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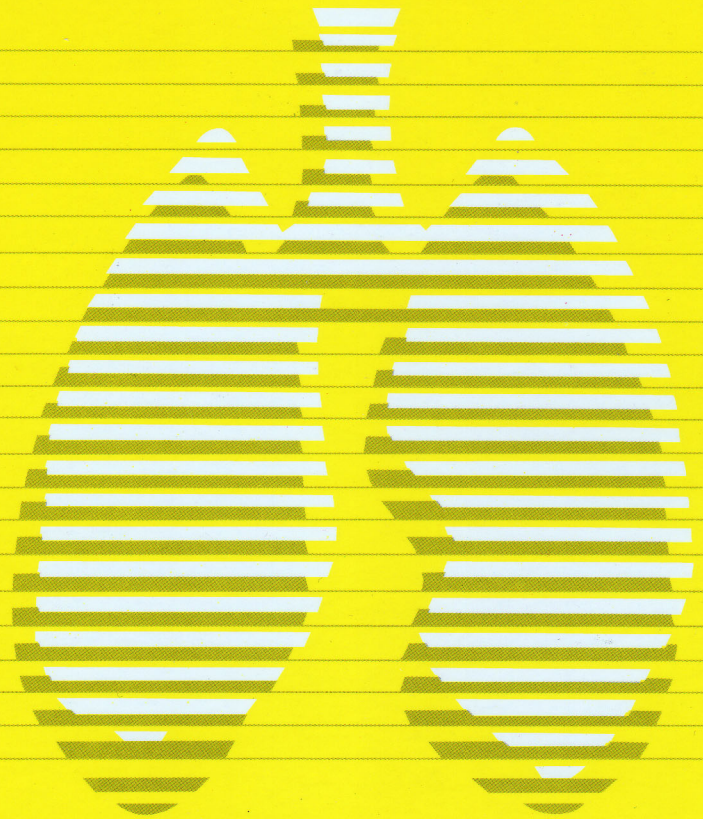

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## 原著



## 病例報告

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# Thoracic Medicine

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## Orginial Articles



## Case Reports

# Comparison of Transbronchial Biopsy and Open Lung Biopsy in Ventilated Patients with Diffuse Pulmonary Infiltrates after Hematopoietic Stem Cell Transplantation

Chen-Yiu Hung, Po-Nan Wang*, Han-Chung Hu, Chung-Chi Huang, Meng-Jer Hsieh, Cheng-Ta Yang, Ying-Hung Tsai**, Kuo-Chin Kao

**Background:** Establishing a specific diagnosis in ventilated patients with diffuse pulmonary infiltration after hematopoietic stem cell transplantation (HSCT) is challenging. The aim of this study was to review and compare our experience with transbronchial biopsy (TBBx) and open lung biopsy (OLB), with a focus on diagnostic yields, the influence of pathological results on altering therapy, and procedure-related complications.

**Patients and Methods:** Data of 20 mechanically ventilated patients with diffuse pulmonary infiltrates receiving lung biopsy (TBBx or OLB) were recorded for analysis. The collected data included general information, pathological results, treatment alterations, complications and clinical outcomes. Characteristics of patients receiving TBBx or OLB were compared using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.

**Results:** Twenty ventilated HSCT patients with diffuse pulmonary infiltrates receiving lung biopsy, including TBBx (N=9) or OLB (N=11), were enrolled. The most frequent pathologic results were diffuse alveolar damage (DAD) in 4 patients, diffuse alveolar hemorrhage (DAH) in 3 patients, aspergillosis in 3 patients, and *Pneumocystis jiroveci* pneumonia (PJP) in 3 patients. The rate of treatment alteration in OLB patients was higher than in TBBx patients, although the difference was not significant (82% versus 56%; $p$=0.34). One of the 11 OLB patients (9%) had subcutaneous emphysema due to chest tube dysfunction. The overall ICU survival rate of the patients receiving lung biopsy was 15% (3/20).

**Conclusion:** TBBx and OLB had a high diagnostic yield rate for some selected ventilated HSCT patients with diffuse pulmonary infiltrates. Patients that underwent OLB had more adequate specimens, more pathological results, and greater rates of treatment alteration than those receiving TBBx, especially after a non-diagnostic BAL examination. The surgical complication rate of the OLB patients was low and acceptable. Further prospective,

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randomized controlled studies are warranted to define the specific role of OLB. ***(Thorac Med 2012; 27: 131-142)***

Key words: transbronchial biopsy (TBBx), open lung biopsy (OLB), hematopoietic stem cell transplantation (HSCT), treatment alteration; complication

## Introduction

Hematopoietic stem cell transplantation (HSCT) has been a successful treatment for many hematological disorders. The toxicity of the conditioning regimen, immunosuppression, and graft-versus-host disease (GVHD) often cause high rates of severe complications and critical illness that require mechanical ventilation in the intensive care unit (ICU) [1-2]. Pulmonary complications account for considerable mortality when associated with respiratory failure after HSCT [3]. A better outcome for these ventilated HSCT patients depends on identifying the cause of the pulmonary infiltrates and giving specific treatment as soon as possible.

Diffuse pulmonary infiltrates of uncertain etiology in HSCT patients present a diagnostic and therapeutic challenge [4-5]. Invasive fungal infections and late viral infections are now the overriding concerns. Bronchoscopy is often requested to evaluate the etiology of respiratory symptoms and chest radiographic abnormalities in these HSCT patients. However, the reported diagnostic yields were highly variable, and their influence on therapeutic decisions and related complications may be multifactorial [4-9]. For this reason, lung biopsy, including transbronchial biopsy (TBBx) or open lung biopsy (OLB), is performed to try to establish an accurate diagnosis in some selected HSCT patients.

The aim of this study was to review our experience with TBBx and OLB in the evaluation of diffuse pulmonary infiltrates in adult HSCT patients with respiratory failure. Particular emphasis was placed on diagnostic yields, the influence of pathological results on alteration of therapy, and procedure-related complications in TBBx patients compared with OLB patients.

## Patients and Methods

### *Patients*

From January 2000 to December 2010, 361 adult patients underwent HSCT at a tertiary care referral center. Sixty-six HSCT patients who were mechanically ventilated and admitted to the ICU were screened during the study period. Only the first admission episode was analyzed for patients with multiple ICU admissions during the study period. Patients that underwent lung biopsy, including TBBx and OLB, and presented with diffuse lung infiltration or ground glass attenuation in high-resolution computed tomography (HRCT) of the chest were included. We excluded patients with hypovolemic shock, cardiogenic shock, pneumonia with focal infiltration and septic shock without lung infiltration on HRCT. Patients with severe thrombocytopenia (<20,000 cell/L), or prolonged prothrombin time-international normalized ratio (PT-INR) or partial thromboplastin time greater than 2 times normal range were also excluded. The local institutional review

board approved this study (IRB no: 99-2134B). A waiver of consent was granted given the retrospective nature of the study.

***Radiological and bronchoalveolar lavage examinations***

All patients who developed diffuse pulmonary infiltration or pulmonary infection by an unknown pathogen received HRCT of the chest on the first day of ICU admission. Flexible fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) was performed after completion of the HRCT of the chest. The location for BAL sampling was selected on the basis of HRCT findings. BAL was performed according to American Thoracic Society guidelines [5] by introducing 200 ml of sterile warm (37$^{o}$C) saline solution into a lung sub-segment and aspirating it back in 4 50-ml aliquots. Each BAL specimen was sent for bacterial, mycobacterial, fungal and virological exam. Specimens were also sent for cytology and iron stain analysis. All 20 patients received BAL examinations first. TBBx was performed immediately after BAL if a noninfectious etiology of the diffuse pulmonary infiltrates, including rapid progression, a relatively symmetric distribution, or ground-glass attenuation in HRCT of the chest, was suspected [10]. OLB was performed 3-4 days later if BAL results showed an uncertain diagnosis or there was a poor clinical response to treatment. The contraindications of TBBx or OLB were severe thrombocytopenia (<20,000 cell/L), PT-INR or partial thromboplastin time greater than 2 times normal, or mean arterial pressure less than 65 mmHg. The decision to perform TBBx or OLB was made by senior intensivists in charge of the ICUs.

***Transbronchial biopsy and open lung biopsy***

TBBx was performed using a flexible fiberoptic bronchoscope introduced into the endotracheal tube through a double swivel connector and wedged in the affected lung segment for imaging. The forceps (FB-19C-1; Olympus Optical Co.) were advanced into the same lung segment as for BAL. From 3 to 5 biopsy specimens, as determined by the operator, were retrieved in the TBBx. OLB was performed in an operating room by a thoracic surgeon after achievement of general anesthesia and through a 7-cm minithoracotomy. The site and number of lung biopsy specimens were determined by the image findings on the HRCT of the chest. Two biopsy specimens, 2 to 3 cm in each margin were usually obtained. Biopsy specimens were swabbed for aerobic and anaerobic bacterial, fungal, and mycobacterial cultures. Sections were routinely stained with hematoxylin and eosin. Acid-fast, Gomori methenamine silver, Gram's stain, or other special stains were added if necessary. Each tissue specimen was cultured and examined by a pulmonary pathologist.

***Data collection***

The medical records of each identified patient were reviewed, and the data were recorded on standardized forms. The collected data included the following: (1) general information (age, gender, date of HSCT, and indication and type of HSCT); (2) acute physiology and chronic health evaluation (APACHE) II score and the sequential organ failure assessment (SOFA) score [11] within the first 24 hours of ICU admission; (3) pathological results of TBBx and OLB; (4) complications of TBBx and OLB, including the development of bleeding, pneumothorax, fever, cardiac arrhythmia, hypoxemia,

hypotension, subcutaneous emphysema, bronchopleural fistula and death within 24 hours of the procedures; (5) clinical outcomes (changes in therapy and ICU survival).

***Definition***

Neutropenia was defined as a neutrophil count of <500 cells/ml lasting more than 10 days. Graft versus host disease (GVHD) was divided into acute and chronic types. Acute GVHD was defined as occurring 2-4 weeks after myeloablative chemotherapy and generally occurring before day 100 [12]. Chronic GVHD was determined with a 0-3-point score (none, mild, moderate, severe) that reflected the clinical effect in any number of different organs, including the skin, liver, eyes, mouth, respiratory tract, and esophagus [12]. The clinical definition of acute respiratory distress syndrome (ARDS) included the acute onset of bilateral pulmonary infiltrates, a ratio of arterial partial pressure of oxygen ($PaO_2$) to fraction of inspired oxygen ($FiO_2$) of 200 mmHg or less, and no evidence of left atrial hypertension [13]. Severe sepsis was defined as sepsis-induced tissue hypo-perfusion or organ dysfunction. Septic shock was defined as sepsis-induced hypotension persisting, despite adequate fluid resuscitation [14].

***Statistical analysis***

Data were analyzed with SPSS 13.0 (SPSS Inc. Chicago, II, USA). The characteristics of HSCT patients requiring ICU with and without TBBx or OLB were compared using the Chi-square test for categorical variables and independent t-test for continuous variables. If the cells of a 2×2 table had an expected count of less than 5, Fisher's Exact Test was used. All tests were 2-tailed, and the data were considered statistically significant if the *p*-value was <0.05.

## Results

Of the 361 patients who underwent HSCT during the study period, 66 had respiratory failure requiring mechanical ventilation and admission to the ICU. Twenty ventilated HSCT patients with diffuse pulmonary infiltrates that had undergone lung biopsy, including TBBx or OLB, were enrolled. Forty-six patients with diffuse pulmonary infiltrates were excluded for the following reasons: severe thrombocytopenia in 2 patients, hypovolemic shock in 4, cardiogenic shock in 4, septic shock without pulmonary infiltrates in 10, and pneumonia with focal pulmonary infiltrates in 26 patients. Transbronchial biopsy was performed in 9 patients and OLB in 11. The duration to lung biopsy after HSCT was within 30 days in 5 patients, 30 to 100 days in 4, and more than 100 days in 11 patients. As for the baseline characteristics of the HSCT patients that had undergone TBBx or OLB, most were young (mean, 29.6 years old), male (70%) and had received allogenic HSCT (85%) (Table 1). High incidences of neutropenia (80%), GVHD (acute and chronic, 85%), ARDS (55%), and severe sepsis and septic shock (40%) were diagnosed at ICU admission. The mean APACHE II score was 22.5 and mean SOFA score was 10.7. None of the above baseline characteristics of the TBBx and OLB patients achieved statistical significance.

All 20 patients underwent BAL for microbiological and cytological examinations before the lung biopsy procedure. All of the BAL examinations of the 9 TBBx patients were negative. For the 11 OLB patients, the BAL examinations were negative in 9 and positive in 2. The BAL fungus culture yielded aspergillosis

**Table 1.** Comparison of Characteristics of Patients with Transbronchial Biopsy and Open Lung Biopsy

| | | Total (N=20) | TBBx (N=9) | OLB (N=11) | *p* value |
|---|---|---|---|---|---|
| Age (year) | | 29.6 ± 1.8 | 30.0 ± 3.2 | 29.9 ± 2.5 | 0.97 |
| Gender | Male | 14 (70%) | 7 (77.8%) | 7 (63.6%) | 0.64 |
| | Female | 6 (30%) | 2 (22.2%) | 4 (36.4%) | |
| HSCT | Allogenic | 17 (85%) | 9 (100%) | 8 (72.7%) | 0.21 |
| | Autologous | 3 (15%) | 0 | 3 (27.3%) | |
| Neutropenia | | 16 (80%) | 6 (66.7%) | 10 (90.9%) | 0.28 |
| GVHD | | 17 (85%) | 7 (77.8%) | 10 (90.9%) | 0.57 |
| Days of ICU admission after HSCT | | 133.9 ± 27.0 | 116.9 ± 33.0 | 143.3 ± 46.8 | 0.65 |
| ARDS | | 11 (55%) | 6 (66.7%) | 5 (45.4%) | 0.40 |
| Severe sepsis or septic shock | | 8 (40%) | 4 (44.4%) | 4 (36.3%) | 1.00 |
| APACHE II score | | 22.5 ± 1.9 | 25.0 ± 2.8 | 20.4 ± 2.6 | 0.25 |
| SOFA score | | 10.7 ± 0.8 | 11.4 ± 1.5 | 10.0 ± 0.8 | 0.42 |
| Positive sputum culture before biopsy | | 7 (35%) | 5 (55.6%) | 2 (18.1%) | 0.15 |

*$p$-value < 0.05

[+] Data represent the mean ± S.D or the number of patients with the ratio in parentheses

HSCT: hematopoietic stem cell transplantation; ICU: intensive care unit; GVHD: graft versus host disease; APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; ARDS: acute respiratory distress syndrome; TBBx: transbronchial biopsy; OLB: open lung biopsy

and the OLB revealed invasive aspergillosis in 1 patient. The BAL microscopy examination with Gomori methenamine silver staining showed *Pneumocystis jiroveci* pneumonia (PJP), and OLB revealed hypersensitivity pneumonitis and PJP in another patient.

With regard to the pathological results of TBBx or OLB, adequate specimens were obtained in 11 of 11 (100%) OLB patients and in 7 of 9 (78%) TBBx patients. Two patients with TBBx had inadequate specimens due to the small size. The most frequent pathologic findings were diffuse alveolar damage (DAD) in 4 OLB patients, diffuse alveolar hemorrhage (DAH) in 3 patients (1 with TBBx and 2 with OLB), aspergillosis in 3 patients (1 with TBBx and 2 with OLB), PJP in 3 patients with OLB and cytomegalovirus (CMV) pneumonia in 2 patients with TBBx (Table 2).

Overall, TBBx and OLB findings led to an alteration of therapy for 14 of 20 patients (70%) (Table 3). The rate of therapy alteration in OLB patients was higher than in TBBx patients, although the difference was not significant (82% versus 56%; $p$=0.34). Of the 5 TBBx patients with a change of therapy, amphotericin B for aspergillosis was added in 1, corticosteroid for DAH and interstitial pneumonitis was added in 2, and ganciclovir for CMV pneumonitis was added in 2. Three of the 9 OLB patients with a change of therapy added co-trimoxazole for PJP, 2 added corticosteroid for DAH, 2 added voriconazole for aspergillosis, 1 added corticosteroid for hypersensitivity pneumonitis, and 1 added corticosteroid for bronchiolitis obliterans. Treatment was not changed for 6 of 20 patients (30%).

No procedure-related complications, such

**Table 2.** Characteristics of Patients, Biopsy Method and Pathologic Result

| Patient | Age | Gender | Underlying disease | Pathologic result | Method |
|---|---|---|---|---|---|
| 1 | 29 | M | CML, accelerated phase | Diffuse alveolar hemorrhage | TBBx |
| 2 | 23 | F | DLBL, stage IIIB | Aspergillosis | TBBx |
| 3 | 43 | M | T-lymphoblastic lymphoma, stage IIIEA | CMV infection | TBBx |
| 4 | 34 | M | CML | Focal alveolar damage, CMV infection | TBBx |
| 5 | 34 | M | CML | Interstitial pneumonitis | TBBx |
| 6 | 25 | M | AML, M2, t(8:21) | Right upper lobe sub-segment small airway obstruction with blood clot | TBBx |
| 7 | 27 | M | AML, M2 | Interstitial lung fibrosis | TBBx |
| 8 | 41 | M | Mantle cell lymphoma, stage IV | Inadequate specimen | TBBx |
| 9 | 18 | M | Hodgkin's disease, stage IIIA | Inadequate specimen | TBBx |
| 10 | 32 | M | CML | Diffuse alveolar damage | OLB |
| 11 | 43 | F | Mycosis fungoides | Diffuse alveolar damage with diffuse alveolar hemorrhage | OLB |
| 12 | 32 | M | CML | Diffuse alveolar damage, diffuse alveolar hemorrhage | OLB |
| 13 | 34 | M | AML, M5a | Diffuse alveolar damage and *Pneumocystis jiroveci* pneumonia | OLB |
| 14 | 28 | M | CML | Aspergillosis | OLB |
| 15 | 33 | M | AML, M2 | Aspergillosis | OLB |
| 16 | 24 | F | AML, M6 | *Pneumocystis jiroveci* pneumonia, hypersensitivity pneumonitis | OLB |
| 17 | 27 | M | ALL, L2 | *Pneumocystis jiroveci* pneumonia | OLB |
| 18 | 23 | F | AML, M1 | Bronchiolitis obliterans | OLB |
| 19 | 28 | M | Hodgkin's disease, stage IIIA | Interstitial pneumonitis and multifocal fibrosis | OLB |
| 20 | 17 | M | ALL T1-lineage, L1 | Acute interstitial fibrosis with alveolar cell hyperplasia | OLB |

M: male; F: female; CML: chronic myeloid leukemia; DLBL: diffuse large B cell lymphoma; AML: acute myeloid leukemia; ALL: acute lymphoid leukemia; CMV: cytomegalovirus; TBBx: trans-bronchial lung biopsy; OLB: open lung biopsy

as bleeding, pneumothorax, fever, cardiac arrhythmia or hypoxemia, occurred in any of the 9 TBBx patients. One of the 11 OLB patients had subcutaneous emphysema after operation due to chest tube dysfunction (1/11, 9%). There were no procedure-related complications, such

**Table 3.** Comparison of Transbronchial Biopsy and Open Lung Biopsy with/without Alteration of Therapy

| | TBBx (N=9) | OLB (N=11) |
|---|---|---|
| No therapy alteration | 4 (44%) | 2 (18%) |
| Therapy alteration | 5 (56%) | 9 (82%) |
| Add antifungal agent | 1 (11%) | 2 (18%) |
| Add corticosteroid | 2 (22%) | 4 (36%) |
| Add co-trimoxazole | 0 (0%) | 3 (27%) |
| Add ganciclovir | 2 (22%) | 0 (0%) |

*Data represent the number of patients with the ratio in parentheses
TBBx: transbronchial biopsy; OLB: open lung biopsy

as hypotension, bleeding, pneumothorax, subcutaneous emphysema or bronchopleural fistula, in the 10 remaining OLB patients.

The overall ICU survival rate of these HSCT patients with diffuse pulmonary infiltrates receiving lung biopsy was 15% (3/20). The 9 TBBx patients died in the ICU. Multiple organ failure was the leading cause of death in 6 patients, followed by septic shock in 2 and ARDS in 1. For the 11 OLB patients, the ICU survival rate was 27% (3/11). The 3 patients that survived were diagnosed as CMV pneumonia, DAH and bronchiolitis obliternas, respectively, and all 3 underwent a change of therapy after OLB.

## Discussion

This retrospective study demonstrated that lung biopsy methods such as TBBx and OLB were acceptable tools in diagnosing diffuse pulmonary infiltrates in some selected HSCT patients with mechanical ventilation. The overall rate of alteration of therapy was 70% in these patients, and the rate of diagnostic yield with treatment alteration was 82% in OLB patients and 56% in TBBx patients. Furthermore, the rate of procedure-related complications was 9% in OLB patients.

Establishing the diagnosis of diffuse pulmonary infiltrates in several infectious and non-infectious diseases that present with similar clinical and radiologic features is challenging, especially in immunocompromised patients [15]. Achieving an earlier diagnosis may potentially improve the outcome of these patients and does contribute information that is useful to clinicians in decision-making [16-17]. It is more difficult for immunocompromised critically ill patients with intubation to get a specific diagnosis without a pathological report [18-20]. Lung biopsy, such as TBBx and OLB, can increase the diagnostic rate, especially in atypical lung infections, by sampling adequate lung tissue, and it can be done rapidly [21]. In this study, TBBx or OLB was performed within 3 days after BAL in the ICU (data not shown), and the pathological results influenced clinical decisions in 16 of 20 patients. Lung biopsy also can identify some diseases such as DAH, hypersensitivity pneumonitis and bronchiolitis obliterans organizing pneumonia, which are more responsive to corticosteroid therapy [19].

With the better prophylaxis against Pneumocystis species, CMV, and fungal infection after HSCT, the etiology of diffuse pulmonary

infiltrates in HSCT patients has changed recently [3]. Bronchoscopy may not be as sensitive as lung biopsy for the diagnosis of other atypical infections and unknown etiologies of interstitial lung disease [19,22-26]. For immunocompromised patients with pulmonary infiltrates, bronchoscopy had a high diagnostic yield [15]. The diagnostic yield of BAL and TBBx was similar (38% versus 38%), and the combined diagnostic yield of BAL and TBBx was higher than that of BAL alone (70% versus 38%, $p<0.001$). The potential advantages of TBBx compared with OLB are that it costs less, allows for repeated sampling, and can be performed under bronchoscopic guidance. However TBBx is limited by the small sample size, sampling errors, and the obtaining of a nonspecific pathological diagnosis. For ARDS patients, OLB was more beneficial in terms of modifying therapy in immunocompromised patients, rather than immunocompetent patients [15,27]. The diagnostic yield of OLB has been estimated to be 46-85% in immunocompromised patients with pulmonary infiltrates [15]. For HSCT patients with pulmonary infiltrates, most diagnoses were obtained by BAL alone, whereas TBBx provided additional specific information in less than 10% of patients [28]. Few studies have evaluated TBBx and OLB in ventilated HSCT patients with pulmonary infiltrates. For HSCT patients without a BAL diagnostic yield, we found that OLB had a tendency to contribute a higher rate of specific diagnoses and alteration of therapy than TBBx (82% versus 56%, $p=0.34$). In one report, 2 patients received OLB after a positive BAL report; 1 had an Aspergillus species infection and OLB confirmed a "proven" rather than "probable" invasive fungal infection [29]. The reason for OLB in the other patient with a PJP infection was the poor clinical response to antibiotic and steroid treatment for 3 days [29].

In immunocompromised patients, BAL was more likely to establish the diagnosis when the pulmonary infiltrate was due to an infectious agent (81%) rather than a non-infectious process (40%) [15]. In addition, surgical lung biopsy provided a diagnosis in most patients (12/17 patients, 71%), and a non-infectious diagnosis was more common than an infectious diagnosis (5/17 patients, 29%) [15]. In HSCT patients with pulmonary infiltrates, surgical lung biopsy also obtained more non-infectious diagnoses (22/27 patients, 81%) than infectious diagnoses (5/27 patients, 19%) [28]. In our study of ventilated HSCT patients with pulmonary infiltrates, both OLB (7/11, 64%) and TBBx (4/9, 44%) patients had more non-infectious diagnoses.

The operative complication rates for OLB ranged from 17-39% in ARDS patients [17]. No instance of prolonged air leak or death was attributed to OLB in 14 selected immunocompromised patients [15]. Few studies have discussed the complication rate of OLB in HSCT patients. In our study, the coagulation profiles of all patients were corrected to keep the platelet count above $50\times10^9$ cells/L, the PT-INR less than 1.5 times normal and partial thromboplastin time within the normal range. Only 1 patient (1/11 patients, 9%) suffered a procedure-related complication of subcutaneous emphysema from OLB. Improvements in operative techniques and postoperative supportive care have made OLB a safer and better tolerated procedure than before [18,30].

Mortality among HSCT patients was not influenced by whether bronchoscopy provided a specific diagnosis and resulted in a change in therapeutic management [15]. Early OLB was found to benefit the diagnosis of interstitial pneumonitis, but not improve the clinical

outcome in immunocompromised patients [31]. In our previous study, the ICU survival rate of immunocompromised early-stage ARDS patients receiving OLB was better than that for immunocompetent patients (71% versus 33%) [10]. However, among the critically ill HSCT patients in this study, the ICU survival rate was 15% for the 11 OLB patients, and 0% for the 9 TBBx patients. Because of the small sample size in both groups, it is difficult to conclude that OLB had a survival benefit greater than TBBx in ventilated HSCT patients with pulmonary infiltrates.

Several limitations of the current study should be considered. First, with the retrospective nature of this study, the relationship between TBBx or OLB and the survival benefit could not be ascertained. However, the finding of a specific diagnosis would permit the institution of a specific therapy, assuming that such a therapy is available. Second, the results of this study cannot be generally applied to all HSCT patients with pulmonary infiltrates. The patients undergoing TBBx or OLB were not randomized and those referred for TBBx or OLB were unlikely to be a representative sample of our HSCT population. The selection bias of patients and clinicians would be expected to increase the possibility of alteration of therapy. Finally, we were unable to decide the accurate sensitivity or specificity of TBBx or OLB due to the lack of a "gold standard" test in this setting. Even OLB cannot identify the etiology of pulmonary infiltrates in every ventilated HSCT patients. Nevertheless, this study can provide useful information for clinicians regarding the significance of TBBx or OLB in this difficult clinical setting. Further large-scale, prospective controlled studies should be undertaken to investigate the benefit of TBBx or OLB in ventilated patients with diffuse pulmonary infiltrates after HSCT.

## Conclusion

In conclusion, this retrospective study demonstrated that TBBx and OLB had a high diagnostic yield rate and an acceptable complication rate for some selected ventilated HSCT patients with diffuse pulmonary infiltrates. Patients who received OLB had more adequate specimens and more pathological results than those undergoing TBBx, especially after a non-diagnostic BAL examination. The rates of treatment alteration were 82% in OLB patients and 56% in TBBx patients. The surgical complication rate of OLB was low and acceptable. Further prospective, randomized controlled studies are warranted to define the specific role of OLB in ventilated HSCT with diffuse pulmonary infiltrates, and to establish the optimal indications for this procedure.

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# 比較經支氣管鏡肺切片及開肺切片在造血幹細胞移植後使用呼吸器病人的研究

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**前言**：造血幹細胞移植後呼吸衰竭常常會造成嚴重的併發症和很高的死亡率。由於這一群病人相對是免疫力低下的族群，造成肺部浸潤的原因常常是多樣性且不易診斷。這個回溯性研究比較經支氣管鏡進行肺切片或開肺切片在這一類病人的病理診斷，治療改變，併發症和預後的分析。

**方法**：這個研究收集了20位因瀰漫性肺部浸潤導致呼吸衰竭進到加護病房的病人接受了經支氣管鏡肺切片或開肺切片。我們記錄下病人基本資料，病理切片結果，治療的改變，併發症和預後的資料，同時利用Fisher's exact test和Mann-Whitney U test做變數分析。

**結果**：瀰漫性肺泡破壞，瀰漫性肺泡出血，麴黴病（Aspergillosis），肺囊蟲肺炎（*Pneumocystis jiroveci* pneumonia），巨形細胞病毒肺炎（CMV pneumonitis）佔了多數病理診斷。開肺切片比經支氣管鏡肺切片有較高的診斷率和治療上的改變（82% versus 56%）。開肺切片只有一位個案有嚴重的皮下氣腫，顯示這個檢查的安全性是可以被接受的。

**結論**：大多數瀰漫性肺部浸潤使用呼吸器的病人在切片之後得到一個特定的診斷並且有治療的改變。特別是在做完支氣管沖洗術的病人若沒有確定診斷，開肺切片比經支氣管鏡肺切片有較高的診斷率和治療上的改變。這篇研究顯示開肺切片都可以得到適當的檢體與支氣管鏡肺切片都有高的安全性。未來在評估這一類病人，開肺切片的角色仍需進一步前瞻性研究。*(胸腔醫學* ***2012; 27: 131-142)***

關鍵詞：經支氣管鏡肺切片，開肺切片，造血幹細胞移植，治療改變，併發症

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# $FEV_1$ Response to Bronchodilation with HFA Fenoterol and CFC Fenoterol by Inhalation

Wen-Kuei Chang, Ching-Lung Liu, Ming-Jen Peng

**Objectives:** Chlorofluorocarbon metered-dose inhalers (CFC-MDIs) have been reformulated, and now, the non-ozone-depleting propellant, hydrofluoroalkane, is used in metered-dose inhalers (HFA-MDIs). The aim of the study was to evaluate the bronchodilation response of the 2 products.

**Methods:** We assessed bronchodilation by measuring $FEV_1$ before and after inhalation of fenoterol CFC-MDI 400 mcg (2 puffs), fenoterol HFA-MDI 200 mcg (2 puffs) or fenoterol HFA-MDI 400 mcg (4 puffs) delivered using a spacer.

**Results:** Of the 3449 outpatients tested, those who had a positive bronchodilator result, defined as $\Delta FEV_1$ >12% and 200 mL, were enrolled in the study. The percentage of positive bronchodilation results in the fenoterol CFC-MDI (400 mcg) group was 19.0% (108/569), that in the fenoterol HFA-MDI (200 mcg) group was 14.4% (138/957) and in the HFA-MDI (400 mcg) group was 15.9% (148/928). $FEV_1$ responses to bronchodilation (absolute $\Delta FEV_1$) were similar between the fenoterol CFC-MDI (400 mcg) group, fenoterol HFA-MDI (400 mcg) group, and fenoterol HFA-MDI (400 mcg) group (380.7 ± 176.5 mL vs. 344.1 ± 132.0 mL vs. 340.2 ± 142.6 mL, $p$=0.072).

**Conclusions:** This study shows that fenoterol HFA-MDI and fenoterol CFC-MDI provide a comparable bronchodilation response. Inhaled fenoterol 400 mcg is better than fenoterol 200 mcg for testing the reversibility of airflow limitation. ***(Thorac Med 2012; 27: 143-149)***

Key words: bronchodilation, chlorofluorocarbon (CFC), fenoterol, metered-dose inhaler (MDI), hydrofluoroalkane (HFA)

## Introduction

It is well-known that chlorofluorocarbons (CFCs) used as propellants in metered-dose inhalers (MDIs) deplete stratospheric ozone and result in serious public health concerns. CFC fenoterol has been reformulated, and now, the non-ozone-depleting propellant, hydrofluoroalkane (HFA), is used [1]. Of the currently marketed bronchodilator products, CFC-containing MDIs produce extremely forceful and cold plumes, while several HFA-containing MDIs produce much softer and warmer plumes. Furthermore, HFA-containing MDIs that have a low spray force also have lower throat and higher lung deposition [2]. Some previous stud-

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ies concerning the clinical response to these 2 propellants' formulation showed an equivalent effect [3-5].

Spirometry and the bronchodilator test are essential for the diagnosis and severity staging of obstructive lung diseases. The rapid-acting bronchodilator, for example, 200-400 mcg inhaled fenoterol [6], is widely used to test the reversibility of airflow limitation [7]. In December 2009, we replaced fenoterol CFC-MDI (Berotec, 200 mcg/puff; Boehringer Ingelheim) 400 mcg (2 puffs) with fenoterol HFA-MDI (Berotec N, 100 mcg/puff; Boehringer Ingelheim) 200 mcg (2 puffs) for bronchodilator testing. The result of a comparison of the positive rates of the tests between 2008 and 2009 showed a decrease in the positive rate (19.0% vs. 14.4%). After thorough discussion with colleagues, an inadequate fenoterol HFA-MDI dosage was suspected to be the cause of this phenomenon. Therefore, we decided to change the dosage of fenoterol HFA-MDI to 400 mcg (4 puffs) beginning in December 2010. We hypothesized that the forced expiratory volume in 1 second ($FEV_1$) response to bronchodilator inhalation with each of fenoterol HFA-MDI and fenoterol CFC-MDI would be different. The aim of this study was to evaluate the effect of the bronchodilation response by comparing different bronchodilator spirometric data.

## Materials and Methods

### *Patients*

Patients eligible for enrollment were those who had undergone bronchodilator spirometry in an outpatient setting at a local teaching hospital in Taitung, Taiwan, and at a tertiary care medical center in Tamsui, Taiwan, from January to November in 2008, 2009 and 2010. Patients were excluded if they were less than 18 years of age or had a poor performance in pulmonary function testing (peak expiratory flow (PEF) <40% of predicted).

### *Pulmonary function tests and bronchodilator test*

Pulmonary function measurements were performed according to the American Thoracic Society guidelines [8-10]. No bronchodilators, neither β-adrenergic agonists nor theophylline, were administered within 8 hours before the study. All patients also underwent spirometry and lung volume measurements using either the nitrogen washout method (Vmax 22; SensorMedics; Yorba Linda, CA) in the Taitung hospital or a body plethysmograph (Vmax 22 and Autobox 6200; SensorMedics; Yorba Linda, CA) in the Tamsui hospital. Predicted and percent-predicted values were calculated for $FEV_1$, FVC, and the $FEV_1$/FVC ratio using the reference values recommended by Knudson *et al*. [11].

Bronchodilator reversibility tests were performed based on the largest $FEV_1$ and forced vital capacity (FVC) from the best of 3 spirograms recorded on a single-breath bellows spirometer. All subjects then inhaled a short-acting bronchodilator, fenoterol, using with a spacer, guided by a well-trained technician [12]. Spirometry was performed and repeated after a 15 to 20-minute delay. A positive bronchodilator response was defined as improvement of the $FEV_1$ by >12% and 200 mL over baseline during a single testing session. Changes in $FEV_1$ of >10% but <12% and >100 ml but <200 ml were considered equivocal. Any results less than that were considered a negative response. Subjects with a positive bronchodilator response constituted our study population.

### *Study design*

The study was designed to compare the bronchodilator response to 3 different methods of delivery based on changes from baseline $FEV_1$. We collected data retrospectively on subjects evaluated from January through November using fenoterol CFC-MDI (Berotec®, 200 mcg/puff; Boehringer Ingelheim) 400 mcg (2 puffs) in 2008 and fenoterol HFA-MDI (Berotec® N, 100 mcg/puff; Boehringer Ingelheim) 200 mcg (2 puffs) in 2009 (Figure 1). Beginning in January 2010, the subjects were asked to use fenoterol HFA-MDI (Berotec® N, 100 mcg/puff; Boehringer Ingelheim) 400 mcg (4 puffs) for bronchodilator testing. The 3 delivery methods compared in the study thus comprised fenoterol CFC-MDI (400 mcg), HFA-MDI (200 mcg), and HFA-MDI (400 mcg).

### *Statistical Analysis*

All data are expressed as mean ± standard deviation. Changes in $FEV_1$ are expressed as absolute and percent changes from baseline. Univariate analysis was conducted using the Pearson $\chi^2$ test for categorical variables and the Mann-Whitney U test for continuous variables. Analysis of variance, followed by Fisher's protected least significant difference *post hoc* test and ANOVA, was used to compare differences among the 3 different delivery method groups. A $p$ value $<0.05$ was considered statistically significant. Differences between groups were tabulated and analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

## Results

A total of 3449 patients underwent pulmo-

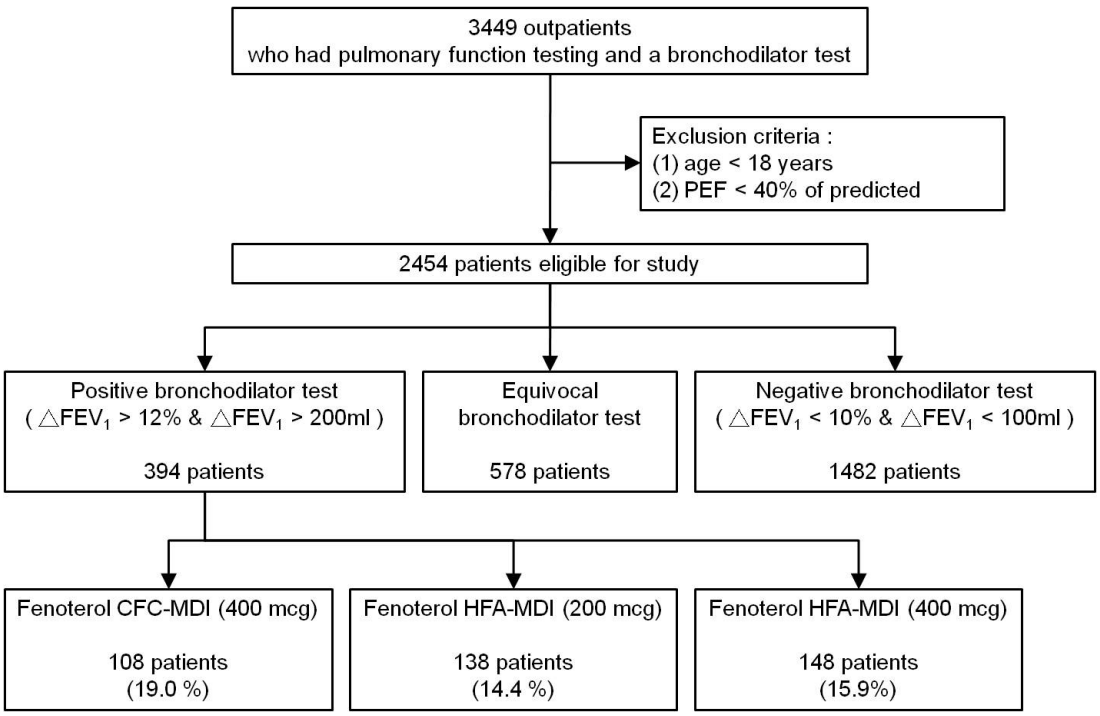


**Fig. 1.** Flow chart of the study population. CFC: chlorofluorocarbon; HFA: hydrofluoroalkane; MDI: metered-dose inhaler; PEF: peak expiratory flow; $\Delta FEV_1$: changes in forced expiratory volume in 1 second.

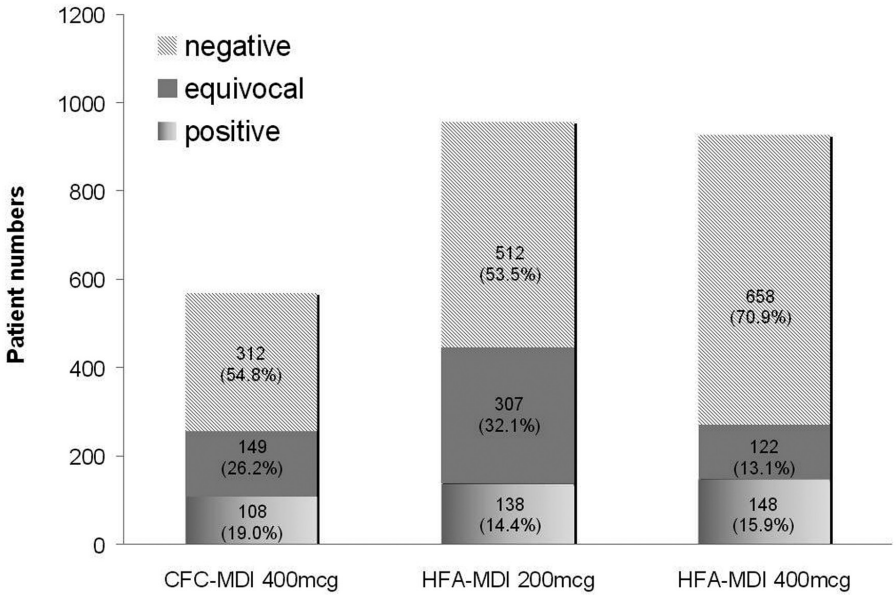


**Fig. 2.** Bronchodilator responses (positive, equivocal, and negative) of subjects inhaling 3 different bronchodilators.

nary function measurements with bronchodilator tests during the study period, and 2454 patients were eligible for the study (Figure 1). Of these eligible patients, the response to bronchodilators was positive in 108/569 (19.0%) individuals in 2008, 138/957 (14.4%) in 2009, and 148/928 (15.9%) in 2010; these then constituted the study population (Figure 2). The positive bronchodilator response rate, using fenoterol HFA-MDI (200 mcg), was significantly decreased in 2009. The equivocal response rate, however, showed an increase in 2009 (32.1%, 307/957) when compared to 2008 (26.2%, 149/569) and 2010 (13.1%, 122/928) (Figure 2).

Demographic and baseline clinical characteristics (Table 1) showed that there were no statistically significant differences between fenoterol CFC-MDI (400 mcg), HFA-MDI (200 mcg), and HFA-MDI (400 mcg) in terms of age, gender, pre-dose $FEV_1$, and post-dose $FEV_1$. However, statistically significant differences were found between fenoterol CFC-MDI (400 mcg), HFA-MDI (200 mcg), and HFA-MDI (400 mcg) in FEV1/FVC ratio (pre-dose: 67.9 ± 12.2% vs. 67.8 ± 12.8% vs. 63.2 ± 11.8%, $p$=0.002; post-dose: 74.0 ± 11.3% vs. 72.9 ± 12.3% vs. 68.1 ± 12.3%, $p$<0.001) (Table 1).

Subjects who used fenoterol CFC-MDI (400 mcg) showed no significant differences in bronchodilation response when compared with those using HFA-MDI (200 mcg) and HFA-MDI (400 mcg) ($\Delta FEV_1$: 380.7 ± 176.5 mL vs. 344.1 ± 132.0 mL vs. 340.2 ± 142.6 mL, $p$=0.072) (Table 1).

## Discussion

This study demonstrated that the bronchodilator response to inhaled fenoterol HFA-MDI is equivalent to that of fenoterol CFC-MDI in terms of $FEV_1$ changes in response to bronchodilation. The only difference we found

**Table 1.** Patient characteristics, baseline values and bronchodilator response of the study population (n = 394) with a positive bronchodilator test.

| | Fenoterol CFC-MDI 400 mcg (N = 108) | Fenoterol HFA-MDI 200 mcg (N = 138) | Fenoterol HFA-MDI 400 mcg (N = 148) | *p* value |
|---|---|---|---|---|
| Male / Woman, n | 60 / 48 | 73 / 65 | 100 / 48 | 0.058 |
| Age, yr | 52.9 ± 17.7 | 52.0 ± 17.3 | 55.5 ± 18.0 | 0.219 |
| Height, cm | 161.9 ± 9.0 | 162.7 ± 8.4 | 163.1 ± 8.2 | 0.501 |
| Weight, kg | 66.0 ± 15.0 | 66.9 ± 13.9 | 69.0 ± 16.6 | 0.253 |
| Pre-dose $FEV_1$, % | 67.1 ± 17.1 | 66.6 ± 16.4 | 66.9 ± 15.8 | 0.981 |
| Pre-dose $FEV_1$/FVC, % | 67.9 ± 12.2 | 67.8 ± 12.8 | 63.2 ± 11.8$^{+\#}$ | 0.002* |
| Post-dose $FEV_1$, % | 81.7 ± 18.9 | 79.6 ± 18.5 | 79.8 ± 17.8 | 0.631 |
| Post-dose $FEV_1$/FVC, % | 74.0 ± 11.3 | 72.9 ± 12.3 | 68.1 ± 12.3$^{+\#}$ | < 0.001* |
| Bronchodilation responses | | | | |
| $\Delta FEV_1$, ml | 380.7 ± 176.5 | 344.1 ± 132.0 | 340.2 ± 142.6 | 0.072 |

Data are presented as mean ± SD. CFC = chlorofluorocarbon; $FEV_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity; HFA = hydrofluoroalkane; MDI = metered dose inhaler.

* $p<0.05$ was considered significant.

$^{+}$ $p<0.01$ compared to fenoterol CFC-MDI 400 mcg group.

$^{\#}$ $p<0.01$ compared to fenoterol HFA-MDI 200 mcg group.

among our groups was that fenoterol HFA-MDI (200 mcg) resulted in a lower bronchodilation response rate in bronchodilator testing. This suggests that an inadequate fenoterol HFA-MDI dosage might decrease potential bronchodilation. For bronchodilation assessment, inhaled fenoterol HFA-MDI 400 mcg is better than HFA-MDI 200 mcg to test the reversibility of airflow limitation [13].

The modern HFA-MDIs, e.g., Proventil-HFA, have a lower initial spray velocity, which could also be the reason for the smaller plume in the mouth. A previous study showed that a salbutamol/HFA formula had a lower oral deposition (56%) but a higher lung deposition (24%) at an inspiration flow of 30 L/min, but a salbutamol/CFC formula showed a higher deposition in the oropharyngeal airway (78%) and a 16% deposition in the lung [14]. However, the improvement in lung deposition did not correlate closely with the increase in bronchodilation. In addition, the threshold for a short-acting $\beta_2$-agonist to trigger positive bronchodilation might be individually different. Because of these possibilities, we changed the dosage of HFA fenoterol from 200 mcg to 400 mcg, and the positive rate of the bronchodilator test then increased from 2009 to 2010. Thus, the present findings of acute reversibility tests in the laboratory cannot be used to predict the clinical benefit of therapeutic interventions; we suggest using 400 mcg fenoterol HFA-MDI for assessing bronchodilation, and more reversibility will be detected.

The significantly lower pre-dose $FEV_1$/FVC and lower post-dose $FEV_1$/FVC among patients in 2010 who received bronchodilator spirometry via fenoterol HFA-MDI 400 mcg might suggest that the patients also had more severe airway obstruction. This could be the reason why the

positive rate in the HFA-MDI 400 mcg group was lower than that in the CFC-MDI 400 mcg group. The higher equivocal rate in the HFA-MDI 200 mcg group, compared with equivocal rates in 2008 and 2010, may be related to the lower detection rate of airway reversibility in the HFA-MDI 200 mcg group.

The limitation of this study may be the differences in populations during these 3 years, which may have resulted in a bias of baseline obstructive lung defects and other airway diseases. The difference in climate between Tamsui and Taitung may also have contributed to the unexpected effect of the results of bronchodilator spirometry.

In conclusion, this study has shown that subjects that inhaled 200 or 400 mcg fenoterol, HFA-MDI and CFC-MDI had comparable bronchodilation responses. However, an inadequate HFA fenoterol dosage may limit bronchodilation in some patients, and result in decreasing positive rates in the bronchodilator test. Our results suggest that inhaled fenoterol HFA-MDI 400 mcg is better than HFA-MDI 200 mcg in testing the reversibility of airflow limitation.

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# 吸入 HFA Fenoterol 和 CFC Fenoterol 引起 $FEV_1$ 改變及支氣管擴張作用

張文魁　劉景隆　彭明仁

**前言**：Fenoterol CFC metered-dose inhalers (CFC-MDIs) 已被換成不會耗竭臭氧的Fenoterol hydrofluoroalkane metered-dose inhalers (HFA-MDIs)。本研究的目的便在於評估兩種劑型對於支氣管擴張的反應。

**方法**：我們以吸入Fenoterol CFC-MDI 400 mcg, Fenoterol HFA-MDI 200 mcg, Fenoterol HFA-MDI 400 mcg 前後$FEV_1$的改變來評估支氣管擴張的反應。

**結果**：在3449位接受檢查的病患中，對支氣管擴張測試結果呈陽性 ($FEV_1$改變 >12% 且 >200 ml) 者即納入本研究中。Fenoterol CFC-MDI 400 mcg組的支氣管擴張測試陽性率為19.0% (108/569)，fenoterol HFA-MDI 200 mcg組的陽性率為14.4% (138/957)，fenoterol HFA-MDI 400 mcg組的陽性率為15.9% (148/928)。支氣管擴張對於$FEV_1$的影響在CFC-MDI 400 mcg組、HFA-MDI 200 mcg組、HFA-MDI 400 mcg組之間的結果相當 (380.7 ± 176.5 mL vs. 344.1 ± 132.0 mL vs. 340.2 ± 142.6 mL, $p$=0.072 )。

**結論**：HFA Fenoterol及CFC Fenoterol對於支氣管擴張的效果相當。吸入性fenoterol 400 mcg較fenoterol 200 mcg更適合用於測試氣流限制的可逆性。*(胸腔醫學* ***2012; 27: 143-149)***

關鍵詞：支氣管擴張，chlorofluorocarbon (CFC), fenoterol, metered-dose inhaler (MDI), hydrofluroalkane (HFA)

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# Comparison of Abrams and Tru-cut Needle Biopsies in Diagnosing Pleural Effusion in an Area with a High Prevalence of Tuberculosis

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You-Lung Chang, Chao-En Huang

There are only a limited number of reports comparing the Abrams needle with the Tru-cut needle in diagnosing pleural effusion of an undetermined etiology. This retrospective study aimed to investigate whether ultrasound-assisted Tru-cut biopsy is superior to standard Abrams needle pleural biopsy, especially in an area with a high prevalence of tuberculosis. Of 193 patients with pleural effusion of an undetermined etiology after initial thoracentesis, 116 received Abrams needle biopsy and 77 underwent ultrasound-assisted Tru-cut biopsy. The results of both biopsy procedures were compared. There were no immediate or late complications among the patients, except 1 in the Tru-cut group who had minimal pneumothorax. The size of the specimen obtained by the Abrams needle was significantly larger than that from the Tru-cut needle (34 vs. 5 $mm^3$, $p<0.001$). There was no difference in the sensitivity of diagnosing tuberculous pleurisy (56% vs. 53%, $p=0.723$) and malignancy (47% vs. 31%, $p=0.312$) between the 2 biopsy procedures. However, the rate of diagnosis of tuberculous pleurisy was higher using the Abrams needle than by Tru-cut biopsy when tissue culture was done (79% vs. 53%, $p=0.027$). In conclusion, both Abrams needle and ultrasound-assisted Tru-cut needle pleural biopsies are useful in diagnosing patients with pleural effusions of undetermined etiology with minimal complications. Abrams needle biopsy is more likely to obtain a large amount of pleural tissue and has a higher TB culture rate, so it should be the choice for closed biopsy in diagnosing pleural tuberculosis. ***(Thorac Med 2012; 27: 150-158)***

Key words: Abrams needle biopsy, Tru-cut needle biopsy, undetermined pleural effusion, malignancy, tuberculosis

## Introduction

Pleural effusion is frequently encountered in clinical practice and usually results in dyspnea or chest pain. For most patients, the cause can be determined by a detailed history, physical examination, and laboratory pleural fluid analysis [1]. Nevertheless, some exudative

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pleural effusions remain undiagnosed after initial thoracentesis and pleural fluid analysis. Pleural biopsy is then indicated for diagnosis. In the past 5 decades, Abrams needle biopsy has been the most widely used procedure [2]. Since it is relatively safe, inexpensive, and easily performed, it is considered the standard tool in obtaining pleural tissue for examination.

Tru-cut needle biopsy is another frequently used procedure in clinical practice. When used with ultrasound guidance, it is considered to be better than the Abrams needle in obtaining pleural tissue for determining the cause of pleural effusion [3-5]. However, reports comparing the Tru-cut needle biopsy with the Abrams needle biopsy in diagnosing pleural effusion of undetermined etiology (PEUE) are very limited, particularly in areas with a high prevalence of tuberculosis (TB), such as Southeast Asia.

This study was conducted in an area with a high TB prevalence to investigate whether the diagnostic yield of ultrasound-assisted Tru-cut biopsy is superior to that of Abrams needle biopsy in patients with PEUE after initial thoracentesis.

## Materials and Methods

### *Patients*

All patients aged ≥17 years who presented to the hospital with pleural effusion between July 2006 and March 2009 were considered as possible candidates for this retrospective study. The patients with pleural effusion underwent diagnostic thoracentesis after informed consent was given. Those with exudative pleural effusion but without a definite diagnosis after initial pleural fluid and cytology analysis were enrolled. Exudative pleural effusion was defined as a pleural/serum protein ratio >0.5, a pleural/serum lactate dehydrogenase (LDH) ratio >0.6, or pleural LDH >2/3 of the upper normal limit of plasma (211 U/L). After chart review, 193 patients were enrolled. The E-Da Hospital Research Ethics Committee approved the study.

### *Biopsy procedures*

Before the biopsy procedures, all patients were examined with a linear, convex and sector ultrasound transducer with a frequency of 3.5-5.0 MHz (model SSD 63, Aloka, Tokyo, Japan) to determine the maximal parietal pleural thickness and amount of pleural effusion. The patients were subdivided into 2 groups based on the parietal pleural thickness: those with <5 mm and those with ≥5 mm. In addition, the amount of pleural effusion was defined as small if the effusion was within 1 imaging field of the transducer, moderate if the effusion exceeded 1 but was limited to 2 imaging fields, and large if it exceeded 2 imaging fields [6].

Abrams needle biopsies were performed after local anesthesia as previously described [2]. The biopsy point chosen depended on the location of the maximal amount of pleural effusion as shown by sonography. Three to 6 biopsy specimens were obtained and immediately fixed in formalin for later histological analysis. Tru-cut biopsies were performed with an 18-gauge Tru-cut needle (Super Cor™, Angiotech, Gainesville, Florida, USA) after sonographic identification of the maximal thickness and location of a safe area. The same number of biopsy specimens were obtained and processed identically to those obtained by Abrams needle biopsies. Only 110 patients had specimens for microbiologic investigation.

Experienced physicians, all of whom had at least 3 years of experience in performing the respective procedures, performed the biopsies.

The patients underwent either 1 of the 2 biopsy procedures in accordance with the duty list of the physicians. The tissue specimens were processed by experienced pathologists who were blinded to the biopsy procedure. They measured the tissue specimens and classified them as malignant, tuberculous, or other benign disease. Patients with an equivocal diagnosis were followed up for at least 6 months and the final diagnosis was made based on the clinical course and other laboratory data.

### *Statistical analysis*

Data normality was assessed using the Shapiro-Wilk test. Normally distributed numerical variables are presented as mean ± SD, while skewed data are expressed by median values with an inter-quartile range (IQR; 25% and 75%). Between-group comparisons of continuous data were performed using Student's *t* test or Wilcoxon rank-sum test, as appropriate. Categorical variables were compared using Fisher's exact or the Chi-square test. A 2-sided $p<0.05$ was considered statistically significant. Statistical analyses were performed with commercially available software (SPSS version 12.0; SPSS Inc, Chicago, IL, USA).

## Results

Of the 193 patients with PEUE after initial pleural fluid analysis, 116 underwent Abrams needle biopsy and 77, Tru-cut biopsy. Patient characteristics are shown in Table 1. There was a significant difference in the amount of pleural effusion and pleural thickness between the 2 groups. The Tru-cut biopsy group had larger amounts of pleural effusion and more patients with a pleural thickness ≥5 mm.

The final diagnoses of all patients are shown in Table 2. Those with tuberculous pleurisy not confirmed by biopsies were diagnosed by follow-up sputum and pleural fluid and tissue cultures, as well as compatible clinical features that are associated with successful anti-TB treatment. Those with malignant pleural effusion not confirmed by the biopsy were subsequently diagnosed by computed tomography (CT)-guided biopsy, bronchoscopic examination in association with endobronchial biopsy, or repetitive pleural fluid cytology analyses. As such, 97 patients were diagnosed as having tuberculous pleurisy; 64 of them had specimens for tuberculous culture, and 47 patients were diagnosed as having malignant pleural effusion.

**Table 1.** Patient characteristics

| | Abrams needle biopsy (n=116) | Tru-cut needle biopsy (n=77) | *p* value |
|---|---|---|---|
| Age (years) | 67.0 ± 14.4 | 67.8 ± 14.6 | 0.706 |
| Male gender (%) | 67.2 | 75.3 | 0.228 |
| Pleural effusion amount | | | 0.013 |
| Small (%) | 21 | 12 | |
| Moderate (%) | 49 | 38 | |
| Large (%) | 30 | 50 | |
| Pleural thickness ≥ 5 mm (%) | 38.3 | 50.6 | 0.049 |

Data are expressed as mean ± SD and %.

Seventeen patients with an unknown etiology were followed up for more than 6 months and no malignancy or TB was discovered.

The results of Abrams needle and Tru-cut needle biopsies in relation to the final diagnoses and size of the biopsy specimen are shown in Table 3. The pleural biopsy specimens obtained by Abrams needle biopsy provided a histological diagnosis in 48 of 91 patients (52.8%), while the Tru-cut biopsy specimens provided a histological diagnosis in 25 of 53 patients (47.2%).The size of the specimen was significantly larger in the Abrams needle group (34 vs. 5 $mm^3$). However, the diagnostic yield between the 2 groups was not significantly different. There was no significant difference in the diagnostic sensitivity for tuberculous pleurisy and malignant pleurisy between the 2 procedures.

The sensitivity, specificity, and predictive values of the Abrams needle and Tru-cut needle pleural biopsies are shown in Table 4. The initial diagnostic rate between the 2 biopsy groups was not statistically different.

In half of the patients, the PEUE was due to TB infection. Sixty-four of the 97 confirmed tuberculous pleurisy patients had pleural biopsy with tissue culture (34 in the Abrams needle group and 30 in the Tru-cut biopsy group). The characteristics of these 64 patients are shown in Table 5. There were no significant differences in the amount of pleural effusion and pleural thickness between the 2 groups.

The size of the specimen and diagnostic yield of the patients with tissue and pleural fluid culture are shown in Table 6. Of these patients, 62 had pleural fluid cultures, with 30% positive for mycobacterium. In the Abrams needle group, 15 of 34 patients with tuberculous pleu-

**Table 2.** Final diagnoses of all patients with pleural effusion of undetermined etiology

| | Abrams needle biopsy | Tru-cut needle biopsy |
|---|---|---|
| Malignant neoplasm | 34 | 13 |
| Tuberculous pleurisy | 57 | 40 |
| Pneumonia | 5 | 4 |
| Congestive heart failure | 2 | 4 |
| Chronic empyema | 1 | 3 |
| Liver cirrhosis | 4 | 2 |
| Chronic renal failure | 5 | 2 |
| Unknown etiology | 8 | 9 |

Diagnoses are based on biopsy findings and more than 12 months of clinical follow-up.

**Table 3.** Differences in the size of the biopsy specimen and initial histologic diagnosis of tuberculous pleurisy and malignancy

| | Abrams needle biopsy | Tru-cut needle biopsy | *p* value |
|---|---|---|---|
| Size of specimen ($mm^3$) | 34 (12-60) | 5 (3-8) | <0.001 |
| Tuberculous pleurisy | 32/57 (56%) | 21/40 (53%) | 0.723 |
| Malignancy | 16/34 (47%) | 4/13 (31%) | 0.312 |

Data are expressed as mediam (inter-quartile range) for size of specimen. For tuberculous pleurisy and malignancy, data are presented as number diagnosed histologically/number of final diagnosis.

**Table 4.** Sensitivity, specificity, and predictive values for the initial histological diagnosis of tuberculous pleurisy and malignancy

| | Abrams needle biopsy | | Tru-cut needle biopsy | |
|---|---|---|---|---|
| | Tuberculous pleurisy | Malignancy | Tuberculous pleurisy | Malignancy |
| Sensitivity (%) | 56 | 47 | 53 | 31 |
| Specificity (%) | 100 | 100 | 100 | 100 |
| PPV (%) | 100 | 100 | 100 | 100 |
| NPV (%) | 70 | 82 | 66 | 88 |

Abbreviations: PPV, positive predictive value; NPV, negative predictive value

**Table 5.** Characteristics of tuberculosis patients with tissue culture (n=64)

| | Abrams needle biopsy (n=34) | Tru-cut needle biopsy (n=30) | *p* value |
|---|---|---|---|
| Age (years) | 67.8 ± 12.6 | 68.6 ± 14.0 | 0.802 |
| Male gender (%) | 79.4 | 80.0 | 0.95 |
| Pleural effusion amount | | | 0.893 |
| Small (%) | 18 | 13 | |
| Moderate (%) | 44 | 47 | |
| Large (%) | 38 | 40 | |
| Pleural thickness ≥ 5 mm (%) | 38.2 | 23.3 | 0.199 |

Data are expressed as mean ± SD and %.

**Table 6.** Size of biopsy specimen and diagnostic yield of tuberculous pleurisy in patients with tissue (n=64) and effusion (n=62) cultures

| | Abrams needle biopsy (n=34) | Tru-cut needle biopsy (n=30) | *p* value |
|---|---|---|---|
| Size of specimen ($mm^3$) | 24 (8-48) | 4 (3-7) | <0.001 |
| Effusion culture | 10/32 (31%) | 8/30 (27%) | 0.691 |
| Tissue culture | 15/34 (44%) | 5/30 (17%) | 0.018 |
| Histological tuberculosis | 23/34 (68%) | 16/30 (53%) | 0.242 |
| Histology/tissue/effusion culture | 28/32 (88%) | 19/30 (63%) | 0.038 |

Data are expressed as mediam (inter-quartile range) for size of specimen. Tuberculous pleurisy data are presented as number diagnosed histologically/number of final diagnoses.

ral effusion had positive tissue culture, as did 5 of 30 patients with tuberculous pleural effusion in the Tru-cut biopsy group. There was a significant difference in the tissue culture rate between the 2 groups.

By combining the tissue culture and histological examination, a diagnosis was made in 67% of patients with tuberculous pleurisy (79% of the Abrams needle biopsy group and 53% of the Tru-cut biopsy group). By combining the tissue and pleural fluid culture, the diagnostic yield was 28 of 32 (88%) in the Abrams needle group and 19 of 30 (63%) in the Tru-cut group. There were no immediate or late complications

related to the biopsy procedures, except 1 Tru-cut biopsy patient who had minimal pneumothorax.

## Discussion

The present study demonstrates that both ultrasound-assisted Tru-cut pleural biopsy and Abrams needle pleural biopsy are useful tools for diagnosing tuberculous and malignant pleural effusions. Both procedures can be safely performed by experienced personnel. In addition, although ultrasound-assisted Tru-cut biopsy yields a smaller tissue sample size, it is not inferior to the Abrams needle biopsy in diagnosing PEUE. However, Abrams needle biopsy provides a higher tissue culture rate ($p$=0.018). Combined with pathology and tissue culture, the Abrams needle biopsy is superior to the Tru-cut biopsy in diagnosing tuberculous pleural effusion ($p$=0.027).

Pleural biopsy is usually indicated in patients with PEUE after initial non-diagnostic pleural fluid analysis. Of the number of techniques currently available for pleural biopsy, Abrams needle biopsy is the most frequently used. It has been demonstrated to have a high diagnostic yield for malignant disease and tuberculous pleural effusion. On the other hand, image-guided Tru-cut biopsy and thoracoscopy have been demonstrated to be just as effective in determining the cause of pleural effusion [7-9]. There is currently no pleural biopsy procedure that is considered to be the standard.

Previous studies have shown that closed pleural biopsy using an Abrams needle is able to achieve a diagnosis in 57-80% of tuberculous pleural effusions and in 40-75% of malignancies [10-11]. However, Chang *et al*. [4] showed that only 20% of tuberculous pleurisy can be determined by Abrams needle biopsy, while 86% can be achieved by Tru-cut needle biopsy, suggesting that Tru-cut needle biopsy is superior. McLeod *et al*. [3], in a head-to-head comparison study of Abrams needle and Tru-cut needle biopsies in obtaining pleural specimens, concluded that the Tru-cut needle biopsy is particularly useful in the presence of thickened pleura. As such, Tru-cut needle biopsy seems superior to Abrams needle biopsy with regard to determining the etiology of pleural effusions.

Results obtained in a closed pleural biopsy with an Abrams needle may be operator-dependent. Chakrabarti *et al*. [11] demonstrated that Abrams needle biopsies reveal the causes of pleural effusions with a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 38%, 100%, 100%, and 51%, respectively. Christopher *et al*. [5] showed that when a blind pleural biopsy is obtained using a Tru-cut needle, the sensitivity for diagnosing tuberculous pleurisy is 75%, and that for malignant effusion is 71%.

In the current study, the diagnostic sensitivities for tuberculous pleurisy and malignancy were compatible with those of previous reports. The combination of pleural fluid culture and closed pleural biopsy with Abrams needles and tissue culture may be adequate to establish a diagnosis of pleural TB. In this study, 88% of tuberculous pleurisy was diagnosed with the combination of histological examination and tissue/pleural effusion culture for TB in the Abrams needle biopsy group, while 63.3% was diagnosed with the same combination in the Tru-cut needle biopsy group. There was a significant difference in the diagnostic rate between the 2 procedures ($p$=0.027).

The combination of culture and biopsy can yield a diagnostic rate of 60-95% for tubercu-

lous pleurisy [12-14]. This is a particularly useful method of diagnosing TB-induced pleural effusion in an area with a high TB prevalence like Southeast Asia. Half of the PEUE in this study population -- one that lives in an area with a high TB prevalence -- was caused by TB infection, and pleural fluid cultures were positive for mycobacterium in 31% of confirmed cases. Together with tissue culture and histological examination, 76% of patients with tuberculous pleurisy were diagnosed. There was a significant difference in diagnostic power between the 2 biopsy procedures. This indicates that Abrams needle biopsy, instead of Tru-cut needle biopsy, as well as TB cultures, should be performed to determine the etiology of pleural effusions in areas where the TB prevalence is high.

Abrams needle biopsy may be superior to Tru-cut needle biopsy in diagnostic power since the Abrams needle obtains larger tissue samples. Koegelenberg and colleagues have demonstrated that ultrasound-assisted pleural biopsies performed with an Abrams needle are more likely to have significantly higher diagnostic sensitivity for pleural tuberculosis [15]. However, results in the current study do not support this hypothesis, as there was no significant difference in the diagnostic rate. Nevertheless, combined with tissue culture, the Abrams needle has a proven superior yield for culture of *M. tuberculosis* and diagnostic sensitivity, compared to the Tru-cut needle biopsy with tissue culture. The cost of the Tru-cut needle was NT$680 in Taiwan; since the Abrams needle can be reused, the Tru-cut needle is relatively more costly.

Complications with closed pleural biopsy are infrequently reported, but include pneumothorax (4-11%), hemothorax (1-5%), and vasovagal reaction (1-5%) [4,11,16]. There was only 1 patient with minimal pneumothorax in the Tru-cut group in this study, suggesting that experienced personnel may lower the complication rate of invasive procedures.

There are some limitations to this study that are worth mentioning. First, this was a retrospective study, which may result in missing data. Another limitation is the small number of patients, since the cause of pleural effusion is determined after an initial pleural effusion analysis in most cases.

## Conclusion

This study demonstrates that both ultrasound-assisted Tru-cut pleural biopsy and Abrams needle pleural biopsy can assist in the diagnoses of pleural TB and malignant pleural effusion with minimal complications. There was no significant difference in the diagnostic rate between the 2 procedures, despite the fact that smaller tissue samples were obtained by Tru-cut needle biopsy. However, Abrams needle biopsy with tissue culture is more likely to contain large pleural tissues and significantly higher diagnostic sensitivity for pleural TB.

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# 比較兩種不同切片方式 Abrams 及 Tru-cut needle biopsies 在高結核病盛行地區肋膜積液的診斷率

邱建通　賴永發　魏裕峰　吳俊廷　張祐綸　黃照恩

**前言**：目前的文獻報告對於比較Abrams needle及Tru-cut needle biopsies在肋膜積液的診斷率上仍不多。所以這個研究目的是比較Tru-cut biopsy在高結核病盛行的地區對於肋膜積液的診斷率是否真的較Abrams needle biopsy為佳。

**方法**：經由回塑性的病例研究，總共有193個病人在本院接受了肋膜切片的檢查，其中116人接受了Abrams needle biopsy，另外77個病人接受了Tru-cut biopsy。除了有一個接受Tru-cut biopsy的病人發生了氣胸之外，其餘病人均無併發症。

**結果**：在檢體的比較上，由Abrams needle biopsy取得的檢體明顯大於Tru-cut biopsy（34 vs. 5 $mm^3$, $p<0.001$）。但兩者取得的檢體在病理組織診斷結核病（56% vs. 53%, $p=0.723$）或惡性腫瘤（47% vs. 31%, $p=0.312$）上並無差異。然而，在診斷結核性肋膜炎方面若病理組織合併組織培養，則Abrams needle biopsy明顯優於Tru-cut biopsy（79% vs. 53%, $p=0.027$）。

**結論**：Tru-cut及Abrams needle biopsy在肋膜積液病因的診斷上都是很有幫助的，而且很少發生併發症。Abrams needle biopsy可以取得較大的組織切片，有較高的機會培養出結核菌，針對結核性肋膜炎的診斷上是為優先選擇。*(胸腔醫學* ***2012; 27: 150-158)***

關鍵詞：Abrams needle切片，Tru-cut切片，未診斷肋膜積液，惡性腫瘤，結核病

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# Choroid Metastasis from Primary Lung Cancer in 26-year-old Male Successfully Treated with Pemetrexed – Case Report and Literature Review

Wei-An Chang*, Chih-Jen Yang*,**, Po-Yen Lee***, Jhi-Jhu Huang*,**, Inn-Wen Chong*,**, Ming-Shyan Huang*,**

Choroid metastasis from primary lung cancer is rare and has a poor prognosis. It can be treated with an external beam of radiation or by laser photocoagulation. However, visual defects or blindness are possible complications related to radiotherapy. Chemotherapy for such a condition has not been widely reported. We report a 26-year-old patient who had stage IV lung adenocarcinoma and suffered from progressive blurred vision during a scheduled chemotherapy regimen. Fundoscopy, fluorescence angiography and optic coherence tomography indicated choroidal metastasis of both eyes. We prescribed a platinum double chemotherapy regimen with pemetrexed and cisplatin. A follow-up examination demonstrated complete remission of the choroid metastasis. Herein, we report the first case of lung cancer with choroid metastasis that underwent complete remission after pemetrexed administration. We share our experience and conduct a literature review. ***(Thorac Med 2012; 27: 159-166)***

Key words: choroid metastasis, lung cancer, pemetrexed

## Introduction

Lung cancer is the most common cause of cancer-related mortality worldwide, and in Taiwan, as well. It may metastasize and involve many organs, such as the brain, bones, adrenal glands and liver. Choroid metastasis has rarely been documented. In a previous study, choroidal metastasis was found to commonly occur in advanced metastatic lung cancer [1], and it is a sign of a poor prognosis [2]. External beam radiation therapy (EBRT) is considered to be the first choice of treatment for choroidal metastasis [3-5]. Chemotherapy treatment for this condition has not been widely reported. Herein, we report a young male with lung adenocarcinoma and who suffered from choroid metastasis. Fortunately, complete regression was obtained after systemic chemotherapy treatment with pemetrexed. To the best of our knowledge,

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based on a thorough Medline search, this is the first report of pemetrexed being used for such a special patient.

## Case Report

This 26-year-old male was diagnosed as having lung adenocarcinoma in August 2010. He was reasonably healthy, but his uncle and grandmother had both suffered from lung cancer. In addition, he was also a heavy smoker, smoking about 1 pack per day for 4 years. He was an engineer and denied having any chemical exposure. He came to our chest outpatient department on 21 July 2010 due to chest pain and cough for 2 weeks. The chest X-ray showed a right-side hilar tumor and a right-side low lung mass (Figure 1). Further chest computerized tomography (CT) revealed a huge mass occluding the trunchus intermedius, accompanied with some large lymph nodes in the ipislateral mediastinal, peribronchial and subcarinal area. Bronchoscopy was performed soon afterwards

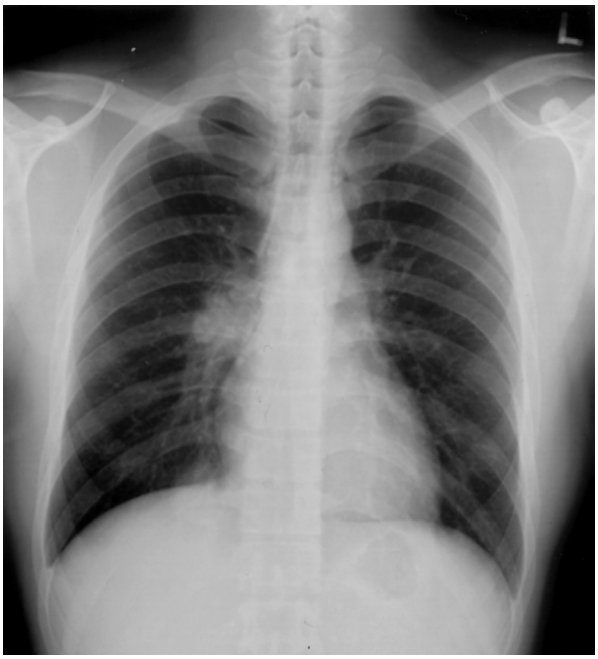

**Fig. 1.** Chest X-ray showed a right hilar tumor and a mass in the right lower lung.

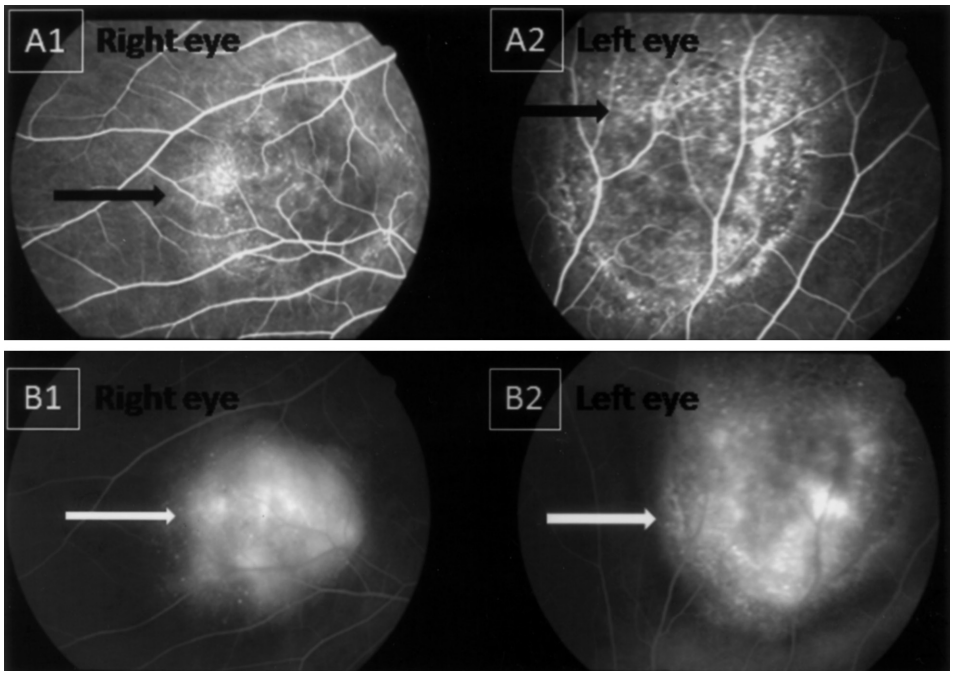


**Fig. 2.** Fluorescent angiography showed early hyperfluorescence (black arrows in A1 and A2), late stain and late leakage in the lesions of both eyes (white arrows in B1 and B2).

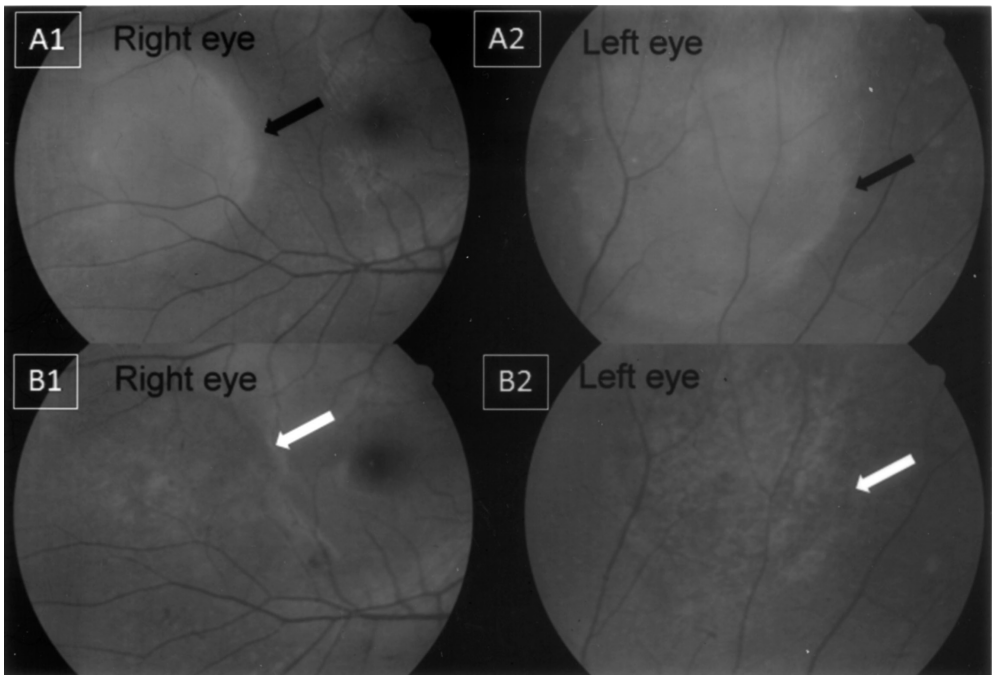


**Fig. 3.** Fundoscopy showed bilateral retro-retinal mass-like lesions with fluid accumulation (the black arrows) before treatment with pemetrexed (A1 and A2). After treatment with 2 cycles of pemetrexed, regression of the choroid tumor was noted (white arrows in B1 and B2).

and showed swollen and hyperemic bronchial mucosal change with hypervascularity at the proximal end of the trunchus intermedius. Transbronchial biopsy showed adenocarcinoma and immunohistochemical staining was positive for CK7 and TTF-1, indicating lung origin. For staging, positron emission tomography (PET) showed a huge lung mass with a high standardized uptake value (SUVmax). Unfortunately, bone and kidney metastasis were also found. Taking the above data together, the patient was diagnosed as having lung adenocarcinoma, T2b N2 M1b, stage IV. In addition, his EGFR gene was wild type. A bronchial stent was implanted due to obstructive pneumonitis, and he underwent concurrent chemoradiotherapy with vinorelbine and cisplatin immediately afterwards.

On 12 November, he was admitted as scheduled for another course of chemotherapy. He complained of having progressively blurred vision and diplopia in his left eye before this hospitalization. He claimed that he was almost blind in his left eye. Therefore, we arranged fundoscopy, fluorescence angiography (FAG) and optic coherence tomography for him. The fundoscopy showed a bilateral retro-retinal mass with fluid accumulation (Figures 3 A1& A2). The FAG disclosed early hyperfluorescence, late staining and late leakage in the lesions of both eyes (Figure 2). Furthermore, optic coherence tomography showed retro-retinal space thickening in both eyes (Figure 4A). The above evidence indicated that he had rare choroid metastasis in both eyes, resulting from his primary lung adenocarcinoma.

The patient hesitated to undergo radiotherapy for the suspected adenocarcinoma with

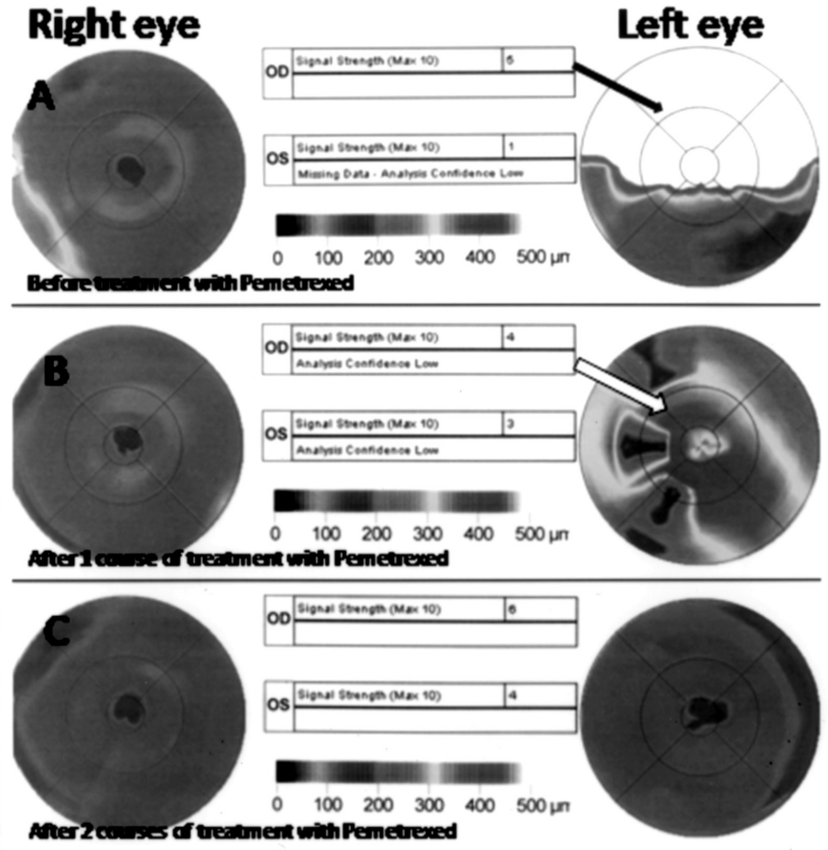


**Fig. 4.** Optic coherence tomography showed retro-retinal space thickening in both eyes. The white area represents the thickest area of the fundus of the eyes (black arrow in A). After 1 cycle of treatment with pemetrexed, the white area turned yellow and green, meaning that the fundus had become less thick (white arrow in B). After the 2nd cycle of treatment with pemetrexed, the thickened area of the fundus became green and blue, meaning that the thickness of the fundus had returned to normal, and indicating regression of the choroid tumor (C).

choroid metastasis because of macular involvement and the possibility of blindness as a result of radiotherapy. Therefore, because of disease progression, we decided to replace the current chemotherapy with pemetrexed 500 mg/$m^2$ and cisplatin 75 mg/$m^2$. After the 1st cycle of treatment, the follow-up optic coherence tomography showed improvement in the retro-retinal space thickening (Figure 4B), though his subjective symptom did not improve . After the 2nd cycle of chemotherapy, he felt his visual field getting much better, and the repeated fundoscopy and optic coherence tomography demonstrated the dramatic resolution of the choroid tumor on both eyes (Figure 3 B1&B2, Figure 4C).

The excellent response indicated that chemotherapy with pemetrexed may be a promising option in cases of choroid metastasis that have developed from primary lung cancer. The patient no longer complained of blurred vision, but experienced somewhat decreased visual activity after treatment with pemetrexed, and there was no more recurrence in the follow-up

by ophthalmologists. However, he expired 4 months later because of pneumonia-related sepsis.

## Discussion

The choroid is located between the retina and sclera, and is a vascular, pigmented tissue layer. The choroid provides the vascular supply to the outer part of the retina [2]. Metastatic tumors are the most common intra-ocular malignancy and the choroid is the most common site. The uveal tract is the most commonly involved site in the metastasis of primary non-ocular tumors. Intraocular metastasis is generally located in the posterior uvea because of the abundant supply of posterior ciliary arteries to the choroid. Recent clinical and autopsy studies have reported that 9.3-10% of patients who died of cancer had ocular metastasis, and that most metastases were localized in the choroid. The route of metastasis to the choroid is hematogenous [2]. Nevertheless, choroid metastasis is rare and often asymptomatic. The first choroidal metastasis case was described by Perl *et al*. in 1872 [6]. Breast cancers are the most common primary tumors to have choroid metastasis, followed by lung carcinoma [2,6-8]. Choroidal metastasis can also be detected in other primary cancers, such as esophageal, ovarian, colon [8], prostate, and pancreatic cancer, and hepatocellular carcinoma [9]. Choroidal metastasis from primary tumors is representative of a poor outcome [2] and most patients die within months of diagnosis. Mean survival is approximately 10 months, and the 5-year survival rate is 24% overall [10-11]. Kreusel *et al*. reported a retrospective review of 22 consecutive patients with symptomatic choroidal metastasis that resulted from lung cancer; 36% of patients with lung cancer had been diagnosed before the occurrence of choroid metastasis. Choroidal metastasis was often unilateral, solitary and located close to or at the posterior pole in the majority of patients. In 20% to 40% of cases, the lesions were bilateral. The report also indicated that median survival after diagnosis of symptomatic choroid metastasis was 13 months, in contrast to 2 months in lung cancer patients with choroidal metastasis identified in an ocular screening study [12].

The clinical presentations of choroidal metastases include blurred vision, decreased visual acuity, tenderness, flashes, floaters, metamorphopsia and scotomas [2,6]. Among these symptoms, blurred vision and decreased visual acuity are the most common [2,6]. Carcinoma metastatic to the choroid can cause visual dysfunction due to the accumulation of subretinal fluid and/or the tumoral involvement of the macular region. However, some patients with choroidal metastases are asymptomatic [6].

The differential diagnosis of a choroidal mass includes choroidal neovascularization, primary choroidal malignant melanoma, choroidal metastasis, inflammatory granulomas and hemangioma. The related diagnostic procedures include slit-lamp biomicroscopy, ophthalmoscopy, ultrasonography, FAG, CT and magnetic resonance imaging [2]. Typical ophthalmoscopic features include 1 or multiple creamy yellow choroidal lesions associated in some advanced cases with secondary retinal detachment [6,13]. With fluorescein angiography, these lesions are usually fluorescent in the early phases of the study and become progressively hyperfluorescent in the late phases. B-scan ultrasound shows an echogenic sub-retinal mass with diffuse, ill-defined borders.

There are many methods of treatment for choroidal metastasis, including radiotherapy,

laser photocoagulation, photodynamic therapy [9,14], transpupillary thermotherapy, chemotherapy, and enucleation [3]. The major determinants of survival after the diagnosis of choroidal metastasis are the primary tumor type and local tumor invasion at the time of diagnosis. EBRT is the most common choice of treatment for choroidal metastasis, because the choroid is radiosensitive. The doses of EBRT required for the successful palliation of choroidal metastasis for most primary tumors is 30 grays in daily fractions of 300 centigrays. However, higher doses of radiotherapy may result in a higher rate of orbital complications [4-5].

The use of chemotherapy alone for choroidal metastasis has not been widely reported. The choice of drugs for each patient depends on the type of primary cancer. For lung cancer, several different kinds of chemotherapy have been attempted, such as gefitinib [15], paclitaxel [16], gemcitabine plus carboplatin [17], topotecan and cisplatin [18]. Ben *et al*. reported a patient with non-small-cell lung cancer with choroid metastasis and complete regression that was treated with a systemic combination of bevacizumab, gemcitabine and carboplatin [19]. Kim *et al*. reported another patient who had complete regression with a combination of bevacizumab and oral erlotinib [20]. To the best of our knowledge, we have reported the first case of a patient with choroid metastasis from primary lung cancer who demonstrated complete regression after pemetrexed plus cisplatin treatment. Platinum doublet chemotherapy has a synergistic effect and is the standard regimen for lung cancer treatment up to now. Our patient had received just 2 cycles of platinum doublet chemotherapy. Therefore, we decided to prescribe a pemetrexed-based platinum doublet for him. Pemetrexed alone may also have been effective for him and further study is necessary.

In conclusion, choroidal metastasis from primary lung cancer is rare, but possible. EBRT is the most common choice of treatment, but may result in permanent orbital complications. Systemic chemotherapy is 1 of the treatment options currently available and pemetrexed is 1 of the drugs of choice for such rare complications in similar cases of lung cancer.

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# 在一位 26 歲肺癌患者合併眼球脈絡膜轉移，成功使用 Pemetrexed 治療—案例報告及文獻回顧

張維安* 楊志仁*,** 李柏延*** 黃吉志*,** 鍾飲文*,** 黃明賢*,**

肺癌合併眼球脈絡膜轉移被認為是較差預後的象徵。針對眼球脈絡膜轉移的第一線治療方法為放射線治療，但可能會併發視力缺損甚至於全盲，另外也可以使用手術、雷射以及化學治療。化學治療並非廣泛使用，回顧之前的文獻，尚無以Pemetrexed成功治療肺癌合併眼球脈絡膜的報告。這位26歲男性被診斷為肺腺癌，經過化學治療之後疾病仍持續進展並出現新的眼力模糊，經過一系列眼科檢查，發現是罕見的眼球脈絡膜轉移，推測是轉移自原本的肺腺癌。經過Pemetrexed的治療之後，病人的視力完全回復，且眼底檢查也顯示眼球脈絡膜轉移癌完全消散。就我們所知，這是第一個肺癌合併眼球脈絡膜轉移且成功地以Pemetrexed治療的病人，我們分享此經驗並作文獻回顧。*(胸腔醫學* ***2012; 27: 159-166)***

關鍵詞：脈絡膜轉移，肺癌，愛寧達（Pemetrexed）

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# Use of Interventional Bronchoscopy to Manage Solitary Bronchial Squamous Papilloma with Malignant Change – A Case Report

Ya-Chun Chang*, Hung-Chen Chen*, Chin-Chao Wang*,**, Yu-Hsiu Chung*, Tung-Ying Chao*, Yi-Hsi Wang*

We reported a 74-year-old male patient with multiple comorbidities (diabetes mellitus, hypertension and stroke) who underwent endovascular aortic replacement due to abdominal aortic aneurism. In the postoperative follow-up, a nodule in the left main bronchus was found. Bronchoscopy confirmed a polyp-like lesion in the orifice of the left upper lobe. The biopsy report revealed a squamous cell papilloma with moderate dysplasia. Following that, electrocautery was performed monthly. The 3rd biopsy report revealed papillary squamous cell carcinoma. The patient then underwent positron emission tomography-computed tomography, which showed fluorodeoxyglucose-avid lesions in the left upper lobe and pretracheal lymph node. The patient refused operation and continued to undergo electrocautery. The biopsy report before the 5$^{th}$ electrocautery procedure began found no malignancy. Since then, he has been followed up regularly in our clinic with autofluorescence endoscopy. ***(Thorac Med 2012; 27: 167-172)***

Key words: solitary bronchial squamous papilloma, electrocautery, autofluorescence endoscopy

## Introduction

Solitary bronchial squamous papillomas are rare tumors that account for 7-8% of all benign lung tumors. Previous studies have suggested that this type of benign tumor is liable to transform into squamous cell carcinoma at its base. We report a 74-year-old man with a solitary bronchial squamous papilloma with malignant change who underwent interventional bronchoscopy with electrocautery rather than surgical intervention, and was followed up with autofluorescence endoscopy.

## Case Report

The patient was a 74-year-old man with a history of diabetes mellitus, hypertension, and

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stroke. He had an asymptomatic bladder stone and was being followed up at Paochien Hospital. During the regular follow-up, an abdominal aortic aneurysm was noted. Therefore, he was transferred to our hospital for further evaluation and management.

During hospitalization, on 26 October 2010, he received an endovascular aortic replacement. The initial chest x-ray is presented in Figure 1. The postoperative computed tomography angiography revealed sputum or a nodule in the left bronchus and bronchoscopy was suggested for further evaluation (Figure 2). The bronchoscopy examination found that the bilateral main bronchi and bronchial trees were normal, except for a polyp-like lesion on the left upper lobe (Figure 3). The lesion was free of coating, not bleeding, and had no ulceration at the left upper lobe orifice; however, it obstructed the passage of the bronchoscope. Autofluorescence endoscopy was then done (Figure 4) and a bronchial biopsy was also performed. The initial pathology report of the lesion was of a squamous cell papilloma with moderate dysplasia. No definite stromal invasion was discernible and a close follow-up was suggested. Therefore, interventional bronchoscopy with electrocautery was used to treat the lesion and autofluorescence endoscopy was used in the follow-up. One month later, bronchoscopy was performed again, and revealed an endobronchial lesion on

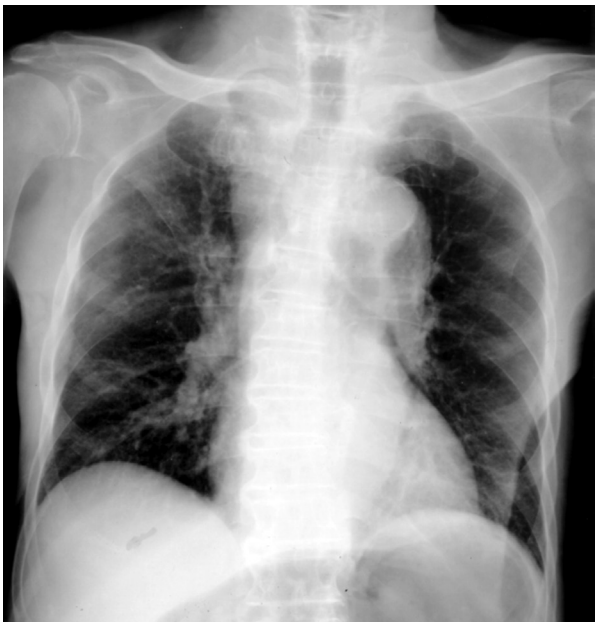

**Fig. 1.** The initial chest x-ray obtained on Oct 18, 2010

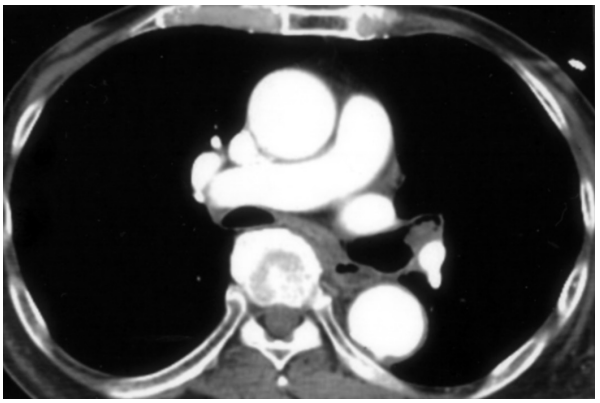

**Fig. 2.** Sputum or a nodule in the left bronchus revealed by chest computed tomography

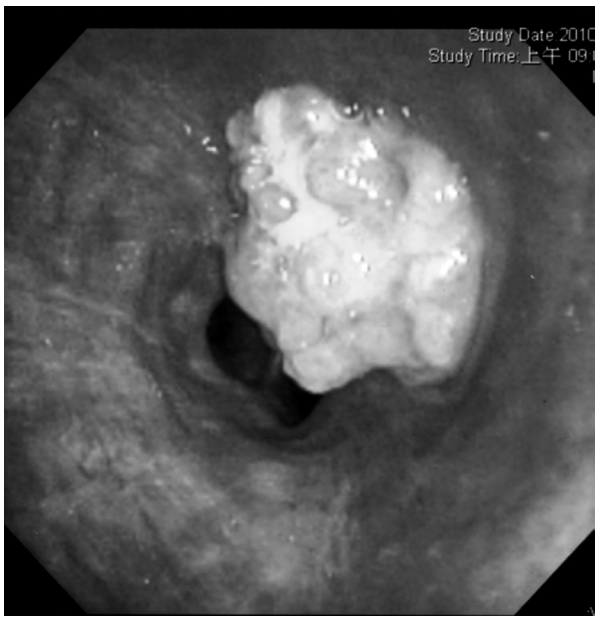


**Fig. 3.** Bronchoscope finding before electrocautery

the left distal main bronchus that had slightly increased in size. After electrocautery was used for the tumor, lingular lobe and apical posterior segment of left upper lobe were noted. The 2nd pathology report revealed papillary squamous cell carcinoma *in situ*. The specimen consisted of more than 10 tissue fragments measuring up to 0.7 ×0.5×0.5 cm. The section showed tumor fragments composed of papillae lined by neoplastic squamous cells bearing irregular nuclei and an increasing number of mitotic figures. No definite tumor invasion was identified on the most recent slide. However, a possible underlying tumor invasion could not be excluded based on the limited biopsy specimen. A regular follow-up was arranged at 1 month intervals. The 3rd biopsy revealed papillary squamous cell carcinoma. The section revealed fragments of bronchial tissue, necrotic debris, and papillary fronds of neoplastic squamous cells growing over a fibrovascular core. A positron emission tomography - computed tomography scan revealed a fluorodeoxyglucose (FDG)-avid lesion in the upper left lung and FDG-avid lesions in the left pulmonary hilar lymph node and pretracheal lymph node. Since the patient and his family refused a lobectomy, interventional bronchoscopy with electrocautery was used for treatment. Autofluorescence endoscopy was used for follow-up. During the follow-up, the tumor size regressed (Figure 5). Autofluorescence endoscopy revealed a magenta lesion at the left anterior segment (Figure 6). However, the 5th biopsy was negative for malignancy. The use of autofluorescence endoscopy continued during the follow-up.

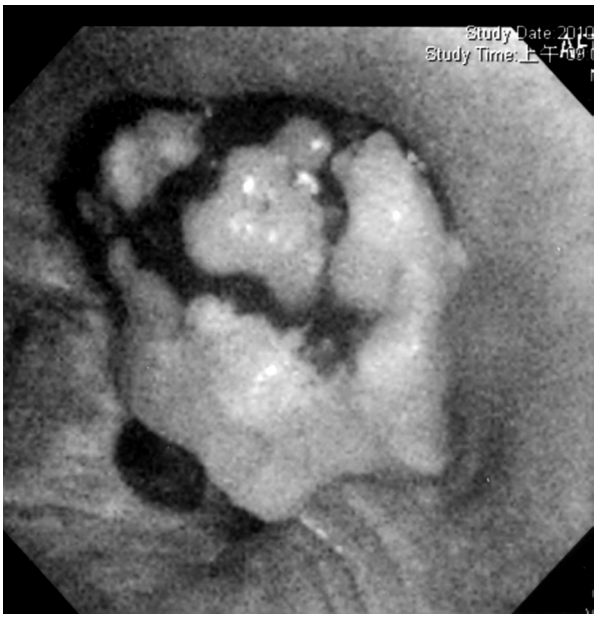

**Fig. 4.** Autofluorescence endoscopy finding before electrocautery

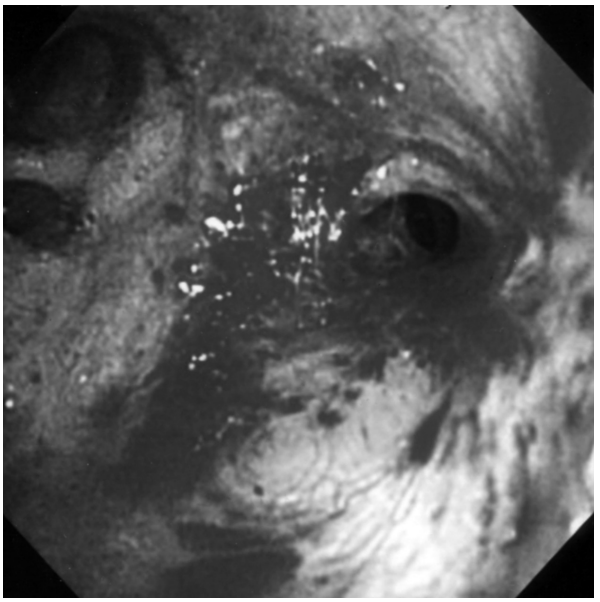

**Fig. 5.** Bronchoscope finding after electrocautery revealed no endobronchial lesion

## Discussion

Solitary bronchial squamous papillomas are rare tumors that account for 7-8% of all benign lung tumors [1]. They are seen more frequently in men and generally appear between 50 and 70 years of age. More than half of the patients

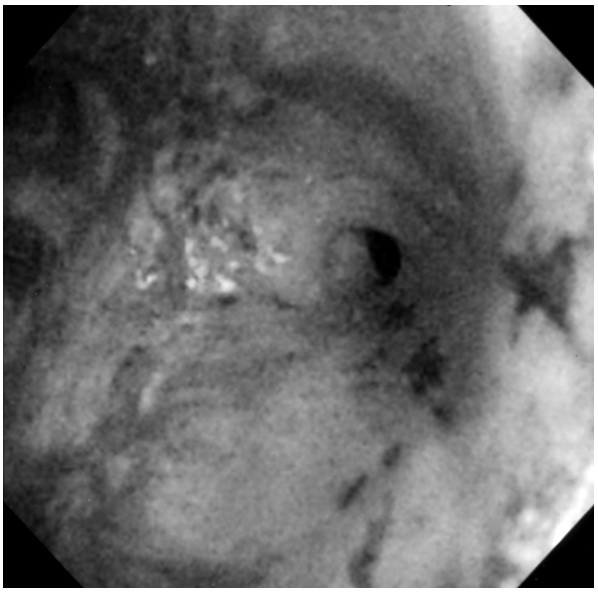

**Fig. 6.** Autofluorescence endoscopy finding after electrocautery revealed a positive magenta lesion

are cigarette smokers [2]. Previous studies have suggested that this type of benign tumor is liable to transform into squamous cell carcinoma at its base, and it should be considered as a precancerous lesion [3].

The tumor causes a variety of symptoms including cough, dyspnea, hemoptysis, recurrent pneumonia, and asthma [1]. Once squamous cell papilloma is diagnosed, potential malignancy becomes a major concern [4]. Squamous cell carcinoma identified within papillomas shows prominent cellular pleomorphism, loss of maturation, increased dyskeratosis and hyperkeratosis, and most importantly, invasion into adjacent lymphatic tissues through the bronchial wall [5]. However, Flieder *et al*. reported difficulty in grading dysplasia in squamous papillomas due to their epithelial architectural distortion, inflammation, and occasional koilocytic changes [6]. Therefore, when a case of squamous cell papilloma is diagnosed, squamous cell carcinoma needs to be excluded.

Squamous cell papilloma is closedly related to human papillomavirus (HPV) [7]. Flieder *et al*. [6] and Popper *et al*. [8] found that 1 of the serotypes -- HPV 6,11,16,18,31,33, or 35 -- will infect 71-100% of these papillomas, and the serotype may predict the malignant potential of the papilloma. The risk of malignant conversion of papillomas is increased with HPV serotype 16 or 18 [8]. HPV serotypes 6 and 11 are considered to have a weaker malignant potential [8-9].

Surgical resection is the "gold standard" for treatment, but since solitary bronchial squamous papillomas are considered benign tumors [10], conservative treatment may be sufficient to obtain a complete cure [4]. Such treatments include photodynamic therapy, YAG laser vaporization, and electrosurgical snare. The electrocautery snare can be used to obtain large biopsies of airway lesions, to debulk and remove malignant tissue in the airway, and to treat benign lesions. In addition, no complications have been reported while utilizing the snare [11]. Therefore, we used interventional bronchoscopy with electrocautery for further management in this case. After a series of interventional bronchoscopy procedures, the 5$^{th}$ lung biopsy was found to be negative for malignancy.

Zimmermann *et al*. reported recurrent papilloma of the bronchus after an incomplete endoscopic resection [12]. Therefore, regular follow-ups need to be arranged. In this case, we used autofluorescence endoscopy during the follow-up until the tumor was totally resected.

From this case, we learned that solitary bronchial squamous papilloma is a precancerous lesion and needs regular follow-up. In addition, interventional bronchoscopy with electrocautery can be used to manage it. However, due to its potential for local recurrence, autofluo-

rescence endoscopy should be used during the follow-up.

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# 使用治療性支氣管鏡來處置肺部癌化的鱗狀乳頭瘤：病例報告

張雅淳* 陳泓丞* 王金洲*,** 鍾聿修* 趙東瀛* 王逸熙*

一位74歲男性病患，伴有多種共病症（糖尿病、高血壓、中風），因腹主動脈瘤接受支架手術。在術後例行檢查中發現左主支氣管有小結節，接著接受支氣管鏡檢查確定左上葉開口處有一息肉狀結節。切片報告為鱗狀乳突瘤伴有中等程度異常（dysplasia)。於是病患接受多次雷射燒灼治療，每次間隔一個月。第三次燒灼前切片報告為鱗狀上皮細胞癌，因此續接受正子電腦斷層（PET-CT），正子結果為左上肺葉病灶和氣管前淋巴結信號增強。病患拒手術切除，續維持原先燒灼治療。在第五次燒灼前切片已沒有惡性細胞，目前在門診以自體螢光支氣管鏡定期追蹤。*(胸腔醫學* ***2012; 27: 167-172)***

關鍵詞：鱗狀乳頭瘤，雷射燒灼治療，自體螢光支氣管鏡

*長庚大學醫學院高雄長庚紀念醫院 內科部 胸腔內科，**高雄醫學大學 職業安全衛生研究所
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# Ectopic Thymus in the Middle Mediastinum: A Case Report and Literature Review

Kuo-Shao Sun, Chung-Ta Lee*, Yau-Lin Tseng**, Han-Yu Chang

The case of a young ethnic Chinese male who presented with rare ectopic thymic tissue in the middle mediastinum is reported and the related literature reviewed. The most common tumors found in the middle mediastinum are mediastinum cyst, bronchogenic cyst, lymphoma and pericardial cyst; most thymic tumors are found in the anterior-superior mediastinum area and less then 4% are found elsewhere. Ectopic thymic tumors in the middle mediastinum are the rarest. Computed tomography has high sensitivity and specificity for thymic tissue, and the gold standard treatment is radical resection. The World Health Organization histological grading and Masaoka staging system for thymoma remain the most important indicators for survival. ***(Thorac Med 2012; 27: 173-180)***

Key words: ectopic thymus, middle mediastinum tumor, thymoma

## Introduction

The thymus is an important organ associated with the immune system. Any errors occurring during embryological migration will result in ectopic thymus. Abnormal thymus is also a common cause of anterior mediastinum mass. However, only very few cases have described ectopic thymus tissue in the middle mediastinum. Herein, we report an unusual case of ectopic thymic tissue in the middle mediastinum.

## Case Report

An 18-year-old male was referred to our clinic for an abnormal shadow detected on plain chest x-ray (CXR) film during a medical check-up in April 2010. He had no clinical discomfort. He was a chronic smoker, consuming 10 cigarettes per day for the past 3 years. His medical and family history was unremarkable. The same shadow was identified 5 years ago on his previous CXR. No obvious interval growth was noted during serial CXR films. Physical exam, neurology exam and biochemistry survey findings were unremarkable. Chest radiographs (Figure 1) showed a right-side paratracheal tumor-like shadow with a well-defined border. Contrast computed tomography (CT) scan of the chest (Figure 2) revealed a 4.7 cm heterogeneous infiltrating mass in the superior-middle mediastinum at the right paratracheal region.

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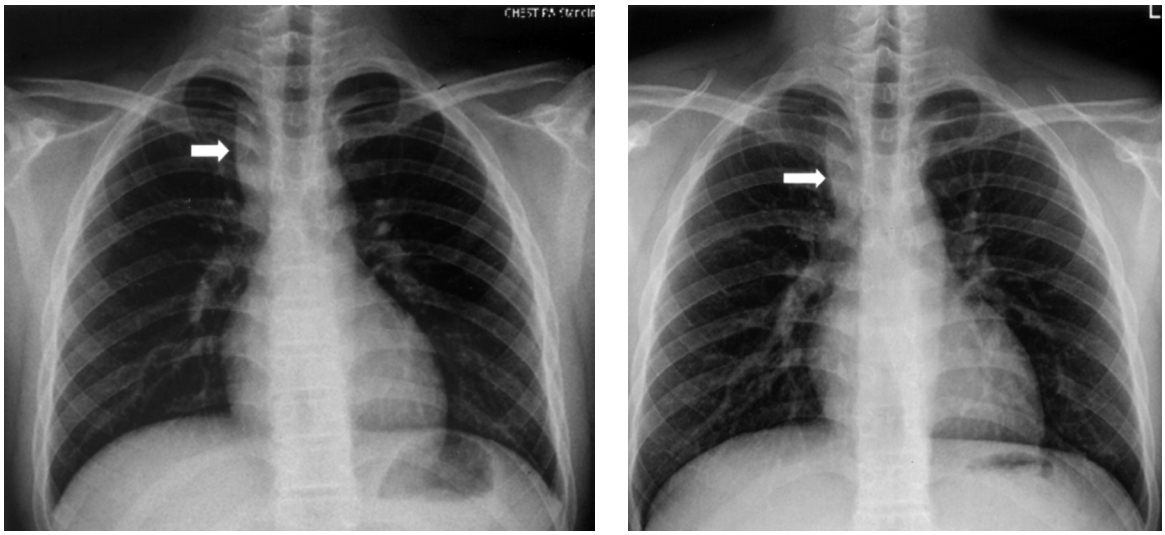
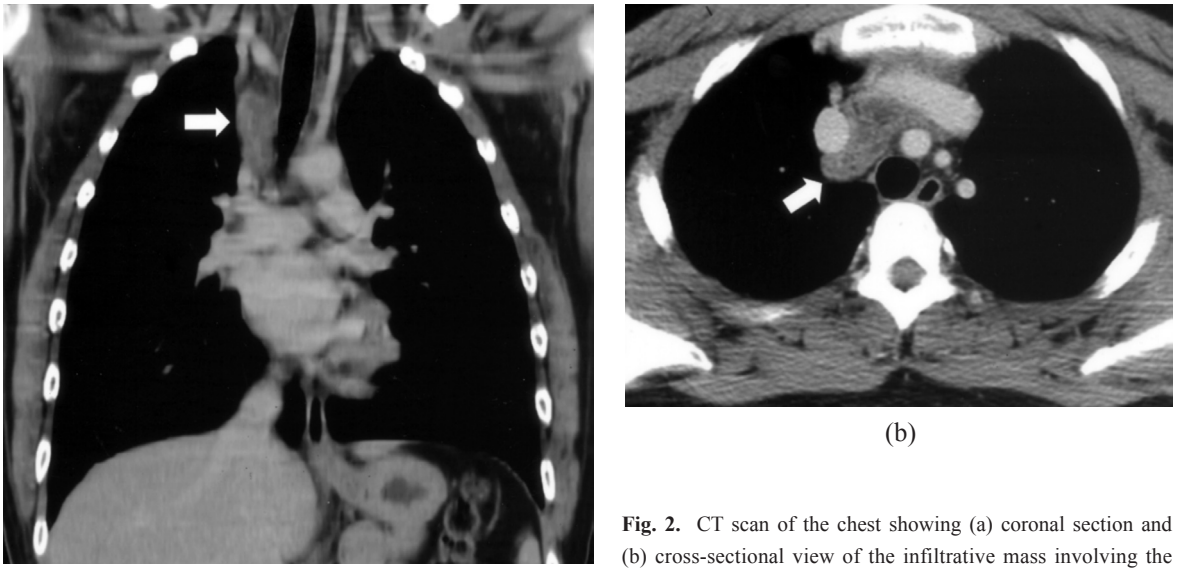


(a) (b)

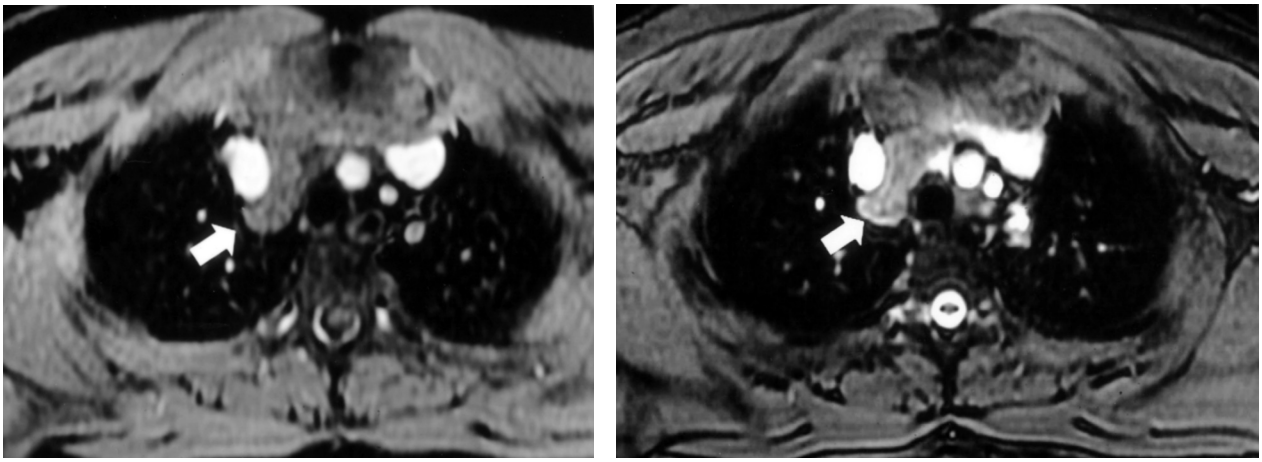
**Fig. 1.** Chest radiograph (posterior-anterior view) taken on (a) 2005/09/24 and (b) 2010/04/13 showed a right paratracheal mass without interval change in size or density.



(a) (b)

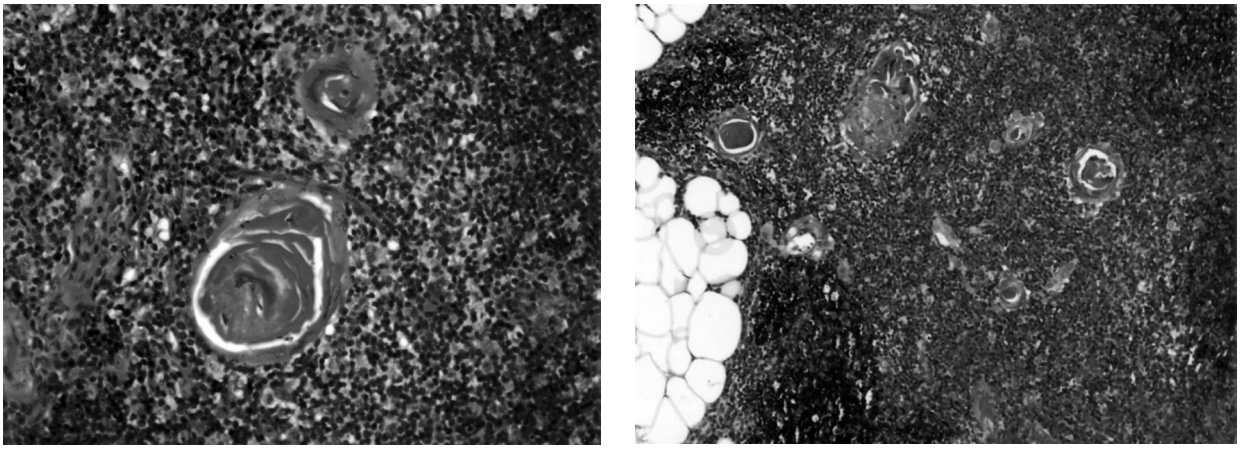
**Fig. 2.** CT scan of the chest showing (a) coronal section and (b) cross-sectional view of the infiltrative mass involving the superior and middle mediastinum.

The mass lesion at the middle mediastinum was suspected to be thymus hyperplasia, thymolipoma or lymphoma. However, no enlarged lymph node was detected and the fat plane was intact without invasion of the surrounding structures. Magnetic resonance imaging (MRI) of the chest (Figure 3) showed an infiltrative lesion involving the superior and middle mediastinum at the right paratracheal region, about 4.5 cm at its greatest dimension, with iso-signal intensity on the T2-weighted image and low signal intensity on the T1-weighted image.



(a) (b)

**Fig. 3.** Contrast MRI showed an infiltrative lesion involving the superior and middle mediastinum at the right paratracheal region, about 4.5 cm at its greatest dimension, with iso-signal intensity on the T2-weighted image (a) and low signal intensity on the T1-weighted image (b).



(a) (b)

**Fig. 4.** Pathology of the tumor, showing a section of tissue that is composed of nearly normal thymic tissue with thymic lobules; some of the thymic stroma is replaced by adipose tissue (400X).

After admission, video-assisted thoracoscopic surgery (VATS) was performed, and in addition to grossly normal-looking thymus tissue at the anterior mediastinum, a 4×4×5 cm, well-encapsulated, multilobulated fat tissue-like mass at the middle mediastinum was found and resected uneventfully. The mass was well-encapsulated without invasion of the surrounding structures. Histologically, it was composed of near normal thymic tissue with thymic lobules and adipose tissue (Figure 4). Postoperative recovery was uneventful and no recurrence was noted during follow-up.

## Discussion

Normal thymus tissue has been reported in the anterior-superior mediastinum and accounted for 13% of all mediastinal masses; it is the most common primary tumor in the anterior mediastinum [1-2]. Thymic masses include thymoma, normal ectopic thymic tissue, cyst, carcinoma, thymolipoma, and neuroendocrine tumor. Seventy-five percent of thymus tumors are found in the anterior mediastinal region and the rest are scattered over the superior mediastinum, posterior mediastinum, neck area, lung, base of the skull and pleural cavity [3-6]. Ectopic thymic growth at the middle mediastinum is very rare.

Thymic epithelium arises bilaterally from the third and sometimes from the 4$^{th}$ bronchial pouches in the embryonic state and migrates into the anterior superior mediastinum. Ectopic thymic tissue may arise either from a failure of normal migration during the course of embryological development or aberrant migration of the accessory thymic lobe. The confusion regarding thymoma and thymic cancer results from the fact that thymoma can also invade surrounding structures, and even metastasize and require radio-chemotherapy. Thymoma is much more common clinically and tends to be indolent and have a better prognosis than thymic cancer [7].

To the best of our knowledge, only 8 cases of ectopic thymic tissue found in the middle mediastinum have been reported in the English literature. The details of the reported cases are summarized in Table 1. In brief, 7 were ectopic thymomas, 1 was a thymic cyst [8], and ours was the only case with nearly normal thymic tissue. Six patients were female and 3 were male. Ages ranged from 18 to 71 years, with the majority above 53 years; our patient was the youngest. Most of the patients were asymptomatic, except 1 that presented with precordial discomfort [9]. None of the 9 patients had signs or symptoms of myasthenia gravis. Physical exam and biochemistry studies were all unremarkable. The tumors had a mean size of 6.5 cm (range, 3.5-10 cm). All patients had an abnormal shadow on CXR, which led to further exams, such as CT scan and MRI. As for pre-operative studies, all had chest CT scan and MRI, and 1 patient had a positron emission tomography (PET) scan which showed increased uptake in acetate instead of fluorodeoxyglucose (FDG) [10]. None of the patients had a bronchoscopic study or fine needle aspiration biopsy. Under non-contrast CT of the chest, the image was of a homogenous fat tissue mass, and with contrast enhancement, a heterogeneous mass; none had calcification. Histology revealed that 6 cases were type AB thymoma, 1 was a cyst and 1 had an unusual histology subtype that did not fit a WHO classification [11]; our case was classified as normal thymic tissue. According to the Masaoka staging system, 6 cases were stage I and 1 was stage II. Among the 9 patients, 4 underwent operation soon after the first abnormal image, but 5 received surgery several years afterward. The delay was due to the relatively asymptomatic status. Later on, resection was performed because of the progressively enlarging mass. With the exception of 1 case with an unusual histology type [11] and 1 with normal thymic tissue, none of the others showed increased tumor invasion with delayed surgery. Among the 9 cases, only 1 patient with Masaoka stage II had postoperative radiotherapy. All the other patients had an uneventful post-operative recovery, and there were no recurrences 6 months after operation.

**Table 1.** Case reports of middle mediastinal thymoma and ectopic thymic tissue

| Reference | Age/gender | Time delay before operation[+] | Tumor size Images | Surgery | Type/stage Histology | Recurrence (6 months) |
|---|---|---|---|---|---|---|
| Kenji K *et al*. 2002 [24] | 60/F | 7.5 ys | 5×3×3 cm CT/MRI | Right thoracotomy | AB/II Thymoma | Not mentioned |
| Masato K *et al*. 2004 [25] | 60/F | Nil | 6×5×4 cm CT/MRI | Median sternotomy | AB/I Thymoma | No recurrence |
| Salvatore M *et al*. 2004 [8] | 53/M | 3 ys | 7 cm CT/MRI | Not mention | AB/I Mixed thymoma | Not mentioned |
| Salvatore M *et al*. 2004 [8] | 33/F | Nil | 5 cm CT/MRI | Not mentioned | Thymic cyst | Not mentioned |
| Jaroslaw K *et al*. 2006 [11] | 69/F | 15 ys | 10×10×7 cm CT | Antero-lateral thoracotomy | *** Metaplastic thymoma | Not mentioned |
| Hiroshige N *et al*. 2007 [9] | 69/F | Nil | 7×4 cm CT/MRI | VATS | AB/I Thymoma | No recurrence |
| Huang Tw *et al*. 2007 [12] | 71/F | 6 ys | 7×6×4 cm CT | Median sternotomy | A/I Thymoma | No recurrence |
| Hiroyuki S *et al*. 2009 [10] | 61/M | Nil | 3.8×3 cm CT/MRI/PET | VATS | AB/I Thymoma | No recurrence |
| Present case | 18/M | 5 ys | 4×4×5 cm CT/MRI | VATS | Near normal thymic tissue | No recurrence |

[+] Time duration from first abnormal image till time of surgery.

*** Rare histology type, not classified by current classifications.

The cardinal radiological feature of thymoma is an opacity abutting the mediastinum on CXR. Of the radiographic studies, CT scan with contrast has a sensitivity and specificity of up to 97% [13-15]. Moreover, the CT scan allows a better distinction between tissue planes and assists in detecting tumor invasion. Although the CT scan is a good predictor of invasion to surrounding structures, there are blind spots. For example, adhesion can mimic invasion and invasion can be missed due to partial blind spots, such as pleural, and the lower portion of the posterior mediastinum. Brown *et al*. analyzed 69 thymoma images and found no radiological correlation of findings to confidently differentiate malignant and benign lesions [14]. The lesion usually appeared as a solid homogenous fat mass under non-contrast CT and enhanced homogeneously, unless necrosis and hemorrhage had occurred. MRI is useful in evaluating thymoma and the surrounding structures, and usually demonstrates a low or iso-signal intensity in T1-weighted images and slightly higher signal intensity on T2-weighted images. In general, malignant thymoma in the anterior mediastinum has an inhomogeneous signal on T2-weighted images, which could be due to hemorrhage or cystic change [16]. PET-CT was used with 1 of the patients with WHO type AB and Masaoka type I, and showed highly positive

c-acetate uptake and only slightly positive F-FDG uptake [1]. It was presumed that c-acetate uptake suggests low-grade malignancy, such as thymoma, and is more useful than F-FDG in detecting thymoma [17]. In the end, because of the pitfalls of image studies, the gold standard for staging remains surgical intervention and histological examination.

Surgery is the gold standard for treatment, and complete resection had a 100% local control rate in stage 1 [16,18]. Different surgical approaches, such as sternotomy or VATS, have all been successful in previous experience. Stage I does not usually require postoperative radiotherapy, and radiotherapy as adjuvant therapy in patients with stage II disease or above is still controversial; large randomized studies are needed to confirm the benefit [19]. Thymoma is generally responsive to chemotherapy. In locally invasive, bulky disease, cisplatin-based combination chemotherapy (cyclophosphamide, adriamycin and cisplatin) has been effective [20-22].

The WHO and Masaoka have both developed a classification system to determine the treatment regimens and predict survival. The former focuses on tumor histology, while the latter focuses on tumor invasion. Both are useful tools, but the Masaoka staging system is used to stratify 5-year survival rates. The overall survival rate for patients with invasive thymoma is almost as good as that for patients with non-invasive tumors if radical excision is achieved.

The most common tumors found in the middle mediastinum are mediastinum cyst, bronchogenic cyst, lymphoma and pericardial cyst. Thymic growth is rarely found in this region, but thymic tissue has malignant potential with a 20% recurrence rate. Thus, ectopic thymus growth in the middle mediastinum should be considered in the differential diagnosis of middle mediastinum tumors.

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# 異位性中縱膈腔胸線瘤：個案報告及文獻回顧

孫國紹　李忠達*　曾堯麟**　張漢煜

在此提出的病歷報告是一位18歲年青的亞洲男性患有異位性中縱膈腔胸線併文獻回顧。回顧文獻，中縱隔腔中最常見的腫瘤是縱隔囊泡，支氣管性的囊泡，淋巴癌和心包膜囊泡。大多數的胸線組織都分佈在前縱隔或上縱隔這兩個區域，只有少於4% 的胸線組織會落在這兩個地方以外。異生的胸線組織中又以生長在中縱隔的最少見。電腦斷層掃描對胸線組織的檢查有很高的敏感性和專一性。目前，最好的治療方式是外科手術切除。對於評估疾病預後，仍是以世界衛生組織擬定的病理分期和Masaoka學者所發表的腫瘤對鄰近組織侵犯程度分期為主要指標。*(胸腔醫學* ***2012; 27: 173-180)***

關鍵詞：異位性胸線，中縱膈腔腫瘤，胸線瘤

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# Tracheal Schwannoma Presenting with Chronic Dyspnea – A Case Report

Chun-Wei Teng*, Chia-Hung Chen*, Wei-Chih Liao*, Chih-Yen Tu*,**, Chuen-Ming Shih*, Wu-Huei Hsu*

Primary tracheal schwannomas are extremely rare among tracheal neoplasms. We present the case of a 36-year-old female who had progressive dyspnea for 1 year. Upper airway obstruction with stridor was noticed after admission. Her pulmonary function test revealed the typical pattern of fixed airway obstruction. CXR and CT scan all showed a mass lesion in the upper trachea. Bronchoscopy was performed and revealed a protruding mass just below the vocal cords. The patient underwent surgical resection of the tracheal tumor, and the final diagnosis was benign tracheal schwannoma. This case demonstrates a rare disease with common dyspnea symptoms. Primary tracheal tumors should be considered in the differential diagnosis of respiratory distress of an unknown origin. ***(Thorac Med 2012; 27: 181-186)***

Key words: tracheal neoplasm, schwannoma, neurogenic tumor

## Introduction

Primary tracheal tumors are rare, and the majority is malignant [1]. Tracheal schwannomas are benign neoplasms accounting for less than 0.5% of all tracheal tumors. They are more common in young adults and their clinical presentations are usually non-specific. In this report, we describe a 36-year-old woman with progressive dyspnea for 1 year, and a final diagnosis of tracheal schwannoma.

## Case Report

A 36-year-old woman presented with progressive dyspnea for 1 year. She had been healthy in the past, but developed a chronic cough and exertional dyspnea 1 year previous to admission. Moreover, the patient had experienced intermittent stridor in the most recent 2 months. Upon admission, upper airway obstruction with mild stridor was noted. We arranged for a pulmonary function test, which demonstrated the typical pattern of fixed airway obstruction (Figure 1). Her chest x-ray (CXR) (Figure 2A) and computed tomography (CT)

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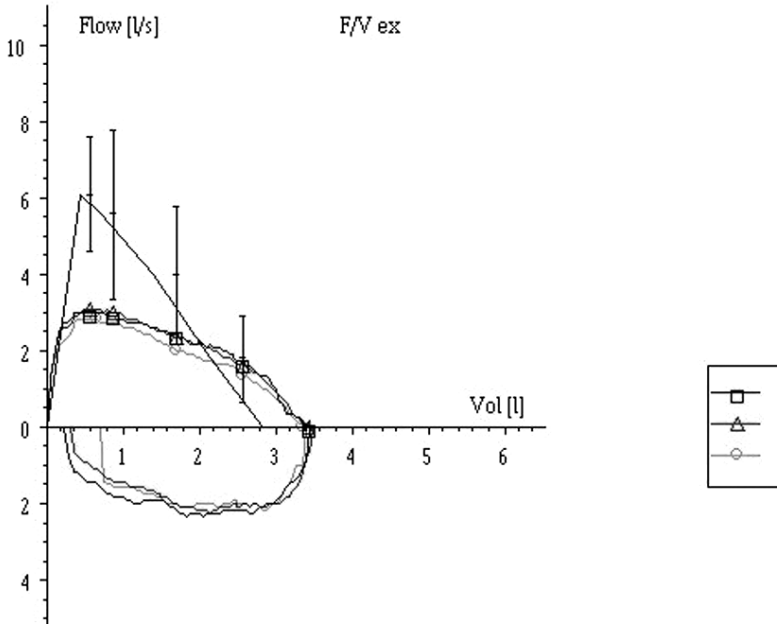



**Fig. 1.** Pulmonary function test revealed the typical pattern of fixed airway obstruction.

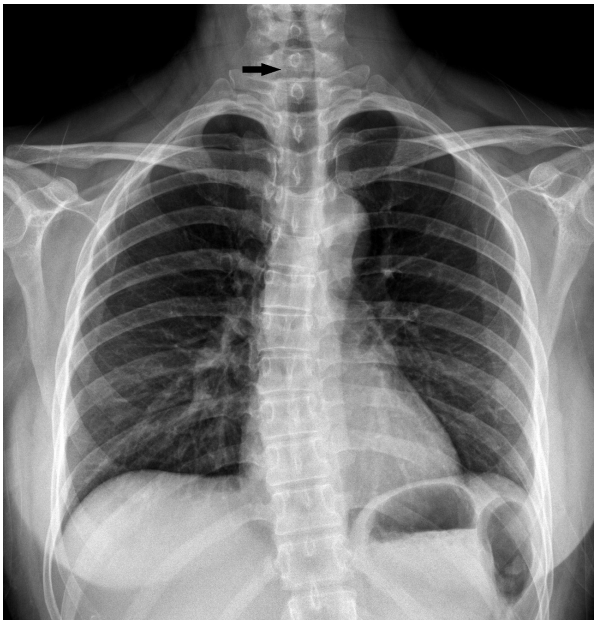


**Fig. 2A.** CXR revealed a tracheal tumor (black arrow).

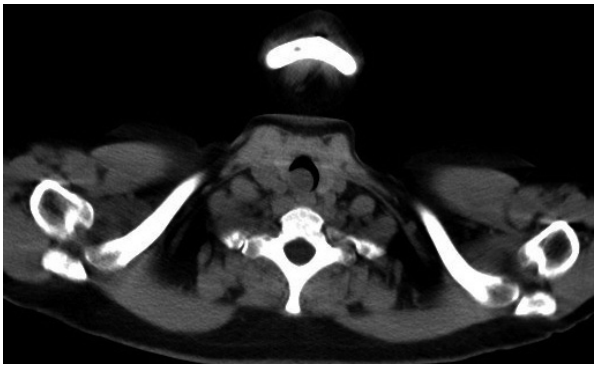


**Fig. 2B.** CT revealed a polypoid mass arising from the right posterior tracheal wall, occupying a large part of the tracheal lumen.

(Figure 2B) revealed an upper tracheal mass lesion. A protruding tumor arising from the posterior wall of the trachea, 2 cm distal to the vocal cords was found through bronchoscopy. Bronchoscopy-aided biopsy with electrocautery for tracheal tumor resection was not feasible due to respiratory distress with cyanosis, which occurred during the procedure.

The patient then underwent surgical intervention for resection of the tracheal tumor. An encapsulated and elastic tumor was found

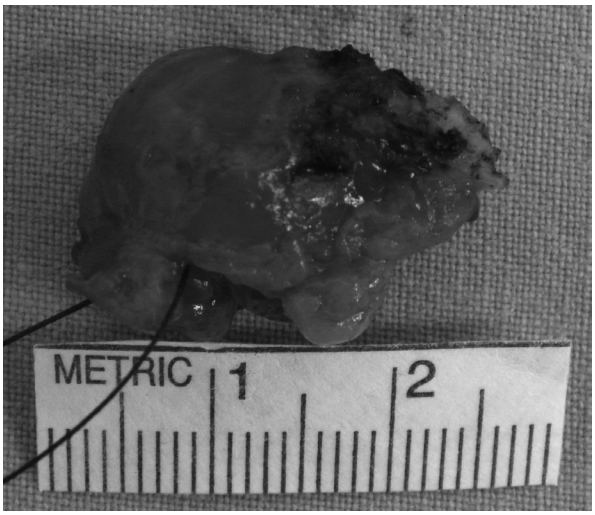
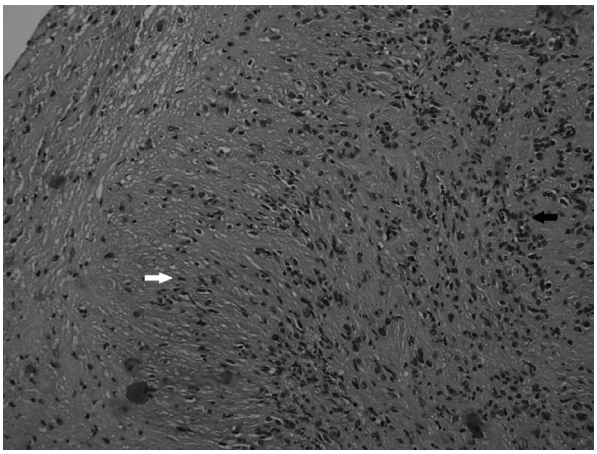



**Fig. 3.** An encapsulated and elastic tumor in the trachea was resected.

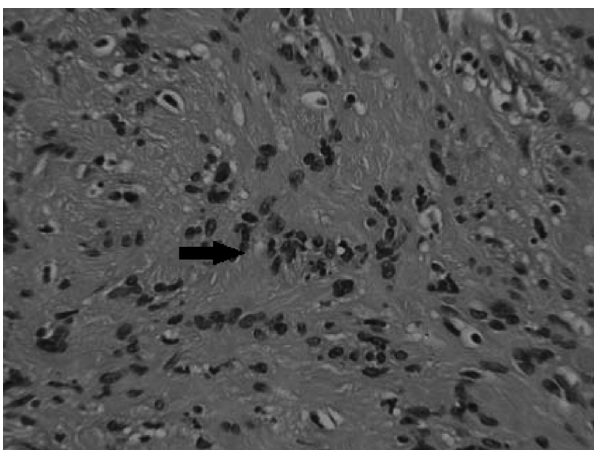
in the intraluminal section (Figure 3), and was confirmed microscopically to be a tracheal schwannoma. This well-defined tumor was composed of both cellular Antoni A and myxoid, hypocellular Antoni B areas. Verocay bodies characterized by nuclear palisading of neoplastic cells were also noted. The immunohistochemical study revealed positive findings for S-100 protein, which is highly specific for schwannoma (Figure 4). After receiving adequate therapy, the patient was discharged without any surgical complications. During the 6 months of follow-up, the patient was in good health and there was no evidence of local tumor recurrence.

## Discussion

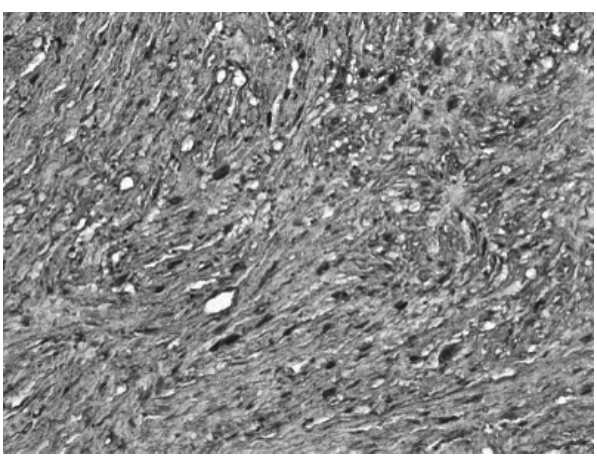
Primary tracheal tumors are rare among pulmonary neoplasms. Two-thirds of primary tracheal tumors are of the adenoid cystic carcinoma and squamous cell carcinoma types, with the remaining 1/3 belonging to a heterogeneous



(A)



(B)



(C)

**Fig. 4.** Microscopic examination: (A) Compact Antoni A tissue (black arrow) abutting a loose-textured Antoni B component (white arrow) (200 X, H & E). (B) Verocay bodies in Antoni A tissue with palisading nuclei (black arrow) (400 X, H & E). (C) Immunohistochemical stain revealed strong positivity for S-100 protein.

group composed of malignant, intermediate and benign lesions with different cell origins [1-2]. Tracheal schwannoma is an encapsulated neurogenic tumor that attaches to the nerve sheath, with solitary and benign characteristics [1,3]. Most cases involve young adults or children, and the most commonly involved site is the distal third of the trachea, followed by the proximal and middle thirds in decreasing order [1,3]. The other neurogenic tumor, neurofibroma, should also be considered in the differential diagnosis. Schwannomas differ from neurofibromas in that they are solitary and rarely associated with von Recklinghausen's disease, whereas neurofibromas are usually found in multiples and are frequently associated with this rare disease [1,4-5]. Microscopic analysis reveals that schwannomas have Antoni A and B areas, with high and low cellularity, respectively. Foci of palisaded nuclei, called Verocay bodies, may be seen in highly differentiated Antoni A areas. Antoni B areas are far less orderly and less cellular. The spindle or oval cells are arranged in loosely textured matrices. Immunohistochemical stains have revealed strong positivity of S-100 protein, which is highly specific for schwannomas [2-3,6].

The clinical course of tracheal tumors depends on their location, size and the degree of airway obstruction [7]. As with all tracheal tumors, the non-specific symptoms, including chronic cough and wheezing dyspnea, usually lead to a delayed diagnosis [2]. Fatal conditions, such as severe stridor, will develop until the tumor causes obvious tracheal obstruction. In addition, a normal CXR finding is noted in more than 50% of all cases; therefore, these patients are usually inappropriately treated as having chronic bronchitis or asthma [2]. However, a pulmonary function test may reveal the typical pattern of fixed airway obstruction, which can provide us with some clues to these diseases.

Chest CT is more efficient than CXR for the evaluation of tracheal schwannomas. The features on CT are well-demarcated, and there is a low density mass before contrast injection, with homogeneous and excessive contrast enhancement after contrast injection. However, these features are not specific for schwannoma. Nevertheless, CT is accurate in defining the location, degree of intra- and extra-tracheal extension and tumor size. Magnetic resonance images (MRI) also have a superior effect in helping identify tracheal schwannomas [3,8]. Overall, CT and MRI examinations can provide more complete information about tumor size, location and extension.

Flexible or rigid bronchoscopy is one of the most important procedures for the diagnosis of primary tracheal tumors [2-3]. The choice of treatment should be influenced by the clinical presentation, whether the tumor is pedunculated or sessile, and the presence or absence of an extratracheal component. Laser resection and bronchoscopic surveillance is most likely appropriate if the tumor is pedunculated and has no demonstrable extratracheal components, whereas tracheal resection and primary anastomosis is advised for more involved tumors [1].

Finally, surgical resection is the standard treatment for all benign tracheal tumors, including schwannoma [2,9]. Recurrence is unlikely after surgical resection [10]. The prognosis for patients with trachea schwannoma is excellent after adequate treatment is provided. However, long-term follow-up is still necessary for this type of patient.

## Conclusion

Primary tracheal schwannomas are extremely rare. Non-specific symptoms usually lead to a delayed diagnosis until severe upper airway obstruction develops. A chest CT or MRI can provide more detailed information with regard to tracheal tumors. Bronchoscopic examination is initially recommended in cases with a suspicion of such diseases. Finally, surgical resection is the "gold standard" for treatment. The prognosis is generally excellent with long-term follow-up.

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# 以慢性呼吸困難來表現的氣管許旺細胞瘤：病例報告

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原發性氣管許旺細胞瘤在氣管腫瘤裡是極度罕見的。我們報告一位36歲的女性，主訴為持續一年的慢性呼吸困難，而病患在住院後同時也被發現有喘鳴的症狀。我們安排了肺功能檢查也證實了典型的上呼吸道阻塞的圖型。胸部X光與電腦斷層掃描都顯示了位於上段氣管的腫瘤病灶，而支氣管鏡檢查也證實了位於聲帶下方氣管腫瘤的存在。最後病患接受了外科腫瘤切除手術，而最終的病理診斷為良性的許旺細胞瘤。這個病例顯示了一個合併常見症狀的罕見疾病，因此氣管腫瘤也必須納入不明原因呼吸困難的鑑別診斷之一。*(胸腔醫學* ***2012; 27: 181-186****)*

關鍵詞：氣管腫瘤，許旺細胞瘤，神經性腫瘤

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# Enlargement of a Bone Island of the Rib: A Case Report and Literature Review

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A bone island, known as an enostosis, is a benign entity usually found incidentally on image studies. Bone islands typically appear as sclerotic, round-to-ovoid intramedullary nodules and consist of normal-appearing compact bones surrounded by cancellous bones. The exact etiology of bone islands is not clear. Clinically, the importance of diagnosing bone islands is to distinguish them from more important lesions such as fibrous dysplasia, osteoblastoma, osteosarcoma, ostoma or even lung lesions, especially when noted in the rib. Sometimes bone islands grow, mimicking a worrisome pathological process. We report the case of a young woman with a bone island of the ribs, which showed progressive enlargement on a series of chest film examinations. ***(Thorac Med 2012; 27: 187-193)***

Key words: bone island, enostosis

## Introduction

An enostosis, also known as a bone island, is a focus of mature compact bones within the cancellous bone. The benign entity was first described by Stieda *et al*. in 1905 [1]. The etiology of the benign lesion is not clear, but it is probably a developmental error reflecting a failure of resorption in the process of endochondral ossification [2]. Bone islands can be found anywhere in the body, except in the cranial bones [3]. Generally, bone islands are located in long bones, such as the hip, femur, pelvis, tibia, finger, and rib. They are more frequently found in adults than in children, and occur in both sexes. Bone islands are typically between 1 mm and 2 cm in diameter, although some case reports present the so-called "giant bone islands" [3-5], defined by Gold *et al*. as those 2 cm or greater in diameter [6]. Bone islands may grow, reduce in size, disappear or remain stable. In general, bone islands are typically asymptomatic and accidentally found on x-rays performed for other purposes. However, some giant bone islands may be symptomatic or even accompanied by bone necrosis of the femoral head area, and require hemi-arthroplasty [5,7]. The lesion has also been described clinically as a compact "island", and its anomaly emphasized to distinguish it from other lesions in the differential diagnosis [8]. The most important step is to differentiate the bone island from pathological

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processes such as fibrous dysplasia, osteoblastoma and osteosarcoma. The former is benign, and the latter pathological processes look like bone islands at first. It is difficult to differentiate between the benign lesion and other pathological processes because the bone islands are still growing and enlarging in a few cases, mimicking a pathological lesion. Moreover, the origin of the enlarging bone island of the rib -- whether it is bone or parenchymal in origin -- is a challenge for the clinician to distinguish.

## Case Report

A 31-year-old female, an editor, was generally in good health and denied any other systemic disease. She had no chest pain, cough or dyspnea problem. She visited the chest outpatient department for an evaluation of the accidental finding of a nodule on the plain chest film at a mobile mass radiography clinic (Figure 1a).

During the review of her medical history, the patient denied specific complaints and any other discomfort. There was neither operation nor medication history. The patient's appetite was good and she denied body weight loss during the past few years. The physical examination was normal without any specific findings. Chest x-rays (CXR) revealed a radiodense nodule about 10 mm in diameter at the right lower lung field, overlapping the right peripheral area of the 6$^{th}$ rib. The nodule moved simultaneously with the right 6$^{th}$ rib in both lordotic and oblique CXR (Figure 2).

A computed tomography (CT) scan of the chest showed a hyperdense lesion at the right 6$^{th}$ rib with no other finding in the lung parenchyma area (Figure 3). The radionuclide bone image was normal without radionuclide uptake

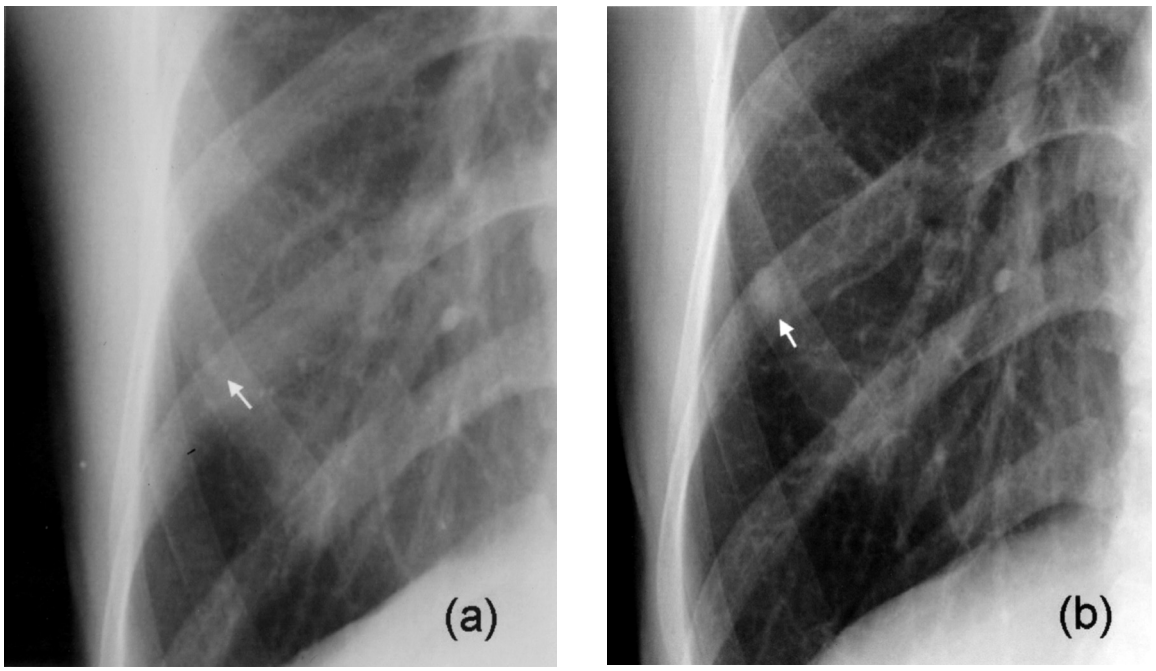



**Fig. 1.** Growing bone island. (a) Initial routine chest radiograph showed a 1.0 cm diameter lesion in the right anterior 6$^{th}$ rib. (b) Follow-up chest radiograph 5 years later showed that the lesion had increased to 1.5 cm in diameter.

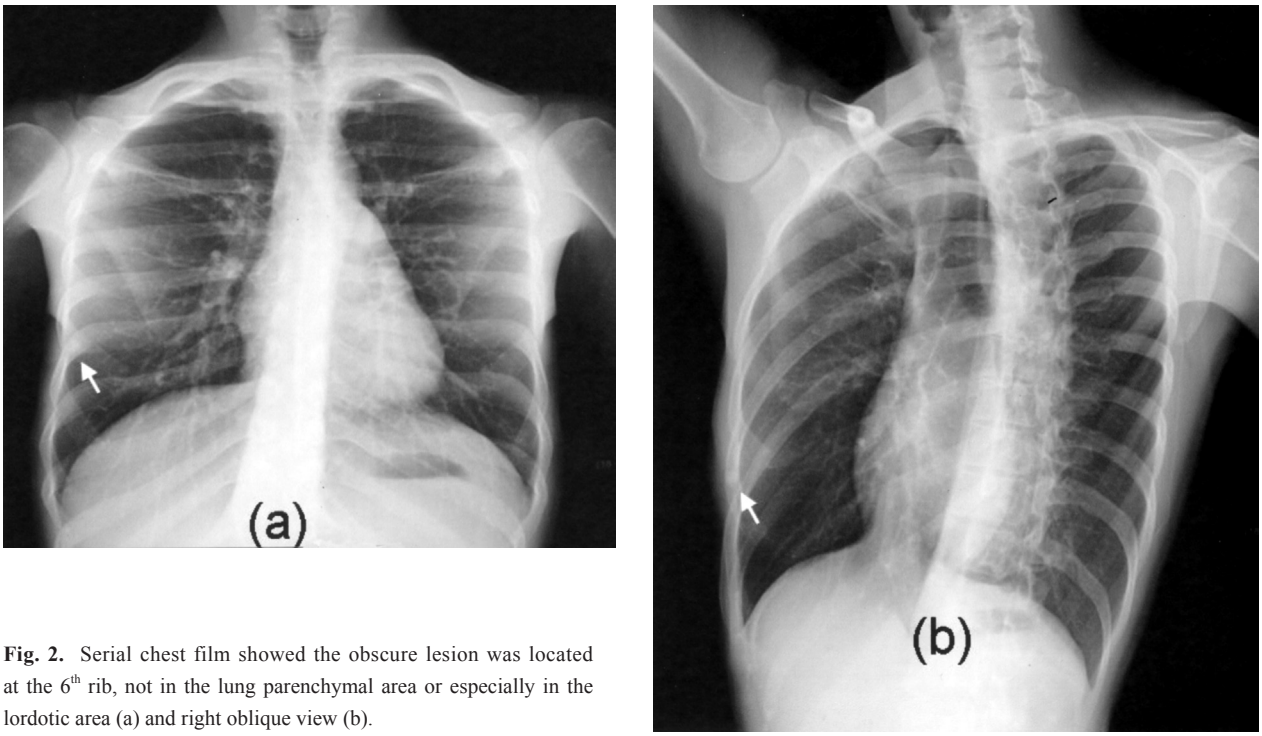
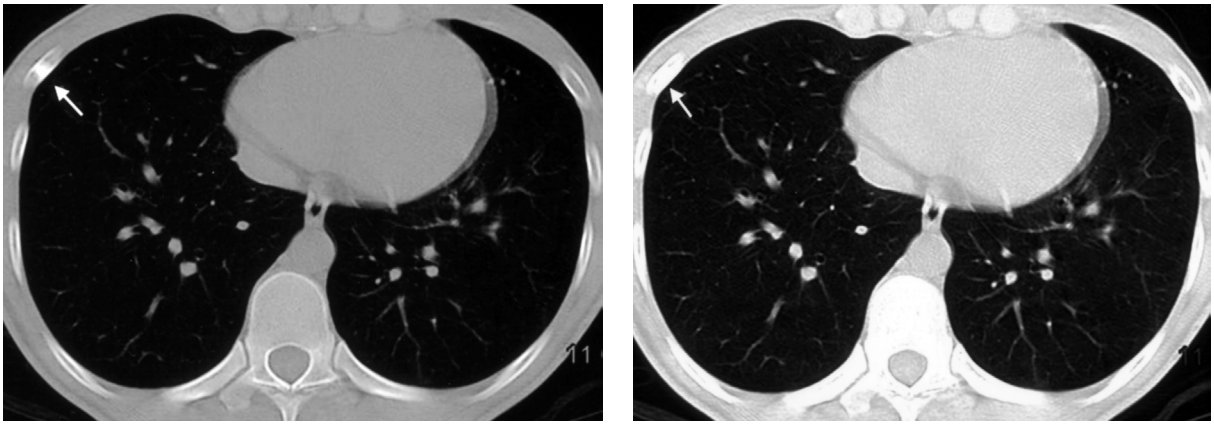



**Fig. 2.** Serial chest film showed the obscure lesion was located at the 6th rib, not in the lung parenchymal area or especially in the lordotic area (a) and right oblique view (b).



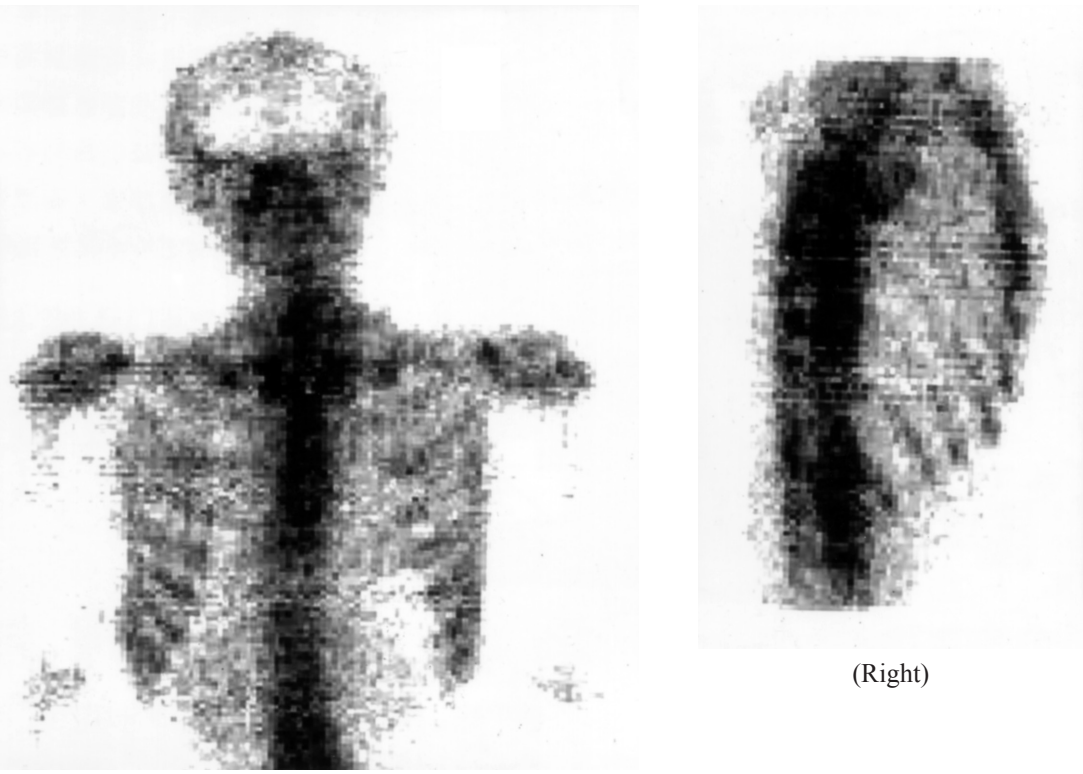
(a) (b)

**Fig. 3.** Computed tomography (CT) scan of the chest showing a hyperdense lesion at the right 6th rib in the bone window (a) and in the lung window (b).

in the right 6th rib lesion (Figure 4). Subsequent follow-up studies showed that the lesion had increased to 15 mm during a 5-year period (Figure 1b). No malignant features were discovered.

## Discussion

Bone islands are defined as cortical bone formations in the spongiosa. They are found throughout the body, especially in the long



(Right)

**Fig. 4.** A $^{99m}$Tc-MDP bone scan reveals no increased radionuclide uptake in the right 6$^{th}$ rib.

bones, and present as an ovoid, round or long focus in the cancellous bone. The majority of bone islands does not exceed 2 cm and causes no symptoms clinically. However, some investigators have also reported large bone islands, called "giant" bone islands, with a lesion larger than 2 cm [14]. The largest bone island reported was 10.5 cm in the femur in 1995 [9]. Usually bone islands are asymptomatic, but Masahiko *et al*. reported a rare case of giant bone islands of the femur concurrent with femoral head necrosis and pain [7]. However, the pain in this patient likely originated from the osteonecrosis rather than the sclerotic change in the femoral neck. Park *et al*. also reported a case of giant painful bone islands, with curettage of the lesion used to relieve the pain. He also reviewed 8 cases of giant bone islands with varying degrees of pain [5], suggesting that the greater the size of the bone islands, the higher the likelihood of induced symptoms.

The most common incidental finding of bone islands is on the x-ray, which shows them as dense, round-to-ovoid lesions. Also, they do not involve any soft tissue, damage or destruction of the cortex, or periosteal reaction. Some radiating spicules tend to surround the bone's spongy trabeculae peripherally without protruding from the bone surface, unlike in osteoma or osteosarcoma. CT scan is useful for studying bone lesions, and for evaluating the density and destructive change of the bone and the pattern of osteoclastic or osteoblastic changes. Bone islands showed isointense, intramedullary lesions

without extension or destruction of the linear cortex [9]. Some reports of magnetic resonance imaging (MRI) described the low signal intensity of bone islands on both T1- and T2-weighted MRI sequences [10]. Bone scintigraphy is a nuclear scanning test used to identify certain abnormalities in bone lesions, especially in bone metastasis from other origins. Most bone islands are seen as normal bones without increased uptake on radionuclide bone scans. However, a few cases exhibited an increased accumulation of $^{99m}$Tc pyrophosphate [11-12]. Sickles *et al*. postulated 2 reasons for positive bone scans: first, the large volume of lesions greater than 3 cm in diameter and second, the increased tracer accumulation in growing bone islands with significant osteoblastic activity [11]. Generally, bone islands cannot be visualized on bone scan because their metabolic activity is the same as that of the surrounding cancellous bones [13]. The growing bone island is thought to have higher metabolic activity with the possibility of increased radionuclide uptake on bone scan. Nevertheless, an enlarging bone island does not always reflect a positive bone scan, even in "giant bone islands" [3]. The increased size and growth of bone islands seem not to be essential factors in a positive bone scan. The increased uptake by some bone islands may relate to their greater osteoblastic activity [2]. Thus, when we suspect bone islands with a positive radionucleotide scan, we continue to follow up their size and image morphology. If we have other considerations, or new findings that conflict with the diagnosis of bone islands, bone biopsy for a definite diagnosis is indicated. In our case, the small bone island with interval growth showed a normal radionuclide bone scan without increased uptake.

The key point is to distinguish clinically between benign and malignant lesions. Although the "gold standard" in the diagnosis of bone islands is the histology, bone biopsy is not necessary in all cases of bone islands. Generally, using all parameters -- including the clinical and radiographic presentations, as well as scintigraphic findings and follow-up examinations -- allows for clear differentiation of a bone island [2]. Bone islands are characteristically asymptomatic and on x-rays appear as dense, sclerotic lesions with a border of radiating spicules. In our case, we first differentiated the bone island from the rib in the lung parenchymal area by using different postures for the x-rays. Then, we identified the growing bone lesion as a bone island by its characteristics of being asymptomatic, isolated, and having no radionuclide uptake. In conclusion, the correct diagnosis of bone islands should be based on the individual clinical situation and on the morphological features on x-ray and CT, regardless of the interval growth.

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# 肋骨內成長的骨島：病例報告及文獻回顧

李世瑜　張漢煜

骨島又被稱為內生骨疣，是一種良性的表現，通常是在做影像檢查時意外發現的。骨島通常發生在長形的骨頭上，主要的特徵是硬化的骨髓內結節，形狀是圓形至卵圓形，確切的病因目前仍然不明確。在臨床上的重要性是去區分良性的骨島與其他可能的骨頭病變，如纖維發育不良，骨母細胞瘤，骨肉瘤等，甚至於如果骨島發生在肋骨上，從影像上還要跟肺部的可能病灶做分辨，特別是隨著時間而變大的骨島，會模擬令人擔憂的病理變化。在此，我們描述一個年輕女性在追蹤胸部X光檢查下，肋骨內的骨島漸漸的成長與變化。藉由這樣的病例報告，提醒臨床醫師應該依據病人的個別狀況及影像的變化來正確診斷骨島。*(胸腔醫學* ***2012; 27: 187-193)***

關鍵詞：骨島，enostosis

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# Broken Stylet in Tracheobronchial Tree as a Complication of Endotracheal Intubation

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Many clinicians use an intubating stylet to facilitate endotracheal intubation, which is a common life-saving procedure in clinical practice. We reported the case of a patient with a broken metallic stylet that was retained in the tracheobronchial tree as a complication of endotracheal intubation, and was initially unnoticed. Difficulty in passing a suction catheter through the endotracheal tube and increased airway pressure under the mechanical ventilator setting aroused the awareness of the physician, and a follow-up chest radiograph confirmed the presence of a retained fragment of the broken stylet. The broken stylet was later successfully removed using fiberoptic bronchoscopy. No other report on the successful bronchoscopic removal of a broken metallic stylet from the endotracheal tube was found in a literature review. Doctors should be conscious of the possibility of a broken stylet when the suction catheter has a difficult passage or there is increased airway resistance. ***(Thorac Med 2012; 27: 194-198)***

Key words: endotracheal intubation, broken stylet, complication, bronchoscopy

## Introduction

Endotracheal intubation is a common life-saving procedure in the clinical practice of emergency and critical care medicine. Physicians should be conscious of its possible complications.

Many clinicians use an intubating stylet to facilitate endotracheal intubation. However, do clinicians always check the integrity of the device after the procedure? Broken stylets that remain in the airway have been reported before, but all incidences were detected immediately. Herein, we report the case of a broken metallic stylet that was retained in the tracheobronchial tree as a complication of endotracheal intubation. The retained stylet was initially unnoticed and was later successfully removed with the assistance of fiberoptic bronchoscopy.

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## Case Report

A 72-year-old female was sent to our emergency department because of consciousness disturbance for 2 days after falling down. She was comatose with a Glasgow coma scale rating of E1V1M3. Physical examination revealed no other obvious abnormal findings, and she had stable vital signs. All laboratory data were within the normal range. Computed tomography of the brain revealed bilateral subarachnoid hemorrhage. Elective endotracheal intubation was performed to maintain the airway due to the poor neurological status, and she was admitted to the surgical intensive care unit.

However, difficulty in passing the suction catheter via the endotracheal tube and increased airway pressure under mechanical ventilator support were noted. Chest radiograph revealed a linear opacity within the endotracheal tube (Figure 1).

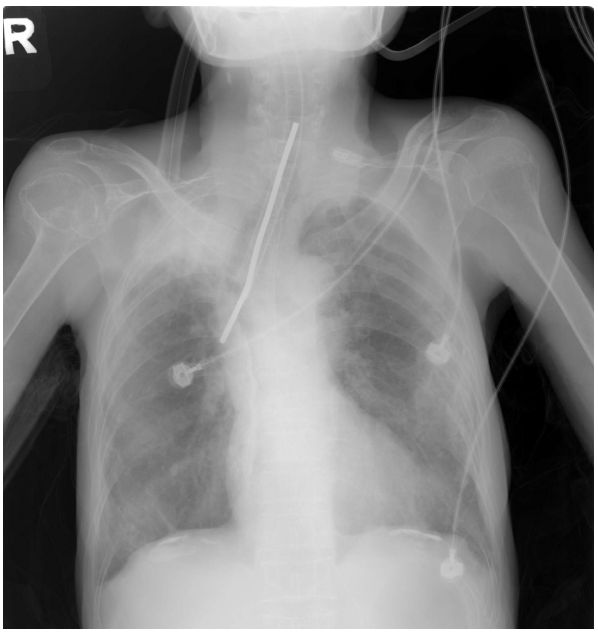


**Fig. 1.** Chest radiograph after intubation revealed a linear opacity (fragment of the broken stylet) inside the endotracheal tube.

Fiberoptic bronchoscopy was performed emergently and revealed the fragment of the broken metallic stylet within the endotracheal tube. The fragment was clipped by the biopsy forceps and was pulled out carefully. Once the tip of the fragment was seen in the oral cavity, we clamped the endotracheal tube and the fragment together with a Kelly forceps. Extubation, followed by re-intubation with a new endotracheal tube, was performed.

## Discussion

Intubating stylets are often used to facilitate endotracheal intubation, especially in difficult airways. Disposable plastic sheath-covered stylets or plastic bougies are advocated, while reusable metallic stylets are still in use in many places.

Airway obstruction by the sheared plastic sheath coating the metallic stylet has rarely been reported before, with most cases in a neonatal setting (Table 1) [1-8]. Broken metallic stylets with subsequent migration into the tracheobronchial tree during emergent endotracheal intubation have also been reported (Table 1) [9-12]. This hazardous complication related to malfunction of the equipment carries the potentially fatal risk of respiratory obstruction. Material fatigue resulting from multiple reuses of the stylet plays a critical role in the occurrence of a broken reusable stylet during intubation. This phenomenon may occur with both metallic and plastic sheath-covered stylets. With regular checking of the equipment and cautious use, this problem may be avoided.

In a recent report of similar circumstances, the broken tip of the metallic stylet was successfully removed directly by extracting the endotracheal tube [9]. Because of a concern about

**Table 1.** Previously reported cases of broken intubating stylet*

| Author, Year | Subgroup | Stylet | Discovery+ | Outcome |
|---|---|---|---|---|
| (Our case) | adult | MS | delayed | bronchoscopic removal |
| Schaffranietz *et al.*, 2009 [1] | adult | PSS | immediate | bronchoscopic removal |
| Koodiyedath *et al*., 2008 [2] | neonate | PSS | delayed | bronchoscopic removal |
| Sharma *et al*., 2008 [9] | adult | MS | delayed | removed together with ETT |
| Chiou *et al*., 2007 [3] | neonate | PSS | delayed | removed with optical forceps under telescopic vision |
| Yokohama *et al*., 2004 [10] | adult | MS | delayed | discharged with stool later |
| Lim *et al*., 2003 [11] | adult | MS | delayed | expectorated while coughing later |
| Sinha *et al*., 1999 [4] | adult | PSS | early | removed together with ETT |
| Bhargava *et al*., 1998 [5] | infant | PSS | early | removed together with ETT |
| Rabb *et al*., 1998 [6] | neonate | PSS | delayed | removed together with ETT |
| Sharma *et al*., 1994 [12] | adult | MS | early | removed together with ETT |
| Zmyslowski *et al*., 1989 [7] | neonate | PSS | early | removed together with ETT |
| Cook *et al*., 1985 [8] | infant | PSS | early | removed together with ETT |

* MS: metallic stylet; PSS: plastic sheath-covered stylet; ETT: endotracheal tube

+ Early discovery is defined as noticing the broken intubating stylet during or right after the process of intubation. Delayed discovery is defined as noticing this complication later.

the risk of a fragment remaining in the trachea, bronchoscopic traction of the fragment was performed in our case. No other reports on the successful bronchoscopic removal of a broken metallic stylet from the endotracheal tube were found in a literature review.

Doctors should be conscious of possible endotracheal foreign bodies, including a broken stylet, when the difficult passage of a suction catheter or increased airway resistance is encountered. During intubation, the integrity of the stylet must always be checked immediately after its withdrawal, and the follow-up chest radiograph must be read carefully immediately thereafter to detect possible complications of intubation.

Although a broken stylet rarely occurs, strategies to prevent this and similar potentially lethal problems must be devised and followed. Standard operating procedures for regular equipment checks and a protocol of peri-intubation care must be set up to improve healthcare quality and patient safety. In addition, it is recommended that a system to report equipment malfunction to the institution, the companies that make the equipment, and even the national body, be established.

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# 卡在氣管支氣管中的斷裂通條—氣管內插管的併發症

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氣管內插管是臨床上常用以維持生命的技術。許多臨床醫師使用通條來幫助氣管內插管的順利進行。我們報告一個氣管內插管時併發通條斷裂並卡在氣管支氣管中的病例。這個合併症在起初並未被察覺，而後由於抽痰時發現抽痰管不易放入，且呼吸器上顯示氣道壓力上升，檢視胸部X光片才發現卡在氣管支氣管中的通條斷片。此斷裂的通條隨後即在支氣管鏡輔助下取出。文獻搜尋顯示這是第一個成功在支氣管鏡輔助下取出氣管支氣管中通條斷片的報告。臨床醫師在發現氣管內插管的病人若抽痰時抽痰管不易放入或呼吸器上顯示氣道壓力上升時，應該警覺氣道內異物的可能性，而通條斷片即是其中一種。*(胸腔醫學* ***2012; 27: 194-198)***

關鍵詞：氣管內插管，通條斷裂，併發症，支氣管鏡

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