 gm/dl, PLT 33000/cmm, WBC 100/cmm, bands 10%, segments 20%, monocytes 20%, lymphocytes 30%, and atypical lymphocytes 20%. Sputum and blood bacterial cultures were all negative. The CXR showed bilateral lower lung infiltration. Teicoplanin and Fortum were given under the impression of nosocomial pneumonia. However, her disease progressed and RUL cavitations (Figure 1, 2) were found. Fungus infection could not be ruled out. So fluconazole IVF was added. Her lung condition worsened, and she developed respiratory failure 2 weeks later. Bronchoscopy was performed and the bronchial alveolar lavage (BAL) stain showed some fungus molds. The BAL cell count showed macrophages 76% and neutrophils 2%. TB, pneumocystis carinii (PCP), cryptococcus, and cytology studies were all negative. We changed fluconazole to amphotericin B.

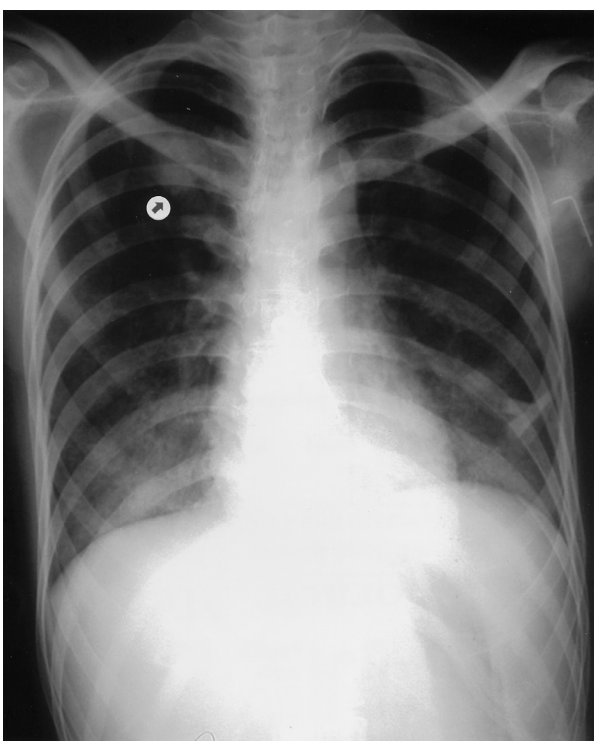


Fig. 1. The CXR of case 1 shows bilateral lower lung infiltration and a cavitation in the right upper lobe.

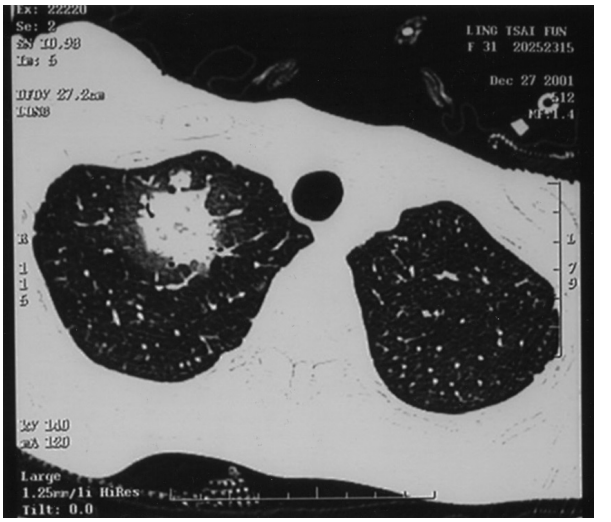


Fig. 2. The chest CT of case 1 reveals a right lobe cavitation.

Her condition progressed to acute respiratory distress syndrome (ARDS) 3 days later, and she died due to septic shock. The RUL lung necropsy (Figure 3) showed invasive pulmonary aspergillosis (IPA). The BAL fungus culture also revealed *Aspergillus Flavus* 2 days after she died.

Case 2

This 34-years-old male was diagnosed with bilineage leukemia (AML M2 and ALL pre-B) in Apr. 2001, and he underwent an allogeneic stem cell transplantation on Jan. 2002. He also suffered from skin GVHD in Feb. 2002, and cyclosporine and a higher dose of methylpredinsolone was administrated to control this condition.

On March 28, 2003 he was admitted under the impression of community-acquired pneumonia. His initial symptom was right-side chest pain. The CXR and chest CT revealed RLL infiltration. The pneumonia was treated with penicillin and ceftriaxone, however, he then developed a change in consciousness and had a seizure 1 week later. The brain CT showed multiple low attenuations in the brain stem, and bilateral cerebral hemispheres. Bleeding was noted within the lesions, and a brain abscess was suspected. Blood and sputum bacterial cultures were all negative. We changed his antibiotic treatment to teicoplanin, meropenem and amphotericin B due

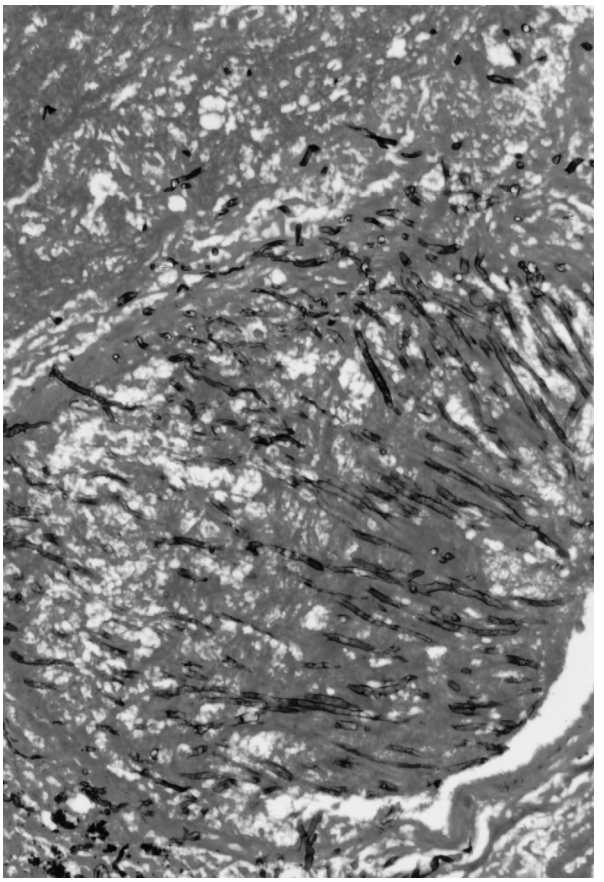


Fig. 3. Photomicrography of a necropsy lung specimen (case 1) reveals abundant long fungal hyphae of Aspergillus infiltrating through a vessel wall. (GMS stain 200X)

to the failure of previous treatment. Nevertheless, he developed respiratory failure 1 week later.

An open lung biopsy was performed due to necrotizing pneumonitis with negative bronchial lavage studies. The biopsy showed IPA and the brain CT was compatible with this diagnosis. The patient died 1 day after the lung biopsy, due to refractory septic shock, without any associated complication of the lung biopsy.

Case 3

This 58-years-old male was diagnosed with systemic sclerosis 20 years before, and has been on long-term low dose-steroid treatment (prednisolone 0.5mg/kg/day) these 2 years.

He was admitted with symptoms of fever, cough, and breathlessness for 3 months. The CXR showed RLL infiltration. The arterial blood gas data was PH 7.43, CO_2 34.7, O_2 49.9, HCO_3 25.4, and SAT 87.9 under FiO_2 35%. Our initial impression was that he had a severe form of community-acquired pneumonia. We treated him with vancomycion and ciprofloxacin to cover oxacillin-resistant staphylococcus, Gram-negative bacilli and *Pseudomonas spp.* His condition did not improve despite treatment. The sputum bacterial cultures were all negative. A chest CT was done later and interstitial pneumonitis and pulmonary fibrosis was suspected. We arranged bronchial alveolar lavage, and the Gram stain revealed yeast-like material. The lavage fluid cell count yielded macrophages 68%, and neutrophils 32%. TB, PCP, cytology, and bacterial cultures were all negative. The fungus culture showed light *Candida albicans*. Oral fluconazole treatment was started as candidiasis was suspected.

The patient developed dyspnea, with a progression to hypoxemic respiratory failure requiring intubation and a mechanical ventilator. Persistent hypoxemia was noted despite supplementation of 100% O_2. The patient died due to septic shock and multiple organ failure. The blood and sputum bacterial cultures were all negative. A RLL necropsy was performed, and it showed IPA. The sputum fungus culture revealed *Aspergillus niger* 1 week after he died.

Discussion

Invasive aspergillosis (IA) has been reported in 5% to 24% of patients during chemotherapy-induced granulocytopenia [4]. Unfortunately, the outcome of invasive or disseminated infection is poor. Better diagnostic tests and treatments are urgently needed.

Invasive pulmonary aspergillosis (IPA) often occurs in immunosuppressed cases with important identified risk factors such as neutropenia, corticosteroid use, and broad-spectrum antibiotics use as shown in our cases (2 AML and a case with long-term steroid use). Other known risk factors include alcohol or marijuana use, underlying lung disease,

and a prior episode of PCP.

Fever, non-productive cough, pleuritic chest pain, and pleural friction rub are the characteristic presentations of IPA. They are found in 30% of all IA cases. In our case 1 and case 2, chest pain was the initial complaint. Following the presentation of pleuritic chest pain, their condition deteriorated within 1 week with the development of respiratory failure. In such cases, chest radiograms often show focal or diffuse infiltrates, but may also be normal. Chest CT scans are more sensitive than radiograms [2], and may reveal nodular lesions surrounded by a zone of attenuation, producing a halo effect. Frequently, a vague infiltration is first noted during granulocytopenia with progression to a classic wedge-shaped infarct or a nodular lesion with cavitations after bone marrow recovery.

Diagnosis of IPA before death may be difficult. CT scans may assist in the early diagnosis and BAL is useful in patients with CT abnormalities. Open lung biopsy is considered a standard diagnostic tool in evaluating pulmonary infiltrates in immunocompromised patients, if the sputum and BAL examination results are negative [5]. Our case 2 was the only case of IPA in which the diagnosis was made while the patient was alive. The sensitivity of open lung biopsy ranges from 60% to 83% [5], and this may be related to the biopsy position. In the 3 cases presented herein, open lung biopsy was the only method that confirmed the diagnosis before the patients died. Biopsy data is available the next day in our hospital, and is more rapid than the fungus culture. Complications include bleeding, pneumothorax, wound infection, and respiratory failure; procedure-related mortality is less than 1% [5]. In our experience over the past 2 years, and in about 45 ICU open lung biopsy cases, the major complication has been hypoxemia during the transfer from the ICU to the operating room. With the use of a portable ventilator use (LTV-1000; PEEP 10-15 cm H_2O), this problem has almost been resolved. (Unpublished data)

If histological confirmation is unavailable in such patients, the recovery of *Aspergillus* or fungus molds, with no other pathogens from the BAL, is probably sufficient evidence for instituting antifungal therapy. In one study of 15 HIV-infected patients, the diagnosis of IPA was made in this manner, and *Aspergillus* infection was later confirmed histologically or at the postmortem examination [6]. In our case 1, we saw fungus molds first, so we treated her as having a fungus infection immediately. This suspicion was confirmed with the necropsy.

IA is characterized by a progression of the infection across tissue planes. One hallmark is vascular invasion with subsequent infarction and tissue necrosis. The specimen in case 3 demonstrated the picture clearly. Presumably, fungal cell surface components bind to vessel wall components, including the basement membrane, extra cellular matrix, and cellular constituent, causing tissue ischemia and infarction.

IA is becoming a leading cause of death due to infection after allogeneic BMT [3]. This increased incidence is not completely understood; it may reflect the use of intensified preparative regimens to avoid rejection or relapse, and result from the intensification of immunosuppressive therapy given to prevent or treat GVHD.

Patients with localized infection have been found to have a considerably lower case fatality rate than those with disseminated disease. A persistently high case mortality for invasive aspergillosis has been shown despite the availability of newer formulations of amphotericin B [7] and improved management of the underlying disease and conditions. Underlying patient conditions, early diagnosis, and the site of infection remain important prognostic factors.

The total duration of therapy is dependent upon the location of the infection, the patient's underlying disease, and the response to therapy. A common strategy is to start with amphotericin B and then to administer itraconazole once the patient is stabilized. In some patients, therapy can be discontinued once the neutrophil count exceeds 500 cells/mm^3 [8]. More commonly, however, continuation of therapy is required until the signs and symptoms of infection have resolved for at least two weeks. How-

ever, it was too late to start amphotericin B for our case 1. In the experience of case 3, oral fluconazole was not a reliable treatment for invasive aspergillosis.

Recently, newer anti-fungal drugs, such as the synthesis of beta (1,3)-D-glucan inhibitor (Caspofungin (MK-0991; Cancidas)), may be helpful in such cases and provide fewer side effects. Combination therapy with conventional treatment could be synergistic [9].

In conclusion, invasive pulmonary aspergillosis has a poor prognosis, especially in high-risk groups (CD4 cell count < 100/uL; patients with cancer and prolonged, profound neutropenia (absolute neutrophil count < 100/uL)) [10,11]. We should suspect this disease whenever the bacterial cultures are all negative or if a patient's clinical condition deteriorates despite adequate antibiotic treatment. Chest CT scan is a more sensitive examination than radiograms. Video assisted open lung biopsy is also a relatively safe procedure. Pathological diagnosis is often rapid than cultures. We could agree that only early diagnosis and aggressive treatment could improve the prognosis in these cases [1,3].

References

1. Perea S, Patterson TF. Invasive aspergillus infections in hematologic malignancy patients. Seminars in Respiratory Infections 2002; 17: 99-106.
2. Dnning DW: Invasive aspergillosis. Clin Infect Dis 1998; 26: 781-803.
3. Ribaud P, Chastang C, Latge JP, *et al*. Survival and prognostic factors of invasive aspergillosis after allogeneic bone marrow transplantation. Clin Infect Dis 1999 ; 28: 322-30.
4. Wheat LJ, Goldman M and Sarosi G: State-of-the-art review of pulmonary fungal infections. Seminars in Respiratory Infections 2002; 17: 158-81.
5. Somboonwit C and Greene JN: Diagnostic methodologies for invasive fungal infections in hematopoietic stem-cell transplant recipients. Seminars in Respiratory Infections 2002; 17: 151-7.
6. Llortholay O, Meyoha MC, Dupont B, *et al*. Invasive aspergillosis in patients with acquired immunodeficiency syndrome: Report of 33 cases. Am J med 1993; 95: 177-87.
7. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis 2001 ; 32: 358-66.
8. Karp JE, Burch PA, Merz WG. An approach to intensive anti-leukemia therapy in patients with previous invasive aspergillosis. Am J Med 1988; 85: 203-11.
9. Groll AH, Walsh TJ. Poential new antifungal agents. Curr Opin Infect Dis 1997; 10: 449-58.
10. Perfect J, Schell W. The new fungal opportunistics are coming. Clin Infect Dis 1996; 22: 112-8.
11. Morrison VA, Haake RJ, Weisfort DJ. Non-candida fungal infections after bone marrow transplantation: Risk factors and outcome. Am J Med 1994; 96: 497-503.

免疫妥協侵犯性肺麴菌病患併發呼吸衰竭—3 病例報告

鄭朝馨　張明哲　黃秀芬*　黃崇旂

如何早期診斷和積極治療侵犯性肺麴菌病一直是棘手的問題,我們報導三位病例，前兩位是白血病患，其中一位是死後屍體檢驗發現，另一例是開胸肺部切片診斷，第三例是全身性罕皮症患者，他也是經由屍體檢驗診斷侵犯性肺麴菌病。每當免疫妥協的病人在適當的抗生素治療下，病情惡化但是細菌培養都是陰性時，我們必須懷疑這個診斷；電腦斷層要比 X 光敏感，胸腔鏡肺切片相對上是個安全的檢查，而且病理學的檢查結果往往比培養來的迅速。*(胸腔醫學 2003; 18: 525-530)*

關鍵詞：侵犯性麴菌病，免疫妥協宿主，內視鏡開胸肺部切片

林口長庚醫院　胸腔內科一科　病理科 *
索取抽印本請聯絡：黃崇旂醫師，林口長庚醫院　胸腔內科一科，桃園縣龜山鄉復興街 5 號

Concomitant Active Pulmonary Tuberculosis and Tuberculous Tenosynovitis of the Wrist: A Case Report

Rong-Sow Lee, Chia-Wen Shih*, Jia-Horng Wang, Ming-Sheng Chern**

Tuberculous tenosynovitis is an uncommon extrapulmonary tuberculosis. The insidious onset and slow progression of symptoms usually result in delayed diagnosis. Surgical debridement and histologic and bacteriologic studies are essential to make the diagnosis. Antituberculous treatment combined with surgical debridement is mandatory to obtain satisfactory results with therapy. Herein, we present the case of a 79-year-old male with pulmonary tuberculosis and concomitant tuberculous tenosynovitis. Although the diagnosis of tuberculous tenosynovitis was delayed for 3 months, the patient still had a satisfactory result with treatment via adequate surgical debridement and anti-tuberculous therapy. Tuberculosis should be included in the differential diagnoses of chronic tenosynovitis of unknown cause whenever active pulmonary tuberculosis exists. ***(Thorac Med 2003; 18: 531-536)***

Key words: Tuberculosis, Tenosynovitis, Wrist

Introduction

Tuberculosis is an endemic disease worldwide. In addition to being an important health care problem in developing countries, an increasing number of cases of tuberculosis has been noted in developed countries in recent years [1,2]. Tuberculosis can affect not only pulmonary, but also extrapulmonary, tissues. Tuberculous tenosynovitis is an example of an uncommon extrapulmonary infection; indolent symptoms and the slow progressive course of the disease make early diagnosis difficult. We report a case of delayed diagnosis of tuberculous tenosynovitis with an initial presentation of chronic swelling, pain, and limited motion of the left wrist. The diagnosis was not established until a positive pathological finding had been obtained.

Case Report

A 79-year-old male had a history of chronic hepatitis C and B for many years. He had poor appetite, productive cough with scanty sputum, and progressive swelling and pain of the left wrist for 3 months prior to admission. He had been treated with non-steroidal anti-inflammatory drugs and physical rehabilitation under the impression of osteoarthritis of the left wrist. He was admitted to our hospital because of body weight loss of 10 kg within 3 months and poor appetite. Physical examination

Respiratory Therapy Department, **Department of Radiology, Veterans General Hospital-Taipei, *Department of Pathology, Lo-Tung Pohai Hospital
Address reprint requests to: Dr. Jia-Horng Wang, Respiratory Therapy Department, Veterans General Hospital-Taipei, 201, Section 2, Shih-Pai Road, Taipei, Taiwan

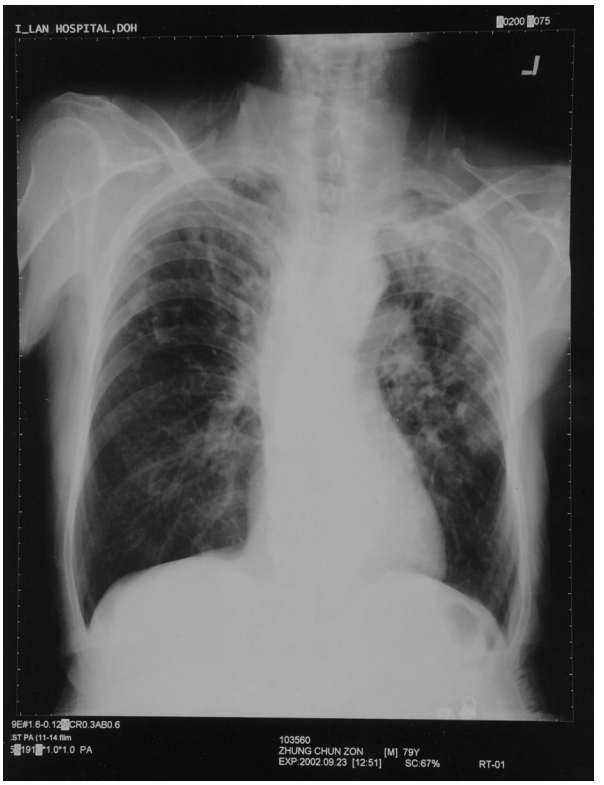


Fig. 1. Chest radiograph shows fibronodular opacities in both upper lobes and left perihilar region. Small cavities were also suspected in the left upper lobe.

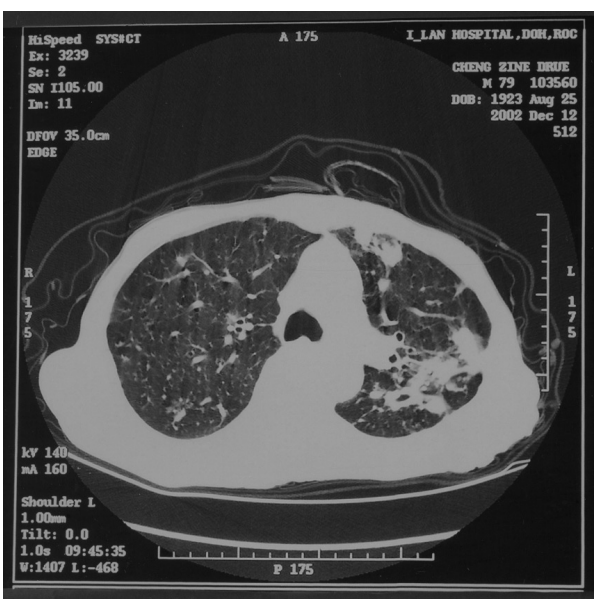


Fig. 2. Thin section high-resolution CT at the carina level shows multiple ill-defined nodules in both upper lobes with more prominence in the left side. A small cavity was evident in the left upper lobe. Pulmonary tuberculosis was highly suggested.

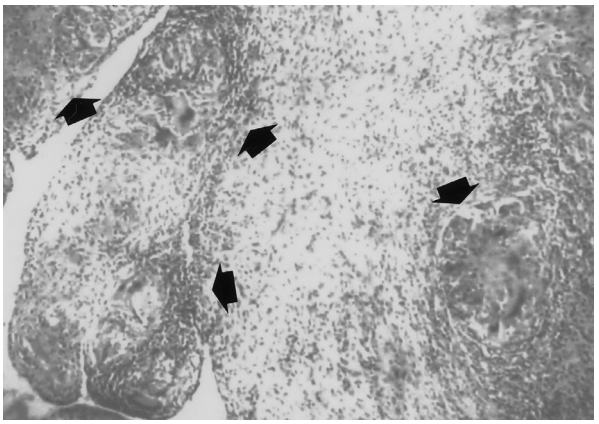


Fig. 3. Histological section of the specimen from the tenosynovectomy. Many granulomas are noted (arrows). (hematoxyline and eosin, X 40)

revealed nothing particular except an ill-defined tender and reddish swelling in the left wrist with a limited range of motion of the joint. The hemogram revealed a normal blood cell count except an elevated erythrocyte sedimentation rate (ESR; 124 mm/hr). Serum chemical analysis revealed hypertransaminasemia (aspartate transaminase [AST]: 69 U/l), hypoalbuminemia (Alb: 2.9 g/dl), and azotemia (BUN: 33mg/dl, Cr: 1.6 mg/dl). The serum immunological study revealed positive hepatitis B surface antigen (HBsAg) and anti-hepatitis C virus (HCV). The chest radiograph showed multiple, ill-defined nodular lesions in both upper zones, and fibrosis and thickening of the pleura. The sputum smear for acid-fast bacilli was negative, but culture grew

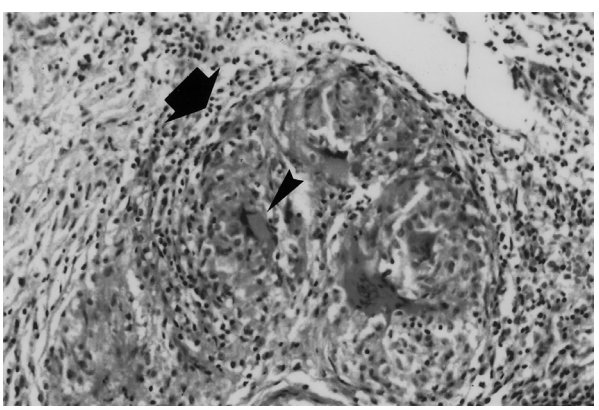


Fig. 4. Histological section of the specimen from the tenosynovectomy. Granuloma (arrow) with lymphocytes, epitheloid cells and Langerhan's giant cells(arrow head). (hematoxylin and eosin, X 200)

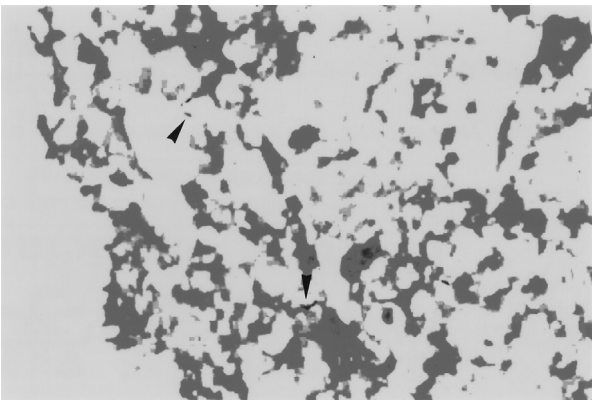


Fig. 5. Histological section of the specimen from the tenosynovectomy. The acid-fast stain shows some red-colored bacilli (arrow heads). (acid-fast stain, X 1000)

Mycobacterium tuberculosis. Tenosynovectomy showed a left wrist abscess accumulation between the flexor tendons and retinaculum, especially between the flexor carpi radialis, palmaris longus, and median nerve, and many rice bodies. A biopsy of the tenosynovium of the left wrist was performed. Histological examination of the specimen showed chronic granulomatous inflammation with positive findings of acid-fast bacilli, but a culture of the soft tissue for acid-fast bacillus was negative.

The diagnosis of pulmonary tuberculosis with tuberculous tenosynovitis was established, and the patient was initially treated with isoniazid, rifampin, ethambutol, and pyrazinamide. However, a development in the icteric sclera was noted after 7 days of antituberculous treatment. The patient was admitted and treated with streptomycin, fluoroquinolone, and ethambutol. The abdominal sonography showed no obstructive hepatobiliary disease. After the subsidence of the hypertransaminasemia and hyperbilirubinemia (serum total bilirubin: 4.59 mg/dl, direct bilirubin: 3.5 mg/dl), isoniazid and pyrazinamide were restarted and streptomycin was discontinued. In addition, the patient received a tenosynovectomy while in the hospital.

After 2 months of antituberculous treatment, the swelling and pain of the left wrist subsided, and the range of motion of the joint improved. Subsidence of constitutional symptoms and cough was also noted, and the follow-up sputum smear for acid-fast bacilli was negative.

Discussion

Extrapulmonary involvement has occured in 17% of cases of tuberculosis [3], and musculoskeletal infection has occured in less than 2% of cases [4,5]. These cases usually present with monoarthritis of the traumatic weight-bearing joints, such as the vertebrae, hip, or knee, and can also involve both the bone and joint [4,5]. Tuberculosis can affect the bone, joint, tendon sheath, or soft tissue portion of these sites, as in the case of tenosynovitis; tendons in the wrist are the most common sites [4-8].

It is well documented that tuberculous tenosynovitis of the hand causes less than 5% of all tuberculous infections of the musculoskeletal system [8]. Predisposing factors include old age, low socioeconomic status, malnutrition, alcohol abuse, history of tuberculosis or exposure to tuberculosis, immunocompromise, and prior trauma. People older than 60 years are thought to be at higher risk than those who are younger. Long-term local or systemic use of corticosteroids for some chronic diseases, such as collagen vascular disease or chronic pulmonary disease, is considered a high risk for the disease. In addition, the spread of human immunodeficiency virus (HIV) infection has made tuberculosis more common. Prior trauma is a well-recognized risk for non-tuberculous mycobacterial infection of the tenosynovium [9,10,13,15]. Most patients with a tenosynovium have a history of pulmonary or extrapulmonary tuberculosis [4,10]. Prior gastrectomy is not thought to be a risk factor for extrapulmonary tuberculosis if there is no history of pulmonary tuberculosis [9].

The pathogenesis of tuberculous tenosynovitis is not completely understood. The disease may be the result of the reactivation of seeded bacteria that spread to musculoskeletal sites after pulmonary tuberculosis, or of a direct seeding of the bacteria to the lesions [4,12]. The clinical manifestations of tuberculous tenosynovitis are indolent, variable, and not characteristic. Progressive swelling around the wrist is the earliest and most common symptom of

the disease. Pain and tenderness are the next most common presenting symptoms. A limitation of the range of motion of the affected joint may occur. Local neurological symptoms, such as paresthesia or numbness, may be present if the median nerve is involved. The presence of constitutional symptoms, such as weight loss, poor appetite, or fever, are uncommon, except when generalized tuberculosis is present [5,7].

No more than 50% of articular infections exist with active pulmonary tuberculosis at the same time [4,7]. About 50% of patients have a normal chest radiograph [5], and the local radiograph shows swelling of the soft tissue [9]. Magnetic resonance imaging (MRI) may be helpful for early diagnosis [11]. The tuberculin skin test may be positive or negative [7]. Establishment of the diagnosis of tuberculous tenosynovitis depends on the culture of *M. tuberculosis* or characteristic pathological findings from infected soft tissue obtained from aspiration, open biopsy, or tenosynovectomy [5,7,9,10]. Adequate surgical treatment includes debridement or tenosynovectomy with antituberculous medical treatment. The antituberculous regimen consists of isoniazid and rifampin for 6 months and pyrazinamide for the first 2 months; the therapeutic response is usually good, and functioning of the affected joint is preserved [5,7-10,13,14]. A high rate of recurrence up to 60% of patients receiving isolated surgical or medical treatment alone has been noted [13, 14], and the concomitant existence of active tuberculosis in other sites of the body may indicate a decreased therapeutic response [7].

Our patient presented with the characteristics of tuberculous tenosynovitis; he is a male, older than 60 years, and is a survivor of chronic hepatitis B and C. His nutritional status at initial presentation was poor, with significant weight loss and hypoalbuminemia. The chest radiograph indicated the predisposing factor of a history of tuberculosis [9]. In addition, a chronic, scanty productive cough, and the growth of *M. tuberculosis* in the sputum culture for acid-fast bacillus indicated active pulmonary tuberculosis at his initial presentation. The progressive swelling and painful sensation in his left wrist, as well as the poor response to non-steroidal anti-inflammatory drugs and physical rehabilitation, indicated an unknown cause of chronic inflammatory disease. The histological finding of chronic granulomatous inflammatory disease suggested the differential diagnoses of tuberculosis, fungal infection, sarcoidosis, non-tuberculous mycobacteriosis, collagen vascular disease, or foreign body reaction. However, the presence of "rice bodies" during tenosynovectomy suggested the possibility of tuberculous involvement of the tenosynovium [14], and the positive finding of acid-fast bacilli in the excised tenosynovium specimen strongly suggested the diagnosis of tuberculous tenosynovitis. Unfortunately, the patient's chronic hepatitis and hypersensitivity to antituberculous agents resulted in jaundice. We discontinued the hepatotoxic agents to preserve his hepatic function. The smooth rechallenge of isoniazid and pyrazinamide strongly suggested that he was hypersensitive to rifampin. He subsequently responded well to antituberculous and surgical treatment. The rapid improvement of the pulmonary tuberculosis and tuberculous tenosynovitis was similar to the results reported by others [5,8-10,15].

In conclusion, tuberculous tenosynovitis is an uncommon disease, especially when it coexists with active pulmonary tuberculosis. Early diagnosis of the disease remains a challenge for the physician because of its insidious onset and indolent progression. It is important to identify predisposing factors and establish the diagnosis of the disease. Adequate surgical and antituberculous medical treatment should begin as soon as possible, regardless of whether active pulmonary tuberculosis exists, to relieve symptoms and preserve the full range of motion and functioning of the affected joint before arthritis or osteomyelitis occurs. In addition, close observation is important because of the high rate of recurrence with surgical or medical treatment alone.

References

1. Buckner CB, Leithiser RE, Walker CW, *et al*. The changing

epidemiology of tuberculosis and other mycobacterial infections in the United States: implications for the radiologist. American Journal of Roentgenolog 1991; 156(2): 255-64.

2. Alrajhi AA, Al-Barrak AM. Extrapulmonary tuberculosis, epidemiology and patterns in Saudi Arabia. Saudi Medical Journal 2002; 23(5): 503-8.
3. Centers for Disease Control and Prevention: Reported tuberculosis in the United States, 1997. Atlanta: Centers for Disease Control and Prevention, 1998.
4. Sen P, Kapila R, Salaki J, *et al*. The diagnosis enigma of extrapulmonary tuberculosis. J Chronic Dis 1977; 30(6): 331-50.
5. Lakhanpal S, Linscheid RL, Ferguson RH, *et al*. Tuberculosis fascitis with tenosynovitis. J Rheumatol 1987; 14: 621-4.
6. Walker UA, Gutfleisch J, Peter HH. Case number 23: tuberculosis tenosynovitis. Ann Rheum Dis 2002; 61(5): 384.
7. Bickel WH, Kimbrough RF, Dahlin DC. Tuberculous tenosynovitis. JAMA 1953; 151: 31-5
8. Fnini S, Ouarab M, Rafai M, *et al*. An uncommon occupational accident: tuberculous tenosynovitis of the extensor tendons of the hand. Chirurgie de la Main 1999; 18(4): 309-12.
9. Jackson RH, King JW. Tenosynovitis of the hand: a forgotten manifestation of tuberculosis. Reviews of Infectious Disease 1989; 11(4): 616-8.
10. Al Soub H. Tuberculous tenosynovitis: a rare manifestation of a common disease. International Journal of Clinical Practice 1998; 52(1): 56-8.
11. Sueyoshi E, Ueitani M, Hayashi K, *et al*. Tuberculous tenosynovitis of the wrist: MRI findings in three patients. Skeletal Radiology 1996; 25(6): 569-72.
12. Soler R, Rodriguez E, Remuinan C, *et al*. MRI of musculoskeletal extraspinal tuberculosis. Journal of Computer Asisted Tomography 2001; 25(2): 177-83.
13. Regnard PJ, Barry P, Isselin J. Mycobacterial tenosynovitis of the flexor tendons of the hand. A report of five cases. Journal of Hand 1996; Surgery -British Volume 21(3): 351-4.
14. Hoffman KL, Bergman AG, Hoffman DK, *et al*. Tuberculous tenosynovitis of the flexor tendons of the wrist: MR imaging with pathologic correlation. Skeletal Radiology 1996; 25(2): 186-8.
15. Garcia Cebrian F. Tuberculous tenosynovitis. [Editorial] Chest 1988; 94(5): 1119.

肺結核合併腕結核性腱鞘炎：病例報告

李榮壽　施洽雯*　王家弘　陳名聖**

結核性腱鞘炎是罕見的肺外結核病。由於發病時癥狀不明顯且病程進展緩慢，通常造成診斷延誤。為正確診斷，外科擴瘡術併組織學及細菌學檢查是必要的。且經由適度的手術併抗結核藥物治療通常產生令人滿意的治療結果。在此我們報告一例 79 歲男性病患同時罹患肺結核合併腕結核性腱鞘炎，結核性腱鞘炎經三個月延遲後才被確認。然而經適度的手術及抗結核藥物治療呈現令人滿意的治療結果。慢性腱鞘炎不論是否同時罹患活動性肺結核，鑑別診斷均應包括結核病。***(胸腔醫學 2003; 18: 531-536)***

關鍵詞：結核病，腱鞘炎，腕

台北榮民總醫院　呼吸治療科　放射線部 **　羅東博愛醫院　病理科 *
索取抽印本請聯絡：王家弘醫師，台北榮民總醫院　呼吸治療科，台北市石牌路二段 201 號

Endobronchial Hamartoma – Correlation between Ultrasonographic and Pathologic Features with A Literature Review

Pei-Ching Oon, Yuang-Shuang Liaw*, Yih-Leong Chang**

Although pulmonary hamartomas are common benign tumors of the lungs, endobronchial hamartomas are very rare in women. We present a middle-aged woman with an endobronchial hamartoma and obstructive pneumonitis. The correlations between the ultrasonographic and pathologic features are the first described in the literature. The characteristic findings included a well-defined, iso- to hyperechoic central tumor with a regular margin, in one wedge-shaped hypoechoic heterogeneous consolidation. She underwent surgical removal of the tumor. No recurrence was noted after ten months of follow-up. ***(Thorac Med 2003; 18: 537-542)***

Key words: endobronchial hamartoma, ultrasonographic findings, pathology

Introduction

Hamartomas, first reported by Albrecht in 1904, are mesenchymal clonal neoplasms composed predominantly of both fat and cartilage, found in the lungs [1-3]. Recently, cytogenetic studies have identified chromosomal bands of recombination located at positions 6p21 and 14q24 in the hamartoma. The incidence of pulmonary hamartomas in a general population was reported as 0.25% [4]. The frequency of an endobronchial location has been reported from 1.1% to 6% [5-7]. A male preponderance was observed among those with endobronchial hamartomas [8]. However, in the largest series of pulmonary hamartomas in Chinese patients (n=24), no endobronchial location was noted [9]. We report a Chinese woman with an endobronchial hamartoma who presented as obstructive pneumonitis. The correlations between her ultrasonographic pictures and pathologic features are described herein, for the first time in the literature.

Case Report

A 47-year-old non-smoking woman presented with chronic dry cough for two months. There was no fever, chills, rhinorrhea, nasal congestion, or dyspnea. A weight loss of 5 kilograms within one month was noted. Chest radiographs revealed a mass at the B6 of the right lower lobe (RLL), with segmental atelectasis (Figure 1A). On admission, her body temperature was 36.2°C, pulse rate 84 beats/min, respiratory rate 20 breaths/min, and blood pressure 110/70 mmHg. No neck lymphadenopathy was detected. The breath sounds were decreased in the right lower lung field, but the heart

Department of Internal Medicine, En Chu Kong Hospital; Departments of Internal Medicine* and Pathology**, National Taiwan University Hospital, Taipei
Address reprint requests to: Dr. Yuang-Shuang Liaw, Department of Internal Medicine, National Taiwan University, Taipei, Taiwan, No. 7, Chung-Shan South Road, Taipei 100, Taiwan

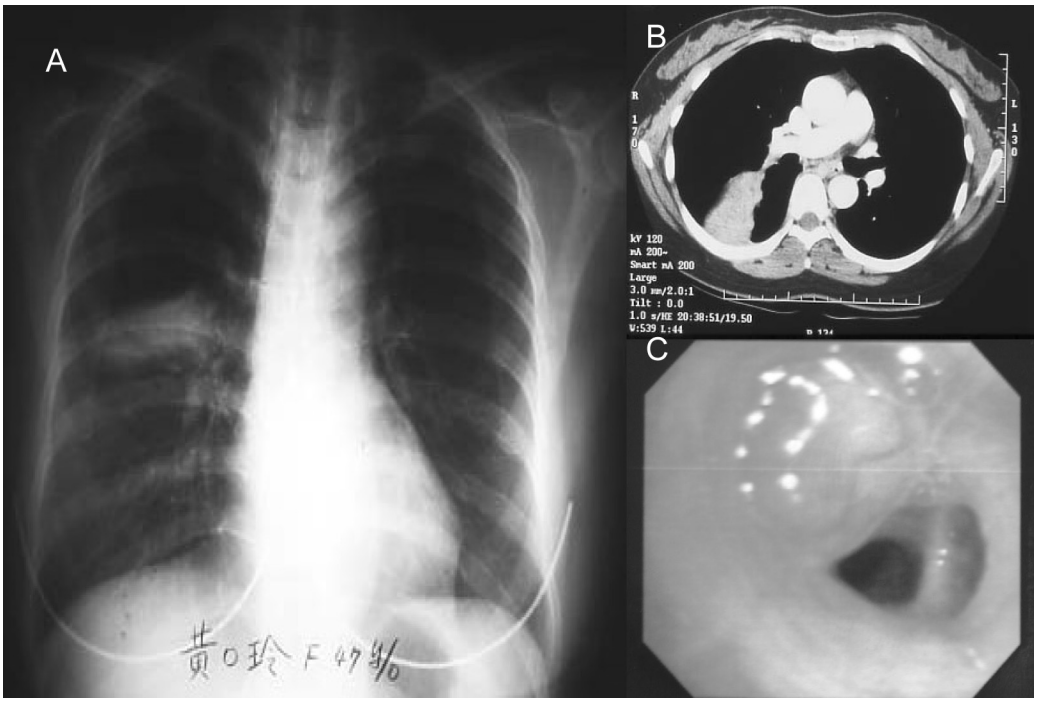


Fig. 1. Image studies of the patient. (A) Chest radiograph showing a mass with segmental atelectasis of the right B6. (B) Chest CT showing an enhanced triangular opacification at the right B6. (C) Bronchoscopic picture showing a pinkish smooth-surface endobronchial tumor at the right B6c.

beat was regular without audible murmurs. Physical examination of the other parts of the body was unremarkable. Computed tomography (CT) of the chest showed a triangular opacification in the right B6, with obstructive pneumonitis (Figure 1B). Endobronchial carcinoid tumor or tuberculosis (TB) with obstructive pneumonitis was suspected. Bronchoscopy disclosed an endobronchial tumor with a smooth surface at the orifice of the right B6c, resulting in total occlusion of the bronchus (Figure 1C). Washing and brushing cytology of the tumor were negative for malignant cells. Acid fast stain of the specimen was also negative. Bronchoscopic biopsy of the tumor showed fibromyxoid tissue and submucosal chronic inflammation (Figure 3A). The chest ultrasonograph revealed one 6.4×6.1 cm wedge-shaped consolidation at the RLL. An iso- to hyperechoic, well-defined central tumor with a regular margin was seen at the apex of the wedge-shaped consolidated lesion (Figure 2A). Echo-guided aspiration of the central tumor was performed, but was inconclusive. Since two consecutive invasive procedures (echo-guided aspiration and bronchoscopic biopsy) did not reveal a definite diagnosis, and malignancy could not be ruled out confidently, surgical intervention was arranged. The patient underwent a right B6 segmentectomy via a posterolateral thoracotomy. A soft, whitish tumor was found at the orifice of the right B6c with yellowish, turbid material in the S6. Grossly, a 0.8×0.5×0.5 cm polypoid tumor was seen in the bronchial lumen, causing inflamed, spongy changes in the tissue distal to the obstruction (Figure 2B). Microscopically, the polypoid tumor was composed of mostly primitive mesenchymal cells within the myxoid stroma, admixed with mature adipose tissue. A small focus of chondroid cells with areas of ossification was also noted (Figure 3B). The adjacent lung parenchyma revealed obstructive pneumonia with mixed acute and chronic inflammation, foamy histiocytes, and lymphoid aggregation. The histologic diagnosis was an endobronchial hamartoma with obstructive

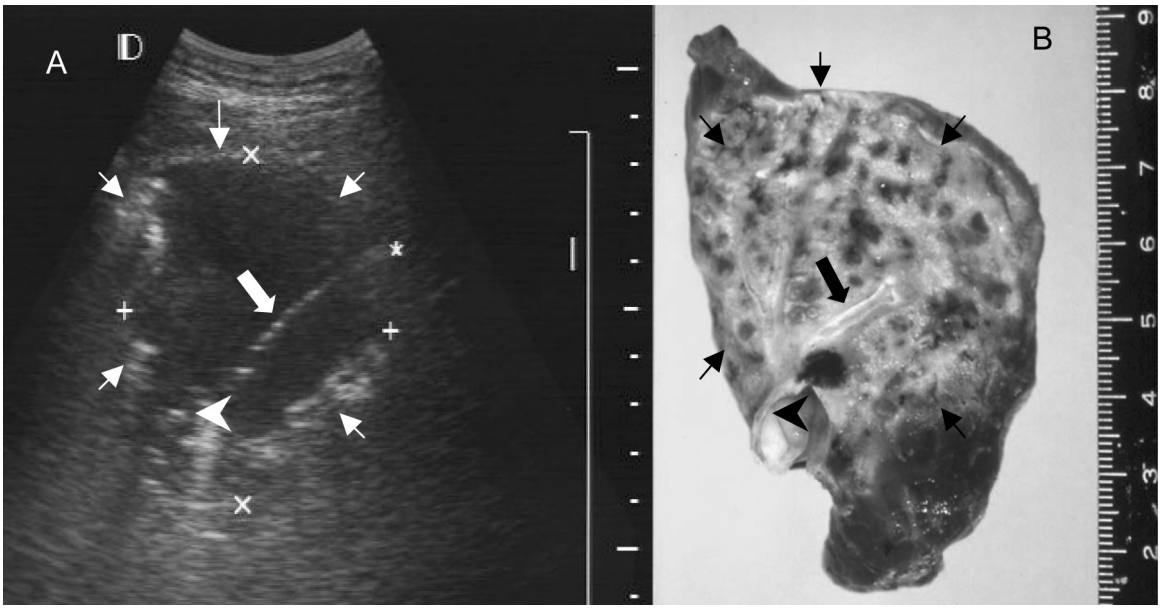


Fig. 2. (A) Ultrasonograph of the patient showing a wedge-shaped consolidation (arrow), a hyperechoic branching bronchus (bold arrow) and an iso- to hyperehoic heterogeneous central tumor with regular margin (arrowhead) at the apex of the triangular consolidation, correlating with (B) the yellowish, inflamed, spongy tissue (arrow), the branching bronchus (bold arrow) and the pinkish, solid endobronchial tumor (arrowhead) in the resected lung tissue.

pneumonitis. The patient recovered fully after the operation, and she has been well in the ambulatory clinical follow-ups.

Discussion

Hamartomas are benign neoplasms most often

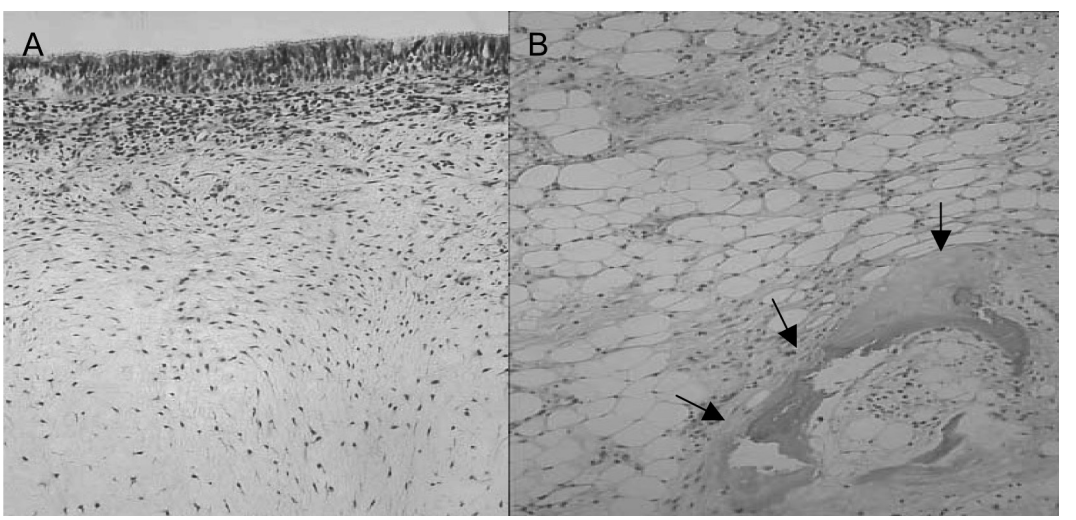


Fig. 3. Histologic examination of (A) specimen obtained by bronchoscopic biopsy of the endobronchial tumor, showing fibromyxoid tissue beneath the columnar epithelium and submucosal chronic inflammation, (H&E, 33X, original magnification) (B) specimen obtained by B6 segmentectomy of the tumor, showing primitive mesenchymal cells within the myxoid stroma admixed with mature adipose tissue, and a small focus of chondroid cells with areas of ossification (black arrows) (H & E, 33x, original magnification).

found in the liver and the lungs. They are generally less than 4 cm, slow-growing, and peripherally located in the lungs. Up to 15% of them are calcified [10]. Endobronchial localization is very rare. Among the 215 patients with pulmonary hamartomas reported by Gjevre et al, only 1.4% had an endobronchial location [6], and an endobronchial location was seen in only one of the 89 patients (1.1%) reported by Hansen et al [5]. Zheng et al reported 24 cases of pulmonary hamartomas in China, and none of them was found inside the bronchus [9].

Endobronchial hamartomas are mainly noted in patients between the 5th and 7th decades, with a male preponderance (male to female ratio was about 6:1 in the series reported by Cosio et al) [8,11]. Most patients with endobronchial hamartomas suffered from recurrent pneumonia, hemoptysis, cough, and/or dyspnea. Because of its intraluminal growth, chest radiographs of these patients have often shown atelectasis with obstructive pneumonitis or recurrent pneumonia [8,11]. No specific imaging feature has ever been concluded. The pathologic picture of this patient correlated well with the ultrasonographic pictures, in which the inflamed tissue distal to the obstruction correlated with the wedge-shaped hypoechoic consolidation shown in the ultrasonograph (arrow in Figures 2A and 2B), the branching bronchus appeared as a hyperechoic branch (bold arrow in Figures 2A and 2B), and the intraluminal tumor was seen as a well-defined, iso- to hyperechoic central tumor with a regular margin in the ultrasonograph (arrowhead in Figures 2A and 2B). These characteristic pictures could be differentiated from malignant tumors, as there was a central tumor with an irregular margin at the triangular tip of the consolidated shadow [12]. In the case of the hamartoma, an iso- to hyperechoic, well-defined central tumor was found.

Bronchoscopic biopsy is the diagnostic method of choice for endobronchial tumors. The endoscopic features are the presence of an exophytic or polypoidal mass with a smooth surface, without submucosal infiltration [8,11]. However, biopsy with a fiberscope was greatly impeded by the extreme hardness of the mass, and the yield rate was only 28.6% [11].

Since hamartomas are benign tumors with a very low risk of malignancy, a low rate of recurrence, and minimal involvement of adjacent tissues, the resection of endobronchial hamartomas by a rigid bronchoscope with laser therapy has been attempted successfully [8,13]. However, Huang et al reported two cases with endobronchial hamartomas who had to be treated with pneumonectomy due to extensive lung parenchymal destruction, caused by chronic bronchial obstruction [14]. Therefore, if (1) malignancy cannot be ruled out; (2) there is total occlusion of the bronchus by the endobronchial tumor; (3) lung parenchyma distal to the obstructive hamartoma is atelectatic and damaged; (4) the endobronchial lesion is accompanied by severe symptoms such as massive hemoptysis; or (5) tumor growth is documented, early thoracotomy or thoracoscopy with minimal tissue destruction is recommended [5,7,9-10,14 -15].

In summary, a rare endobronchial hamartoma is reported in a middle-aged Chinese woman. The ultrasonograph of the endobronchial hamartoma, described herein, is the first described in the literature. The well-defined iso- to hyperechoic central tumor with a regular margin can be differentiated from a malignant intraluminal tumor with obstructive pneumonitis.

References

1. Albrecht E. Ueber harmatoma. Verh Dtsch Ges Pathol 1904; 7: 153-7.
2. Goldsworthy NE. Chondroma of lung (hamartoma chondromatous polmonis), with report of case. J Pathol Bacteriol 1934; 39: 291-8.
3. Fletcher JA, Pinkus GS, Donovan K *et al*. Clonal rearrangement of chromosome band 6p21 in the mesenchymal component of pulmonary chondroid hamartoma. Cancer Res 1992; 52: 6224-8.
4. McDonald JR, Harrington SW, Clagett OT. Hamartoma of the lung. J Thorac Surg 1945; 14: 128-43.
5. Hansen CP, Holtveg H, Francis D *et al*. Pulmonary hamartoma. J Thorac Cardiovasc Surg 1992; 104: 674-8.

6. Gjevre JA, Myers JL, Prakash UB. Pulmonary hamartomas. Mayo Clin Proc 1996; 71: 14-20.
7. Minasian H. Uncommon pulmonary hamartomas. Thorax 1977; 32: 360-4.
8. Cosio BG, Villena V, Echave-Sustaeta J *et al*. Endobronchial hamartoma. Chest 2002; 122: 202-5.
9. Zheng RH, Chou DH, Shi MX. Hamartoma of the lung: An analysis of 24 cases. Chung Hua Chieh Ho Ho Hu His Tsa Chih 1994; 17: 86-7.
10. Yalcin S, Kars A, Firat P *et al*. Multiple bilateral chondromatous hamartomas of the lung – a rare entity mimicking metastatic carcinoma. Respiration 1997; 64: 364-6.
11. Borro JM, Moya J, Botella JA *et al*. Endobronchial hamartoma. Scand J Thor Cardiovasc Surg 1989; 23: 285-7.
12. Yang PC, Luh KT, Wu HD *et al*. Lung tumors associated with obstructive pneumonitis: US studies. Radiology 1990; 174: 717-20.
13. Ortiz-Saracho J, Picher J, Garcia-Rull S *et al*. Endobronchial hamartoma resected by rigid bronchoscope. Eur J Cardiothorac Surg 1993; 7: 445-6.
14. Huang KC, Chen CY, Chen CL *et al*. Endobronchial hamartoma – report of two cases. Chin Med J 1988; 42: 65-70.
15. Otani Y, Yoshida I, Kawashima O *et al*. Benign tumors of the lung: A 20-year surgical experience. Jpn J Surg 1997; 27: 310-2.

氣管內缺陷瘤—超音波和病理之相關性和文獻回顧

溫佩卿　廖永祥*　張逸良**

缺陷瘤雖然是常見的肺部良性腫瘤，但女性氣管內的缺陷瘤卻是非常罕見。我們報告一名中年女性氣管內缺陷瘤合併阻塞性肺炎；本病例首次在文獻上報告氣管內缺陷瘤的超音波表徵和病理之間的相關性。氣管內缺陷瘤在超音波影像學上的表徵為位於楔形低回音狀阻塞性肺炎的中心處，邊緣清楚，具同或高回音的腫瘤。病人接受手術切除腫瘤後追蹤十個月無復發。 ***（胸腔醫學 2003; 18: 537-542）***

關鍵詞：氣管內缺陷瘤，超音波，病理

恩主公醫院　內科部　台大醫院　內科部 *　台大醫院　病理部 **
索取抽印本請聯絡：廖永祥醫師，台大醫院　內科部，台北市中山南路 7 號