# The Incidence of Cough-variant Asthma in Patients with Chronic Cough of Unknown Origin

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**Background:** Cough is a noisy and troublesome symptom which leads sufferers to search for medical help. In some circumstances, doctors treat chronic cough patients as asthmatics, due to the clinical picture or audible wheezing. Although the incidence of asthma has been increasing in recent years, under-treatment may allow the development of irreversible airflow limitation as a result of airway remodeling. It is well known that asthma should not be over-treated. Unnecessary administration of a bronchodilator, such as β2 agonist and theophylline, may cause hand tremor, palpitation and headache. Excess exposure to corticosteroids also may lead to some local or systemic side effects.

**Methods:** In this study, we included 44 patients who had suffered from chronic cough for more than 8 weeks. All patients demonstrated chronic cough, initially negative chest X ray findings, no smoking history, no ACEI consumption history, and clear breathing sounds during physical examination. Sputum special stain for eosinophil count and a bronchial provocation test were performed in selected patients.

**Results:** Ten (22.7%) of the participants were asthmatics, and 3 (6.8%) were patients with eosinophilic bronchitis. Only 29.5% of the participants benefited from corticosteroid treatment.

**Conclusion:** Chronic cough is an unreliable symptom for diagnosing asthma, and may lead to over-treatment. Treatment with corticosteroid or β2 agonist in patients with chronic cough should be more conservative, unless sufficient evidence of asthma has been obtained. ***(Thorac Med 2006; 21: 225-231)***

Key words: chronic cough, cough-variant asthma, eosinophilic bronchitis

## Introduction

Cough is an important defensive mechanism that helps clear excessive secretions and foreign materials from the airways [1]. However, in some pathological conditions, cough is noisy and troublesome. It may cause some complications and lead the patient to seek medical attention. Chronic cough lasting for more than 8 weeks usually implies underlying diseases [2]. In 1 report, the 3 most common causes of chronic cough of unknown origin were asthma, gastroesophageal reflux and post-nasal dripping. This is the so called “diagnostic triad”, if there are no abnormal

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chest roentgenographic findings and if the patient is a non-smoker [2].

Asthma is 1 of the 3 most common causes of chronic cough in adult non-smokers. In cough-variant asthma [3] cough is the cardinal symptom, without detectable airflow limitation. In such cases, a bronchial provocation test and a sputum differential cell count are 2 useful tools for the differential diagnosis. In this study, we sought to clarify the incidence of asthma in patients with chronic cough.

## Methods and Subjects

### *Patient population*

Forty-four patients (19 male and 25 female) with chronic cough lasting more than 8 weeks were enrolled from our outpatient clinics (Table 1). Their ages ranged from 28 to 79 (mean, 58.39 ± 14.06) years; their average FEV1 was 2.10 ± 0.63L and average FEV1/FVC, 78.55±8.87%. All patients were non-smokers and had normal chest roentgenographic findings. Those who had had upper respiratory tract infection within the previous 2 months, recent angiotensin-converting enzyme inhibitor (ACEI) consumption, or a documented history of asthma, were excluded.

### *Study design*

The evaluation protocol included a detailed history-taking and physical examination, a baseline pulmonary function test and methacholine provocation test, and a sputum differential cell count (sputum obtained by self-coughing out or hypertonic saline induction) (Figure 1) [4].

Cough-variant asthma was diagnosed by a positive or borderline methacholine provocation test (PC20 < 16 mg/dl) [5], and/or an increased percentage (≥ 5%) of sputum eosinophil and a history of same. Eosinophilic bronchitis was diagnosed by an elevated sputum eosinophil level of more than 5% without airway hyperresponsiveness.

Post-nasal dripping (PND) was diagnosed mainly by clinical symptoms. Patients were asked if they had a sensation of mucous dripping down to their throats or if they felt the necessity to clear their throats frequently. The results of empirical anti-histamine treatment were used to confirm the impression of post-nasal dripping.

Frank gastroesophageal reflux disorder (GERD) was diagnosed by the clinical symptoms [6] of the heartburn sensation, worsening cough after heavy meals, sour taste in the mouth, and symptoms relieved by taking prokinetic agents as well as H2 blockers. If the GERD symptom persisted, or PND and asthma were not likely, we would arrange 24-hour PH monitoring and a gastroscopy for further evaluation. The "unknown" group included those with chronic cough

**Table 1.** Baseline demographic data in 5 groups

| Group | No. of Patients | Percentage of patients (%) | M/F | Age (y/o) | FEV1 (L) | FEV1/FVC% |
|---|---|---|---|---|---|---|
| Cough-variant asthma | 10 | 22.7 | 6/4 | 61.8 ± 10.7 | 1.94 ± 0.68 | 73.3 ± 7.35 |
| Post-nasal dripping | 11 | 25.0 | 4/7 | 55.7 ± 17.8 | 2.06 ± 0.76 | 76.18 ± 11.46 |
| Eosinophilic bronchitis | 3 | 6.8 | 1/2 | 49 ± 19 | 2.31 ± 0.22 | 78.33 ± 4.04 |
| GERD | 7 | 15.9 | 3/4 | 63.3 ± 7.87 | 2.16 ± 0.46 | 87.29 ± 5.31 |
| Unknown | 13 | 29.5 | 5/8 | 57.5 ± 14.6 | 2.18 ± 0.66 | 79.92 ± 6.36 |
| Total | 44 | 100 | 19/25 | 58.39 ± 14.06 | 2.10 ± 0.63 | 78.55 ± 8.87 |

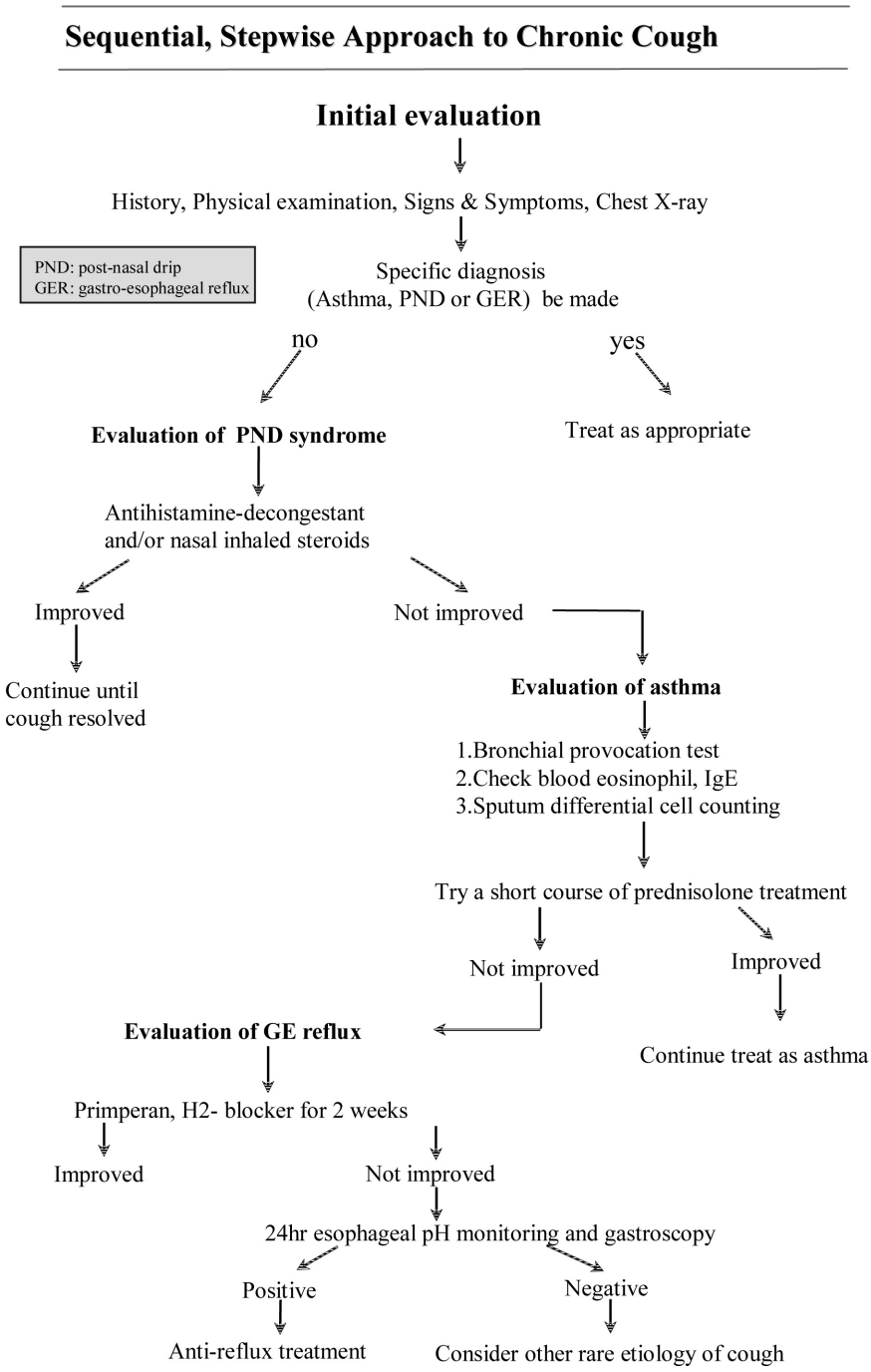


**Fig. 1.** Flow chart approach to chronic cough (modified from Pratter *et al.* Ann Intern Med 1993; 119: 977-83)

with causes other than the 4 diagnoses mentioned above.

***Data results and analysis***

After a series of examinations, the major cause of cough was found to be cough-variant asthma in 10 (22.7%) patients, eosinophilic bronchitis in 3 (6.8%), post-nasal dripping in 11

**Table 2.** Sputum eosinophil percentage in patients with cough of unknown origin

| | Diagnosis | | | | |
|---|---|---|---|---|---|
| Eosinophil % (sputum) | Asthma | PND | GERD | Eosinophilic bronchitis | Unknown |
| Mean | 20.20 | 0.33 | 1.00 | 12.00 | 1.00 |
| N | 5 | 3 | 3 | 3 | 5 |
| Standard deviation | 22.52 | 0.58 | 1.73 | 5.29 | 2.24 |

**Table 3.** Bronchial provocation test results in patients with cough of unknown origin

| Diagnosis | SPT Positive | SPT Borderline | SPT Negative |
|---|---|---|---|
| Asthma | 3 | 7 | 0 |
| PND | 1 | 0 | 9 |
| GERD | 0 | 2 | 5 |
| Eosinophilic bronchitis | 0 | 0 | 3 |
| Unknown | 0 | 2 | 11 |
| Total | 4 | 11 | 28 |

Results of bronchial provocation test: Positive: PC20 < 4 mg/dl, Borderline: PC20: 4-16 mg/dl, Negative: PC20: > 16 mg/dl

(25%), and symptomatic GERD in 7 patients (15.9%) (Table 1). In 5 of the cough-variant asthma patients, the mean percentage of sputum eosinophils was 20.2% (Table 2); the other 5 patients did not have sputum available for further study. Three patients in the cough-variant asthma group demonstrated positive bronchial provocation results and 7 had borderline results (Table 3).

In the eosinophilic bronchitis group, the mean percentage of sputum eosinophils was 12%, and none of the patients demonstrated airway hyperresposiveness. In the PND group, the mean percentage of eosinophil was 0.33%, and only 1 patient showed a positive provocation test. A sputum eosinophil count was not done in 25 participants, since sputum was unavailable or unnecessary for a sputum examination. One participant missed the provocation test because the initial pulmonary function test showed an obstructive type of ventilatory impairment.

## Discussion

Cough of unknown origin is multiple organ-related, and asthma is only 1 probability. One study reported that over half of the patients with cough had underlying lung disorders, such as chronic obstructive pulmonary disease (COPD), bronchiectasis, pulmonary fibrosis, or lung cancer [7]. Among these, the most common causes of chronic cough with normal chest radiography findings were asthma, esophageal disease, and rhinitis, otherwise known as the "diagnostic triad". The other unknown causes of chronic cough are eosinophilic bronchitis, ACEI-induced cough, occupational exposure to an irritant, post-infectious cough, and rarely, psychogenic, or "habit", coughs [2, 8].

The term "cough-variant asthma" was originally used in 1972 [3]. Another researcher reported 6 patients with chronic cough and airway hyperresponsiveness, but no airway obstruction or wheezing [9].

In 1998, researchers defined eosinophilic bronchitis as airway eosinophilia without bronchial hyperresponsiveness [10]. However, wheezing, worsening of the pulmonary function, chronic airway inflammation, and remodeling have been reported in a patient with non-asthmatic eosinophlilic bronchitis [11-12]. Thus, follow-up observation for these patients is mandatory, because of the tendency to become clinical asthma.

This study showed the incidence of cough-variant asthma in our patients to be 22.7%. However, using different enrolment criteria, previous reports have shown a wide variation in the incidence of cough-variant asthma, as a cause of cough of unknown origin, ranging from 7% to 75% [13-14]. Another study reported that 6 of their 86 cough patients were asthmatics. The researchers did not exclude patients who had consumed ACEI, and enrolled 1 case of interstitial lung disease; the methacholine challenge test was not performed [13]. In a study of 78 participants, which included 59 asthma patients that were much younger than those of the previous study, patients with wheezing noticed by doctors were enrolled [14]. In our study, older participants (more than 28 years old) were enrolled, and patients who had audible wheezing sounds during the visit were excluded.

The results of our study showed that the incidence of post-nasal dripping was not as high as that of the previous studies. This may have been because post-nasal dripping is easier to diagnose and manage at a local hospital. Fifteen (34.9%) of the participants in this study had positive to borderline provocation tests--4 (9.3%) were positive and 11 (25.6%), borderline. Airway hypersensitivity to methacholine has been found in patients with reflux esophagitis [15]. Two of our patients with reflux esophagitis demonstrated borderline methacholine test results. Despite the possibility of overlapping diagnoses, these 2 cases showed symptomatic improvement after prescribing prokinetic agents and an H2 blocker, so we chose the main diagnosis as final diagnosis. Transient airway hypersensitivity may exist for months after acute viral respiratory infections [16], the diagnosis of cough-variant asthma should be delayed at least 8 weeks after a recent upper respiratory tract infection. Some of the studies mentioned above showed that a higher incidence of cough-variant asthma did not exclude recent upper respiratory tract infection.

Thirteen of our participants did not fit the above 4 diagnoses and were classified as an "unknown" group. The possible causative agents in this group may have included silent esophageal reflux, silent post-nasal dripping, psychogenic cough, irritants, or a "habit" cough.

In order to distinguish asthma from other causes of chronic cough, more sensitive measurements, such as exhaled nitric oxide, should be considered [17]. Although the clinical values were confirmed only in asthma with acute exacerbation and in monitoring the effects of steroid treatment [18-20], early detection of "sub-clinical asthma" by exhaled NO may prevent the risk of developing clinical asthma.

Many doctors use bronchodilators and even systemic/inhaled corticosteroids to treat cough, especially in patients who complain of chronic cough with self-audible wheezing. Both of the medications can cause adverse effects, such as hand tremor, headache, palpitation, dry mouth, dysphonia, and oral candiasis. Although cough-variant asthma may improve with bronchodilator treatment for 1 week, complete resolution of the symptom will still require inhaled corticosteroid for more than 8 weeks [21]. It is mandatory to make a clear diagnosis of cough of unknown origin, and then specific management can be

implemented to prevent exposure to unnecessary medications.

In conclusion, chronic cough of unknown origin should not be the only reason to prescribe empirical corticosteroid or bronchodilator, unless more data is available to confirm the diagnosis.

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# 咳嗽變異型氣喘在不明原因慢性咳嗽中的發生率

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**前言**：咳嗽是一個惱人的症狀並常促使患者尋求醫療協助。有時候醫師會把慢性咳嗽的患者當做氣喘治療，雖然氣喘發生率逐年增加，雖然治療不足會造成不可逆的呼吸道氣流阻塞及呼吸道重塑，但過度使用治療氣喘藥物也是有害的。使用不必要的支氣管擴張劑，像$\beta$ -agonist 與 theophylline 類藥物，會引起手抖、心悸及頭痛。過度使用類固醇也會導致局部或全身性的副作用。

**方法**：我們選擇 44 個慢性咳嗽超過八週的病人，胸部 X 光片正常、無抽菸史、無使用 ACEI 類降高血壓藥物、胸部理學檢查呈現乾淨呼吸聲。檢查痰液中嗜伊紅性白血球的數量與支氣管激發試驗。

**結果**：10 (22.7%) 個受試者診斷為氣喘，3 (6.8%) 個受試者診斷為嗜伊紅性支氣管炎。總共只有 13 (29.5%) 個受試者會因使用類固醇藥物而受益。

**結論**：只靠慢性咳嗽就診斷氣喘，似乎不太可靠。因此當我們沒有進一步的證據時，應該更謹慎且保守的用類固醇藥物來治療慢性咳嗽。*(胸腔醫學* ***2006; 21: 225-231)***

關鍵詞：慢性咳嗽，咳嗽變異型氣喘，嗜伊紅性支氣管炎

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# The Value of Fiberoptic Bronchoscopy in the Diagnosis of Central and Peripheral Lung Cancer

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**Background:** Flexible fiberoptic bronchoscopy combined with bronchial brushing (BB), bronchial washing (BW) and endobronchial biopsies (EBB) has been widely performed to achieve diagnoses of lung cancer. Our study was designed to evaluate the diagnostic yield of BB, BW and EBB in central and peripheral lung cancers.

**Methods:** A total of 295 patients who presented with a central or peripheral lung mass in the chest radiography were proven to have a malignancy, based on the final cytology and histology reports, and the clinical evidence. Each patient received a bronchoscopy with BB, BW, or EBB, or a combination of these procedures. In all, 191 patients with a central type of lung cancer had a visible endobronchial lesion, and 104 patients had a peripheral type which was not visible to bronchoscopy. The tumor size of the peripheral lung cancer was recorded.

**Results:** The overall diagnostic yield in the central lung cancer group (81.7%) was significantly higher than that of the peripheral lung cancer group (29.8%, $p < 0.0001$). Each EBB and BB procedure significantly increased the diagnostic accuracy of central lung cancer compared to that of peripheral lung cancer. The BW diagnostic rate showed no difference between central and peripheral lung cancer. The diagnostic rate of the combined procedures was significantly increased in central lung cancer, but not in peripheral lung cancer. The conventional EBB, BW, or BB procedures achieved a higher diagnostic yield for peripheral lung cancer with a tumor size > 3 cm (39.7%) than for a tumor size less than 3cm (19.6%, $p = 0.005$).

**Conclusions:** In conclusion, the combination of BB and EBB has a satisfactory diagnostic yield in central lung cancer. In peripheral types of lung cancer, conventional procedures alone cannot achieve a good result. Bronchoalveolar lavage, transbronchial lung biopsy, and transbronchial needle aspiration with or without endobronchial ultrasonography will provide more accurate diagnostic sensitivity. ***(Thorac Med 2006; 21: 232-238)***

Key words: bronchoscopy, lung cancer, bronchial brushing, bronchial washing, endobronchial biopsy

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## Introduction

Flexible fiberoptic bronchoscopy (FFB) is a well-established and useful diagnostic tool for lung tumors [1-2]. To achieve a diagnosis, 3 conventional techniques: bronchial brushing (BB), bronchial washing (BW) and endobronchial biopsies (EBB), individually or in combination, have been widely used. The diagnostic yield with these conventional sampling methods has varied in different series, but was higher in central-type (range: from 79% to 96%) and lower in peripheral-type lung cancer (range: from 48% to 74%) [1, 3-8]. For peripheral lung cancer, several methods, such as fluoroscopy guidance, multiple brushings with immediate stain cytology, bronchoalveolar lavage (BAL), transbronchial needle aspiration (TBNA), or transbronchial lung biopsy (TBLB), have been established to increase the diagnostic yield [6, 8-11]. Herein, we report on study of the diagnostic yield of BB, BW and EBB applications in central and peripheral lung cancers.

## Methods

### *Study population*

From September 2002 to October 2004, the data of a total of 393 patients at Chang-Gung Memorial Hospital proven to have lung cancer in the final cytological or histological reports were studied retrospectively. FFB was performed in 295 patients (201 men and 94 women), aged from 33 to 87 years (mean: 65 years). The location of the tumor was determined initially by conventional chest radiography or computed tomography. Informed consent was obtained before the procedures. FFB without fluoroscopic guidance was then performed transnasally after local anesthesia with 2% xylocaine. The heart rate and oxygen saturation of each patient was monitored by a pulse oximeter during the examination. An individual procedure, or a combination of the 3 conventional techniques EBB, BB, or BW, was performed to establish the final diagnosis.

The patients were divided into central or peripheral lung cancer groups, defined as tumors visible (exophytic mass or irregular mucosa) or invisible to bronchoscopy. One hundred and ninety-one of the 295 patients had a central type with a visible endobronchial lesion; the other 104 patients had a peripheral type. The diagnostic yield of the individual or multiple sampling procedures in the central and peripheral lung cancer groups was calculated.

The tumor size based on chest radiography or computed tomography in the peripheral lung cancer group was recorded. Forty-six of 104 patients had a main tumor less than or equal to 3 cm. The other 58 patients had a main tumor more than 3 cm. The diagnostic yield in these 2 groups was also calculated.

### *Statistical analysis*

The data were expressed as mean ± SD. The chi-square test was used to compare differences between the diagnostic yields of different sampling procedures in each lung cancer group, and tumor size in the peripheral lung cancer group. A $p$ value less than 0.05 was considered statistically significant.

## Results

Two hundred and ninety-five of 393 patients had underdone at least 1 bronchoscopy. Of these 295 patients, 191 had endobronchial lesions, with cell types including 38 small cell carcinoma and 153 non-small cell carcinoma (65 adenocarcinoma, 54 squamous cell carcinoma, and 34 unde-

**Table 1.** Demographic and cell type in central and peripheral lung cancer

| | Central type n=191 | Peripheral type n=104 | *p* value |
|---|---|---|---|
| Age, mean ± SD | 65.9 ± 11.5 | 63.4 ± 12.2 | 0.07 |
| Male, (%) | 137 (71.7) | 64 (61.5) | 0.07 |
| Cell type | | | |
| Small cell carcinoma | 38 | 1 | < 0.0001 |
| Non-small cell carcinoma | 153 | 103 | |
| Adenocarcinoma | 65 | 68 | < 0.0001 |
| Squamous cell | 54 | 12 | 0.001 |
| Undetermined | 34 | 23 | 0.37 |

termined). The other 104 patients had peripheral lung lesions, with a histological distribution of 1 small cell carcinoma and 103 non-small cell carcinoma (68 adenocarcinoma, 12 squamous cell carcinoma and 23 undetermined) (Table 1). The cell types in the central lung cancer group consisted of a higher percentage of small cell carcinoma than those of the peripheral lung cancer group, while the percentage of adenocarcinoma was higher in the peripheral lung cancer group (Table 1).

One hundred and eighty-seven of 295 patients were proven to have malignancy after the first bronchoscopic examination. The diagnostic yield was 63.2%. The other 108 patients received either a second bronchoscopy, or other procedures to achieve the final diagnosis (9 repeat bronchoscopies, 39 CT-guided biopsies, 18 pleura biopsies, 12 cytologies of pleural effusion, 15 open-lung biopsies, and 15 other procedures) (Table 2).

The overall diagnostic yield in the central lung cancer group was significantly higher than that in the peripheral lung cancer group (81.7% vs 29.8%, $p < 0.001$). Each EBB (77.9% vs 30%, $p = 0.0007$) and BB (72.2% vs 20.4%, $p < 0.0001$) procedure significantly increased the diagnostic accuracy in central lung cancer, compared to that in peripheral lung cancer (Table 3). However, the diagnostic rate of BW showed no difference between central and peripheral lung cancer. The diagnostic rate of the combined procedures- EBB + BB, BB + BW, or EBB + BB + BW, was significantly increased in central lung cancer, compared to peripheral lung cancer (Table 3).

**Table 2.** Final diagnostic procedure of 295 patients with lung cancer

| | n = 295 | % |
|---|---|---|
| Diagnostic methods | | |
| Bronchoscopy (1st) | 187 | 63.4 |
| Repeat bronchoscopy | 9 | 3.0 |
| CT-guided biopsy | 39 | 13.2 |
| PL biopsy | 18 | 6.1 |
| PL cytology | 12 | 4.1 |
| Open lung biopsy | 15 | 5.1 |
| Others | 15 | 5.1 |

Others: including 8 lymph node aspirations, 4 echo-guide biopsies, 1 biopsy from a metastatic site, and 2 from local hospital results

Forty-six of 104 peripheral lung cancer patients had a main tumor less than or equal to 3 cm, and 58 patients had a tumor greater than 3 cm. Conventional EBB, BW, or BB procedures achieved a higher diagnostic yield in peripheral lung cancer with a tumor size > 3 cm (39.7%) in tumors less than 3 cm (19.6%, $p = 0.005$).

**Table 3.** The diagnostic yield of different bronchoscopic procedures in central or peripheral-type lung cancer

| | Central type (n = 191) | | | Peripheral type (n = 104) | | | |
|---|---|---|---|---|---|---|---|
| | positive | negative | % | positive | negative | % | *p* value |
| EBB or BB or BW | 156 | 35 | 81.7 | 31 | 73 | 29.8 | < 0.0001 |
| EBB | 120 | 34 | 77.9 | 3 | 7 | 30.0 | 0.0007 |
| BB | 114 | 44 | 72.2 | 19 | 74 | 20.4 | < 0.0001 |
| BW | 26 | 49 | 34.7 | 24 | 75 | 24.2 | 0.13 |
| EBB + BB | 107 | 15 | 87.7 | 3 | 7 | 30.0 | < 0.0001 |
| BB + BW | 48 | 19 | 71.6 | 25 | 63 | 28.4 | < 0.0001 |
| EBB + BW | 32 | 8 | 80.0 | 2 | 8 | 20.0 | 0.0003 |
| EBB + BB + BW | 28 | 5 | 84.8 | 2 | 5 | 28.6 | 0.0018 |

EBB: endobronchial biopsies, BB: bronchial brushing, BW: bronchial washing

## Discussion

The present study demonstrated that the conventional EBB, BB, and BW procedures via a flexible bronchoscope had a higher diagnostic yield in central lung cancer than in peripheral lung cancer. FBB provides a thorough visual inspection of the airways and can directly approach central-type lung cancer. Therefore, the EBB, BB, or BW procedures were able to easily gain adequate samples to establish the cytological or histological diagnosis. To achieve a higher diagnostic yield, a combination of these procedures was performed simultaneously.

The value of bronchial washing in our series was lower in the diagnosis of central lung cancer. This procedure may have a limitation in obtaining satisfactory cells to establish the diagnosis. Therefore, a combination of EBB or BB is mandatory for an improvement in the diagnostic yield in central-type lung cancer. The addition of TBNA to conventional sampling procedures has increased the overall yield of bronchoscopy for central-type lung cancer in some studies, especially with submucosal infiltration or peribronchial tumors causing external compression [12-14]. Dasgupta *et al*. [13] showed that the diagnostic yield increased from 76% with conventional procedures to 96% with a combination of TBNA and conventional procedures. In addition, other newly-developed techniques using real-time endobronchial ultrasonography (real-time EBUS) also have value in the diagnosis of infiltrated tumors or mediastinal lymph nodes [15].

Using conventional procedures to approach peripheral lung cancer, the diagnostic yield (29.8%) was relatively lower in our study compared to previous studies (ranging from 56% to 80%) (Table 4). BAL, TBLB, and TBNA were proven to be useful in increasing the diagnostic yield in peripheral lung cancer (Table 4). EBUS is another powerful tool that was introduced recently, and that can detect and localize peripheral lung tumors exactly. EBUS can also reduce the number of complications, such as bleeding or pneumothorax, and increase the diagnostic accuracy [21].

The size of the peripheral lung tumor was an important factor in the diagnostic yield of bronchoscopy [6-7]. The higher diagnostic yield of FFB for larger peripheral lung cancers is related, possibly, to the bronchus-tumor relationship. Tsuboi *et al.* [22] found a significant relationship between the size of the tumor and

**Table 4.** Diagnostic yield of flexible bronchoscopy for peripheral lung cancer

| Author (Ref) | Year | Bronchoscopic procedures | No. of patients | Diagnostic yield (%) |
|---|---|---|---|---|
| Shiner *et al* (8) | 1988 | BB, BW, BAL, TBLB | 51 | 74 |
| Pirozynski (16) | 1992 | BAL | 145 | 65 |
| Gasparini *et al* (17) | 1995 | TLBL, TBNA | 750 | 75 |
| Katis *et al* (18) | 1995 | BB, BW, TBLB, TBNA | 37 | 70 |
| Chechani *et al* (19) | 1996 | BB, BW, TBLB, TBNA | 40 | 80 |
| Baaklini *et al* (7) | 2000 | BB, BW, TBLB | 151 | 64 |
| Tang *et al* (10) | 2000 | BAL, TBLB | 37 | 73 |
| Herth *et al* (20) | 2003 | TBNA+EBUS | 242 | 71 |
| Yang *et al* (21) | 2004 | TBLB, TBNA+EBUS | 218 | 56 |
| | | | 1671 | 70* |

*Combined weighted average diagnostic yield of all 9 studies. BB: bronchial brushing, BW: bronchial washing, BAL: bronchoalveolar lavage, TBLB: transbronchial lung biopsy, TBNA: transbronchial needle aspiration, EBUS: endobronchial ultrasound

the number of involved airways. More than 60% of tumors smaller than 3 cm involved only 1 bronchus. In contrast, 3 or more bronchi were involved in 60% of tumors larger than 3 cm. More bronchi in relation to the tumor increase the probability that the bronchoscopy reaches the periphery of the tumor, resulting in a higher diagnostic yield.

Failure to obtain an accurate diagnosis with the initial bronchoscopy for suspected lung cancer often leads to a repeat bronchoscopy or other invasive procedures. This also delays the initiation of definitive treatment, especially in patients with peripheral lung cancer. The average delay was 33.9 days (ranging from 0 to 834 days) from the first bronchoscopy to the final diagnosis. It is mandatory to perform a more invasive procedure via bronchoscopy to achieve a higher diagnostic accuracy.

In conclusion, FFB is a useful diagnostic tool for lung cancers. In patients with endobronchial lesions, a combination of BB and EBB has a satisfactory diagnostic yield. To increase the diagnostic accuracy in patients with submucosal or peribronchial tumors, the addition of TBNA to these conventional procedures may be a better approach. In peripheral-type lung cancers, conventional procedures alone cannot achieve a good result. BAL, TBLB and TBNA with or without EBUS guidance will provide more accurate diagnostic sensitivity.

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# 軟式支氣管鏡在診斷中央型和周邊型肺癌的價值

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**背景**：支氣管鏡檢查術合併支氣管刷拭，支氣管沖洗，以及支氣管切片，被廣泛的應用在肺癌的診斷上。本研究比較這些技術在中央型和周邊型肺癌的診斷上有何異同。

**方法**：本研究納入了胸部 X 光上發現有肺腫瘤且最後診斷為肺癌的病患共 295 人。每一個病患都接受支氣管鏡檢查，其中 191 人屬於中央型肺癌，另外 104 人屬於周邊型。周邊型肺癌病患的腫瘤大小同時加以紀錄。

**結果**：中央型肺癌的診斷率 (81.7%) 明顯比周邊型 (29.8%) 高 ($p < 0.0001$)。就單獨的檢查術比較，支氣管切片和支氣管刷拭明顯增加中央型肺癌的診斷率，但是支氣管鏡沖洗術在中央型和周邊型肺癌的診斷上就沒有差別。中央型肺癌的病患同時合併使用這些檢查技術明顯增加了診斷率。周邊型肺癌的患者如果腫瘤大小超過 3 公分會有較高的診斷率 ($p = 0.005$)。

**結論**：中央型肺癌，合併使用支氣管鏡切片和支氣管鏡刷拭術有最好的診斷率。在周邊型肺癌，單獨使用這些傳統的技術沒有辦法得到很好的診斷結果。可能以支氣管肺泡沖洗術、經支氣管肺切片術、經支氣管細針抽吸術、或支氣管鏡超音波可以得到更好的診斷結果。*(胸腔醫學* ***2006; 21: 232-238)***

關鍵詞：軟式支氣管鏡檢，肺癌，支氣管刷拭，支氣管沖洗，支氣管切片

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# Clinical Antecedents to Cardiopulmonary Resuscitation in the Medical Intensive Care Unit: A Retrospective Study

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Background: The clinical antecedents of cardiopulmonary arrest in the intensive care unit have not been well defined yet.

Methods: We retrospectively reviewed those patients who received cardiopulmonary resuscitation in the medical intensive care unit over a 2-year period. We evaluated a number of pre-arrest conditions to determine if the outcome after cardiopulmonary resuscitation was influenced by any of these parameters.

Results: A total of 45 patients (1.2% of medical intensive care unit admissions) were identified. Among them, 27 (60 %) were successfully resuscitated with recovery of spontaneous circulation, but only 4 patients (8.9 %) survived to hospital discharge. A total of 38 (84 %) and 17 (38 %) of the patients had documented observations of clinical deterioration within 8 and 24 hours of arrest, respectively. Patients developing arrest in the medical intensive care unit have predominantly respiratory and cardiovascular derangements in the underlying disease. Arrest was frequently preceded by a clinical deterioration involving hypotension. Antecedent cardiovascular events (RR = 0.182, $p$ = 0.018), including shock, and expected arrests (RR = 0.125, $p$ = 0.009), were associated with a worse chance of recovery of spontaneous circulation.

Conclusion: Patients receiving cardiopulmonary resuscitation have a poor outcome. Expected arrests and antecedent cardiovascular events are associated with a reduced chance of successful resuscitation. ***(Thorac Med 2006; 21: 239-246)***

Key words: cardiopulmonary resuscitation, intensive care unit

## Introduction

Cardiopulmonary arrest is a condition commonly encountered during practice in the medical intensive care unit (MICU), because of the concentration of seriously ill patients admitted there. Cardiopulmonary resuscitation (CPR) has been widely used for cardiopulmonary arrests occurring both in and out of the hospital [1] since the introduction of closed-chest cardiac massage in 1960. Technological advances during these same 4 decades have led to the extensive development

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of the MICU, but the risk of arrest remains high because of the pertinent severity of the critically ill patients; the mortality of those receiving CPR in the MICU has remained high, as well.

For cardiopulmonary arrests occurring in the general population, a witnessed arrest and a rapid initiation of CPR are 2 important factors that are associated with a favorable outcome [2-3]. MICUs have been equipped with a number of monitoring devices to detect early changes in the condition of patients, for which staff may act promptly to provide adequate management to achieve optimal outcomes. The study of the physiologic abnormalities preceding cardiopulmonary arrest in the MICU might eventually lead to more rational approaches to the prevention of arrest, alternate strategies in resuscitation from arrest, or the timely involvement of patients and family members in decisions to resuscitate. In this study, we sought to investigate and describe the antecedent physiologic abnormalities of MICU patients who received CPR.

## Materials and Methods

We retrospectively reviewed the medical records of the patients who developed cardiopulmonary arrest and received CPR after admission to the 50-bed MICU of National Taiwan University Hospital, between January 2003 and December 2004. Cardiopulmonary arrest was defined by the cessation of cardiac mechanical activity as confirmed by the loss of consciousness and absence of signs of spontaneous circulation. All MICU patients aged 18 years or older with a computerized code for CPR on hospital discharge were evaluated for eligibility for inclusion in this study. The exclusion criteria were: (1) cardiopulmonary arrests occurred within 1 hour after admission to the MICU; (2) cardiopulmonary arrests that occurred while the patients were out of the MICU; (3) CPR performed when the patients were being treated with extracorporeal oxygen support or ventricular aid devices.

The following clinical data were collected for every patient, partly based on the international consensus (Utstein recommendation) for reporting CPR [4]: age, sex, underlying diseases or conditions, reasons for MICU admission, severity scores (APACHE II) on admission to the MICU, dates of hospital and MICU admission and discharge, treatments in the MICU, cardiac rhythm before, during and after CPR, cerebral functions, CPR procedures performed, and MICU and hospital outcome on discharge. The initial rhythms were coded according to the rhythm recorded on the chart or resuscitation note when the collapse took place. The time of events and various interventions were recorded in the resuscitation records. In addition, antecedent events were recorded if they either appeared for the first time or were specifically described as increasing in severity during the 8 and 24 hours preceding cardiac or respiratory arrest. The data were verified and compared with the nursing records. The outcomes measured and analyzed were the return of spontaneous circulation (ROSC) after resuscitation and survival to discharge. ROSC, or "successful resuscitation", was defined as restoration of spontaneous circulation, lasting for >20 min, and providing evidence of more than an occasional gasp, occasional fleeting palpable pulse, or arterial waveform [4].

For statistical analysis, all continuous data were expressed as mean ± SD. Analyses were performed with the SPSS-10 computer software (SPSS, Inc., Chicago, IL). Categorical data were compared with the Chi-square test. A $p$ value of less than 0.05 was considered significant.

## Results

During the 2-year study period, with 3911 admissions to the MICU, a total of 45 episodes (1.2%) of CPR performed on 45 patients were identified. Table 1 shows the demographic and clinical characteristics of the patients. The average age was 63 years (range, 18-87), and the majority of the patients (66%) were male. The most common underlying diseases included diabetes, malignancy, and renal failure, while the most common reasons for MICU admission were pneumonia and septic shock. Mechanical ventilation had been used with 35 patients (78%) prior to resuscitation in the MICU. Cardiac arrest occurred at a mean interval of 9 days after MICU admission (range, 0 to 42 days). Cardiac arrests were unexpected in 33 patients (73%). The median duration of the resuscitation effort was 16 minutes (range, 2-110). ROSC was achieved in 60% of the patients, but only 4 patients (8.9%) survived to hospital discharge (Figure 1). All patients received at least 1 intravenous medication (epinephrine: 100%, atropine: 42%, sodium bicarbonate: 64%) during resuscitation. Cardiac massage was performed in 42 patients (93%) and defibrillation for cardiac arrhythmia was performed in 14 patients (31%). Five patients had a previous "do not resuscitate" order, but still received CPR when the cardiac arrests occurred, mainly due to staff considerations of family decision-making uncertainty. Resuscitative efforts were discontinued after the "do not resuscitate" order was made known to the doctor responding to the arrest.

The clinical antecedents of the cardiopulmonary arrests of the 45 patients are shown in

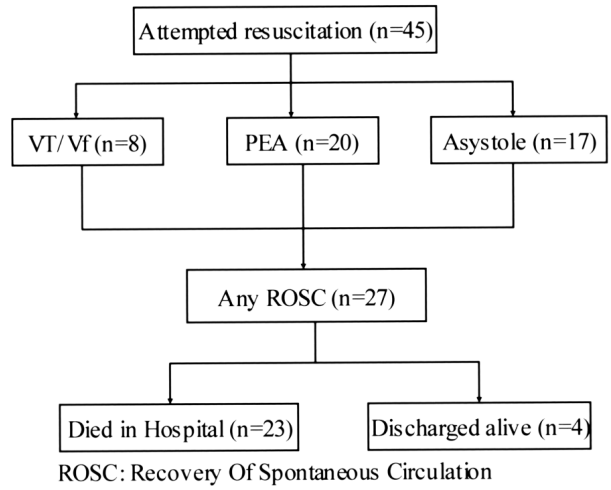


**Fig. 1.** Overall data of the 45 resuscitated patients

**Table 1.** Characteristics of 45 patients receiving resuscitation for cardiopulmonary arrest in the medical intensive care unit

| Characteristic | Data (n = 45) |
|---|---|
| Age, yr, mean ± SD (range) | 63 ± 19 (18-87) |
| Male, n (%) | 30 (67) |
| Underlying conditions | |
| Diabetes, n (%) | 17 (38) |
| Malignancy, n (%) | 15 (33) |
| Renal failure, n (%) | 10 (22) |
| Hypertension, n (%) | 9 (20) |
| Coronary artery disease, n (%) | 8 (18) |
| Congestive heart failure, n (%) | 8 (18) |
| Cardiac arrhythmias, n (%) | 8 (18) |
| Liver cirrhosis, n (%) | 3 (7) |
| Cerebrovascular accident, n (%) | 2 (4) |
| Chronic obstructive pulmonary disease, n (%) | 2 (4) |
| Reason for MICU admission | |
| Pneumonia, n (%) | 15 (33) |
| Septic shock, n (%) | 9 (20) |
| Acute myocardial infarction, n (%) | 6 (13) |
| Gastrointestinal bleeding, n (%) | 5 (11) |
| Post-resuscitation, n (%) | 4 (9) |
| Congestive heart failure, n (%) | 3 (7) |
| Acute renal failure, n (%) | 2 (4) |
| Ventricular tachycardia, n (%) | 1 (2) |
| APACHE II score (range) | 26 ± 10 (9-42) |
| Length of hospitalization, prior to CPR, days (range) | 25 ± 27 (0-113) |

**Table 2.** Clinical antecedents within 8 hours before cardiopulmonary arrests in 45 patients who received CPR in the MICU

| Condition | n |
|---|---|
| Cardiovascular | |
| Hypotension | 17 |
| ST-T segment change on electrocardiogram | 2 |
| Bradycardia, with pacemaker implantation | 1 |
| Cardiac tamponade | 1 |
| Chest pain | 1 |
| Non-sustained ventricular tachycardia | 1 |
| Pulmonary | |
| Tachypnea | 4 |
| Hypoxemic respiratory failure | 3 |
| Pneumothorax | 2 |
| Hypercapnia | 1 |
| Pleural effusion requiring thoracentesis | 1 |
| Other conditions | 4 |
| Metabolic acidosis | 5 |
| Altered consciousness | 1 |
| Seizure | 1 |
| Agitation | 1 |
| Newly onset fever | 1 |

Table 2. At least 1 change in patient behavior in the 8-hour period preceding arrest was found in 38 (84%) records. Observations such as tachypnea, hypotension, GI bleeding, or metabolic acidosis were most common. At least 1 change in patient behavior in the 24-hour period preceding arrest was found in 17 (38%) records. Observations such as hypotension and hypoxic respiratory failure were most common (Table 2).

Univariate and multivariate analyses were performed to determine the factors related to prearrest and arrest conditions that might be associated with the likelihood of ROSC (Table 3). There was no major difference among the outcome groups regarding age, gender, or initial heart rhythm. Patients with antecedent cardiovascular events, including shock, within 24 hours before cardiac arrest had unfavorable ROSC outcomes (relative risk = 0.182, 95% confidence interval: 0.049-0.657; $p = 0.013$). Those who had expected cardiac arrest also had unfavorable outcomes (RR = 0.125, 95% CI 0.027-0.568; $p = 0.006$). This association still remained statistically significant even after multivariate adjustment ($p = 0.018$ for a cardiovascular antecedent and $p = 0.009$ for an expected cardiac arrest). In analyzing the predictive variables for survival in our study population, we found no major difference regarding age, gender, primary admission diagnosis, initial heart rhythm, cause of cardiac arrest, or comorbid conditions.

## Discussion

In this study, we found that the outcome of CPR in the MICU was very poor, despite intensive monitoring, treatment, and the presence of antecedent events in the majority of the patients.

During the study period, 60% of the patients were successfully resuscitated, but only 8.9% survived to hospital discharge. These findings are similar to those of previous reports, with initial response rates of 16% to 45% and survival rates of 0% to 23% for in-hospital arrests [2-3], and initial response rates of 30% to 38% and survival rates of 5% to 11% to discharge for critically ill patients [5, 12]. The MICU patient outcomes after CPR in this study are comparable to the survival range reported in a previous study [13].

This study showed that the most common underlying abnormalities preceding the arrests were those involving the respiratory system, predominantly pneumonia, and cardiovascular disease. The findings are comparable with those of other reports, in which a greater number of cases were associated with cardiac disease, especially coronary artery disease, with a range of approximately 50% [6-7] to 70% [8-9].

**Table 3.** Univariate and multivariate analyses of factors associated with recovery of spontaneous circulation in 45 patients receiving resuscitation in the MICU

| Factor | | Patient | ROSC | Relative Risk | Univariate | Multivariate |
|---|---|---|---|---|---|---|
| | number | number (%) | (95% CI) | *p* value | *p* value | |
| Antecedent | Present | 17 | 6 (35) | 0.182 | 0.013 | 0.018 |
| cardiovascular | Absent | 28 | 21 (75) | (0.049-0.675) | | |
| Antecedent | Present | 5 | 3 (60) | 1.0 | 1.000 | |
| respiratory | Absent | 40 | 24 (60) | (0.150-6.671) | | |
| Antecedent sepsis | Present | 7 | 5 (71) | 1.818 | 0.684 | |
| | Absent | 38 | 22 (58) | (0.312-10.586) | | |
| Expected arrest | Yes | 12 | 3 (25) | 0.125 | 0.006 | 0.009 |
| | No | 33 | 24 (73) | (0.027-0.568) | | |
| Asystole | Yes | 17 | 11 (65) | 1.375 | 0.757 | |
| | No | 28 | 16 (57) | (0.396-4.775) | | |
| Pulseless VT/Vf | Present | 8 | 6 (75) | 2.286 | 0.445 | |
| | Absent | 37 | 21 (57) | (0.406-12.86) | | |
| DC shock performed | Yes | 14 | 8 (57) | 0.842 | 1.000 | |
| | No | 31 | 19 (61) | (0.234-3.034) | | |
| Cardiac massage | Yes | 42 | 24 (57) | 1.750 | 0.264 | 0.999 |
| | No | 3 | 3 (100) | (1.347-2.274) | | |
| Malignancy | Present | 15 | 9 (60) | 1.000 | 1.000 | |
| | Absent | 30 | 18 (60) | (0.282-3.544) | | |
| Male sex | Yes | 30 | 19 (63) | 1.511 | 0.538 | |
| | No | 16 | 8 (53) | (0.430-5.313) | | |
| Age > 65 years | Yes | 27 | 17 (56) | 1.360 | 0.758 | |
| | No | 18 | 10 (63) | (0.404-4.580) | | |

Differences in patient population and place, i.e., the general wards and the MICU, may influence the manifestation prior to an arrest, and the response to resuscitation efforts.

In this study, the progressive derangements and abnormalities in patient behavior in the hours preceding arrest might differ from previous concepts in which cardiopulmonary arrest occurred as an acute, isolated event. Actually, 84% of the cases from the chart review documented acute deterioration of the patient's condition. The abnormalities most often involved hypotension. In 1 study, none of the patients whose cardiac arrest was preceded by a declining clinical course survived to discharge from the hospital [14]. Similar findings have been reported in general medical cohorts and cancer patients [15]. In our population, this finding seems to be attributable to the fact that the patients with antecedent cardiovascular events and with expected cardiac arrest tended to have lower cardiac arrest survival rates. This association should be explored further in a larger study. The high proportion of cardiac arrests without a concomitantly high survival indicates that even interventions made immediately at the time of arrest are generally too little or too late. The effectiveness of earlier interventions in improving survival remains to be tested. How-

ever, some data [10-11] suggest that it is not necessarily the absence of pertinent information that is a problem, but the response to this information.

The mortality associated with cardiopulmonary arrest in this study was high; 14 patients (including the 2 patients with 'do not resuscitate' orders), or approximately one-third of the total group studied was expected to die during hospitalization as a result of advanced and untreatable disease. While the accuracy of these predictions is not absolute, the medical benefit of proceeding with full resuscitation in these patients is doubtful because of a uniformly unsuccessful outcome. A variety of prognostic factors have been implicated for poor outcome in an MICU population after CPR. These include prearrest hypotension, sepsis, an elevated APACHE II score on MICU admission, duration of resuscitation, metastatic cancer, increased creatinine level, initial cardiac rhythm other than ventricular tachycardia, fibrillation or non-ventricular tachyarrhythmia, steroid administration, and the reason for MICU admission [16-17]. These prognostic factors reflect the severity of the current illness and the multi-organ dysfunction syndrome (MODS) in MICU patients as the main factors influencing survival [18]. This may explain our low rate of long-term survival. Only 1 of our patients with an APACHE II score > 40 on MICU admission (14%) survived to discharge after CPR. The small size of our study population precludes a more thorough analysis of predictors of outcome. Variables that were not significantly different among the groups may have had an important effect that we were unable to detect. In other words, lack of significance in this study should not be interpreted to mean no effect.

Survival from in-hospital cardiopulmonary arrest has apparently changed very little since the introduction of CPR. The likelihood of a new technology or technique to change this mortality seems remote, given the variety of derangements that precede and contribute to cardiopulmonary arrest. The central questions of resuscitation research so far as the MICU population is concerned should be to what degree do cardiopulmonary arrests in the MICU represent predictable events, to what degree can prediction lead to intervention that prevents arrest, and to what degree does the prevention of arrest reduce mortality. The observation of deterioration in the vital signs and clinical condition of these patients prior to arrest supports the idea that cardiopulmonary arrest is neither a sudden nor unpredictable event.

Although our initial successful CPR rate was high, the survival to hospital discharge rate was disappointing in our MICU population. It seems that, although ICU patients are better monitored and are treated in a timely fashion, they are disadvantaged by chronic underlying disease and severe current medical illness leading to a worse outcome after CPR. Larger prospective and control-matched studies are needed to evaluate specific prognostic factors, including predictable events before cardiac arrest, as determinant of CPR efficacy and survival to hospital discharge in an MICU population.

In conclusion, patients receiving cardiopulmonary resuscitation have a very poor prognosis despite a high percentage of successful recovery of spontaneous circulation. Expected arrests and antecedent cardiovascular events are associated with a reduced chance of successful resuscitation.

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# 內科加護病房病人接受心肺復甦術前臨床表徵之回溯性研究

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**背景**：本篇報告探討在加護病房中發生心肺停止前的臨床表徵。

**方法**：本研究收集從 2003 年 1 月至 2004 年 12 月在內科加護病房中接受心肺復甦述的病人，探討相關在接受心肺復甦術後能恢復自主循環的因子。

**結果**：共收集 45 位病人 (佔加護病房總住院人數 1.2%) 接受心肺復甦術，其中 27 人 (60%) 成功恢復自主循環，但僅 4 人 (8.9%) 存活出院。評估心肺停止前病人情況發現 38 人 (84%) 在心肺停止前的 8 小時內曾觀察到臨床情況惡化，而 17 人 (38%) 在心肺停止前的 24 小時內曾觀察到臨床情況惡化。病患原有疾病仍以心臟血管及呼吸道方面為主。在發生心肺停止之前以低血壓為最常見的情況。心血管方面異常 (RR = 0.182, $p = 0.018$) 以及預期發生之急救 (RR = 0.125, $p = 0.009$) 是導致自主循環恢復機會降低之主要因素。

**結論**：在內科加護病房發生心肺停止時，接受急救之預後不佳。預期發生心肺停止並接受急救之病人，以及有前驅心臟血管異常事件的病人，接受心肺復甦術的成功率較低。*(胸腔醫學* ***2006; 21: 239-246****)*

關鍵詞：心肺復甦術，加護病房

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# Ultraflex Airway Stent for the Treatment of Tracheobronchial Stenosis due to Lung Cancer

Chia-Hung Chen, Chih-Yen Tu, Te-Chun Hsia, Shinn-Jye Liang, Hung-Jen Chen, Chuen-Ming Shih

Background: Tracheobronchial stenosis due to inoperable lung cancer is a challenging problem, and usually presents worrisome symptoms. We report a recent 5-month experience with interventional bronchoscopy in this group of patients, and evaluate the benefit of this palliative therapy.

Materials and Methods: From May to November 2005, 5 patients with tracheobronchial stenosis due to lung cancer received interventional bronchoscopy at China Medical University Hospital. We used OLYMPUS PSD-60 unipolar electrode endobronchial electrocautery to dissect tumor tissue which had induced trachobronchial stenosis. After debulking the endobronchial tumor, we used an Ultraflex stent (Boston Scientific; Natick, MA) to maintain airway patency.

Results: The patients comprised 5 males, with ages ranging from 42 to 70 years, and a mean age of 57.4 years; all had squamous cell carcinoma of the lung with endobronchial metastasis causing intrinsic airway obstruction. They also suffered from progressive dyspnea and received interventional bronchoscopy with electrocautery and stents (1 tracheal stent in 1 patient and 5 bronchial stents in 4 patients—1 patient received 2 bronchial stents). All symptoms immediately improved after the interventional procedure. No serious complications such as bleeding or airway perforation were noted.

Conclusions: Even for patients with a very poor prognosis at the terminal stage of lung cancer, electrocautery and a stent implant for tracheobronchial stenosis must always be considered as a worthwhile palliative therapy to provide immediate symptom relief of dyspnea. ***(Thorac Med 2006; 21: 247-254)***

Key words: tracheobronchial stenosis, interventional bronchoscopy, electrocautery, ultraflex airway stent

## Introduction

Tracheobronchial stenosis due to inoperable lung cancer is a challenging problem. It usually presents worrisome symptoms such as dyspnea, cough, and hemoptysis, and may be life-threatening. An estimated 20~30% of patients with lung cancer will develop the complication of tracheobronchial stenosis [1]. This may be either intrinsic or extrinsic to the airway. Multiple therapies are available for tracheobronchial stenosis. Airway stents, external beam radiation, and bra-

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chytherapy are indicated in extrinsic conditions that produce compression of the airway. Electrocautery, laser, cryotherapy, photodynamic therapy, and argon plasma coagulation with or without stents are indicated in intrinsic obstruction [2]. The aim of this study was to evaluate the benefit of electrocautery and stent insertion in a group of patients with tracheobronchial stenosis due to inoperable terminal lung cancer. We report our preliminary experience and emphasize the benefit of electrocautery debulking of airway tumors, and of tracheobronchial stent implants.

## Materials and Methods

### *Patients*

From May to November 2005, 5 patients with tracheobronchial stenosis due to lung cancer received interventional bronchoscopy at China Medical University Hospital. There were 5 males, with ages ranging from 42 to 70 years, and a mean age of 57.4 years. The etiologies were all squamous cell carcinoma of the lung with intrinsic obstruction. In the initial diagnosis, 1 patient was found to have tracheal stenosis, 3 patients had bronchial stenosis, and 1 patient had recurrent lung cancer with airway metastasis 3 months after a right upper lobe lobectomy. All patients had symptoms of airway obstruction (stridor or dyspnea).

### *Interventional bronchoscopy*

We used OLYMPUS PSD-60 unipolar electrode endobronchial electrocautery to coagulate or dissect tumor tissue which had induced tracheobronchial stenosis. We performed the procedure in the bronchoscopy room without general anesthesia or ventilator use; local anesthesia and sedative drugs were administered prior to the procedure. After debulking the airway tumor, we implanted an Ultraflex stent (Boston Scientific; Natick, MA) to maintain airway patency. Its length and diameter were determined after dissection of the endobronchial tumor which had induced airway stenosis. Stents were inserted via the nasal cavity under flexible bronchoscopic-guidance.

## Results

Details regarding patient characteristics and interventional procedures are shown in Table 1. We used endoscopic electrocautery and chose Ultraflex stent emplacement because these procedures could be performed using flexible bronchoscopy. None of our patients received general anesthesia, and the interventional bronchoscopies were all performed in the examination room, without going into the operation room.

Case 1 had suffered from progressive dyspnea for more than 2 weeks. Chest computed tomography (CT) at the local medical department revealed mediastinal lymphadenopathy with central airway obstruction (Figure 1a). The patient was then transferred to our hospital where a chest CT examination could not be performed due to progressive dyspnea in the supine position. Therefore, we arranged a bronchoscopic examination, which revealed a tracheal tumor with tracheal compression and induced upper airway obstruction (Figure 1b). We then implanted a tracheal stent to release the severe tracheal compression from his lung cancer. The pulmonary function improved after stent implantation, as can be seen in Figure 1c.

Case 2 was admitted due to progressive dyspnea for 1 month. After admission, the chest X-ray (CXR) showed a collapsed right lower lung (Figure 2a). The bronchoscope revealed a right lower lobe endobronchial tumor which had

**Table 1.** Details of patient characteristics and interventional procedures

| Case | Gender | Age | Diagnosis: All lung cancers were squamous cell carcinoma | Obstructed site | Stent (Ultraflex): Insertion site | Stent (Ultraflex): Diameter X Length | Outcome: Dyspnea improved |
|---|---|---|---|---|---|---|---|
| 1 | M | 64 | LUL, T4N3M0, stage IIIB | Trachea | Trachea | 18 mm x 40 mm<br>Cover membrane: 25 mm | Yes |
| 2 | M | 70 | RLL, T4N3M1, stage IV | Right intermedius bronchus | RLL<br>R't intermedius | 10 mm x 20 mm<br>12 mm x 20 mm | Yes |
| 3 | M | 42 | RUL, T3N2M1, stage IV | Carina and right main bronchus | Right main bronchus | 18 mm x 40 mm<br>Cover membrane: 25 mm | Yes |
| 4 | M | 63 | RLL, T2N0M0, stage Ib s/p lobectomy with recurrence at RML | Right middle lobe | RML | 10 mm x 20 mm | Yes |
| 5 | M | 48 | LUL, T4N2M1, stage IV | Left lower lobe | LLL | 14 mm x 40 mm<br>Cover membrane: 25 mm | Yes |

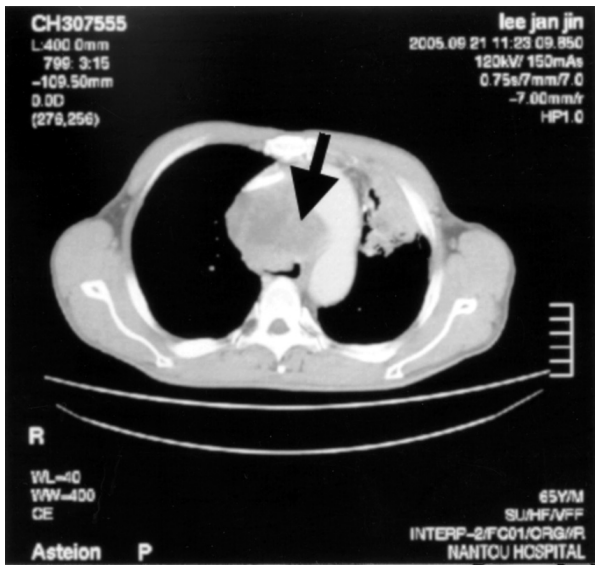


**Fig. 1a.** Chest CT showing a tracheal tumor (arrow site) with tracheal compression

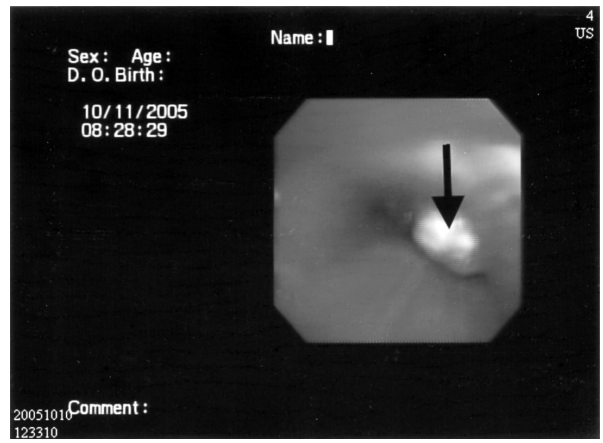


**Fig. 1b.** Bronchoscope showing a tracheal tumor (arrow site) with tracheal compression

induced the collapse. After electrocautery and stent implantation, the CXR showed right lower lung expansion (Figure 2b). The dyspnea also improved after the stent implant.

Case 3 had a Pancoast tumor (squamous cell carcinoma) of the right upper lobe, and underwent a lobectomy 3 months before this admission. He suffered from stridor for 1 week. The bronchoscope showed a recurrent tumor at the carina with a nearly totally occluded airway, as shown in Figure 3a. His dyspnea could not be relieved immediately by traditional radiotherapy or chemotherapy. Electrocautery and a stent implant were then performed, as seen in Figures 3b and 3c. After this treatment, his dyspnea and quality of life improved immediately, and he could receive standard chemotherapy for his recurrent

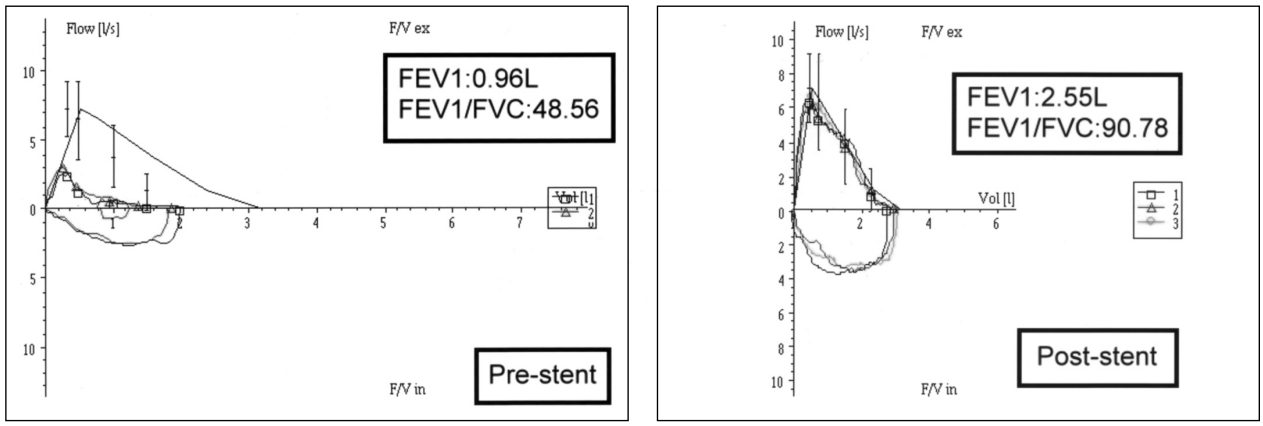


**Fig. 1c.** Flow-volume loop before and after stent emplacement

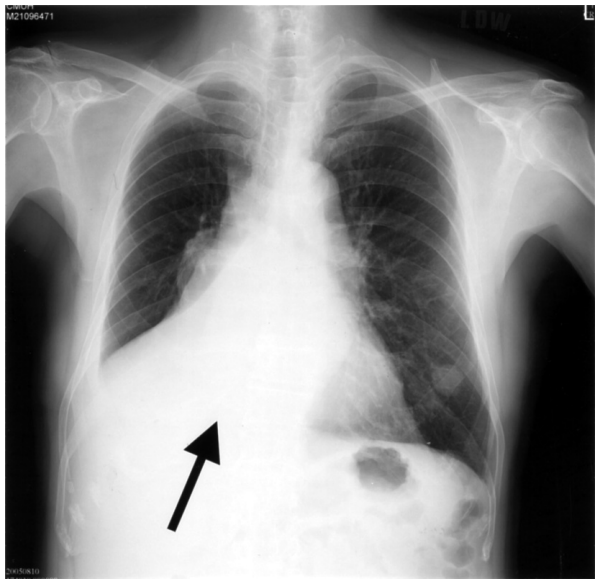

**Fig. 2a.** CXR showing right lower lung collapse

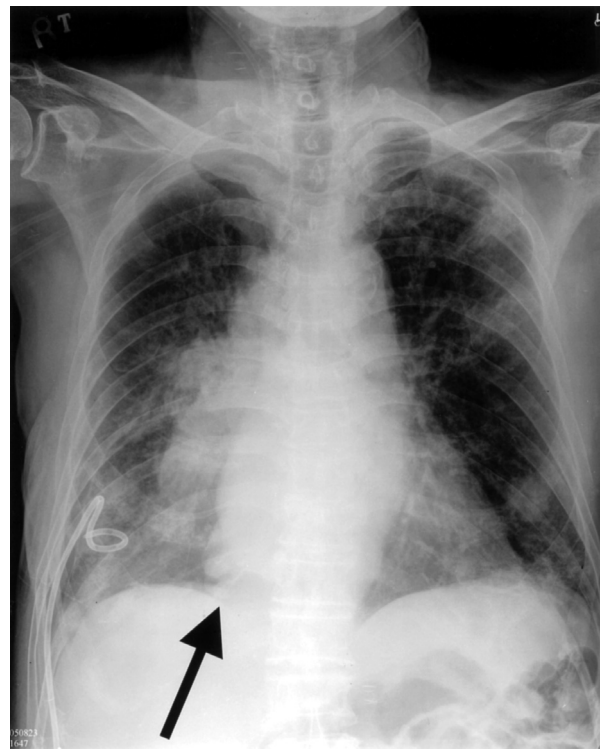

**Fig. 2b.** CXR showing right lower lung expansion after stent emplacement

lung cancer.

## Discussion

Gilfoy first used electrocautery in a tracheobronchial tree in 1932 [3]. Hopper and Jackson popularized its use, using the flexible bronchoscope, for the management of both benign and malignant endobronchial disease [4-5]. The principle of electrocautery involves the use of high-frequency electrical currents via a probe to coagulate or dissect tumor tissue. It is a simple technique, and has the ability to produce rapid palliation and immediate tumor debulking [6].

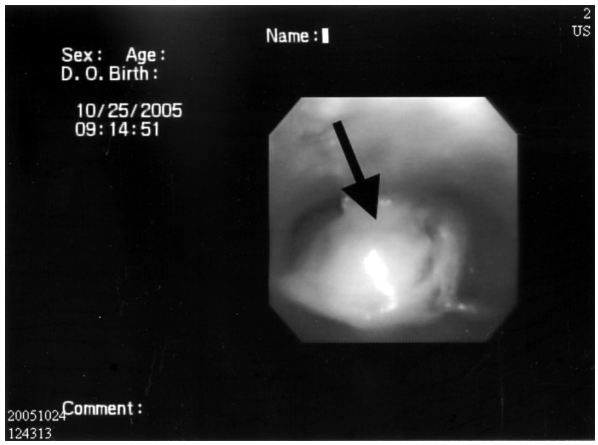


**Fig. 3a.** Bronchoscope showing recurrent lung cancer in the carina (black arrow site)

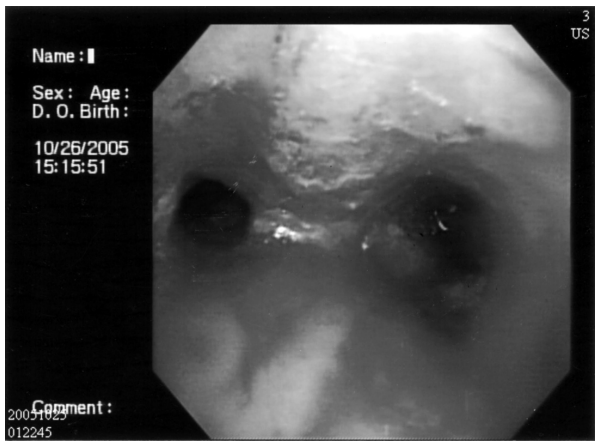


**Fig. 3b.** Patent airway after electrocautery

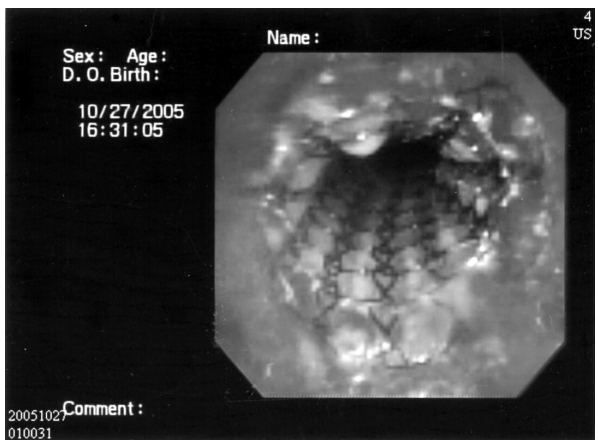


**Fig. 3c.** Stent emplacement

Superficial damage was noted with electrocautery for a short duration, and damage to the cartilage occurred with a longer duration [7]. The side effects of electrocautery include hemorrhage, airway perforation, aspiration pneumonia after debulking due to pus from obstructive pneumonia, and endobronchial fire.

Brachytherapy may induce relatively late responses, and photodynamic therapy and cryotherapy may cause secondary necrosis, so these interventional bronchoscopic procedures are less attractive in patients with airway obstruction due to lung cancer. Lasers (e.g., Nd-YAG) may be another good choice. However, the cost of laser therapy is around 3-fold that of electrocautery [8], and special facilities are necessary for safe laser applications. Not every hospital can provide the facilities for laser therapy, but electrocautery, which is the so-called "poor man's laser", can easily become a standard treatment in almost every hospital.

Airway stents were first described by Trendelenburg and Bond in the late 1800s [9]. Montgomery introduced a silicone T-tube for patients with tracheal stenosis in 1965 [10], and Jean-Francois Dumon introduced completely endoluminal airway stents in 1990 [11]. These have become the most widely used throughout the world during the past decade, due to their being economical and more easily removed. However, silicone stents must be implanted using a rigid bronchoscope under general anesthesia, and their complications, such as stent migration and retained secretion, tend to bother patients.

In 1995, Becker investigated a self-expanding device made of nitinol, the Ultraflex stent (Boston Scientific; Natick, MA), which is more flexible and resembles the physical properties of the cartilages [12]. Nitinol is a nickel and titanium alloy and has superelasticity, so it has the ability

to undergo deformation in size and shape [13]. It also has shape memory deployment, which at cold temperatures, and at higher temperatures, such as body temperature, it regains its original shape [14]. The Ultraflex stent does not show obvious expansion under forced compression, so the risk of airway perforation is lowered. This stent can be safely and quickly emplaced with a flexible bronchoscope, without the need of fluoroscopy. The procedure reduces the radiation exposure of patients and physicians, thus, it is more cost-effective [15]. Recent reports have pointed out the significant reduction of tumor cells [16] and the lack of malignant transformation of initially nontumorous tissue after an Ultraflex stent implant [17]. Stent-related complications include halitosis, perforation of the airway walls, hemoptysis, or granuloma formation at the stent ends. The Ultraflex stent seems to lower the risk of airway perforation due to the fact that it does not change in length once expanded, and that it is flexible enough to change shape when coughing occurs [18].

We presented herein our preliminary endoscopic experience with tracheobronchial stenosis in patients with inoperable lung cancer. In this study, all patients showed improvement in symptoms and CXR imaging, and experienced immediate benefits after electrocautery and stent emplacement. The use of chemotherapy or radiotherapy may lead to a partial response of treated terminal lung cancer, but it cannot immediately relieve the symptoms of airway obstruction, and radiotherapy may cause airway mucosa edema, which progresses to airway obstruction. Hence, we concluded that interventional bronchoscopy, including electrocautery tumor dissection and airway stent implantation, is a worthy palliative treatment for terminal lung cancer with tracheobronchial stenosis.

## Conclusion

Based on our preliminary data, we concluded that even for patients with a very poor prognosis at the terminal lung cancer stage, electrocautery and airway stent emplacement for tracheobronchial stenosis must always be considered, for its ability to provide immediate symptomatic relief of dyspnea, and its role as a worthwhile palliative therapy.

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# 氣管介入性治療對肺癌引起支氣管氣道狹窄之治療經驗

陳家弘　涂智彥　夏德椿　梁信杰　陳鴻仁　施純明

**背景**：肺癌引起的支氣管氣道狹窄若是無法開刀仍舊對醫護人員是一個富有挑戰性的難題。它會使得病人出現嚴重呼吸道阻塞的症狀，使得生活品質大大降低，本文將報告我們過去 5 個月來的初步治療經驗。

**材料與方法**：我們分析從西元 2005 年 5 月至 11 月在台中中國醫藥大學附設醫院接受氣管介入性治療的病人。對於病人所施以的氣管介入性治療包括先使用 OLYMPUS PSD-60 電燒來切除掉導致支氣管氣道阻塞或是狹窄的腫瘤，之後在狹窄的部位再佐以 Ultraflex (Boston Scientific; Natick, MA) 氣管支架支撐。

**結果**：從西元 2005 年 5 月至 11 月，總共有 5 位病人接受氣管介入性的治療， 5 位病人皆是男性，年齡從 42 歲至 70 歲，平均年齡為 57.4 歲，導致支氣管氣道狹窄的原因皆是由於肺部鱗狀上皮細胞癌， 5 位病人皆出現明顯呼吸道阻塞的症狀， 5 位病人中有 1 位接受氣管支架，而有 3 位接受支氣管支架，另外一位病人則接受二支支氣管支架， 5 位病人藉由氣管介入性治療包括電燒切除以及支架置放之後，臨床症狀明顯改善，同時在我們的病人中沒有嚴重的併發症例如氣道破裂或是無法控制出血的產生。

**結論**：對於由於肺癌引起的支氣管氣道狹窄，儘管病人是屬於末期，我們仍舊應該考慮施以氣管介入性治療包括電燒以及支架的置放，因為此種治療可以使得病人的症狀立即改善，使得生活品質得以提升，是一種可以讓病人得到最佳利益的療法。*(胸腔醫學* ***2006; 21: 247-254)***

關鍵詞：支氣管氣道狹窄，氣管介入性治療，電燒，支架

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# Kartagener's Syndrome: A Case Report and Review of the Literature

Kuo-An Wu*, Chung-Yi Liao, Wann-Cherng Perng, Chin-Pyng Wu

Kartagener's syndrome (KS) is a rare congenital malformation, which consists of a classic triad of situs inversus, bronchiectasis, and sinusitis [1]. It is a genetic disorder that is included in either the group of diseases defined as immotile cilia syndrome, or diseases due to primary cilia dyskinesia [2]. These disorders are characterized by the immotility or abnormal beating of the cilia which leads to insufficient mucociliary clearance. KS can cause substantial clinical problems, mainly because of the complications of pulmonary infections.

The patient we encountered was a 58-year-old man with complaints of recurrent productive cough and purulent nasal discharge for about half a year. After a work-up, KS was eventually diagnosed. The patient's symptoms were relieved after treatment with antibiotics and a bronchodilator. We also review the associated literature. ***(Thorac Med 2006; 21: 255-260)***

Key words: Kartagener's syndrome, situs inversus, bronchiectasis, sinusitis, immotile cilia syndrome, dyskinetic cilia syndrome, primary ciliary dyskinesia

## Introduction

Kartagener's syndrome (KS), an autosomal recessive inherited disease, is characterized by the clinical triad of bronchiectasis, sinusitis, and situs inversus [1]. This syndrome occurs with an approximate incidence of 1 in 15,000 people, and is included in the group of diseases defined as dyskinetic cilia syndrome. It is a congenital defect of the cilia and sperm tails, in which ciliary motility is abnormal and mucociliary transport is impaired in organs with these functions. This abnormality is an important cause of chronic respiratory-tract infection and male sterility [3]. Herein, we report the case of a man afflicted with KS.

## Case Report

A 58-year-old male, a public official, was a nonsmoker, and had complained of recurrent productive cough, mucopurulent sputum, rhinorrhea with purulent discharge, and nasal obstruction for about half a year. He visited several clinics for these symptoms, but in vain.

The plain chest film (Figure 1) revealed the cardiac silhouette and stomach air located on the right side. The Water's view radiograph revealed opacity in the left maxillary sinus (Figure 2). High-resolution computed tomography of the

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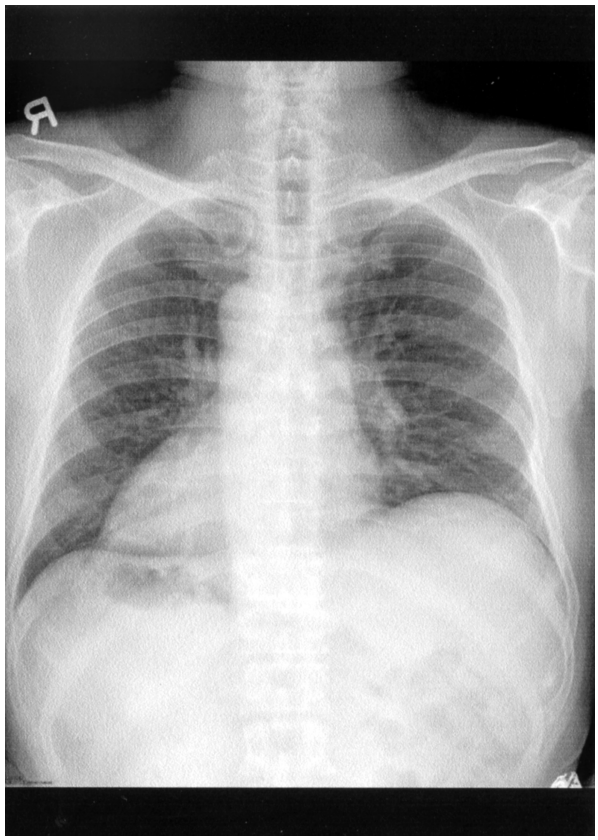

**Fig. 1.** Chest X-ray of the patient illustrates the cardiac silhouette and the stomach air located on the right side.

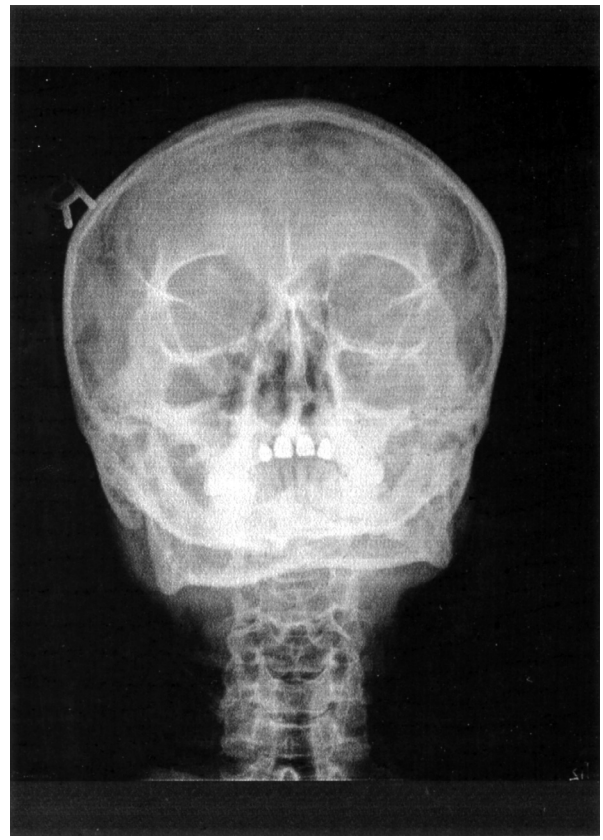

**Fig. 2.** The Water's view radiograph shows opacity of the left maxillary sinus.

chest disclosed abnormal bronchial dilatation, a lack of bronchial trapering, visualization of the peripheral airways, bronchial wall thickening, and centrilobular nodules in the bilateral lower lobes of the lungs (Figure 3). These findings, in addition to situs inversus and sinusitis, suggested the diagnosis of KS. With appropriate oral antibiotics treatment (amoxicillin 875 mg plus clavulanic acid 125 mg 3 times a day) and bronchodilators, the mucopurulent sputum and nasally purulent discharge improved.

## Discussion

KS occurs with an approximate incidence of 1 in 15,000 people, and is characterized by specific ultrastructural defects of the cilia and spermatozoa, resulting in ciliary dyskinesia [4].

In 1901, Oeri first described a clinical association between bronchiectasis and situs inversus [5]. In 1904, this description was further explored by Siewert in his report of a patient with sinusitis, bronchiectasis, and situs inversus [6]. In 1933, after Kartagener's description of the classic features as an etiologic-nosologic entity in his report of 4 cases with sinusitis, bronchiectasis, situs inversus, and male infertility, this rare disorder then became known as Kartagener's syndrome [1]. In 1976, Afzelius published a valuable study demonstrating immotile spermatozoa in an affected patient caused by a deficiency of dynein arms in the flagellar microtubules. His theory,

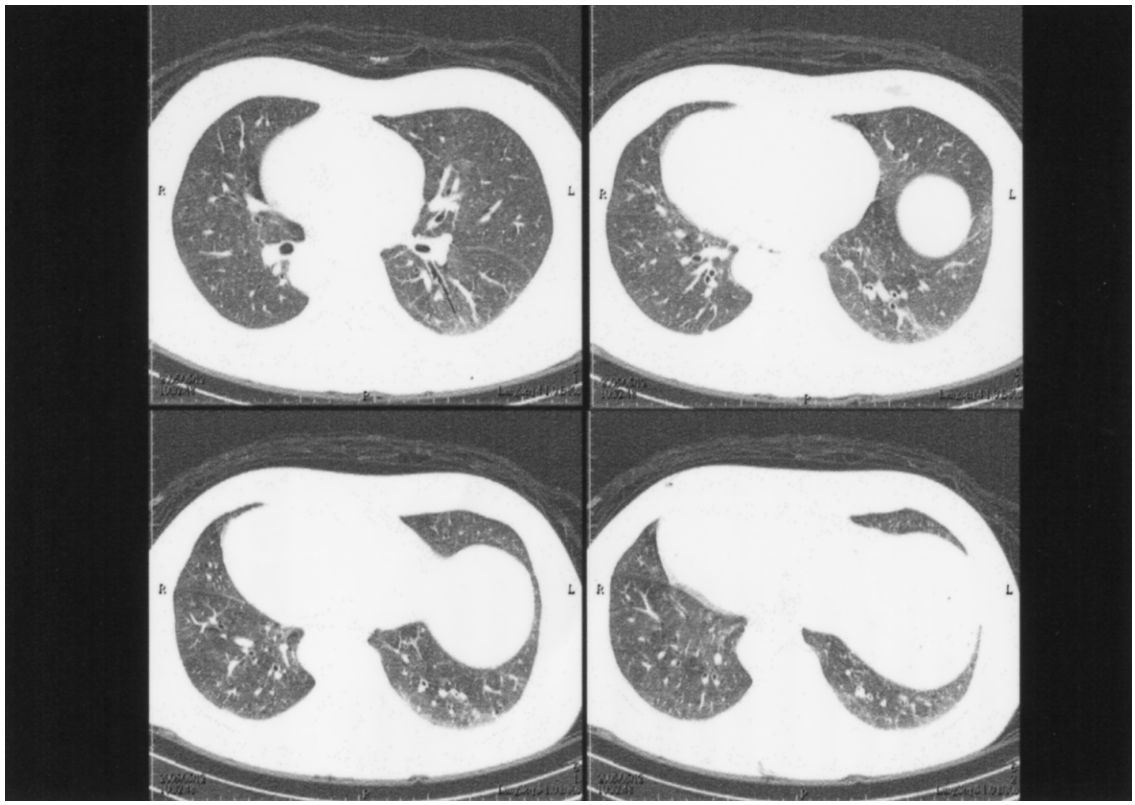

**Fig. 3.** High-resolution CT of the lung demonstrates bronchial dilatation, a lack of bronchial trapering, visualization of the peripheral airways, bronchial wall thickening, and centrilobular nodules in the bilateral lower lobes.

based on his observations, was that, relative to situs inversus, the cilia play a role in the normal dextral rotation of the body organs during embryonic life. In the absence of ciliary movement, the disposition of the body organs is random, being normal in 50% of patients and inverse in 50% [7]. In 1977, Eliasson *et al*. found that congenital ciliary abnormalities were not necessarily associated with situs inversus, and they coined the term "immotile cilia syndrome". In about half of these patients there was also a situs inversus - i.e., Kartagener's syndrome [3]. In 1980, Rossman *et al*. observed the movement in a number of ciliated cells in 3 patients with KS. They found that some ciliated cells are indeed motile. However, since this abnormal movement lacks an effective stroke and occurs in an uncoordinated way, mucociliary transport would not be expected. Thus, the researchers believed that "immotile cilia syndrome" was a misnomer, and that a more appropriate term was "dyskinetic cilia syndrome" [8].

The normal ciliary ultrastructure consists of 9 peripheral and 1 central pair of microtubules and their associated structures, including dynein arms, radial spokes, and nexin links. The adenosine triphosphatase within the dynein arms is responsible for the sliding movement of the ciliary microtubules [4]. The earliest reports characterized the pathophysiologic origin of KS as a defect or the complete absence of dynein arms of the primary energy source, which led to

the immotility or dysmotility of the cilia. Subsequent reports described the absence of or the defects in the ultrastructural components of the cilia, including the outer dynein arms, inner dynein arms, nexin links, radial spokes, spoke heads, and central tubules, as the causes of ciliary dyskinesia [9].

When ciliary dyskinesia occurs in the upper and lower airways, a high risk of chronic infection will develop. Since the dyskinesia of the sperm tail is the same as that in the cilia, these patients will possibly suffer from male sterility. Moreover, because the airways (including the paranasal sinuses and auditory tubes), brain ventricles, oviducts, and vasa efferentia of the testes all have ciliated epithelia, an overall examination of these cilia is strongly recommended once the syndrome with congenital ciliary dyskinesia is recognized.

The most common clinical features of patients with a congenital ciliary defect are productive cough (97.1%), sinusitis (94.1%), and otitis media (76.5%) [9]. In a retrospective survey of chest radiographs of this defect, bronchial wall thickening was often the earliest radiologic manifestation. Other pulmonary radiographic abnormalities include hyperinflation, segmental atelectasis, segmental consolidation, and bronchiectasis. These parenchymal abnormalities or bronchial wall thickening showed a predilection for the anatomic middle lobe (20/30, 66%) [10].

The underlying defect in primary ciliary dyskinesia and KS cannot be corrected, so there is no definitive therapy. Chest physiotherapy and antibiotics for acute respiratory infections are helpful, but prophylactic antibiotics are of little use [10]. Despite the usual benign course of KS, and the aggressive physiotherapy and regular administration of antibiotics, the general condition of patients can suddenly deteriorate to global respiratory failure [11].

Segmental surgical resection of the involved lobes in patients with bronchiectasis might lessen recurrent respiratory symptoms [12], and some reports have demonstrated successful bilateral lung transplantation in patients with KS and progressive global respiratory failure. Bilateral lung transplantation seems to be the therapy of choice in patients with respiratory insufficiency, but without concomitant cardiac anomalies [11, 13-14].

In conclusion, KS should be taken into consideration in the differential diagnosis of a patient with combined situs inversus and recurrent chronic upper or lower respiratory disease.

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# Kartagener 氏症候群—病例報告及文獻回顧

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Kartagener 氏症候群為一罕見之先天性疾病。此症後群包括三種病症：1）內臟反位，2）支氣管擴張症，3）鼻竇炎。這種遺傳性疾病包含在纖毛運動不良症候群或原發性纖毛運動困難的疾病群之中。此症是因為纖毛不活動或不正常的拍動而導致纖毛無法有效地清除呼吸道的分泌物。 Kartagener 氏症候群會引起一些臨床的問題，最主要的併發症是肺部感染。本篇報告一位 58 歲男性因反覆性的咳嗽有痰，合併有膿樣的鼻腔分泌物而到本院求診。經過系列檢查確定診斷為 Kartagener 氏症候群。病人接受抗生素及支氣管擴張劑治療後臨床症狀明顯改善。在此並回顧歷年來對此種病歷相關的文獻報告。*(胸腔醫學 **2006; 21: 255-260**)*

關鍵詞：Kartagener 氏症候群，內臟反位，支氣管擴張症，鼻竇炎，纖毛運動不良症候群，原發性纖毛運動困難

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# Pulmonary Arterial Hypertension Related to Human Immunodeficiency Virus Infection: A Case Report and Literature Review

Shuo-Chueh Chen, Mao-Wang Ho*, Chih-Yen Tu, Pei-ying Pai**, Chuen-Ming Shih

Pulmonary complications of acquired immunodeficiency syndrome (AIDS) represent major causes of mortality in human immunodeficiency virus (HIV)-infected patients. The occurrence in these patients of chronic pulmonary non-infectious complications, such as pulmonary arterial hypertension (PAH), is well established, and the incidence is about 0.5%. But the pathogenesis and treatment of choice are unclear. Herein, we report the case of a 35-year-old man who had PAH related to HIV infection. He received highly active antiretroviral therapy (HAART) and a 2-week daily diltiazem 60 mg treatment, but the pulmonary arterial pressure did not improve. We suggest that if a young patient suffers from dyspnea on exertion due to pulmonary arterial hypertension, with no other common etiology, pulmonary arterial hypertension related to HIV infection should always be kept in mind. ***(Thorac Med 2006; 21: 261-267)***

Key words: pulmonary arterial hypertension, human immunodeficiency virus, highly active antiretroviral therapy

## Introduction

Pulmonary hypertension is a rare condition characterized by an increase in pulmonary vascular resistance that ultimately leads to right ventricular failure. Although it can be idiopathic (primary pulmonary hypertension; PPH), and in some instances familial, it is often associated with other conditions, including connective tissue disease, chronic liver disease, congenital heart disease, pulmonary thromboembolic disease, the use of appetite-suppressant medications, and human immunodeficiency virus (HIV) infection. Pulmonary complications of acquired immunodeficiency syndrome (AIDS) represent major causes of mortality in HIV-infected patients. Despite the advent of highly active antiretroviral therapy (HAART), the lung continues to be the most frequently involved organ in AIDS autopsy cases [1-2]. Non-infectious pulmonary complications, including malignancies and pulmonary arterial hypertension (PAH), and lymphoproliferative disorders, including lymphocytic interstitial pneumonitis and lymphocytic alveolitis [3-4], are seen with increasing frequency in HIV infection. The association between PAH and HIV

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infection is well established [5-7]. Researchers first described a case of pulmonary hypertension associated with HIV infection in 1987 [8]. Since then, approximately 100 patients with HIV infection and otherwise unexplained pulmonary hypertension have been reported. Interestingly, the first several cases occurred in patients with classic hemophilia; based on these early cases, researchers theorized that the etiology of pulmonary hypertension in HIV-infected patients was hemophilia, or perhaps lyophilized factor VIII. However, most of the subsequent cases have been identified in HIV-infected patients without hemophilia; thus, the development of pulmonary hypertension seems, in some way, to be related to the HIV infection itself. Pulmonary hypertension may become more prevalent as improved medical management increases the life expectancy of HIV-infected patients. The incidence of PAH related to HIV infection (PAHRH) is about 0.5% [6-7], which is about 6 to 12 times greater than the incidence of PPH in the general population [9]. Thus, all individuals caring for HIV-infected patients should be aware of this condition. To our knowledge, this is the first case of PAHRH reported in Taiwan. The relevant literature is also reviewed.

## Case Report

A 35-year-old man with a history of hemophilia A and HIV infection visited the cardiology outpatient department (OPD) of our hospital due to progressive dyspnea on exertion for 1 month. He began feeling a gradual onset of shortness of breath when climbing a flight of steps 1 month previous to the visit. There was no fever, productive cough, leg pain or edema, abdominal fullness on exertion, orthopnea, paroxysmal nocturnal dyspnea, wheezing, chest distress, anemia, or tarry stool. He allegedly had hemophilia A when he was 4 years old, due to the presentation of a bleeding tendency. He had been undergoing repeated transfusions of factor VIII for the past 25 years. Recurrent hemoarthrosis had also bothered him for 30 years, and he underwent repeated arthrocenteses and blood transfusions because of it. HIV infection was diagnosed by routine serum screening in March, 1998; the patient had experienced no discomfort at that time. The initial viral load was < 400 RNA copies/ml and the CD4+ cell count was 580 cells/μl. He began receiving antiretroviral therapy in Nov 2001, but the regimen was changed frequently in the beginning due to side effects, such as dizziness and abdominal discomfort. The HAART regimen was changed to Combivir® (containing zidovudine 300 mg and lamivudine 150 mg) and nevirapine in May 2002, and this new regimen was well tolerated. He was regularly followed up at our infectious disease OPD, during which time, the viral load had ranged from < 400 to 550 RNA

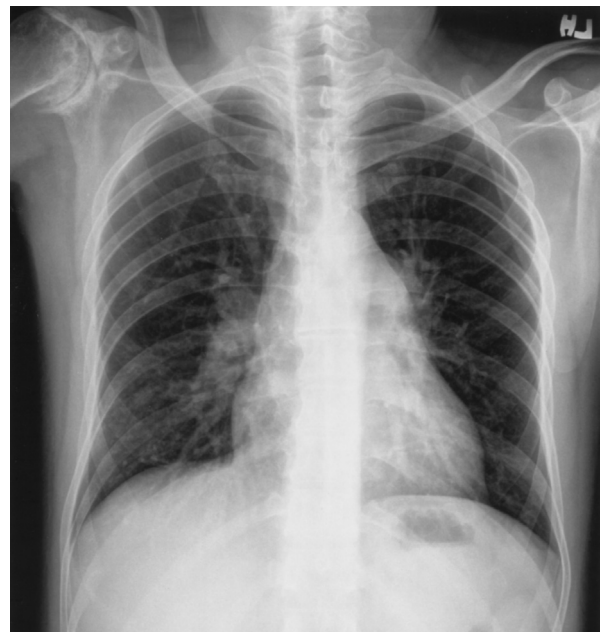
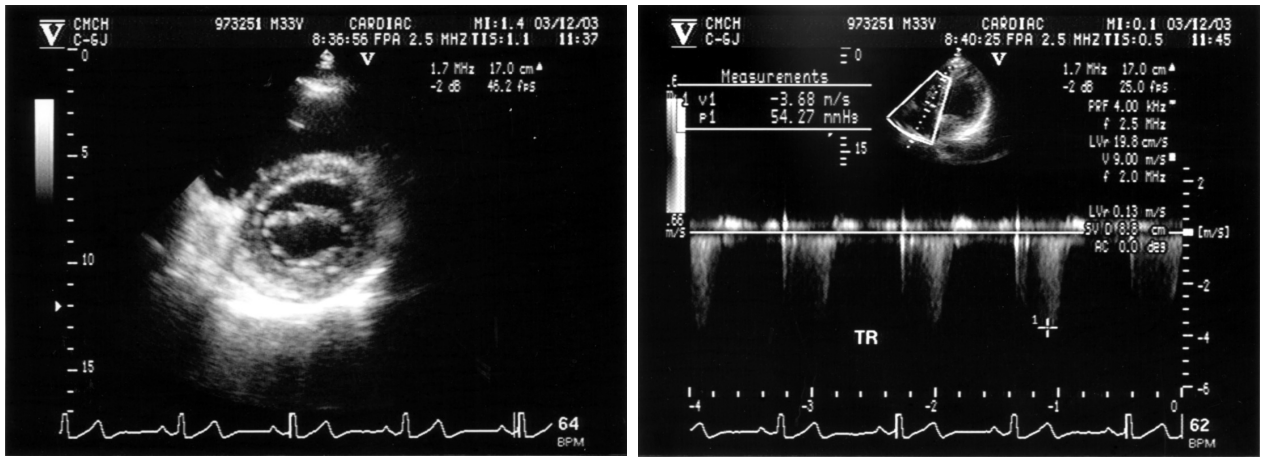


**Fig. 1.** Chest X-ray shows bulging of the bilateral pulmonary truck




(A) (B)

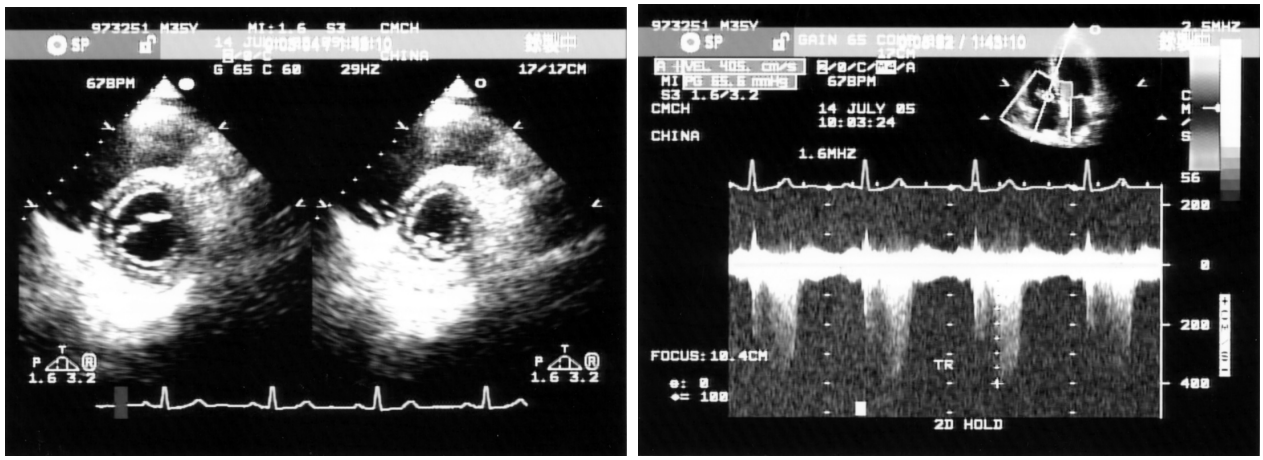
**Fig. 2.** Initial echocardiography revealing the degree of pulmonary arterial hypertension (pulmonary artery pressure: 64 mmHg)

copies/ml and the CD4+ cell count ranged from 580 to 590 cells/μl. The side effects of treatment were hypertriglycemia, hyperuricemia and lipodystrophy. He denied homosexual behavior or intravenous drug use. No AIDS-defined disease, such as *Pneumocystis carinii* pneumonia, candida esophagitis, Kaposi's sarcoma, or non-Hodgkin's lymphoma, was documented during this period. The patient had also had a history of chronic hepatitis C since 1998, without liver cirrhosis or portal hypertension proved by abdominal sonography. There was no history of syphilis, hepatitis B, or gonococcus infection.

At our cardiology OPD, an examination of the patient yielded the following: blood pressure, 123/78 mmHg; body temperature, 36.2°C; pulse rate, 96/min with a regular rhythm; and respiratory rate, 20/min with a normal respiratory pattern. Physical examination revealed normal jugular vein pressure. There was no S3 or S4 on cardiac auscultation. The legs had no edema. He received a chest X-ray examination which demonstrated bilateral pulmonary trunk engorgement without increased pulmonary infiltration (Figure 1). Echocardiography showed moderate pulmonary hypertension (pulmonary arterial pressure: 64 mmHg) and mitral valve prolapse with mild mitral regurgitation (Figure 2). There was no evidence of cardiac chamber dilatation or overt valvular heart disease. Diltiazem 30 mg twice daily was administered, and the HAART regimen was also continued. He discontinued taking diltiazem on his own after 2 weeks, however, due to the subjectively poor response of his shortness of breath. The dyspnea did not show obvious improvement during this time, and the follow-up pulmonary arterial pressure 18 months later, using echocardiography, was 75 mmHg (Figure 3). Tricuspid valve regurgitation had also progressed to a moderate degree. The viral load was 405 copies/ml in June 2005.

## Discussion

Isolated right ventricular hypertrophy with or without right ventricular dilatation is generally related to pulmonary diseases that increase pulmonary vascular resistance, such as recurrent bronchopulmonary infections in HIV-infected patients. However, pulmonary hypertension has




(A) (B)

**Fig. 3.** The follow-up echocardiography revealing the progression of the pulmonary arterial hypertension (pulmonary artery pressure: 75 mmHg)

also been reported in HIV-infected patients without a history of thromboembolic disease, intravenous drug use, or pulmonary infections [10-11]. The clinical symptoms and outcome of patients with right ventricular dysfunction are related to the degree of pulmonary hypertension, varying from mild symptoms, such as dyspnea, chest pain, pedal edema, and syncope, to severe cardiac impairment with cor pulmonale and death [10-11]. It is important to rule out any secondary cause of pulmonary hypertension prior to establishing the diagnosis of HIV-associated pulmonary hypertension. A national prospective study of PPH in the United States excluded the following secondary causes for pulmonary hypertension: pulmonary hypertension within the first year of life; congenital abnormalities of the lung, thorax and diaphragm; congenital or acquired valvular or myocardial heart disease; pulmonary thromboembolic disease as diagnosed by V/Q scan or pulmonary angiogram; sickle cell anemia; a history of intravenous drug abuse; obstructive or interstitial lung disease; arterial hypoxemia associated with hypercapnea; collagen vascular disease; parasitic disease affecting the lungs; pulmonary artery or valve stenosis; and pulmonary venous hypertension with pulmonary capillary wedge pressure greater than 12 mmHg. Additionally, appetite suppressants were also found to be associated with pulmonary hypertension and should always be routinely inquired about. A male predominance (male-to-female ratio of 1.6:1) in PAHRH, and a marked female predominance (female-to-male ratio reported between 1.7:1 and 3:1) in PPH have been reported. The mean age of the PAHRH patients was also younger than that of the PPH patients ($32 \pm 5$ and $42 \pm 7$ years old) [12]. The occurrence of PAHRH is independent of the CD4+ cell count, but it appears to be related to the duration of HIV infection [13].

The pathogenesis of PAHRH remains unclear. There is no evidence that HIV infects pulmonary artery endothelial cells. Neither HIV nor its proteins have been identified in the pulmonary vascular endothelium of patients with PAHRH in the published data [14]. This might be the result of an indirect role of the virus in

stimulating the host to release proinflammatory cytokines or growth factors that would result in PAH [15-16]. Recent studies showed that HIV-gp120 proteins significantly increased endothelin-1 secretion, which is a potent vasoconstrictor and pulmonary artery smooth muscle cell proliferation stimulator, in primary human pulmonary endothelial cells (Kanmogne *et al*., unpublished data). However, only a small percentage of HIV-infected patients develop PAH. This supports the existence of an individual susceptibility to the development of this disease. Morse *et al*. suggested that this susceptibility could have a genetic basis and might be determined by major histocompatibility complex alleles, particularly *HLA-DR6* and *HLA-DR52* [17]. The histopathology of HIV-associated pulmonary vasculopathy is similar to that of PPH [5-6, 10].

Although the probability of survival is significantly lower in HIV-infected patients with PAHRH, compared to those without pulmonary hypertension (median survival: 1.3 versus 2.6 years) [18], the best therapeutic approach for this group of patients is still unknown. Drugs used in the treatment of PAHRH include anticoagulation therapy, diuretics [19], vasodilators (calcium channel blockers [20-21], intravenous epoprostenol [20], sildenafil [23]), and antiretroviral treatment (ART) [20, 24]. According to the Swiss HIV Cohort Study published in 2004, which enrolled 47 patients with PAHRH, HAART therapy achieved a significant improvement in PAH and prolonged survival. The study suggested that HAART therapy be administered to all patients with PAHRH, irrespective of their CD4+ lymphocyte counts [25]. However, the PAH in this patient did not improve despite receiving continuous HAART. The patient's self-discontinuation of diltiazem after 2 weeks may have been the cause.

In conclusion, PAHRH can be a cause of shortness of breath in HIV-infected patients. If a young HIV-infected patient suffers from dyspnea on exertion due to PAH, with no other common etiology, pulmonary arterial hypertension related to HIV infection should always be kept in mind.

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# 人類後天免疫缺陷病毒感染所導致之肺動脈高壓—病例報告及文獻回顧

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愛滋病的肺部併發症是感染人類後天免疫缺陷病毒病人主要致死原因之一。慢性非感染性肺部併發症，如肺動脈高壓，已被充分研究且發生率約 0.5%。但其病態生理學及首選治療仍不清楚。在此我們報告一位 35 歲男性病人，因感染人類後天免疫缺陷病毒而引起肺動脈高壓。病患持續接受高活性抗反轉錄病毒藥物及兩週的 diltiazem(每天 60 毫克)治療但肺動脈高壓仍未好轉。我們建議若有年輕病患因肺動脈高壓產生運動性呼吸困難求診，在排除常見原因後，原發性肺高壓，包括人類後天免疫缺陷病毒感染所引起的肺動脈高壓應列入考慮。*(胸腔醫學 **2006; 21: 261-267**)*

關鍵詞：肺動脈高壓，人類後天免疫缺陷病毒，高活性抗反轉錄病毒藥物

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# Ventilator Autotriggering Caused by Cardiogenic Oscillation — A Case Report

Meng-Yi Chou, Chang-Wen Chen

Ventilator autotriggering refers to the initiation of mechanical breath in the absence of a patient's spontaneous inspiratory effort. In other words, ventilator autotriggering may occur under any condition, whenever the triggering criteria are met. Pressure-triggering and/or flow-triggering are the most frequent modes we have used as triggering variables. Under certain circumstances, ventilator autotriggering may occur and produce harmful effects.

We report a patient with congestive heart failure with recurrent pulmonary edema who received prolonged ventilator support. During the treatment course, tachypnea was noted, despite a high level of sedatives and neuromuscular blocking agents. After measurement of airway pressure, airway flow, and esophageal pressure, tachypnea was proved to be caused by ventilator autotriggering as a result of cardiogenic oscillation. Ventilator autotriggering can be easily eliminated by decreasing the triggering sensitivity. ***(Thorac Med 2006; 21: 268-273)***

Key words: autotriggering, autocycling, cardiogenic oscillation

## Introduction

The selection of the trigger variable in mechanically ventilated patients is very important, in order to improve patient-ventilator interaction. The pressure-triggered and flow-triggered modes are two commonly used triggering variables in modern ventilators. Appropriate selection of the triggering threshold in either mode improves patient-ventilator synchrony and reduces the work of breathing. Higher trigger sensitivity is usually used to decrease the patient's inspiratory workload. However, some untoward effects may occur when the trigger threshold is too sensitive. In this article, we describe a case of ventilator autotriggering caused by cardiogenic oscillation. Unexplained tachypnea in spite of a high level of sedatives and muscle relaxants was the clinical clue for suspicion.

## Case Report

A 67-year-old male patient with recent myocardial infarction was admitted to the surgical intensive care unit of National Cheng Kung University Hospital for planned coronary artery bypass grafting (CABG). The patient could not be weaned from the ventilator because of recurrent pulmonary edema and cardiogenic shock after the operation. Cardiac echo revealed a dilated

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left ventricle and global hypokinesis with an ejection fraction of only 21 percent. He received a tracheostomy three weeks after operation, and was transferred to the medical intensive care unit (MICU) for further weaning.

The ventilator settings in the MICU were pressure-controlled ventilation with a pressure-triggered sensitivity of -1 $cmH_2O$, external positive end-expiratory pressure (PEEP) of 8 $cmH_2O$ and respiratory rate of 22 /min. Due to frequently poor patient-ventilation interaction, the patient was sedated and paralyzed with midazolam and cis-atracurium. While adequate sedation and paralysis were achieved, we noted that the patient's respiratory rate (32/min) was still higher than the preset value (20/min). Autotriggering was thus suspected. To clarify this condition, a standard measurement procedure was performed after informed consent was obtained from his son.

Airflow was recorded with a heated Fleisch No.2 pneumotachograph (Fleisch, Lausanne, Switzerland) connected to a differential pressure transducer (MP 45, ± 2 $cmH_2O$; Validyne Corp., Northridge, CA). The pneumotachograph was inserted between the endotracheal tube and the Y-piece of the ventilator. Tidal volume was derived from digital integration of the flow signal. Airway pressure was measured with a differential pressure transducer (MP 300D, ± 88 $cmH_2O$; Validyne Corp., Northridge, CA). Esophageal pressure was recorded with a balloon catheter connected to a differential pressure transducer (MP 300D, ± 88 $cmH_2O$; Validyne Corp., Northridge, CA). All signals were amplified via a Gould signal conditioner, sampled at 100 Hz, recorded and stored using an analog/numeric data-acquisition system (MP100; Biopac Systems) in a personal computer. Figure 1 shows the tracings and illustration. A respiratory rate up to 32/min was found when the trigger sensitivity was set to -1 $cmH_2O$. Tachypnea disappeared after the pressure-triggering sensitivity was changed to -2 $cmH_2O$. Further analysis can be seen in Figure 2 and Figure 3. The patient eventually died of sepsis, despite treatment.

## Discussion

Ventilator autotriggering [1] is a situation in which mechanical breath is initiated without the patient's spontaneous inspiratory effort. Conditions associated with autotriggering (or autocycling) include random noise in the circuit, leaks in the circuit, pressure/flow fluctuation resulting from water in the circuit, chest tube suction for bronchopleural fistula [2], endotracheal tube cuff leakage [3], and cardiogenic oscillation [4]. When a gas leak exists in the circuit, it can create a negative pressure change in the proximal airway. Also, when chest tube suction is used for a bronchopleural fistula, the negative intra-pleural pressure is transmitted through the fistula to the trachea, dropping proximal airway pressure.

Ventilator autotriggering caused by cardiogenic oscillation was first described by Imanaka [4]. The beating heart may cause intrathoracic pressure change, or compression and expansion of the adjacent lung, and lead to flow fluctuation. This condition can induce ventilator autotriggering if the trigger threshold is set to be too sensitive. In our case, autotriggering caused by cardiogenic oscillation occurred during pressure-triggered ventilation. The absence of inspiratory effort was supported by the esophageal pressure tracing. Autotriggering caused by cardiogenic oscillation could be clearly seen as ventilator-delivered breath was given following a heartbeat-related airway pressure drop. Autotriggering was abolished once the trigger sensitivity was changed

**Fig. 1**

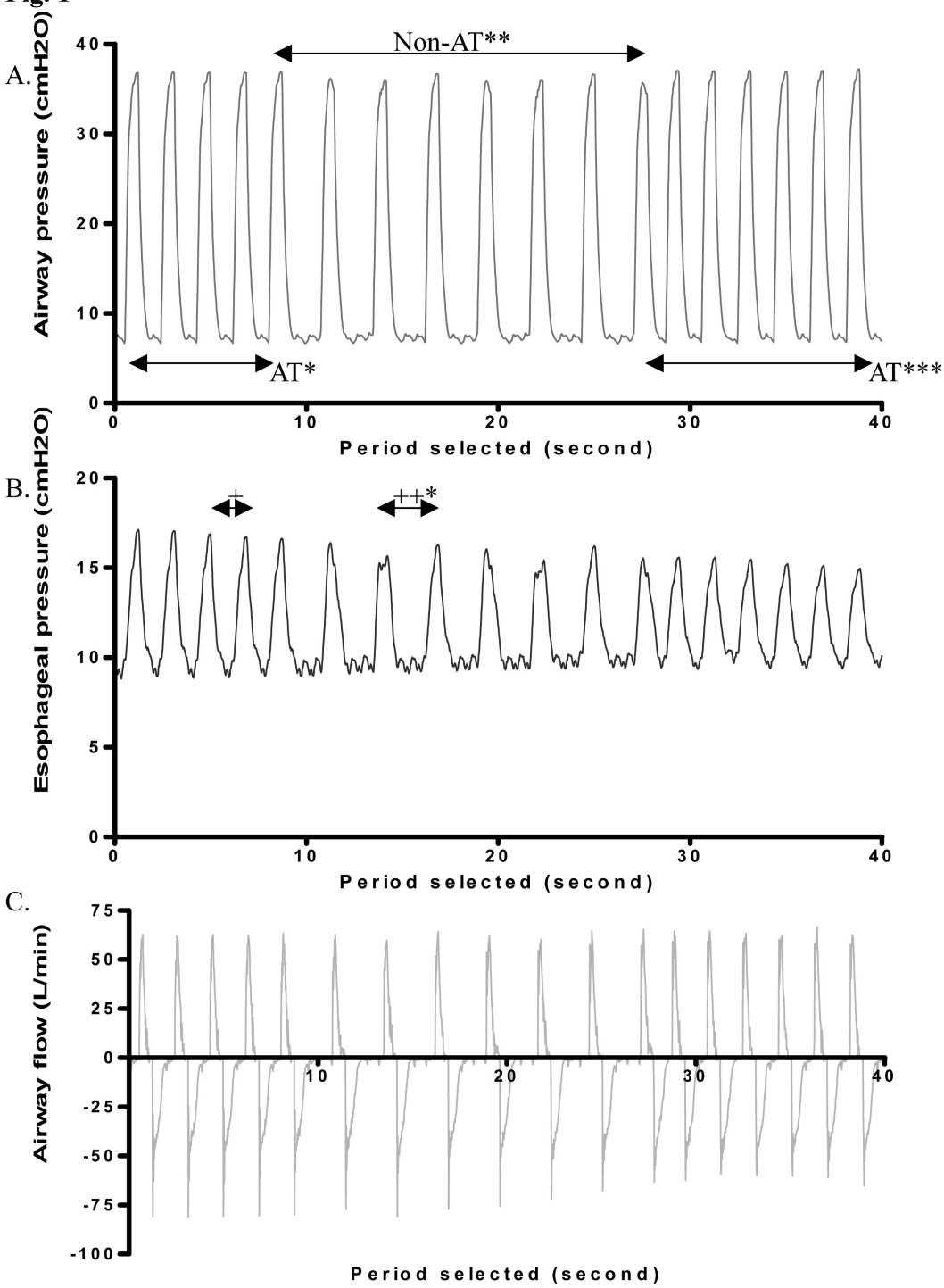


**Fig. 1.** Typical tracing in a selected 40-second period is shown. The "AT*" indicates autotriggering. The "non-AT**' indicates a respiratory rate equal to the ventilator setting. During the AT* period, the pressure-triggering threshold was -1 $cmH_2O$. The measured respiratory rate was about 32 times/min (each breath interval "+" was about 1.86 seconds). During the non-AT** period, the pressure-triggering threshold was changed to -2 $cmH_2O$, and the respiratory rate returned to baseline settings of 22 times/min (each breath interval "++" was about 2.76 seconds). Then, when the threshold was changed to -1 $cmH_2O$ again, the respiratory rate once again became 32 times/min (AT*** period).

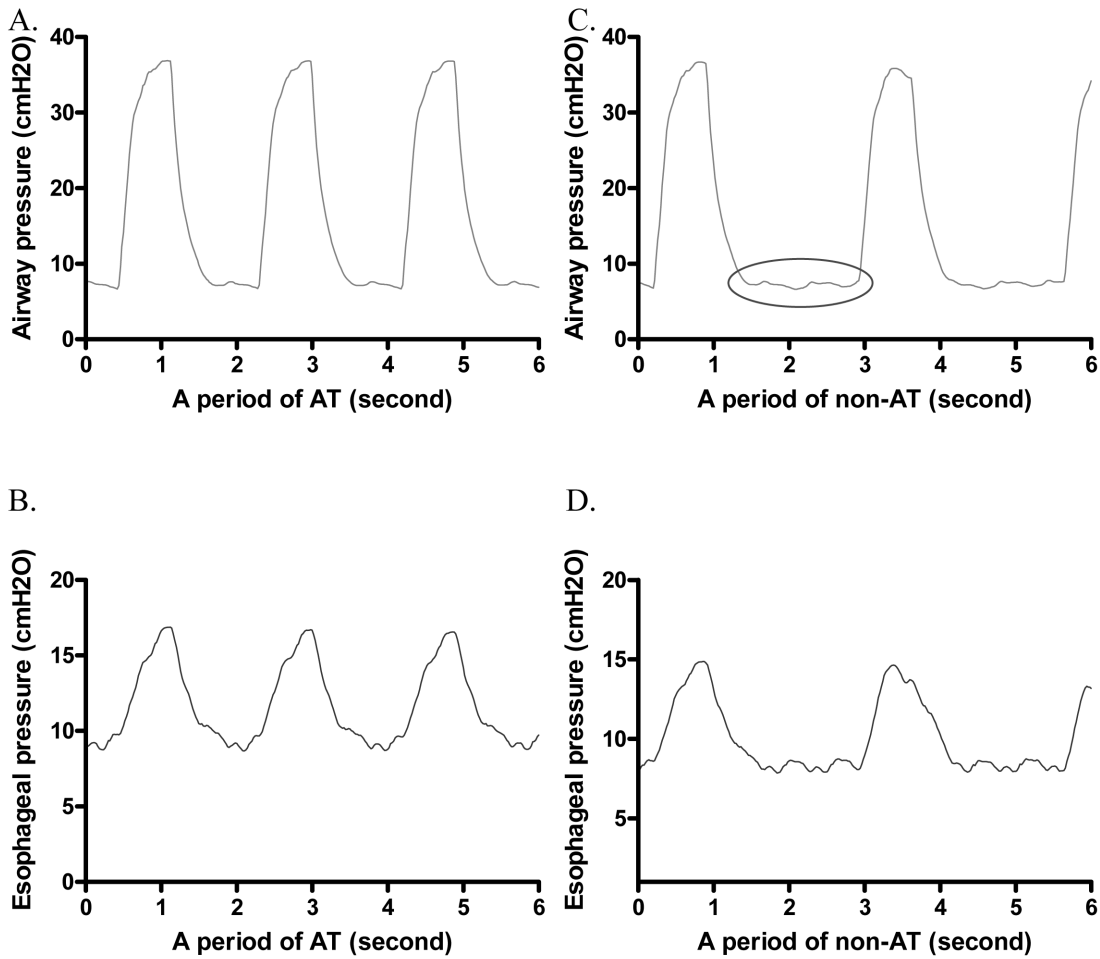


**Fig. 2.** Figures 2-A and 2-B are 6-second periods selected from the "AT*". Figures 2-C and 2-D are 6-second periods selected from the "non-AT**". We can see an obviously different respiratory rate between each. For further analysis, we enlarged the circled areas in Figure 2-C into Figure 3.

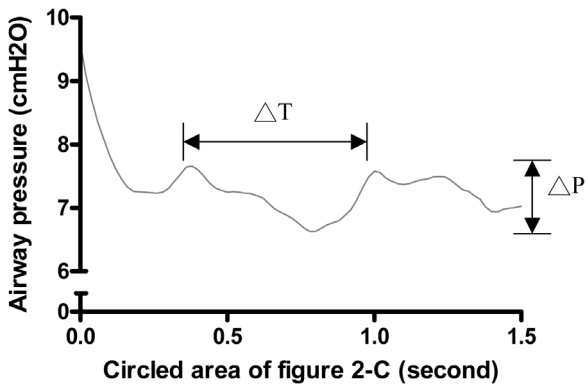


**Fig. 3.** We can see the 2 fluctuating waves. The interval between the 2 waves (△T) was 0.64 second with a frequency of 93 times/second, which was synchronized with our recorded heart rate. The fluctuation was presumed to be caused by cardiac oscillation. The pressure change (△P) measured ranged from 0.96~1.04 $cmH_2O$, just exceeding our pre-set triggering threshold.

to -2 $cmH_2O$.

Ventilator autotriggering is not infrequently met in clinical situations. It should be recognized earlier, because it may result in severe hyperventilation and respiratory alkalosis with a dangerous pH, over-dosage of sedatives and neuromuscular blocking agents, increased intrinsic PEEP, and dynamic hyperinflation. This phenomenon can be easily eliminated based on the cause, by simply titrating down the triggering threshold.

In conclusion, during mechanical ventilation, an insensitive triggering threshold may cause a patient fatigue, but a "too sensitive" triggering

threshold may result in autotriggering. For patients who present with unexplained tachypnea, we should take autotriggering into consideration, especially when the patients are paralyzed.

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# 心臟震顫造成之呼吸器自發性驅動—病例報告

周孟誼　陳昌文

呼吸器自發性驅動意指在病人無呼吸動作時，呼吸器仍給予病人通氣。換言之，在任何情況下只要符合驅動的條件，呼吸器即會給氣。近代呼吸器常使用的驅動條件通常是壓力驅動或者是氣流驅動。在某些情況下，呼吸器自發性驅動可能會發生，並造成病人的傷害。本病例報告中，病人因為嚴重心衰竭及反覆肺水腫而導致無法脫離呼吸器。因為呼吸急促，我們使用了高劑量的安眠劑及肌肉鬆弛劑，但發現病人依舊呈現呼吸急促。在測量了呼吸道壓力、食道壓力以及氣流後，病人呼吸急促的原因證實為心臟震顫造成之呼吸器自發性驅動。此現象只要我們調減驅動閾值的敏感度就可以消弭。*(胸腔醫學* ***2006; 21: 268-273)***

關鍵詞：呼吸器自發性驅動

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# Primary Endobronchial Mucosa-associated Lymphoid Tissue Lymphoma Presenting with Hemoptysis: A Case Report

Chih-Che Chou, Shih-Feng Liu, Jui-Long Wang, Meng-Chih Lin

Primary pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma is an extremely rare disease which can involve the lung parenchyma or bronchi. The most common findings of primary pulmonary MALT lymphoma, using a chest roentgenogram or computerized tomography of the chest, are a solitary nodule or mass with or without air bronchograms. We describe a case of primary pulmonary MALT lymphoma presenting with intermittent hemoptysis and normal chest radiography. Bronchoscopic examination showed a plaque lesion located on the lower trachea just above the carina. ***(Thorac Med 2006; 21: 274-279)***

Key words: primary pulmonary lymphoma, mucosa-associated lymphoid tissue lymphoma, bronchoscope, hemoptysis

## Introduction

Primary pulmonary MALT lymphoma is a rare extranodal lymphoma that is usually of the low-grade B-cell type and is considered to arise from mucosa-associated lymphoid tissue (MALT) of the bronchus, which is histologically distinct from true intrapulmonary lymph nodes. MALT-associated malignant lymphomas develop most frequently in the stomach, and are also found in the bowel, salivary glands, larynx, and thyroid gland [1]. Unlike the model of gastric MALT lymphoma and *Heilcobacter pylori*, no triggering of antigens has been identified in primary pulmonary MALT lymphoma. It can affect the lung parenchyma and bronchi, but only a few case reports have described bronchoscopic findings, especially when lesions involve only the main bronchus [2-3].

## Case Report

A 63-year-old woman, a housewife in southern Taiwan, complained of intermittent hemoptysis for about 1 month. The amount varied from blood-tingled sputum to several milliliters of fresh blood. She was a nonsmoker and had been healthy before this event. She had no history

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of hemoptysis, although she had had 1 episode of gastric ulcer bleeding 2 years previous. There was no fever, chills, body weight loss, epistaxis, epigastralgia, or melena accompanying the hemoptysis during this month. Physical examinations produced unremarkable results. Breathing sounds were clear. She had neither peripheral lymphadenopathy nor hepatosplenomegaly. On investigation, the hemogram, and renal and liver function tests were all within normal limits. There was no abnormal finding on the posteroanterior chest roentgenogram.

She received a bronchoscopic examination for prolonged intermittent hemoptysis. The scope located elevated plaque in the anterior wall of the lower trachea just above the carina, with a small portion extending to the left main bronchus. The surface tended to be whiter than other normal mucosa, and had many bleeding spots (Figure 1). A bronchoscopic biopsy was performed, and the results of histopathology with immunohistochemical analysis were consistent with MALT-associated malignant lymphoma.

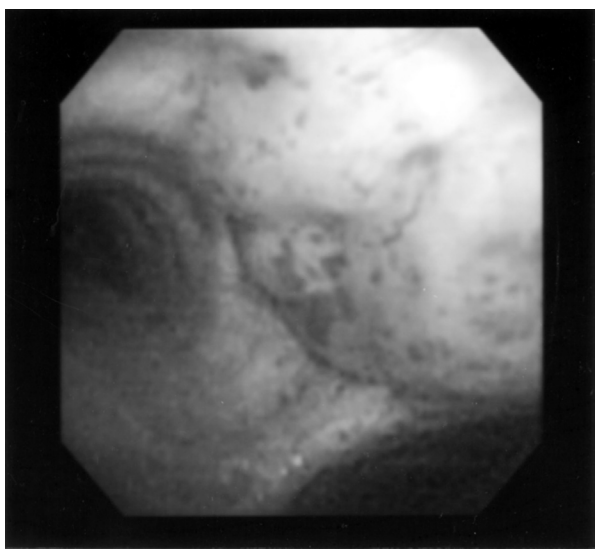

**Fig. 1.** Before radiotherapy, the tumor appeared as an elevated flat plaque located in the anterior wall of the lower trachea just above the carina. Its surface tended to be whiter than other normal mucosa, with many bleeding spots.

She then underwent computerized tomography (CT) examinations of the abdomen and chest. There was no evidence of lymph node involvement, including the thymus, mediastinal nodes, splenic hilar nodes, celiac nodes, portal nodes, paraaortic nodes, iliac nodes and mesenteric nodes. Oral and nasopharynx examinations revealed no abnormalities. Although she had been diagnosed with gastric ulcers 2 years previous, the repeated gastric endoscopy showed no significant change. She also received a bone marrow biopsy from the right posterior iliac crest. The pathology showed no abnormal lymphoid cell infiltration. According to the Ann Arbor staging system, she had stage IE non-Hodgkin's disease. Therefore, she underwent radiotherapy in the carinal and upper mediastinal area with 3600 cGy in 180-cGy fractions. Three months later, she received another bronchoscopic examination. The plaque lesion demonstrated a regressive change in the anterior wall of the lower trachea, compared with the prevous bronchoscopic examination (Figure 2). A biopsy was performed again, but the pathologic report showed no remnants of the previous tumor; the hemoptysis had improved, as well. She received regular follow-up in our outpatient clinic, and there was no evidence of recurrence.

## Discussion

Lymphomatous proliferation disorder can involve the lungs in a primary lesion, especially in non-Hodgkin's lymphomas (NHL). Primary pulmonary lymphoma represents only 0.5-1% of primary pulmonary malignancies, and less than 1% of all lymphoma. About 69%-78% of primary pulmonary lymphoma cases have been reported as MALT-type lymphoma [1-2]. The ages of those

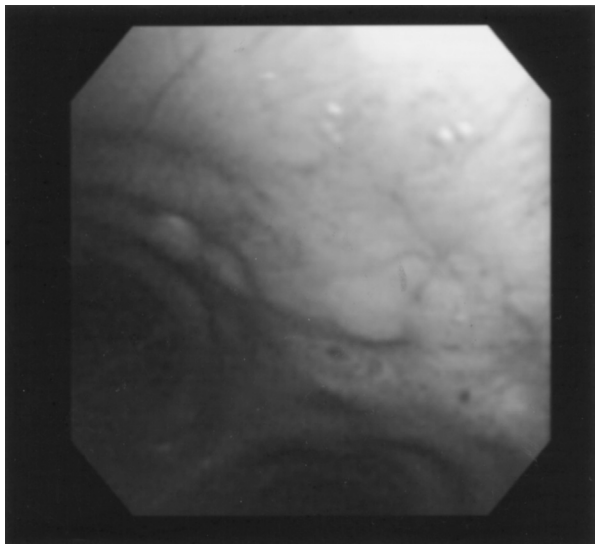

**Fig. 2.** Follow-up bronchoscopic examination after radiotherapy showing a regressive change in the tumor compared with the previous examination.

suffering this disease range from 20-80 years old, but those under 30 years old are rarely affected. The incidence of the disease is equally distributed among men and women.

About half of the patients with primary pulmonary MALT lymphoma are asymptomatic at presentation, and nearly half of these cases are incidentally identified on the basis of abnormal radiological findings. The pulmonary symptoms, such as cough, dyspnea, chest pain, and occasional hemoptysis, are nonspecific, but are more common than the constitutional symptoms, such as body weight loss, fever, night sweats, or fatigue. These symptoms may present for several weeks to months before diagnosis [1-3]. Endobronchial involvement of the disease may cause cough, dyspnea, respiratory distress, atelectasis, obstruction pneumonia, bronchiectasis, or abscess formation due to central airway obstruction. Another form of airway involvement is diffuse submucosal infiltration by tumor cells, and the widespread airway narrowing can cause dyspnea and wheezing, which may be misdiagnosed as asthma [3].

The usual findings in the chest radiographs of patients with primary pulmonary MALT lymphoma are pulmonary nodules and parenchymal consolidation and/or mass. These may be representative of either bilateral or unilateral disease, and the ratio is equal [2, 4]. The lesion is typically 2 to 8 cm in diameter. Up to 50% of cases demonstrate air bronchograms within the mass, or consolidation on the chest radiographs. The lesion is more sensitive to computed tomography. The presence of distended bronchi has the unique radiological appearance of primary pulmonary MALT lymphoma, although the mechanism is not known [1, 3]. Other imaging findings, including diffuse alveolar and interstitial infiltrates, atelectasia, and pleural effusion, are involved in around 10% of cases [1-4].

Usually, the diagnosis of primary pulmonary lymphoma is difficult to make, because of the latent, non-specific clinical presentation and radiographic findings. Although the diagnosis of primary pulmonary MALT lymphoma has been achieved with bronchoalveolar lavage, bronchial biopsy, and transcutaneous biopsy in a few cases, most require thoracoscopic or open lung biopsy [5-7]. Bronchoalveolar lavage fluid appears to be valuable, if lymphocyte alveolitis (lymphoid cell count > 20%) is present [8]. Due to these characteristics of the disorder, the interval between the first clinical or radiological manifestation and diagnosis ranges from 5 months to 8 years [1-3, 8].

Only a few published reports have described the bronchoscopic findings of endobronchial MALT lymphoma. The most common abnormal bronchoscopic findings were inflammatory change of the mucosa and bronchial stenosis [1, 3,8]. In our case, the bronchoscopic findings only

showed elevated plaque in the anterior wall of the lower trachea, without evidence of tumor infiltration.

There were normal findings on the chest radiographs and computed tomography of our patient, and there was no evidence of parenchyma involvement. The only lesion in this case was the endobronchial plaque-like tumor. In a recent review series of 22 cases, 2 patients had additional CT findings of peribronchial thickening, in which they must have had unilateral or bilateral lung parenchyma lesions [2].

The outcome of MALT-type primary pulmonary lymphoma is generally favorable. More than 80% of the cases have a 5-year survival rate, and the median survival rate has been more than 10 years. The overall survival is better than that of other types of non-Hodgkin's lymphoma [1-3]. The clinical features associated with a poor prognosis in a series study of primary pulmonary lymphoma included patients over 60 years of age, elevated serum lactate dehydrogenase, elevated serum $\beta_2$ microglobuin levels, an Eastern Cooperative Oncology Group performance status of 2 to 4, more than 1 extranodal site of involvement, and failure to show a complete response after the first phase of therapy [1, 3, 8]

The optimal management of endobronchial MALT lymphoma—whether surgery, chemotherapy, or radiation therapy alone or in combination--has not been determined. Surgery simultaneously serves both a diagnostic and a therapeutic purpose, and may be the treatment of choice for localized disease. Radiation therapy or single-agent chemotherapy can be used as an alternative to surgery or as an adjunctive treatment for incompletely resected disease. Combination chemotherapy may be considered in symptomatic patients with bulky or disseminated disease [2]. For our patient, surgery was not indicated because the lesion was located around the carina. We chose local radiotherapy for the localized disease of this patient, and 6 months later, there was no evidence of recurrence. Ahmed *et al*. reported 2 cases in which radiotherapy was the primary treatment, of which 1 achieved a complete response [2].

In conclusion, MALT lymphoma is the most common type of primary pulmonary lymphoma, although it is still extremely rare in primary pulmonary malignancies. The common findings in the chest radiograph are pulmonary nodules and parenchymal consolidation and/or mass. Most of the symptoms are non-specific, and patients are often asymptomatic. The diagnosis of primary pulmonary MALT lymphoma is time-consuming. Our case had an unusual manifestation, which was the involvement of the main-stem bronchus with a normal appearance on radiology. Therefore, primary pulmonary MALT lymphoma should be considered in the differential diagnosis of hemoptysis.

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# 以咳血爲表現的原發性氣管內膜相關性淋巴組織淋巴癌：病例報告

周志哲　劉世豐　王瑞隆　林孟志

原發性氣管內黏膜相關性淋巴組織淋巴癌是一種相當罕見的疾病，可能會侵犯肺實質或支氣管。原發性氣管內膜相關性淋巴組織淋巴癌在胸部 X 光片或電腦斷層最常見的表現是單一個肺結節或腫塊合併空氣肺泡造影。在此我們報告一個暗示已咳血為表現，但胸部 X 光片正常。而支氣管鏡檢查的表現是位於氣管隆凸上方單一突起的腫塊。*(胸腔醫學 **2006; 21: 274-279**)*

關鍵詞：原發性肺淋巴癌，黏膜相關性淋巴組織淋巴癌，支氣管鏡，咳血

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# Isolated Cryptococcal Pleural Involvement in a Patient with Renal Tuberculosis — A Case Report

Ming-Tai Wu*, Wen-Liang Yu**, Jiunn-Min Shieh*, Kuo Chen Cheng*,**, Chin-Ming Chen**

*Cryptococcus neoformans* is a ubiquitous fungus commonly found in soil contaminated with pigeon droppings; on inhalation, it can become colonized in the immunocompetent host or cause infections in the immunocompromised host. Clinically, the central nervous system is the most commonly infected site, followed by the lung (pulmonary cryptococcosis). However, there have been only scarce reports of isolated pleural empyema or effusion caused by *C. neoformans* without identified lung lesions in non-human immunodeficiency virus (HIV)-infected patients. Herein, we present a patient with renal tuberculosis and prolonged fever who had an incidental finding of isolated cryptococcal pleural effusion. We suggest that an examination for pleural cryotococosis in immunocompromised patients with unexplained pleural effusion may be warranted. ***(Thorac Med 2006; 21: 280-285)***

Key words: *Cryptococcus neoformans*, pulmonary cryptococcosis, cryptococcal pleural effusion

## Introduction

Although cryptococcal infection in immunocompromised hosts has received more attention recently, 50% of cases could occur in healthy persons. Because of its low incidence, pleural cryptococcosis is often not included in the initial differential diagnosis of the etiology of pleural effusions. Although the most commonly infected site is the central nervous system (CNS), followed by the lung, the usual portal of entry is the lung. There are relatively few reports of pulmonary cryptococcosis in the English literature, and cryptococcal pleural effusion in non-human immunodeficiency virus (HIV)-infected patients has been rarely reported. For immunocompromised hosts, approximately 80% of pulmonary cryptococcal infections included CNS infection, most of which was clinically silent [1]. Herein, we report a rare case of cryptococcal pleural effusion in an immunocompromised host with a prolonged hospital course, and who eventually died of nosocomial infection.

## Case Report

A 65-year-old man with a 10-year medical history of hypertension visited our emergency

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room on May 30, 2004, due to fever, chillness, and voiding difficulty for 10 days. He was discharged with the diagnosis of tuberculosis (TB) of the right kidney, and with a pigtail indwelling for hydronephrosis. The patient received short-term steroid for persistent fever, in addition to anti-TB therapy.

On June 30, 2004, the patient was re-admitted due to the flare-up of fever. On admission, his consciousness was clear. His blood pressure was 193/97 mmHg; pulse rate, 98/min; and temperature, 37.2°C. The neck was supple. Some rhonchi in the bilateral chest regions were audible.

The laboratory data revealed a leukocyte count of 5,900/uL; platelet count, 77,000/uL; blood urea nitrogen (BUN), 73 mg/dL; and serum creatinine, 5.9 mg/dL. The anti-HIV antibody was negative. Chest X-ray revealed right lower lung field atelectasis. The urinary analysis revealed numerous white cells with positive acid-fast staining.

Empiric antibiotic with cefazolin was prescribed and anti-TB drugs were started. Due to progressive dyspnea and persistent metabolic acidosis, he was transferred to the intensive care unit (ICU) on July 4, 2004. Hemodialysis was performed for acute on chronic renal failure with oliguria. After 1 month of ICU stay, generalized anasarca developed with hypoalbuminemia. Thoracocentesis was performed for the right pleural effusion (Figure 2). A pleural effusion routine revealed a bloody appearance with a leukocyte count of 20/uL (lymphocyte 10/ uL and neutrophil 10/uL). Pleural fluid biochemistry showed protein, 1.3mg/dL; sugar, 110mg/dL; and LDH, 810 IU/L. An incidental finding in the pleural routine was positive Indian ink staining. The subsequent blood and pleural effusion cultures yielded *C. neoformans*. Lumbar puncture was not performed due to a huge bedsore in the lumbar-sacral area. Magnetic resonance imaging (MRI) of the brain disclosed no evidence of meningitis or hydrocephalus. His consciousness remained clear. A 10-day course of intravenous amphotericin-B 50 mg daily was administered, followed by intravenous fluconazole 200 mg daily

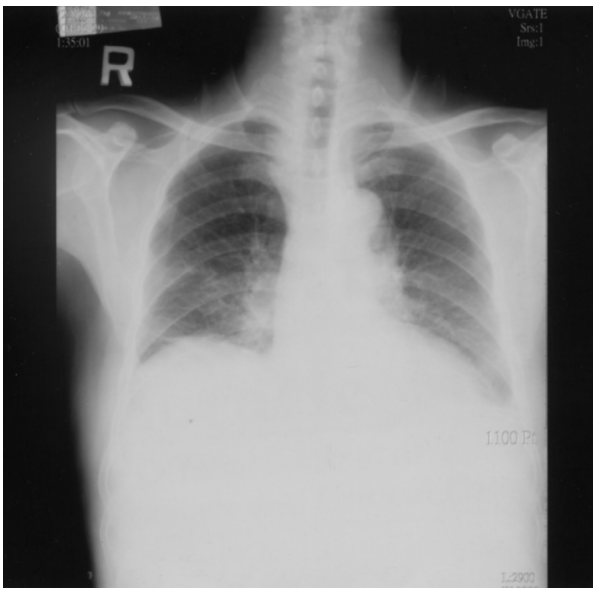


**Fig. 1.** CXR revealing right lower field atelectasis.

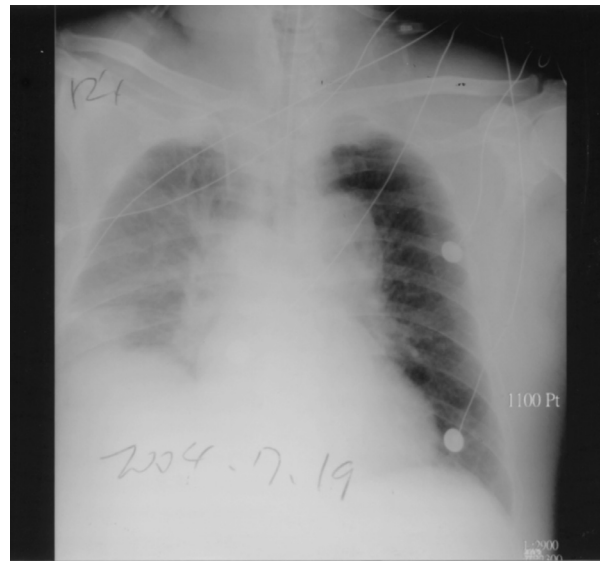


**Fig. 2.** CXR revealing cardiomegaly with right pleural effusion.

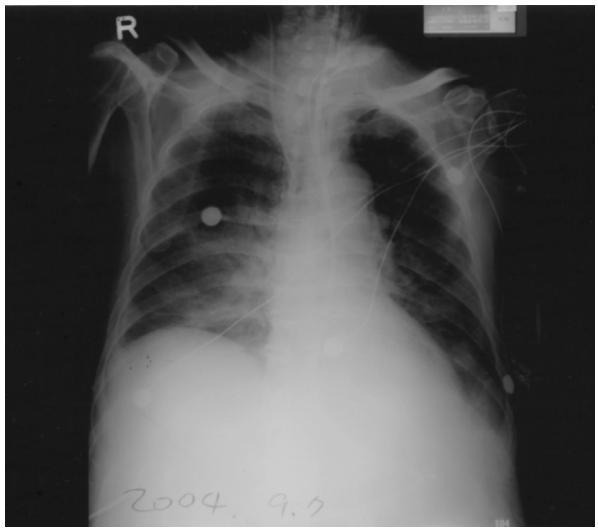


**Fig. 3.** CXR revealing resolution of the right pleural effusion. Some air-space infiltration at the right middle, lower and left middle lung is noted.

due to the patient's intolerance. Six weeks after antifungal treatment, the serum cryptococcal antigen titer had declined, from 1:4096 to 1:128. The follow-up chest film revealed resolution of the right pleural effusion (Figure 3). However, the patient died of nosocomial infection with pan-drug-resistant *Acinetobacter baumannii* septicemia and multiple organ failure 2 weeks after admission.

## Discussion

*C. neoformans* is a type of non-mycelial budding yeast found in soil contaminated with pigeon or chicken excreta. For cryptococcal infection, the most common site is the meninges, and the second is the lung. It is a saprophyte in nature, and usually causes infection in patients with impaired cell-mediated immunity; pleural involvement is usually associated with an underlying lung lesion.

In a review of the English literature, less than 30 articles on cryptococcal pleural effusion could be found, and most were associated with HIV-infected patients. It has been postulated that cryptococcal infection has a greater tendency in patients with steroid or immunosuppressive agent use, hematological malignancy, or an underling parenchymal pulmonary disease, such as chronic obstructive pulmonary disease (COPD) or sarcoidosis [2]. The predisposition to cryptococcal infection in these individuals appears to be secondary to the defect in cell-mediated immunity, which is further suppressed by the capsular polysaccharide produced by the fungus [3]. Our patient might have been in an immuocompromised status with the long-term use of steroid.

Pulmonary cryptococcosis has been defined as having (1) a culture positive for *C. neoformans* from a respiratory specimen, such as sputum or lung biopsy; (2) a positive chest X-ray finding; and (3) clinical symptoms with no other proven etiology [4]. Cryptococcal pleural effusion was defined as a positive effusion culture [4]. Disseminated cryptococcosis has been defined as positive culture(s) from blood, urine or other sterile body fluid [4]. Colonization was defined as a positive respiratory specimen culture without chest X-ray findings, respiratory symptoms, and postmortem confirmation [4]. Culture positive from pleural effusion, but without evidence of systemic disease, was still considered as a localized disease [4].

Primary cryptococcal pleural disease is rare in non-HIV-infected patients, and it could be an indication of a spread of primary subpleural nodules or dissemination in immunocompromised hosts [5]. Of those who have pulmonary cryptococcal pneumonia, 50~80% are immunocompromised hosts [6]. It has been postulated that the release of antigen, rather than organism growth, is responsible for pleural manifestation. Pleural cryptococcosis, if present, almost always has been

associated with underlying lung parenchymal lesions, such as a subpleural nodule, mass, or interstitial infiltrates, alveolar consolidation, and lymphadenopathy. Effusion analysis often revealed bloody or serosanguinous effusive fluid with lymphocyte predominance.

Pulmonary cryptococcosis with pleural effusion is uncommon. About 17% of pulmonary cryptococcosis in healthy patients develops CNS dissemination, if not treated. In 1 study, 69% of immunocompromised hosts had concomitant CNS involvement [6].

Bronchoalveolar lavage is the most sensitive diagnostic procedure for pulmonary cryptococcosis, with a sensitivity rate of 82%; the cryptococcal antigen test is 31% in serum and 26% in CSF [9]; the fluorescent antibody test is not helpful in diagnosing cryptococcal disease. Effusion cell counts vary from 1 to 10,000, with predominant lymphocytosis (80~90%). Chest X-ray patterns of pulmonary cryptococcal infection include lymphadenopathy and nodular interstitial infiltrates, even consolidation or mass. Closed pleural biopsy may afford a rapid method of diagnosing pleural cryptococcal disease [10]. The serum cryptococcal antigen (SCA) titer test may be helpful for decision-making on antifungal therapy, or as a marker of disease activity or organism burden. A positive SCA test may reflect an increased risk for more severe local disease or for dissemination, but the relationship is still unproven [8]. Antigen detection in pleural fluid has been proved useful in documenting local infection. Overall, the cryptococcal antigen test is highly specific, with a low incidence of false positive reactions, and it can be helpful in following up the clinical response to therapy [8].

The immune status and other sites of involvement determine the choice of antifungal therapy for pulmonary cryptococcosis [11]. Aberg et al. suggested fluconazole for 3~6 months for immunocompromised hosts; if there is CNS involvement, amphotericin-B plus flucytosine was recommended [4]. For most HIV-negative patients with cryptococcal pneumonia, azole therapy was probably sufficient [4]. De Clerk et al. recommended fluconazole 200~400mg/day for 3~6 months or itraconazole 200~400mg/day for 6~12 months for mild to moderate disease; amphotericin-B 0.5~1.0 mg/kg/day for 6~10 weeks for severe disease; and surgical resection if medical therapy failed [12]. However, there is no definite conclusion on therapy for pulmonary cryptococcosis or cryptococcal pleural effusion.

In immunocompromised hosts with primary cryptococcal pneumonia and no antifungal treatment, 70% will disseminate to extrapulmonary lesions (especially CNS) in a few months [13]. The mortality rate for cryptococcosis is around 0~15% in immunocompetent hosts, and around 20~85% in immunocompromised hosts. Although rare, spontaneous resolution of pleural cryptococcosis has been reported [13].

In conclusion, *C. neoformans* is present in the sputum more often than is realized. Because of its low incidence, pleural cryptococcosis is often not included in the initial differential diagnosis of the etiology of pleural effusion. We urge that pleural effusion of an uncertain etiology, even in patients with no predisposing disease, should be evaluated with serum cryptococcal antigen and fungal culture.

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# 隱球菌肺肋膜積水—病例報告

吳銘泰* 余文良** 謝俊民* 鄭高珍*,** 陳欽明**

隱球菌是一種黴菌，常見於受鴿子排泄物污染的泥土中；它在健康人身上可形成無害的寄生菌落，也可在免疫不全的人身上造成感染，形成疾病；臨床上中樞神經系統是最常見的感染部位，肺部次之。從文獻記載中，我們發現肺隱球病並不常見，形成隱球菌肺肋膜積水更是少見；這裡我們報告一個病例，希望藉此能對醫療從業人員在臨床治療上有所啟發。*(胸腔醫學 **2006; 21: 280-285**)*

關鍵詞：隱球病，肺隱球病，隱球菌肺肋膜積水

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# Adenocarcinoma of the Lung with Bilateral Hydroureteronephrosis

Wei-Chun Lin, Chao-Hua Chiu, Chun-Ming Tsai

We report a 53-year-old female who was diagnosed with adenocarcinoma of the lung and failed to respond to 2 lines chemotherapy. She developed oliguric acute renal failure within 1 week. A renal sonography disclosed bilateral hydroureteronephrosis. She underwent a bilateral percutaneous nephrostomy with external drainage, and her renal function recovered within 3 days. The most common primary sites of cancers causing ureteral obstruction are the cervix, prostate, bladder and colo-rectum. To our knowledge, few case reports of ureteral obstruction attributable to lung cancer have been published. With the current improvements in lung cancer management, survival time has been significantly prolonged and unusual presentations or complications of lung cancer are becoming more common than before. Physicians should be aware that hydronephrosis could complicate the course of patients with non-small cell lung cancer. ***(Thorac Med 2006; 21: 286-290)***

Key words: lung cancer, hydronephrosis

## Introduction

Lung cancer metastatic to the ureter is rare; there have been only a few reported cases [1-2], with some cases reported in 2 large reviews of autopsies [3-4]. Most cases are asymptomatic, making the diagnosis more difficult prior to death [3-4]. We report herein a case of advanced lung cancer metastatic to the bilateral ureters that manifested with acute renal failure.

## Case Report

A 53-year-old female developed oliguric acute renal failure (blood urea nitrogen/creatinine raised from 25/1.2 mg/dL to 55/4.1 mg/dL) within 1 week. Neither a gross nor a microscopic hematuria was noted. She had been diagnosed with adenocarcinoma of the lung, with brain, adrenal, spleen, skin, bone, opposite lung, and pleural metastases. She had been vigorously treated, and failed to respond to 2 lines of chemotherapy: gemcitabine plus carboplatin for 5 courses and vinorelbine plus ifosfamide for 3 courses, followed by gefitinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor. A renal sonography disclosed bilateral hydronephrosis and proximal hydroureter. She then

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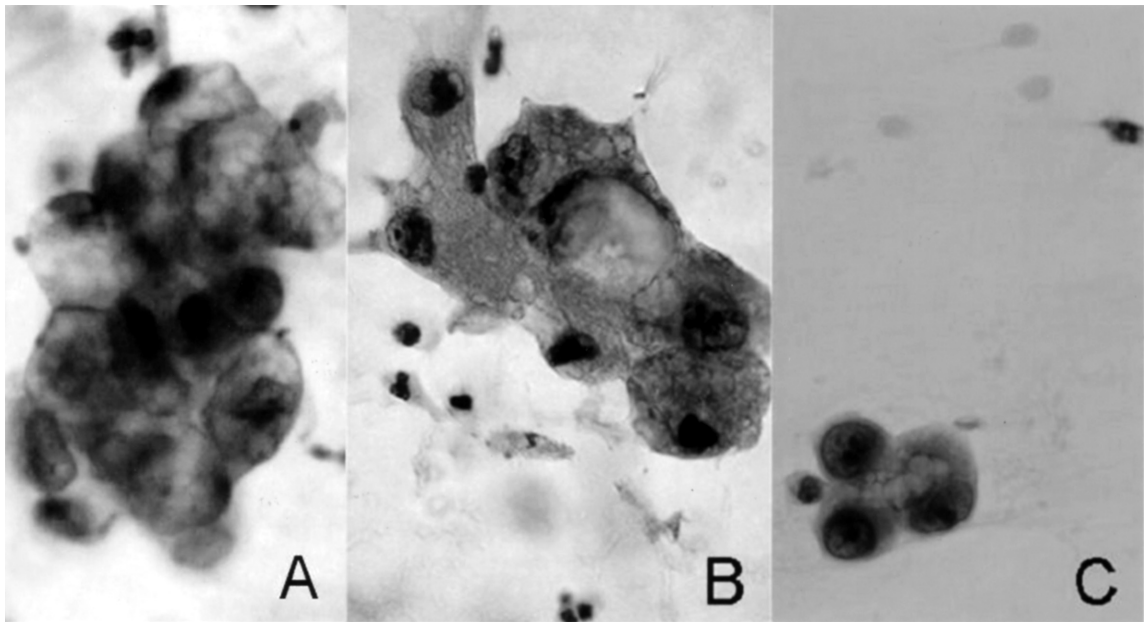


**Fig. 1.** Cytology from the right (A) and left (B) nephrostomies, and the uterine cervix (C) (original magnifications, x 400).

underwent a bilateral percutaneous nephrostomy with external drainage, and her renal function recovered within 3 days. Cytological examination of urine samples collected separately from each kidney disclosed adenocarcinoma. (Figure 1A, 1B). Contrast-enhanced computed tomography (CT) of the lower abdomen disclosed bilateral hydroureters with obstruction at the mid-third and lower third of the right and the left ureters, respectively (Figure 2). No retroperitoneal lymph node or tumor growth was disclosed by abdominal computed tomography (CT) and magnetic resonance imaging (MRI). An ovarian cyst adjacent to but lower than the obstruction level of the right ureter (Figure 2, arrow) showed no change in size and shape, as compared to the CT findings of 1 month before (not shown). Since the urine cytology from the nephrostomy disclosed adenocarcinoma, and the imaging studies (CT, MRI) failed to demonstrate positive radiographic findings of kidney metastasis, retroperitoneal lymphadenopathy or tumor involvement, our first impression was adenocarcinoma of the lung with bilateral ureter metastases. An intra-ureter stent was successfully inserted into the left ureter via ureteroscopy, but the procedure failed in the right ureter due to severe intraureteral adhesive stricture. In addition, there was no ureteroscopic evidence of external compression of the ureters. A couple of days later, bloody discharge from the vagina was found. A Papanicolaou smear of the cervix and vagina revealed adenocarcinoma, likely metastatic in origin (Figure 1C). Unfortunately, this patient died of profound diffuse intravascular dissemination and recurrent cerebral infarcts 4 weeks later. In view of the clinico-radiological findings, the overall picture was in keeping with adenocarcinoma of the lung associated with bilateral ureter and lower female genital tract metastases.

## Discussion

Ureter metastasis is rare; there have been only

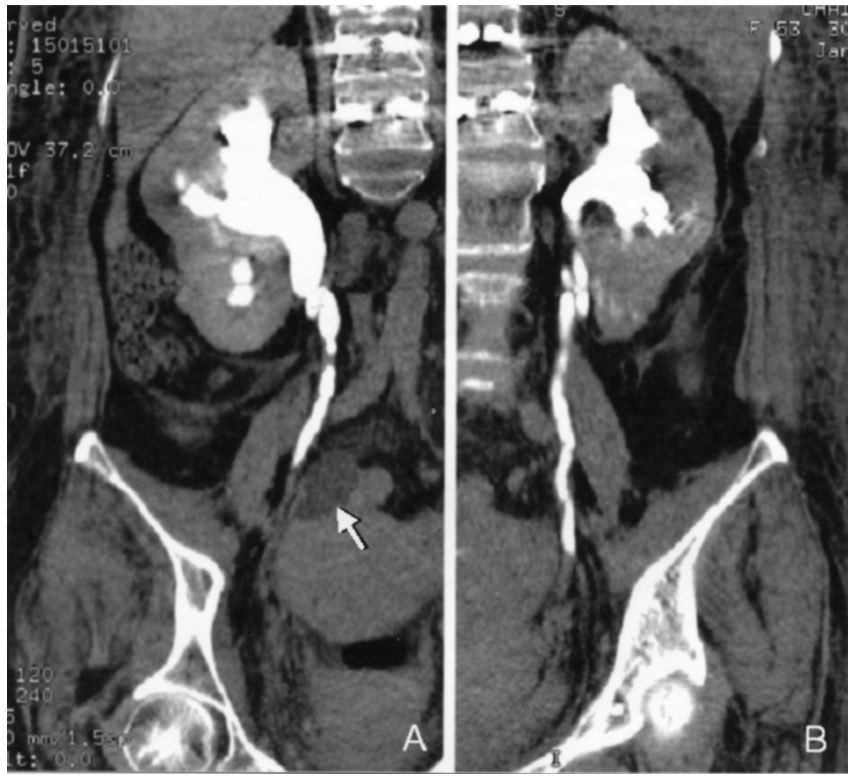


**Fig. 2.** Computed tomography: hydroureteronephrosis noted at the mid-third of the right ureter (A) and the lower third of the left ureter (B). Arrow: ovarian cyst.

a few case reports [1-2] and some cases reported in 2 large reviews of autopsies. One review of 11,698 autopsies yielded 37 cases of histologically-proven ureteral metastases. The lung was the primary site in only 2 cases (5% of the ureteral metastases cases, or 0.02% of the entire autopsy group), whereas the gastrointestinal tract was the primary site in 32%, the cervix in 22%, the breast in 19%, and melanoma in 14% [3]. In another study of 3,200 consecutive autopsies, 3 of 31 cases of ureteral metastatic tumors arose from primary lung tumors (0.1% of the entire autopsy group) [4]. In an additional report of 160 cases of ureteral metastatic tumors, only 4 (2.5%) had primary lung tumors [5]. Most cases are asymptomatic, and the ureteral metastases are discovered incidentally at autopsy. No definite predilection for laterality or ureter segment has been reported. Hematuria was uncommon [4], and usually resulted from tumor involvement and necrosis of the ureter mucosa [6]. Flank pain or back pain is the less specific finding. The laboratory findings are more significant. An elevation of the blood urea nitrogen (and/or creatinine) value may give rise to the suspicion of obstructive nephropathy. The most uniform finding was hydroureteronephrosis proximal to the site of the metastatic lesion [4]. Metastases to the ureter have been rarely discovered prior to death, unless associated with the signs and symptoms of obstruction [2, 4]. There have been very few case reports of ureteral obstruction as an initial finding on presentation, leading to the subsequent diagnosis of primary malignancy [7].

There was a lack of direct evidence to document ureteral metastasis in this case because the patient's family refused an autopsy. Nevertheless, there was no other reasonable etiology for the bilateral hydroureteronephrosis. The CT and MRI studies failed to demonstrate positive radiographic findings of kidney metastasis, retroperitoneal lymphadenopathy, or tumor involvement. Ureteral metastasis usually occurs via the vascular and lymphatic systems to the ureteral wall, and should be distinguished from malignant extension from the retroperitoneal soft tissues or pelvic organs. The ureteral adventitia is the common layer involved in ureteral metastasis, and may cause compression of the ureteral lumen [4-5]. Some authors have emphasized the mechanism of tumor expansion along the ureteral wall, or induced desmoplasia leading to obstruction [8-9]. Hematogenous spreading to the ureteral mucosa is the least metastatic pathway. This explains why hematuria is rarely found in ureteral metastasis.

The female genital tract is an infrequent site of metastasis, particularly for extragenital primaries. We found few case reports in a Medline search. Of those cases reported, the patients presented with intermittent, yellowish vaginal discharge [10] and postmenopausal vaginal bleeding [11]. In our case, physical examinations disclosed atrophic vaginitis with no tumor growth. A Papanicolaou smear revealed a positive finding for malignant cells.

With the current improvement in lung cancer management, survival time has been significantly prolonged and unusual presentations or complications of lung cancer are becoming more common; this should always be kept in mind.

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# 肺腺癌合併兩側輸尿管阻塞及水腎—病例報告

林偉群　邱昭華　蔡俊明

本文報告一肺癌病例於生前被發現有兩側輸尿管及陰道轉移。病患是一位 53 歲女性肺癌患者因為急性腎衰竭住院，腎臟超音波顯示有兩側輸尿管阻塞及腎臟積液，腎功能於經皮置放腎臟 pig-tail 導管引流尿液後恢復正常。尿液細胞學檢查顯示為腺癌細胞。而相關影像學檢查（腹腔電腦斷層及後腹腔核磁共振）顯示無腎臟、後腹腔淋巴結轉移或是後腹腔腫瘤壓迫輸尿管。原發性腫瘤造成輸尿管阻塞常見的是子宮頸癌，攝護腺癌、膀胱癌及大腸直腸癌，肺癌合併兩側輸尿管阻塞及腎臟積液實為少見，只有少數病例是在生前診斷出來。而隨著肺癌治療的進步，肺癌病人的生命延長，預期一些往昔肺癌罕見的臨床表現會愈來愈多，我們報告這樣的病人以提醒大家肺腺癌病人可能有此罕見的輸尿管轉移。*(胸腔醫學* ***2006; 21: 286-290)***

關鍵詞：肺癌，水腎，輸尿管阻塞

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# Congenital Cystic Adenomatoid Malformation in an Adult: A Case Report and Review of the Literature

Fu-Tsai Chung, Chih-Hsia Kuo, Po-Jui Chang, Chun-Yu Lo, Chih-Wei Wang*, Yuan-Chang Liu**, Horng-Chyuan Lin

Congenital Cystic Adenomatoid Malformation (CCAM) is an uncommon congenital pulmonary malformation that mostly affects newborn infants. However, it may sometimes occur in adults without any symptoms, and complete resection, such as lobectomy, is usually necessary for those at high risk of recurrence, malignancy, or possible massive hemorrhage. Herein, we report a case of adult CCAM presenting as a huge mass on a chest roentgenogram. Recurrence of CCAM was found 7 months after wedge resection. The patient then underwent another surgery with a right lower and middle bilobectomy, and has been regularly followed up at clinics, in a stable condition, since then. We reviewed the literature for a discussion of the clinical manifestations, radiology and histopathologic studies, as well as management of CCAM in adults. ***(Thorac Med 2006; 21: 291-297)***

Key words: congenital cystic adenomatoid malformation, adult, lobectomy

## Introduction

Congenital cystic adenomatoid malformation (CCAM) is an uncommon anomaly in lung development, characterized by a proliferation of dilated bronchiolar-like airspaces of varying sizes and distribution [1]. The term CCAM was first introduced in 1949 by Ch'in and Tang [2]. It has no association with race, sex, maternal age, or familial predisposition [3]. It is suggested that CCAM is caused by an overgrowth of the terminal bronchiolar-like tubular structures with subsequent suppression of alveolar growth, resulting from an embryologic insult before the 49th gestation day [4].

In 1977, Stocker and coworkers [1] classified CCAMs into 5 types, by the size and structure of the cysts. Type 0 was defined as bronchial, type 1 as bronchial/bronchiolar, type 2 as bronchiolar, type 3 as bronchiolar/alveolar duct, and type 4 as peripheral. CCAM principally affects newborn infants, and is rarely found beyond adolescence [5-6]. Complete eradication is recommended due to the high risk of recurrence, repeat infection, massive hemorrhage, and possible malignant potential [7]. We present a case of CCAM in an adult with the initial presentation of chest pain. Thoracotomy with wedge resection was perfor-

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med initially, but the tumor recurred 7 months later. Therefore, the patient underwent a complete right lower and middle lobe bilobectomy. We also reviewed the literature regarding CCAM in adults.

## Case Presentation

A 46-year-old woman with no previous history of respiratory problems sought treatment for chest pain lasting for 1 month. She visited our emergency room where a chest roentgenogram revealed a huge cyst in the right lower lobe (Figure 1).

After admission, HRCT of the chest was performed and a huge cyst, measuring about 11x13 cm, with homogenous fluid content and a thin wall, was found (Figure 2). The chest surgeon was consulted and a wedge resection of the right lower lobe was performed. CCAM (Figure 3) was diagnosed by pathologic examination and was classified as type I, based on Stocker's modified classification [1].

After surgery, the chest pain was relieved and she was followed up regularly at the OPD, without complication. The follow-up CXR was unremarkable (Figure 4). However, 7 months later, the chest pain flared up again, and a new radiopaque lesion in the right hilar area was found on another chest X-ray (Figure 5) A right lower

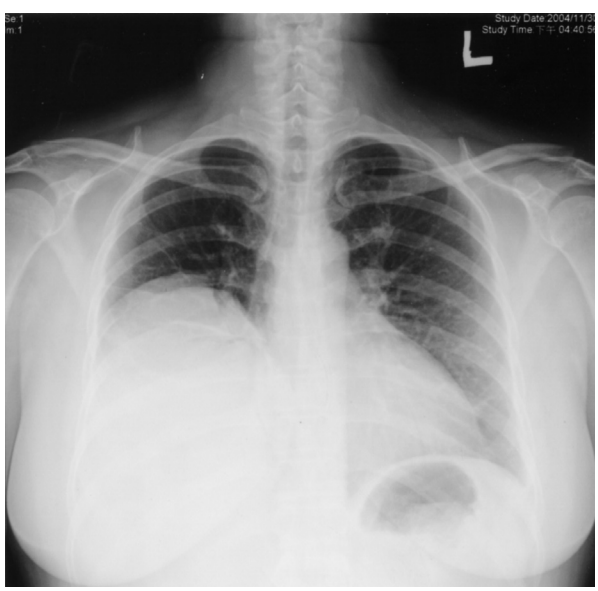

**Fig. 1.** The chest roentgenogram revealing a huge cyst in the right lower lung field.

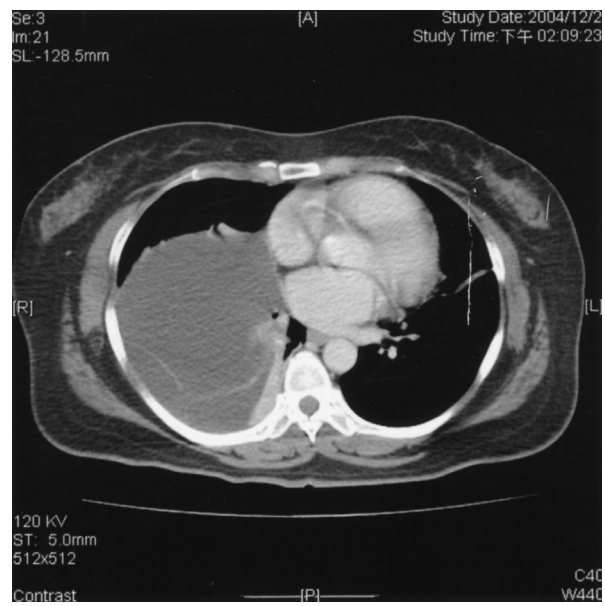


**Fig. 2.** HRCT of the chest showing a huge cyst measuring about 11x13 cm with homogenous fluid content and a thin wall.

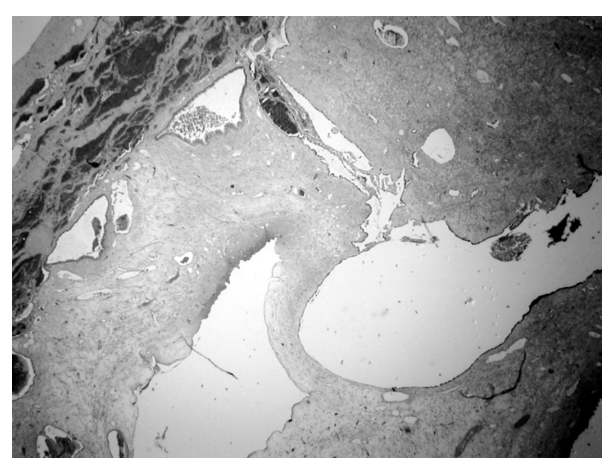

**Fig. 3.** CCAM is confirmed by pathologic examination.

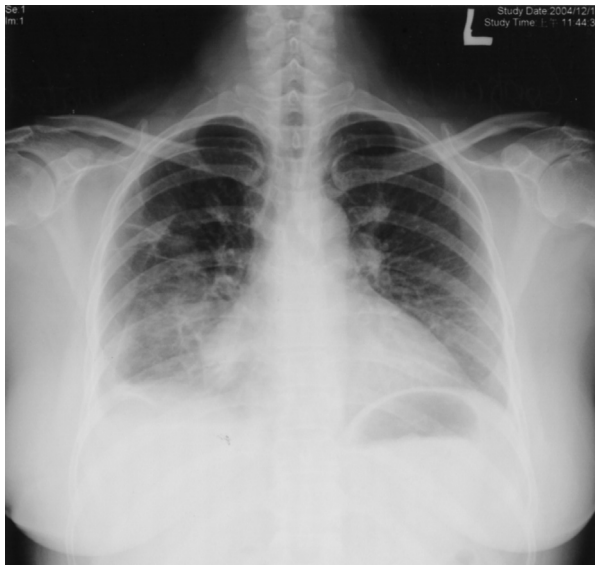

**Fig. 4.** The chest roentgenogram after the first surgery is normal.

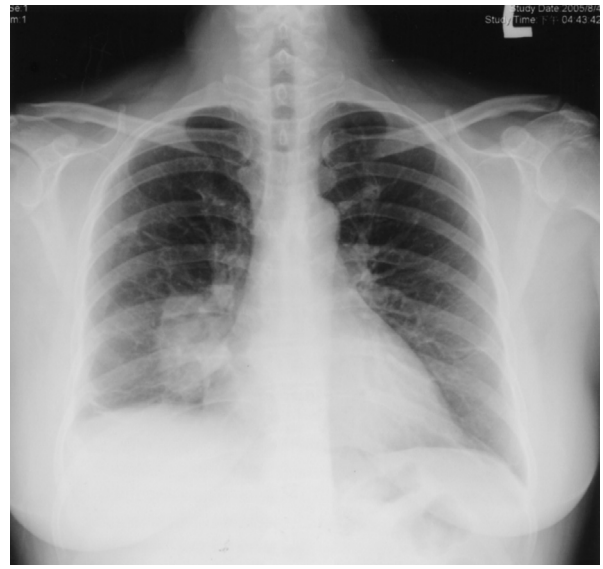

**Fig. 5.** Chest X-ray revealing a new radiopaque lesion in the right hilar area 7 months after wedge resection.

and middle bilobectomy was then performed, and the pathology revealed a recurrent CCAM. She has been regularly followed up at the OPD, in a stable condition, up to this writing.

## Discussion

CCAM is an uncommon embryonic developmental abnormality usually diagnosed in neonates and infants [8]. The reported incidence is between 1:25,000 and 1:35,000 [9]. Its presentation in adulthood is rare, with only 27 cases reported up to now [6]; as such, CCAM in adults is seldom suspected by physicians. The main clinical presentation is repeated respiratory tract infections. Lung abscess in adulthood has been described [10]. In a previous report [6], CCAM in adulthood presented as recurrent pneumonia, or as an incidental finding on a chest roentgenogram without symptoms. The manifestations of our case were a huge mass on the chest CXR and chest pain. Therefore, the clinician should always keep in mind the possibility of CCAM, even in adulthood.

The differential diagnoses of the cystic lesion in our case included bronchogenic cyst, pulmonary sequestrations, congenital parenchymal cysts, or congenital lobar emphysema. Although a CT scan may provide some information before operation, surgical pathology is the best method to confirm the final diagnosis [11]. Although some authors have considered conservative treatment, such as pulmonary sequestration with remobilization and congenital lobar emphysema, for some cystic lesions, complete resection of the lesion is an acceptable treatment leading to a better prognosis. Surgical exploration is imperative for CCAM because of the risk of repeated respiratory infection, bleeding, and possible malignancy, even if the patient has no symptoms.

The potential for malignant transformation to bronchoalveolar carcinoma and pulmonary embryonic rhabdomyosarcoma in CCAM has been described [12]. The extended morphologic classification of CCAMs envisages them

progressively affecting more peripheral tissue. However, very few type 0 or type 4 CCAMs have been reported [13]. Type 4 CCAMs are similar histologically to grade 1 pleuropulmonary blastomas, and in the absence of clear-cut sarcomatous differentiation, there are few guidelines to distinguish them [14]. Therefore, the presence of type 4 CCAM morphology should prompt a thorough search of the cyst wall for evidence of stromal cellularity, with its identification raising concerns regarding malignant transformation or reclassification as a grade 1 pleuropulmonary blastoma.

The pathogenesis of CCAM remains unknown. While some researchers have hypothesized that CCAM results from a failure of interaction between the endoderm and mesoderm, others suggest an imbalance between increased cell proliferation and decreased programmed cell death (apoptosis) within the developing lung. Another group of researchers considers that CCAM is the result of a developmental failure due to a hypovascular development, as seen in other malformations [15].

CCAM was initially classified by Stocker et al. into 3 types, based on gross and microscopic features [1]; however, in 1994, the same authors then modified this classification into 5 pathological types, based on their resemblance to normal anatomical structures from the proximal to distal area (Table 1). The sub-grouping provides useful clinical data with regard to potential malignant transformation. Type 1 CCAMs are occasionally complicated by a carcinomatous transformation. The tumor cells show lepidic growth within the cysts and adjacent lung, and morphologically resemble bronchoalveolar carcinomas (BACs) arising de novo, although recurrence is exceptional. They show lower rates of Ki-67 and p53 staining than BACs arising de novo, but these differences are not statistically significant. Type 4 CCAMs show histologic overlap with grade 1 pleuropulmonary blastomas. Stromal cellularity in a type 4 CCAM, even in the absence of overt malignant features, should raise the possibility of a potentially malignant process. Therefore, follow-up, especially of types 1 and 4 CCAMs, is recommended [16].

The chest radiography of CCAM is nonspecific and depends on the extension of the lesion and its clinical presentation. Consolidations or an intrapulmonary water density mass with well-defined margins have been described. They were indistinguishable from a lobar pneumonia or a lung abscess and pneumatocele. Small CCAM lesions may not be visible on chest roentgenograms.

Computed tomography is the best choice for assessing CCAM lesions. On the CT scan, the type I CCAM is characterized by large cysts (> 1 cm in diameter) that may be air-filled, fluid-filled, or contain air-fluid levels. Areas of enhancement after intravenous contrast injection or areas of low attenuation around the cysts, corresponding to smaller cystic lesions and normal parenchyma, can also be seen. In our case, the initial CT findings included a large cystic area containing fluid in relation to retained fluid secretions. The wide radiological expression of CCAM makes a correct preoperative diagnosis difficult. Radiological findings for the differential diagnosis must be noted for pulmonary sequestration, bronchogenic cyst, cystic bronchiectasis, diaphragmatic hernia, and infected tumors [6].

The treatment of CCAM is essentially surgical. Long-term antibiotics may prevent recurrent infections. However, prolonging antibiotic therapy delays and complicates eventual surgery and leads to antibiotic resistance.

Infants with CCAM who undergo partial

**Table 1.** The Extended Classification of Congenital Cystic Adenomatoid Malformations [11]

| Type | Proportional incidence | Gross appearance | Microscopy | Other features |
|---|---|---|---|---|
| 0 | 1–3% | Solid; the lungs are small and firm throughout | Bronchial-type airways that have cartilage, smooth muscle, and glands are separated by abundant mesenchymal tissue | Neonates; other malformations; poor prognosis |
| 1 | 60–70% | Large cysts (up to 10 cm) | The cysts are lined by pseudo-stratified ciliated cells that are often interspersed with rows of mucous cells | Presentation may be late; respectable; good prognosis; rare cases show carcinomatous change |
| 2 | 10–15% | Sponge-like, composed of multiple small cysts (up to 2 cm) and solid pale tumor-like tissue | The cysts resemble dilated bronchioles separated by normal alveoli; striated muscle in 5% | Neonates; other malformations; poor prognosis |
| 3 | 5% | Solid | There is an excess of bronchiolar structures separated by air spaces that are small, have a cuboidal lining, and resemble rate fetal lung | Neonates; poor prognosis |
| 4 | 15% | Large cysts (up to 10 cm) | The cysts are lined by a flattened epithelium resting on loose mesenchymal tissue | Neonates and infants; good prognosis |

resection of the malformation may present in adulthood with residual disease or even worse—malignant transformation in the residual lung. An unstable epithelium in unresected malformations may be more susceptible to oncogenesis. Sudou *et al*. reported a bronchoalveolar carcinoma in a patient with a VATS lobectomy for adult CCAM, demonstrating the importance of complete resection and of closely following up patients with incomplete resections. Hemopneumothorax, pyopneumothorax and recurrent pneumothorax have been described in association with CCAM. Al-Ghitmi and associates described the presence of bronchiectasis and multiple neuroendocrine nests in a CCAM specimen, which contributed to the hemoptysis [7]. Based on this review of the literature, we concluded that a complete surgical resection is advisable in type 1 CCAM at the time of diagnosis, in both infants and adults, because a delayed or incomplete procedure may expose patients to inflammation, to metaplasia, and finally to neoplasia [17-19].

In our case, the initial partial treatment with a wedge resection of the right lower lobe for CCAM may not be suitable treatment for recurrence 7 months later. We reviewed the literature, and partial treatment, such as segmental resection or wedge resection, was not suggested, for it led to more complications and prolonged hospitalization than complete treatment, such as lobectomy [20]. Although only a few reports have mentioned recurrence after partial treatment for

CCAM, it should be kept in mind as a potential risk.

## Conclusion

CCAM is a rare congenital anomaly of the lower respiratory tract, especially in adults. The diagnosis depends on the imaging study, histopathology and surgery. Because of the high risk of recurrent infection, malignant transformation, possible massive hemorrhage, and easy recurrence, complete resection is the best treatment for all patients, even those without symptoms.

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# 成人先天囊狀類腺畸形—病例報告及文獻回顧

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先天囊狀類腺畸形乃是罕見的先天肺部發育異常，由於產前診斷及治療技術的發展，通常在成年以前即被診斷。雖然少見，其仍被發現可能發生於成人且未伴隨任何症狀。由於它具有高度復發率，且潛存發展成惡性腫瘤及大出血之危險，徹底的切除例如肺葉切除術通常是必須的。我們報告了一例診斷於成人之先天囊狀類腺畸形，經楔狀切除後於門診追蹤七個月後再發，復行雙肺葉切除之徹底治療後，目前於門診追蹤情況穩定。同時針對成人先天囊狀類腺畸形之臨床表現，放射影像學及病理組織學，我們回顧並整理過去的文獻提出此報告。*(胸腔醫學* ***2006; 21: 291-297****)*

關鍵詞：先天囊狀類腺畸形，成人，肺葉切除術

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# Pulmonary Coccidioidomycosis Manifesting as a Single Pulmonary Nodule — A Case Report and Literature Review

Wen-Cheng Chao, Ming-Cheng Chan, Yee-Jee Jan*, Jeng-Yuan Hsu

A previously healthy 40-year-old man with pulmonary coccidioidomycosis presented with a solitary pulmonary nodule. The diagnosis was made by wedge resection with histological proof and a previously positive serology test for coccidioidomycosis IgG. The patient had suffered from left chest pain in 2003 when he worked in Arizona. A left lung nodular lesion was found by chest film, and pulmonary coccidioidomycosis was diagnosed at that time, on the basis of positive serum coccidioidomycosis IgG. He underwent anti-fungal treatment there for about 3 months, and the chest pain subsided. In May 2005, he visited our chest medicine outpatient department because of a recurrence of chest pain. The chest X-ray disclosed a 2.5 cm nodule in the left lung. A wedge resection was performed and histopathology of the lesion demonstrated caesous granulomatous inflammation with some Langerhan's giant cells. The Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) stains disclosed several spherules containing some small endospores. The histopathological picture was compatible with Coccidioides infection. Literature concerning the life cycle, manifestation, diagnosis, treatment, and pulmonary sequelae of coccidioidomycosis is also reviewed. ***(Thorac Med 2006; 21: 298-304)***

Key words: coccidioidomycosis , single pulmonary nodule

## Introduction

Coccidioidomycosis is the infection caused by a dimorphic fungus, *Coccidioides immitis,* and is known for its endemicity to the arid desert region of the southwestern United States, including California, Arizona, Nevada, and New Mexico [1-2]. However, given the more frequent tourist and business travel of late, an increasing number of coccidioidomycosis infections are reported in non-endemic areas [3]. This infection has protean clinical manifestations and is frequently unrecognized, especially in travelers to endemic areas who return to locations where the disease is not typically encountered. It is difficult to make the diagnosis because two-thirds of infections are asymptomatic; the remainder exhibit only non-specific respiratory symptoms, for the most part. Current methods for diagnosing coccidioidomycosis include recovery of *C. immitis* from clinical specimens, detection of specific anti-coccidioidal antibodies in serum or

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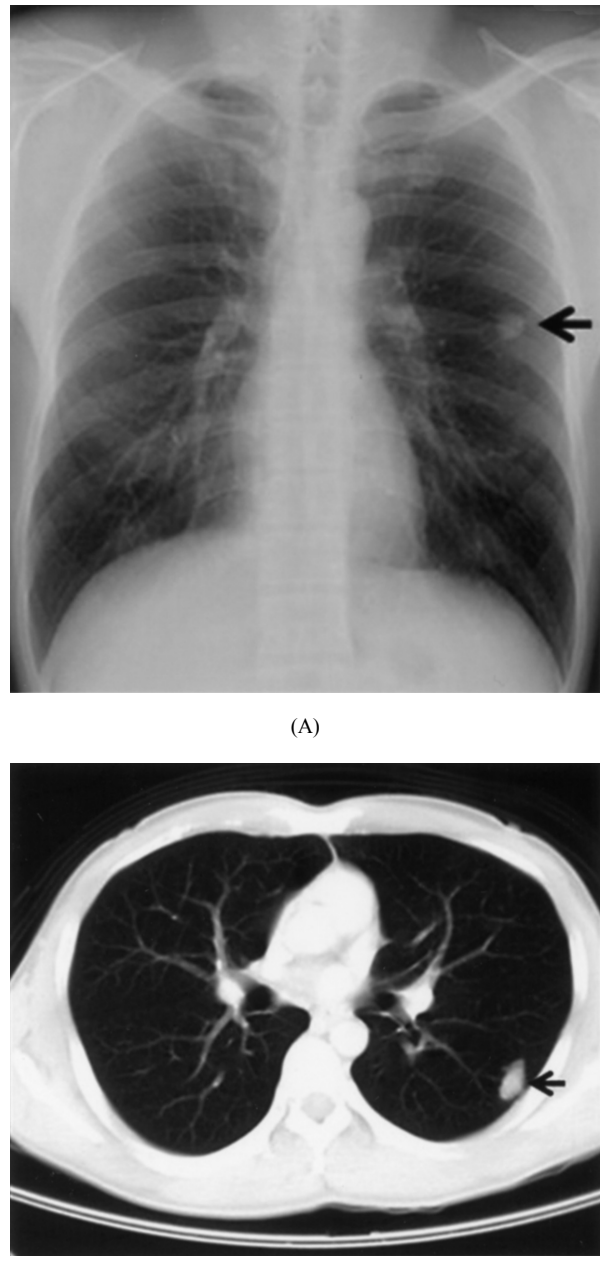
other body fluids, and eliciting dermal delayed-type hypersensitivity (DTH) reactions to coccidioidal antigens [1-2].

Management of this disease involves defining the extent of infection and assessing host factors that predispose to disease severity. Fluconazole, itraconazole, or ketoconazole are common treatment choices, and amphotericin B is often reserved for disseminated or rapidly progressive infection [4]. The symptoms frequently resolve within several weeks, but resolution of the radiographic abnormalities is usually slower. If the radiographic abnormalities persist more than 8 weeks, the term "chronic pulmonary coccidioidomycosis" is designated. The radiographic abnormalities take the form of nodules, cavities or progressive pneumonia. When manifested as nodule(s), lung malignancy should be suspected and a histologic examination is needed [5-6].

## Case Report

A 40-year-old man presented to the chest medicine outpatient clinic of Taichung Veterans General Hospital (VGHTC) with intermittent left lower chest tenderness lasting for several weeks. Two years previous, he had experienced an episode of left chest tenderness when he worked in the desert region of Arizona. The chest X-ray revealed a nodular lesion in the left lung, and the serology test was positive for coccidioidomycosis IgG. He received oral fluconazole at that time, and the chest pain subsided. However, the chest X-ray abnormality persisted despite resolution of the symptom.

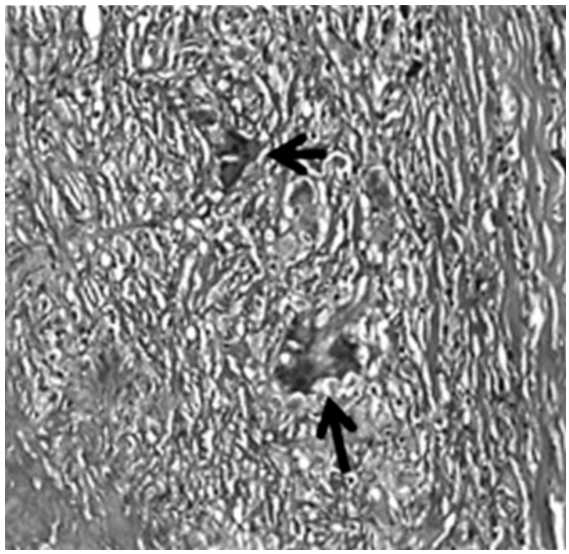
In May 2005, he came to our chest medicine outpatient clinic because of a recurrence of left chest pain. Physical examination revealed him to be a well-developed man with an easy-looking appearance. His blood pressure was 110/80 mmHg, body temperature 37°C, pulse rate 78/min, and respiratory rate 17/min. The breathing sounds were clear bilaterally and no neck lymph node was palpable. He had no fever, cough,



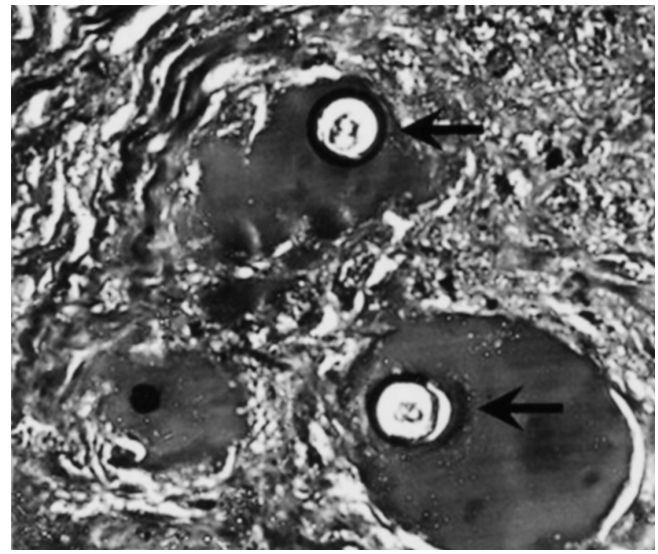
(A)

(B)

**Fig. 1.** (A) Preoperative PA chest radiography and (B) CT scan showing a smooth, well-marginated peripheral nodule (about 2.2 cm x 1.2 cm) in the left lung field.



(A)



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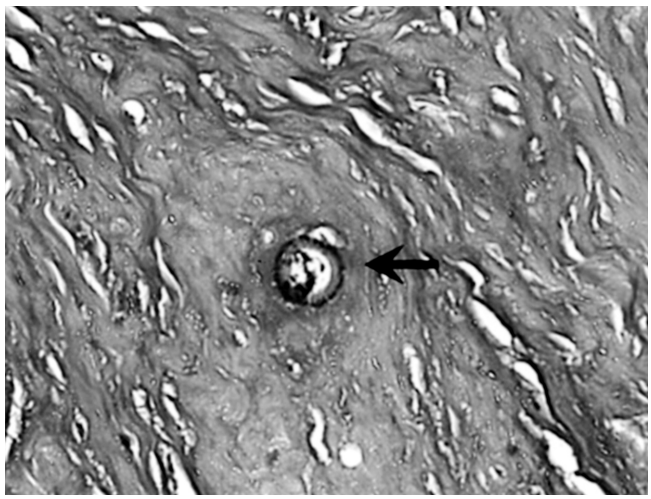

(C)

**Fig. 2.** (A) Histopathology of the specimen of the wedged resection demonstrating Langerhans' giant cells. (hematoxylin and eosin x400); (B) Gomori methenamine silver (GMS) stain and (C) periodic acid-Schiff (PAS) stain disclose several spherules containing some small endospores.

sputum production, or loss of weight. The blood examinations, including a complete blood count, renal function tests, liver function tests, electrolytes, C-reactive protein, and serum Cryptococcus antigen revealed no abnormal finding. The chest X-ray (Figure 1A) disclosed a well-defined 2-cm nodular lesion located in the left middle lung field. The chest computed tomography (CT) also showed a 2.5-cm nodule in the left lower lobe with several small lymph nodes in the aorto-pulmonary window (Figure 1B). Histopathology of a wedge resection of the nodule demonstrated caesous granulomatous inflammation with some Langerhan's giant cells (Figure 2A). The Gomori methenamine silver (GMS) (Figure 2B) and periodic acid-Schiff (PAS) (Figure 2C) stains revealed several spherules containing some small endospores. The histopathological picture was compatible with Coccidioides infection. Mycobacterial and fungus cultures were both negative.

As the lesion had been removed and the patient was rather robust without significant immunosuppression, no further antifungal treatment was given. The post-operative course went smoothly, and there was no further chest pain; the chest X-ray follow-up 2 months after operation was clear.

## Discussion

*C. immitis* is a biphasic fungus that lives as a saprophytic (mycelia-arthroconidial) form in nature or in culture, and as a parasitic (spherule) form in humans and other mammals. *C. immitis* grows a few inches below the surface of the desert soil. With dry conditions, the mycelia become very fragile and are easily fractured by even slight air turbulence. They can remain suspended for prolonged periods of time in the air. The mycelia develop arthroconidia, approximately 3 to 5 μm in size, which are the spores that are inhaled and cause the clinical human infection. Once inside the host, the arthroconidia change into a spherule form, and then greatly enlarge, sometimes becoming 70 μm or more in diameter. The enlarging spherules contain numerous endospores, as can be seen in Figures 2B and 2C. If the mature spherules rupture, endospores are released into the infected tissue; each endospore is potentially capable of producing another spherule [2]. *C. immitis* produces an asymptomatic or a self-limited respiratory illness in up to two-thirds of infected persons. The remaining one-third experiences symptoms of an acute respiratory illness and may have chest pain, cough, fever, and malaise. These symptoms typically develop 1 to 4 weeks after exposure, but are non-specific and cannot be distinguished from other respiratory infectious disease. The majority (perhaps 90%) of patients have a clearing of their primary illness without therapy; with clearing of the disease, lifelong immunity is established [7-8]. Based on the above description, the first episode of chest pain in our case could be explained by *C. immitis* infection, however, his lung lesion did not resolve completely.

The current approaches to diagnosing coccidioidomycosis include recovery of *C. immitis* from clinical specimens, detection of specific anti-coccidioidal antibodies in serum or other body fluids, and eliciting dermal delayed-type hypersensitivity (DTH) reactions to coccidioidal antigens.

The definitive diagnosis of coccidioidomycosis is by tissue culture or by demonstration of spherules in tissue with granulomatous inflammation, as in Figures 2A, 2B and 2C. Without histopathological proof, the definitive diagnosis can be made only by culture with additional tests. The most common test is to prepare a formalin extract of the fungus, and determine if it contains a "coccidioides-specific" antigen, but this method takes 2 or more weeks to complete. Now, the DNA probe offers a quicker and easier way to identify *C immitis*.

Several serologic tests are useful in the diagnosis of coccidioidomycosis and for monitoring disease activity. These tests detect precipitin-reacting antigen (IgM) and the complement-fixing antigens (IgG). Positive IgM, which peaks between the first week and 3 months after exposure, indicates primary infection; IgG appears later, and can disappear if the infection clears. The persistent positive IgG in our patient may be due to the persistent existence of *C immitis* in his lung.

Skin testing can also be done, but is not entirely reliable. About 83% of patients who become infected with *C. immitis* develop dermal hypersensitivity to coccidioidal antigens, as manifested by induration to skin testing. A positive

skin test, however, simply confirms the previous exposure and response to *C. immitis,* and is not diagnostic of ongoing infection [2].

The standard treatment for coccidioidomycosis has not yet been defined. This is due to the lack of controlled studies and the broad spectrum of disease manifestations. Management of patients diagnosed with coccidioidomycosis involves defining the extent of infection and assessing host factors that predispose to disease severity [9-10]. Patients with relatively localized acute pulmonary infections and with no risk factors for complications often require only periodic reassessment to demonstrate resolution of their self-limited process. Amphotericin B is often reserved for patients with respiratory failure due to *C. immitis,* or rapidly progressive coccidioidal infections. With other more chronic manifestations of coccidioidomycosis, treatment with fluconazole, itraconazole, or ketoconazole is common. Duration of therapy often ranges from many months to years, and for some patients, chronic suppressive therapy is needed to prevent relapses [4, 11-12]. This patient had received oral fluconazole for 3 months in the beginning, but discontinued the medication himself due to the lack of further chest pain, despite the incomplete resolution of the lung lesion.

Following primary pneumonia, residual pulmonary nodules may develop in 5% to 10% of cases. These nodules may resolve slowly or persist for years and often prompt lung biopsies to exclude malignancy, as in this case [5]. If a nodule is proved to be *C. immitis* infection by noninvasive means or by fine-needle aspiration, specific antifungal therapy or resection is unnecessary [6]. Thus, in the absence of significant immunosuppression, antifungal therapy is not recommended if the lesion is completely resected and the diagnosis is determined by examination of the excised tissue [4-5]. There was no significant immunosuppression in this patient, so, we did not prescribe any further antifungal therapy after the complete resection of the lesion.

In summary, coccidioidomycosis has protean manifestations, and chronic infection may manifest as lung nodules or cavities. With the more frequent tourist and business travel lately, more and more cases will be encountered in non-endemic areas. A high degree of suspicion and a detailed travel history are very important to identify coccidiodomycosis.

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# 球孢子菌病以單一肺結節表現—病例報告及文獻回顧

趙文震　詹明澄　詹以吉*　許正園

球孢子菌病 (Coccidioidomycosis) 是美國西南方沙漠區域常見黴菌感染，可對免疫力正常或不正常的人造成感染，早期臨床症狀通常很輕微，常見為咳嗽和發燒並無特異性表徵，大多數感染不需藥物治療，但少數病人會有全身性的感染，早期診斷及治療對此部分病人相當重要，另外 5% 至 10% 病人感染過後肺部會遺留下一些結節或空洞。我們在此報告一個免疫力正常患者，該病人兩年前曾於美國亞利桑那工作，當時曾因胸痛於該地住院，影像學檢查發現左肺有結節性病灶且經血清學檢查證實為球孢子菌感染，病人症狀經口服抗黴菌藥物治療後改善，此次病患因胸痛復發且影像學檢查仍然發現左肺有一結節性病灶，經手術切除後證實該結節為球孢子菌感染。我們並且回顧文獻，探討球孢子菌病的生活史、臨床表現、診斷及處置。*(胸腔醫學* ***2006; 21: 298-304)***

關鍵詞：球孢子菌病 (coccidioidomycosis)，肺結節 (pulmonary nodule)

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