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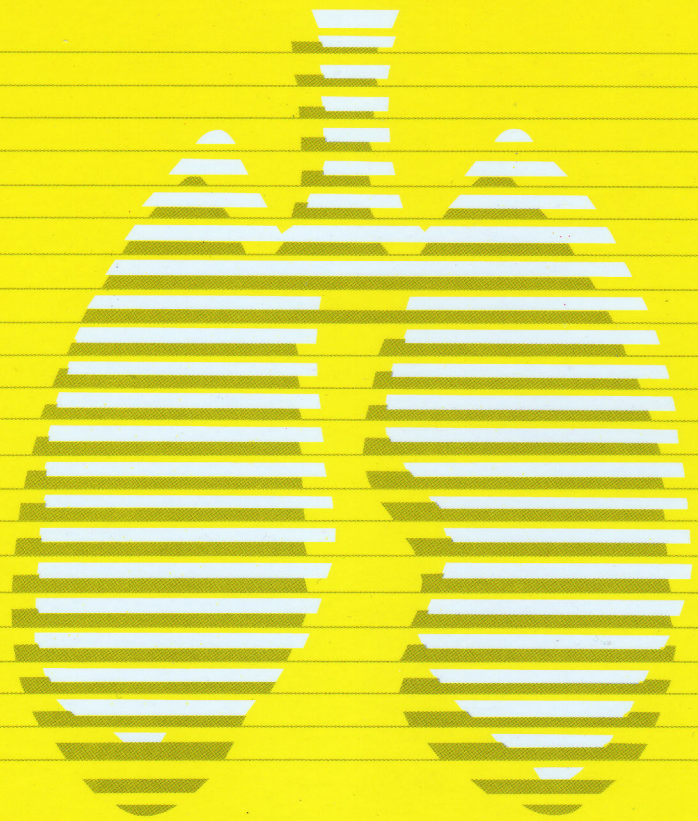

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## 原著



## 病例報告

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The Official Journal of Taiwan Society of Pulmonary and Critical Care Medicine

## Orginial Articles



## Case Reports

# Comparison of Weekly Vinorelbine and Weekly Docetaxel, Each with Cisplatin, for Locally Advanced Non-Small Cell Lung Cancer in Patients with Concurrent Chemoradiotherapy

Chung-Shu Lee, Chih-Hung Chen, Kuo-Chin Kao, Shinn-Yn Lin*, Li-Chung Chiu, Chien-Ying Liu, Ning-Hung Chen, Chung-Chi Huang, Ying-Huang Tsai**, Cheng-Ta Yang

**Background:** Concurrent chemoradiotherapy (CCRT) is 1 of the standard treatments for locally advanced non-small cell lung cancer (NSCLC) patients. The aim of the present study was to evaluate and compare the efficacy and toxicities of weekly vinorelbine and weekly docetaxel plus cisplatin for locally advanced stage III NSCLC patients with CCRT.

**Patients and Methods:** We performed a retrospective review of locally advanced stage III NSCLC patients in a tertiary referral medical center between January 2003 and December 2009. Patients with histologically and/or cytologically confirmed NSCLC with inoperable stage IIIA or IIIB disease who underwent CCRT with a regimen of weekly cisplatin 20 mg/$m^2$ combined with weekly vinorelbine 20 mg/$m^2$ or docetaxel 20 mg/$m^2$ were included. The scheduled dose of thoracic irradiation was 60 Gy in 30 fractions. The collected data included general information, stage, histological types and performance status. Treatment response, including response rate, time to disease progression, survival time and toxicity, was compared in both groups.

**Results:** Ninety-five patients were enrolled for analysis; 26 (27.4%) had stage IIIA and 69 (72.6%) had stage IIIB NSCLC. All clinical characteristics, except stages, were identical in the 2 groups. The portion of stage IIIB patients was significantly higher in the vinorelbine group than that in the docetaxel group (83.3% versus 61.7%, $p$=0.018). The disease control rates and response rates of the vinorelbine and docetaxel groups were 72.9% and 74.5%, and 45.8% and 51.1%, respectively. One of 8 stage IIIA patients (12.5%) in the vinorelbine group and 7 of 18 stage IIIA patients (38.9%) in the docetaxel group were down-staged and subsequently received surgical resection for residual tumors. The median survival time of the patients in both groups was not significantly different (15.6 months versus 22.1 months; $p$=0.07). The incidence of leukopenia was higher in the vinorelbine group (33.3%) than in the docetaxel group (4.3%). We noted that 39.6% of patients in the vinorelbine group and 68.1% in the docetaxel group completed 6 cycles of chemotherapy, respectively. There were 4 toxic

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deaths due to sepsis during the treatment period, 1 in the vinorelbine group and 3 in the docetaxel group.

**Conclusions:** CCRT with a regimen of weekly vinorelbine plus cisplatin or weekly docetaxel plus cisplatin may have similar effects. There was less toxicity and greater tolerance in the docetaxel group. ***(Thorac Med 2013; 28: 260-269)***

Key words: non-small cell lung cancer (NSCLC), concurrent chemoradiotherapy (CCRT), survival, cisplatin, vinorelbine, docetaxel

## Introduction

In Taiwan, lung cancer is the leading cause of cancer-related deaths [1]. Non-small cell lung cancer (NSCLC) is the most prevalent type, accounting for more than 80% of lung cancers. The outcome of NSCLC patients with bulky stage IIIA or IIIB, i.e., locally advanced disease, is poor. The median survival time is 10 and 14 months, and the 5-year-survival rate is 18% and 8% for IIIA and IIIB NSCLC, respectively [2]. The combination of chemotherapy and radiotherapy for NSCLC patients with locally advanced disease has long been evaluated as a standard of care, and has been proven to provide significant benefits with regard to survival [3-4].

Compared with sequential radiochemotherapy, concurrent chemoradiotherapy (CCRT) can provide longer median survival time and better locoregional control for patients with locally advanced NSCLC [5-6]. In CCRT, cisplatin is commonly used as a radiosensitizer [4]. Vinorelbine and docetaxel, 2 of the current, novel 3rd-generation chemotherapy agents for NSCLC, are also effective radiosensitizers *in vitro* [7-8]. Some previous studies have demonstrated the efficacies of vinorelbine or docetaxel combined with tri-weekly cisplatin and radiotherapy in patients with inoperable stage III NSCLC [5-6,9-14]. There is evidence that among stage III NSCLC patients, CCRT with weekly chemotherapy was better tolerated than radiotherapy followed by additional chemotherapy [15].

The objective of this study was limited to evaluating the efficacy of weekly vinorelbine and docetaxel plus cisplatin in stage III NSCLC patients receiving CCRT. This retrospective study aimed to compare the clinical outcomes and toxicity of weekly vinorelbine and docetaxel plus cisplatin as CCRT in locally advanced inoperable stage III NSCLC.

## Patients and Methods

### *Patients*

This study involved collecting and analyzing data for the period January 2003 to December 2009 from the lung cancer registry system in a tertiary referral medical center in Taiwan. We performed a retrospective review of locally advanced inoperable stage III NSCLC patients and followed up their medical outcomes until June 2011. This retrospective study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No.101-0001B). The classification system outlined in

the 2002 American Joint Committee on Cancer (AJCC) 6th edition for TNM staging was used for the enrolled patients [16]. Stage III patients with histologically and/or cytologically confirmed NSCLC without pleural effusion and that met the following criteria: (1) chemo-naïve, (2) inoperable at initial presentation, and (3) underwent curative CCRT with the regimen of weekly vinorelbine or docetaxel plus cisplatin, were included.

Baseline evaluation included the patient's history, physical examination, routine complete blood cell count, biochemistry, chest radiography, chest computed tomography, pathology result and bone scan. Performance status (PS) was calculated using the ECOG performance scoring system scored from 0 to 5.

***Chemotherapy and radiotherapy schedule***

The treatment schedule consisted of cisplatin 20 mg/m$^2$ weekly combined with vinorelbine 20 mg/m$^2$ weekly in the vinorelbine group, and docetaxel 20 mg/m$^2$ weekly with cisplatin 20 mg/m$^2$ weekly in the docetaxel group. The dose of thoracic radiotherapy was 60 Gy scheduled into 30 fractions, 1 fraction a day, 5 days per week. Radiotherapy was initiated on day 1 of chemotherapy. The clinical radiotherapy target area consisted of the primary volume of the gross tumor and node, the ipsilateral hilum region and an elective mediastinum for which the lower edge was 3.0 cm below the carina. The planned radiation target area was a margin plus the clinical radiotherapy target area to ensure that the prescribed dose precisely covered the lesion. After CCRT with a maximum of 6 weekly cycles of chemotherapy, lobectomy might be considered, otherwise 2 to 3 cycles of consolidation chemotherapy with cisplatin 75 mg/m$^2$ combined with vinorelbine 20 mg/m$^2$ every 4 weeks or combined with docetaxel 20 mg/m$^2$ tri-weekly would be administered, depending on the patient's tolerance and the physician's experience, if the patient could not undergo surgery.

Treatment was discontinued if disease progression or unacceptable side effects developed. A maximum of 6 weekly cycles was given to responders with tolerance to treatment. Chemotherapy was postponed until recovery if the granulocyte count was less than 1,000/μL and/or the platelet count was less than 50,000/μL.

***Efficacy and safety evaluations***

Treatment response was assessed based on Version 1.0 of the Response Evaluation Criteria in Solid Tumors (RECIST). Toxicity was evaluated using the World Health Organization (WHO) toxicity grading scale.

The evaluation parameters, including response rate, time to disease progression, overall survival and toxicity profile, were compared between the 2 treatment groups. Time to disease progression was defined as the time interval from the date of initial treatment to the date of disease progression. Survival was calculated from the date of initial treatment to the date of death. Survival and disease progression data up to June 2011 were analyzed. If death or progression had not occurred, survival time and progression time were considered censored.

***Statistical analysis***

The Chi-Square test was used to compare variables between patients within the 2 treatment groups. Overall survival was estimated using the Kaplan-Meier method. Cox regression analysis was used to compare survival rate factors of the 2 regimens. All data were calculated using SPSS version 18.0 statistical software

(PASW Statistics).

## Results

Ninety-five patients with locally advanced NSCLC treated with CCRT with a regimen of weekly cisplatin 20 mg/m$^2$ combined with weekly vinorelbine 20 mg/m$^2$ or docetaxel 20 mg/m$^2$ were registered at our hospital from January 2003 to December 2009. The median age of the patients was 61 years, (range, 53-73 years). Twenty patients (21.1%) had a WHO performance status (PS) of 0 and the remaining 75 patients (78.9%) had a PS of 1. Fifty-two patients (54.7%) had squamous cell carcinoma and 25 (26.3%) had adenocarcinoma in histological type; 26 patients (27.4%) had stage IIIA and 69 (72.6%) had stage IIIB NSCLC. All clinical characteristics, except for stages, were identical in both regimen groups. The portion of stage IIIB patients was significantly higher in the vinorelbine group than that in the docetaxel group ($p$=0.018, 83.3 versus 61.7%, respectively) (Table 1).

### *Response, time to disease progression and survival*

Of the assessable patients treated with cispla-tin and vinorelbine, 1 had a complete response (CR) and 21 achieved a partial response (PR); the overall response rate was 45.8% (95% confidence interval, CI: 31.4% to 60.8%). In the cisplatin and docetaxel group, 24 achieved a PR and the overall response was 51.1% (95% CI: 36.11% to 65.9%). After excluding 9 patients (1 in the vinorelbine group and 8 in the docetaxel group) who underwent surgery after CCRT, the median time to disease progression was 6.1 and 5.9 months for the vinorelbine group (47 patients) and docetaxel group (39 patients) ($p$=0.893), respectively. The median time to disease progression for all patients was 6.0 months, and median overall survival time was 15.6 months and 22.1 months for the vinorelbine group and docetaxel group ($p$=0.07), respectively. At the end of the survival analysis, 23 patients were still alive. The Kaplan-Meier curve for survival is shown in Figure 1. After taking age and pathology result into consideration, there was no significant difference between the 2 groups in survival, using Cox regression analysis ($p$=0.131).

Resected tissues were free of malignancy in 2 (22.2%) of the 9 patients that underwent subsequent surgery: 1 in the vinorelbine group and 1 in the docetaxel group. Furthermore, it was found that 31.9% (15/47) and 15.4% (6/39) of the patients received consolidation therapy in the vinorelbine group and docetaxel group, respectively.

### *Treatment Tolerance and Toxicity*

We found that 97.3% of patients in the vinorelbine group and 80.9% in the docetaxel group received a radiation dose of more than 55 Gy. Further, 39.6% of patients in the vinorelbine group and 68.1% in the docetaxel group completed 6 cycles of chemotherapy, respectively. The average cycle numbers were 4.8 and 5.2 in the vinorelbine group and docetaxel group, respectively. In terms of the grade 3 or 4 hematology and non-hematology toxicities of both groups, the major hematological toxicity was leukopenia. Of the total number of patients, 13 (13.7%) developed grade 3 leukopenia and 5 (5.3%) had grade 4 leukopenia, but no febrile neutropenia was noted. Sixteen patients (16.8%) developed grade 3 esophagitis and 1 (1.1%) suffered from grade 4 esophagitis. There were 4 toxic deaths as a result of sepsis during the

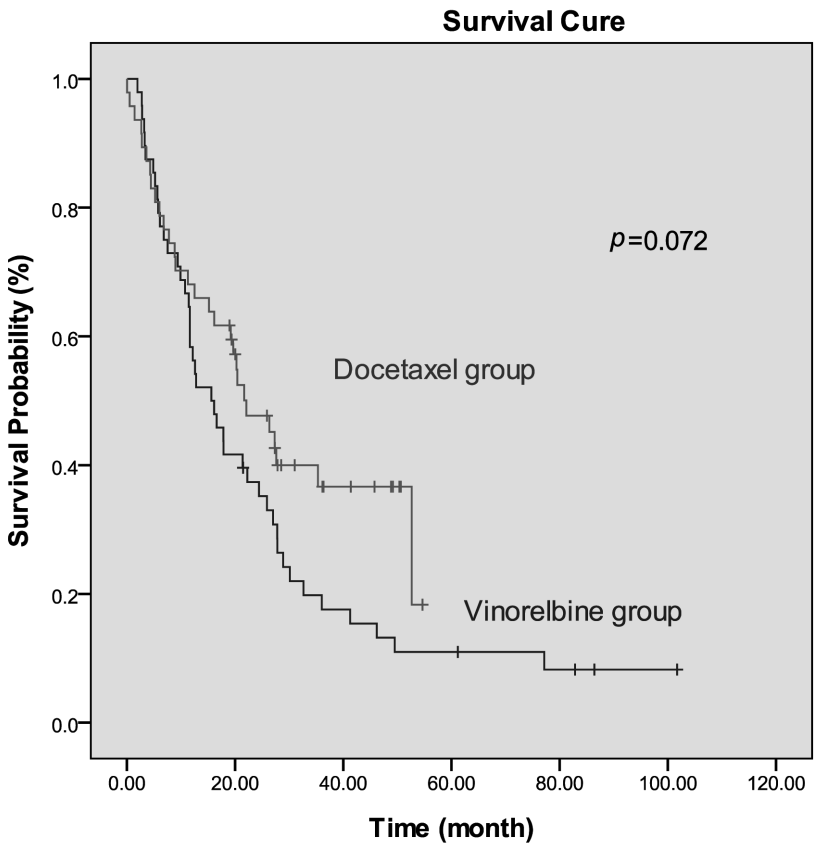


**Fig. 1.** Kaplan-Meier survival curve of the vinorelbine group and docetaxel group. Median survival time: 15.6 and 22.1 months for the vinorelbine group and docetaxel group, respectively, $p$=0.072.

treatment period, 1 in the vinorelbine group and 3 in the docetaxel group. There was a higher incidence of leukopenia in the vinorelbine group, and the major toxicity of the docetaxel group was esophagitis (Table 2).

## Discussion

This study suggested that the regimen of weekly vinorelbine plus cisplatin or weekly docetaxel plus cisplatin can be administered with concurrent radiotherapy as it has fair efficacy and acceptable toxicity for locally advanced inoperable stage III NSCLC patients. In addition, less toxicity and greater tolerance were noted in the docetaxel group, compared with the vinorelbine group.

Locally advanced NSCLC patients are a heterogeneous group and have quite different spectrums of mediastinal invasion and lymph node involvement. There are a variety of controversial therapeutic options for such malignancies, including CCRT, neoadjuvant chemotherapy or chemoradiotherapy before surgery, surgery followed by adjuvant chemotherapy, and sequential chemoradiotherapy [3]. There is still lack of consensus on the standard of care and optimal management protocol for such patients. The treatment decision is often based on the patient's general condition, the initial dis-

**Table 1.** Characteristics of 95 Enrolled Patients with Locally Advanced Non-small Cell Lung Cancer

| Characteristics | N (%) | Vinorelbine (N=48) | Docetaxel (N=47) | *p* value |
|---|---|---|---|---|
| Gender | | | | |
| Male | 74 (77.9%) | 38 (79.2%) | 36 (76.6%) | 0.763 |
| Female | 21 (22.1%) | 10 (20.8%) | 11 (23.4%) | |
| Age (years old) | | | | |
| Median | 60.4 | 59.9 | 60.9 | 0.660 |
| Range | 32-80 | 32-80 | 35-77 | |
| Performance status | | | | |
| ECOG* 0 | 20 (21.1%) | 10 (20.8%) | 10 (21.3%) | 0.958 |
| ECOG 1 | 75 (78.9%) | 38 (79.2%) | 37 (78.7%) | |
| Histological types | | | | |
| Squamous cell carcinoma | 52 (54.7%) | 28 (58.3%) | 24 (51.1%) | 0.756 |
| Adenocarcinoma | 25 (26.3%) | 12 (25.0%) | 13 (27.7%) | |
| Other | 18 (18.9%) | 8 (16.7%) | 10 (21.3%) | |
| Stage | | | | |
| IIIA | 26 (27.4%) | 8 (16.7%) | 18 (38.3%) | 0.018 |
| IIIB | 69 (72.6%) | 40 (83.3%) | 29 (61.7%) | |

*ECOG: Eastern Cooperative Oncology Group

**Table 2.** Grade 3 or 4 Toxicity of CCRT with Weekly Vinorelbine or Docetaxel and Cisplatin

| Toxicity | Vinorelbine (N=48) | Docetaxel (N=47) | |
|---|---|---|---|
| | No (%) | No (%) | *p* |
| Leukopenia | 16 (33.3) | 2 (4.3) | <0.001 |
| Anemia | 5 (10.4) | 8 (17.0) | 0.349 |
| Thrombocytopenia | 1 (2.1) | 3 (6.4) | 0.297 |
| Hepatic | 0 (0.0) | 1 (2.1) | 0.310 |
| Diarrhea | 1 (2.1) | 0 (0.0) | 0.320 |
| Nausea/Vomiting | 13 (27.1) | 8 (17.0) | 0.237 |
| Mucositis | 1 (2.1) | 0 (0.0) | 0.320 |
| Radiation pneumonitis | 3 (6.3) | 1 (2.1) | 0.317 |
| Esophagitis | 6 (12.5) | 11 (23.4) | 0.166 |

ease presentation at diagnosis, the physician's experience and preference, and the facilities available at the hospital. When patients can receive treatment only with a palliative goal in mind, CCRT can provide a statistically significant benefit with regard to overall survival, compared to sequential treatment (Hazard ratio, HR=0.84, $p$=0.004) [5]. CCRT may contribute an absolute survival benefit of 5.7% at 3 years and 4.5% at 5 years, at the cost of increased

grade 3/4 toxicities, especially esophagitis (from 4-18%), during therapy [5].

At the time of diagnosis, physicians may need to choose neoadjuvant treatment with a curative intent followed by surgical resection for certain patients. CCRT was developed to improve locoregional control and to achieve pathological down-staging [5-6,17]. In this study, 8 of 18 (38.9%) patients with IIIA disease received complete resection in the docetaxel group, compared to 1 of 8 patients (12.5%) in the vinorelbine group. Weekly administered schedules, such as that seen in our study, have been shown to be effective in many previous studies, and the recommended doses were docetaxel 20 or 25 mg/m$^2$ and cisplatin 20 or 25 mg/m$^2$ [10-11,14,18]. The dose limiting toxicity was esophagitis. The rate of grade 3/4 esophagitis in our docetaxel group was 23.4%.

Vinorelbine was shown to be as effective as gemcitabine and paclitaxel when combined with cisplatin in a regimen of CCRT. The median progression-free survival for the 3 arms (vinorelbine, gemcitabine, palictaxel) was 11.5, 8.4 and 9.1 months, respectively, and the overall survival was 17.7, 18.3 and 14.8 months, respectively [12]. In addition, there were fewer cases of toxicity and treatment interruptions (grade 3/4 neutropenia 27%, grade 3/4 esophagitis 25%) with the vinorelbine and cisplatin combination [19]. A study conducted by Zatloukal *et al*. that randomized patients using cisplatin and vinorelbine showed significantly better results in terms of time to disease progression (11.9 versus 8.5 months, respectively; $p$=0.024) and survival (16.6 versus 12.9 months, respectively; $p$=0.023) with the CCRT approach than with sequential chemoradiotherapy [13]. But grade 3/4 toxicities were more often found in the concurrent arm than in the sequential arm, especially granulocytopenia (53% versus 19%, respectively) and esophagitis (18% versus 4%, respectively). Our data in the vinorelbine group indicated a similar result with a time to disease progression of 6.1 months and median survival of 15.6 months. Grade 3/4 leukopenia and esophagitis occurred in 33.3% and 12.5% of patients, respectively.

The results of our report indicated that the cisplatin plus docetaxel combination was more tolerable, as 68.1% of patients in the docetaxel group received 6 planned cycles of chemotherapy, compared to 39.6% of patients in the vinorelbine group. Although there was a trend toward longer survival in the docetaxel group (22.1 months vs. 15.6 months in vinorelbine group), the difference did not achieve statistical significance, and time to disease progression for both groups was similar (5.9 vs. 6.1 months, respectively). It is noteworthy that more patients in the docetaxel group were at stage IIIA disease (38.3% vs. 16.7% in the vinorelbine group). Post-CCRT treatment may also affect the prognosis. Eight patients in the vinorelbine group and 17 in the docetaxel group received epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). Furthermore, all patients in the docetaxel group had already received CCRT when EGFR-TKI was introduced into clinical practice in Taiwan; no doubt, the subsequent treatment may have influenced survival [20].

In order to improve treatment outcome, some investigators use an additive treatment approach, either as induction chemotherapy or consolidation chemotherapy. However, there is no strong evidence to support the further improvement of a patient's survival with the additive treatment [12,21-22]. We used 2-3 cycles of chemotherapy after CCRT, but only a small

number of patients received consolidation therapy (15 patients in the vinorelbine group and 6 in the docetaxel group).

There are some limitations that should be addressed with regard to this study. First, this retrospective report reveals a real outcome of ordinary clinical practice, as most of our patients did not meet the restrictive inclusion criteria for most clinical trials. In earlier clinical trials, elderly patients and/or those with serious comorbidities were often excluded from aggressive chemoradiotherapy [5]. A successful therapy needs to find the balance between efficacy and patient tolerance. Collaboration among pulmonary physicians, medical oncologists, radio-oncologists and thoracic surgeons may be of help in selecting more suitable patients for CCRT. Second, there were incomplete evaluation parameters among the collected patient data. Some prognostic factors, such as pulmonary function test, body weight loss, performance status, hemoglobin and radiotherapy dose-volume parameters (V20), may be used to tailor individual treatment [23]. Third, not every enrolled patient received advanced radiation therapy. Advanced radiotherapy techniques like 3-dimensional conformal radiation therapy, image-guided radiation therapy (IGRT), and intensity-modulated radiation therapy (IMRT) can deliver higher radiation doses with less collateral injury to normal tissue. Such techniques may make CCRT more feasible for most patients [24]. Finally, the relatively small number of patients at a single center offers a limited assessment and as a result, our conclusions are difficult to confirm. Larger prospective multicenter studies are needed to achieve results that can be generalized.

## Conclusion

In conclusion, this study revealed that CCRT with the regimen of weekly vinorelbine plus cisplatin or weekly docetaxel plus cisplatin may have similar effects. There was less toxicity and greater tolerance in the docetaxel group.

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# 在局部後期非肺小細胞癌病人接受同步化學放射治療時，比較每週 vinorelbine 和 docetaxel 加上 cisplatin 之差異

李忠恕　陳志弘　高國晉　林信吟 *　邱立忠　劉劍英　陳濘宏　黃崇旂
蔡熒煌 **　楊政達

**前言**：同步使用化學治療和放射治療是治療局部後期非肺小細胞癌之標準方法，在亞洲此方法的成效結果並不充足詳細。這個回溯性研究作了同步放射治療和每週化學治療於兩種不同化學治療成分（cisplatin併vinorelbine或cisplatin併docetaxel）的效力和毒性比較。

**方法**：這個研究收集了 95 位局部後期（stage IIIA or IIIB）非肺小細胞肺癌病人接受了同步放射治療和每週化學治療（cisplatin 併 vinorelbine 或 cisplatin 併 docetaxel）。我們記錄下病人基本背景數據，病理切片結果，治療副作用的資料，同時利用 Chi-Square test、Kaplan-Meier survival curve 和 Cox regression 來分析。

**結果**：這兩組（vinorelbine 組和 docetaxel 組）病人的基本資料除了分期（stage）比例有差別外，其餘是相似的。在 vinorelbine 組和 docetaxel 組中，疾病控制程度分別為 72.9% versus 56% 及治療反應為 45.8% versus 51.1%。在 stage IIIA 病人裡，vinorelbine 組 8 個病人中有 1 個可以接受完全切除手術( 12.5%)，docetaxel 組則是 18 位病人中有 7 位可接受完全切除（38.9%）。全部的病人（含接受手術者），vinorelbine 組和 docetaxel 組的中位存活數分別為 15.6 months versus 22.1 months。白血球低下的發生率在 vinorelbine 組是比較高的（33.3% versus 4.3%）。治療期間有 4 個病人因敗血症而死亡，其中 1 個在 vinorelbine 組，另 3 個在 docetaxel 組。

**結論**：這篇研究顯示在局部後期非肺小細胞癌病人中同步放射治療和每週化學治療（cisplatin 併 vinorelbine 或 cisplatin 併 docetaxel）是安全且有效的。而未來在這類病人的治療成效上，仍需進一步前瞻性研究。*( 胸腔醫學 **2013; 28: 260-269**)*

關鍵詞：非肺小細胞癌，同步放射治療和化學治療，存活率，cisplatin，vinorelbine，docetaxel

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# Concomitant Treatment with Recombinant Human Activated Protein C and Extracorporeal Membrane Oxygenation for Sepsis-related Acute Respiratory Distress Syndrome

Chin-Chih Chang*,**, Shuenn-Wen Kuo*,**, Jang-Ming Lee**, Wen-Je Ko*,**

**Introduction:** Sepsis-related acute respiratory distress syndrome (S-ARDS) is a difficult problem for clinicians. The aim of this study was to evaluate the efficacy and safety of combined treatment with recombinant human activated protein C (rhAPC) and extracorporeal membrane oxygenation (ECMO) for S-ARDS.

**Methods:** We retrospectively analyzed a prospective database in a single institution. Patients with S-ARDS requiring ECMO support were enrolled. RhAPC was given to the patients who met the criteria of our study. Other patients received conventional management. The primary endpoint was all-cause hospital mortality, and the secondary endpoint was serious bleeding complications.

**Results:** A total of 14 patients were enrolled. Five patients received rhAPC and 9 underwent conventional treatments. Two of 5 patients in the rhAPC group (40.0%) and 8 of 9 patients in the control group (88.9%) died in the hospital ($p$=0.095). Two serious bleeding incidents occurred in patients in the control group (22.2%) and none in the rhAPC group ($p$=0.505).

**Conclusion:** Our analyses suggested rhAPC has no significant effect on the reduction of all-cause mortality in patients with S-ARDS requiring ECMO support, although no increase in serious bleeding complications associated with rhAPC treatment was noted. ***(Thorac Med 2013; 28: 270-277)***

Key words: activated protein C, acute respiratory distress syndrome (ARDS), drotrecogin alfa, extracorporeal membrane oxygenation (ECMO), sepsis, Xigris

## Introduction

Acute respiratory distress syndrome (ARDS) is a difficult problem for clinicians. The overall pooled mortality of ARDS was as high as 44.3% in the last decade, without a substantial decrease over time [1]. Many treatment options have been proposed to reduce the mor-

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tality of ARDS, including low tidal volume [2], the prone position [3], surfactant supplements [4], inhaled nitric oxide [5], and corticosteroid [6]. Extracorporeal membrane oxygenation (ECMO) can provide vital support for refractory respiratory failure. In the CESAR trial, management with ECMO reduced the rate of death or disability at 6 months in patients with ARDS, resulting in an absolute reduction from 53% to 37% [7].

Sepsis is the leading cause of ARDS [8]. Recombinant human activated protein C (rhAPC) had been regarded as an effective drug to reduce mortality in patients with severe sepsis [9]. However, it was associated with an increased risk of bleeding [9-11]. In October 2011, Eli Lilly and Company, the manufacturer of rhAPC [drotrecogin alfa (activated), Xigris®], announced the worldwide withdrawal of the product from the market due to a lack of benefit relative to 28-day mortality in the preliminary analyses of the PROWESS-SHOCK study [12]. The purpose of this study was to evaluate the efficacy and safety of combined treatment with rhAPC and ECMO for sepsis-related ARDS (S-ARDS).

## Patients and Methods

The study protocol was approved by the Research Ethics Committee of National Taiwan University Hospital. We retrospectively analyzed a prospective database of the Surgical Intensive Care Unit, National Taiwan University Hospital. We enrolled all patients who had S-ARDS and needed ECMO support. Inclusion criteria for ECMO and rhAPC in the S-ARDS group (Appendix 1) and exclusion criteria for rhAPC (Appendix 2) are presented below. Patients who met the criteria for rhAPC were immediately administered 96-hour continuous rhAPC with drotrecogin alfa (activated) [Xigris®, Eli Lilly and Company (Taiwan), Inc., Taipei, Taiwan] infused at a rate of 24 μg/kg/h. ECMO support with conventional treatment was given to those S-ARDS patients who did not meet the rhAPC criteria but met the ECMO criteria. Heparin was given to all patients in the control group. In the rhAPC group, patients were not given systemic heparinization until the rhAPC treatment course was finished. Heparin-coated circuits were used in every patient in whom ECMO was placed.

Baseline data including demographic information, preexisting conditions, recent surgery, the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores [13], and the partial pressure of arterial oxygen/fraction of inspired oxygen ($PaO_2/FiO_2$) ratio were collected before ECMO support was set up. The primary endpoint was to compare all-cause hospital mortality between patients with rhAPC treatment and those without. We also analyzed data regarding serious bleeding complications in the 2 groups as the secondary endpoint.

### *Statistical analysis*

We compared both groups using Fisher's exact test for categorical variables. The New York Heart Association functional classification [14] was compared with the use of the Chi-square test, and the independent *t* test was used for continuous variables. A $p$ value less than 0.05 was considered significant.

## Results

From August 2005 to February 2008, we had 14 adult patients with S-ARDS requiring ECMO support (mean age 51.3 ± 15.6 years

**Table 1.** Comparison of demographic characteristics at baseline and results of rhAPC and control groups

| | rhAPC group (n=5) | Control group (n=9) | *p* value |
|---|---|---|---|
| Age (year) | 46.9 ± 14.1 | 53.8 ± 13.5 | 0.384 |
| Men | 3 (60.0%) | 8 (88.9%) | 0.505 |
| BMI (kg/m$^2$) | 23.4 ± 2.5 | 24.5 ± 4.3 | 0.615 |
| Preexisting conditions | | | |
| NYHA functional class | | | 1 |
| I | 3 (60.0%) | 6 (66.7%) | |
| II | 2 (40.0%) | 3 (33.3%) | |
| Hypertension | 2 (40.0%) | 3 (33.3%) | 1 |
| Diabetes | 2 (40.0%) | 1 (11.1%) | 0.505 |
| Immunocompromise | 1 (20.0%) | 1 (11.1%) | 1 |
| Liver disease | 2 (40.0%) | 2 (22.2%) | 0.580 |
| Lung disease | 0 | 2 (22.2%) | 0.505 |
| Smoking | 1 (20.0%) | 1 (11.1%) | 1 |
| Dialysis | 0 | 1 (7.7%) | 1 |
| Recent surgery | 3 (60.0%) | 4 (44.4%) | 1 |
| APACHE II | 35.6 ± 10.0 | 37.9 ± 9.2 | 0.616 |
| $PaO_2/FiO_2$ | 70.7 ± 24.4 | 60.5 ± 22.4 | 0.434 |
| ECMO duration (hr) | 455.6 ± 649.9 | 110.1 ± 196.8 | 0.305 |
| Mortality | 2 (40.0%) | 8 (88.9%) | 0.095 |
| Bleeding | 0 | 2 (22.2%) | 0.505 |

Data are expressed as number (%) or mean ± standard deviation. APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: body mass index; CAD: coronary arterial disease; ECMO: extracorporeal membrane oxygenation; $FiO_2$: fraction of inspired oxygen; NYHA: New York Heart Association; $PaO_2$: partial pressure of arterial oxygen; rhAPC: recombinant human activated protein C.

[range: 28-70 years], mean APACHE II score 37.2 ± 8.5). Of these 14 patients, 5 received rhAPC. The demographic characteristics of the control group and the rhAPC group at baseline were similar (Table 1). Of the 5 patients in the rhAPC group, 3 underwent veno-arterial (V-A) ECMO support initially and the other 2 received veno-venoarterial (V-VA) ECMO. In the control group, all 9 patients were treated with V-A ECMO initially. There was no significant difference in the mortality rate between the V-A and V-VA ECMO modes ($p$=0.505). There was also no significant association between initial ECMO modes and groups ($p$=0.110).

Two of the 5 patients in the rhAPC group (40.0%) and 8 of the 9 patients in the control group (88.9%) died in the hospital ($p$=0.095). There were 2 serious bleeding complications in patients in the control group ($p$=0.505). Both events occurred in the brain, causing intracranial hemorrhages, and resulted in death. Heparin was given  all patients in the control group

and 4 of 5 patients in the rhAPC group after the rhAPC treatment course was finished. One patient in the rhAPC group died on the first day of rhAPC infusion, and did not receive systemic heparinization. Without heparinization, furthermore, no evidence of clot formation was noted in the 4 patients' ECMO circuits during the 96-hour rhAPC treatment.

## Discussion

To our knowledge, there is no clinical literature on the efficacy and safety of combined treatment with rhAPC and ECMO for S-ARDS, except some related case reports. Yu and associates successfully treated 2 patients with acute myocarditis and profound septic shock using ECMO and rhAPC [15]. Lamarche and colleagues reported 2 cases in which rhAPC and ECMO were used concomitantly for ARDS and septic shock, and the result was good [16]. There was no bleeding complication in either report. A consistent result in our study was that treatment with rhAPC given to patients with septic ARDS on ECMO was not associated with an increased rate of serious bleeding. Lamarche and colleagues concluded that formal anti-coagulation with intravenous heparin might not be required for ECMO with heparin-bonded circuits in patients who are receiving rhAPC [16]. We observed the same result in our study.

There was no significant effect of rhAPC on the reduction of all-cause mortality in patients with S-ARDS requiring ECMO support, although no increase in serious bleeding complications associated with rhAPC treatment was noted in our study. The PROWESS study first showed rhAPC was associated with reduced mortality in patients with severe sepsis [9]. Other clinical trials, however, did not show a difference in mortality rates between rhAPC and placebo [10,17]. In 2011, preliminary analyses of the PROWESS-SHOCK clinical trial were done by Eli Lilly and Company and revealed no difference in 28-day mortality rates between rhAPC and placebo [26.4% (223/846) vs. 24.2% (202/834); relative risk 1.09; 95% confidence interval (0.92, 1.28); $p$ value=0.31] [12], which led to the worldwide withdrawal of rhAPC from the market.

The reasons why rhAPC was not given to the patients in the control group were as follows. Three of the 9 patients had stayed at intensive care units for more than 48 hours, so they did not meet the inclusion criteria for rhAPC. Furthermore, 1 patient had chronic renal failure dependent on hemodialysis for more than 1 month, and 5 patients had very poor hemodynamics and inevitable death was expected by the physicians. These 6 patients were excluded from rhAPC therapy since they met some of the exclusion criteria of rhAPC.

Our study was limited by the small sample size, and the possibility of selection bias in this non-randomized, non-blinded study could not be avoided.

In conclusion, administration of rhAPC to patients with S-ARDS on ECMO did not significantly reduce mortality, although it was not associated with increasing serious bleeding complications. In patients receiving ECMO with heparin-coated circuits, no systemic heparinization is needed to prevent clotting in circuits when these patients are undergoing intravenous rhAPC treatment.

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**Appendix 1:** Inclusion criteria

1. SIRS criteria

Patients had to have 3 or more of the following qualifications: core temperature ≥ 38°C or ≤ 36°C; heart rate ≥ 90 beats/minute, except in patients with a known medical condition or receiving treatment that would prevent tachycardia; respiratory rate ≥ 20 breaths/minute or a $PaCO_2$ ≤ 32 mmHg or mechanical ventilation for an acute process; white blood cell count of ≥ 12,000 /$mm^3$ or ≤ 4,000 /$mm^3$ or > 10% immature neutrophils.

2. Sepsis criteria

Patients had to have suspected or proven infection and meet the SIRS criteria.

3. Septic ARDS criteria

Patients with sepsis had to have an acute onset of respiratory failure, a chest X-ray with lung infiltration, and a $PaO_2/FiO_2$ < 200 mmHg.

4. ECMO criteria for ARDS

$PaO_2/FiO_2$ < 100 mmHg under a high ventilation setting with 1.0 of $FiO_2$.

5. Criteria for rhAPC

Septic patients had to have stayed in intensive care units for less than 48 hours and have APACHE II scores between 24 and 52 before rhAPC was used.

APACHE II: Acute Physiology and Chronic Health Evaluation II; ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; $FiO_2$: fraction of inspired oxygen; $PaCO_2$: partial pressure of arterial carbon dioxide; $PaO_2$: partial pressure of arterial oxygen; rhAPC: recombinant human activated protein C; SIRS: systemic inflammatory response syndrome.

**Appendix 2:** Exclusion criteria of recombinant human activated protein C

1. Patients who are pregnant.
2. Patients less than 14 years of age.
3. Patients weighing > 135 kg.
4. Patients with a platelet count < 30,000/$mm^3$ or uncontrolled active bleeding.
5. Patients at increased risk for bleeding based on the following:
   A. Any major surgery, defined as surgery that requires general or spinal anesthesia, performed within the 12-hour period immediately preceding study drug infusion, or any postoperative patient who demonstrates evidence of active bleeding, or any patient with planned or anticipated surgery during the study drug infusion period.
   B. History of severe head trauma within the previous 4 weeks that required hospitalization or intracranial surgery.
   C. History of stroke within the previous 3 months, or any history of intracerebral arteriovenous malformation, cerebral aneurysm, or central nervous system mass lesions, or definitive intracranial hemorrhage.
   D. History of congenital bleeding diatheses.
   E. Gastrointestinal bleeding within the last 6 weeks that required medical intervention unless de-

finitive surgery was performed.

6. Patients with a known hypercoagulable condition including activated protein C resistance or a hereditary deficiency of protein C, protein S, or anti-thrombin III.
7. Patients on the following medications:
   A. Thrombolytic therapy within the past 3 days.
   B. Glycoprotein IIb/IIIa antagonists within the past 7 days.
   C. Antithrombin III infusion of > 10,000 units within the past 12 hours.
   D. rhAPC infusion within the past 24 hours.
8. Patients with known or suspected portal hypertension.
9. Presence of an advance directive to withhold life-sustaining treatment, with the exception of cardiopulmonary resuscitation.
10. Patients not expected to survive more than 28 days given their pre-existing medical condition (e.g., widely metastatic cancer) or inevitable death as judged by the physician.
11. Patients with chronic renal failure dependent on either hemodialysis or peritoneal dialysis for more than 1 month.
12. Human immunodeficiency virus-positive patients whose last known CD4 count was $\leq 50/mm^3$.

# 同時以基因重組人類活化 C 蛋白與體外膜氧合器治療與敗血症相關的急性呼吸窘迫症候群

張金池 *,** 郭順文 *,** 李章銘 ** 柯文哲 *,**

**前言**：與敗血症相關的急性呼吸窘迫症候群在臨床治療上仍是一個很困難的問題。本研究的目的是評估同時以基因重組人類活化 C 蛋白與體外膜氧合器治療與敗血症相關的急性呼吸窘迫症候群之療效及安全性。

**方法**：我們以台大醫院中的前瞻性資料庫來做回溯性分析。我們收集了與敗血症相關的急性呼吸窘迫症候群並且使用體外膜氧合器的病人。符合本研究中基因重組人類活化 C 蛋白治療條件的病人接受該藥物治療，其他病人則接受傳統治療。初級終點為全部原因的在醫院死亡率，次級終點為嚴重出血併發症。

**結果**：共有 14 位病人被收入本研究，其中 5 位接受基因重組人類活化 C 蛋白治療（研究組），其他 9 位接受傳統治療（對照組）。研究組中 5 位有 2 位死亡（40.0%），而對照組中 9 位有 8 位死亡（88.9%，$p$=0.095）。在嚴重出血併發症方面，在對照組中有 2 位發生（22.2%），在研究組中則無（$p$=0.505）。

**結論**：在與敗血症相關的急性呼吸窘迫症候群並且使用體外膜氧合器的病人使用基因重組人類活化 C 蛋白治療，對於降低死亡率沒有顯著的成效，雖然在本研究中沒有發現與此藥物相關的嚴重出血併發症。
*( 胸腔醫學 **2013; 28: 270-277**)*

關鍵詞：基因重組人類活化 C 蛋白，體外膜氧合器，葉克膜，敗血症，急性呼吸窘迫症候群，除栓素

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# Diagnosis and Treatment of an Infective Bronchogenic Cyst Using Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration: A Case Report

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Bronchogenic cysts are 1 of the most common bronchopulmonary congenital malformations found in adults. Most would agree that symptomatic or infected cysts should be surgically removed. We report a 58-year-old male with fever and a mediastinal mass, who was diagnosed with infected bronchogenic cyst and treated with a combination of antibiotics and drainage by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). This case suggests that EBUS-TBNA can be an effective alternative treatment to surgery in the management of infective bronchogenic cysts. ***(Thorac Med 2013; 28: 278-282)***

Key words: bronchogenic cyst, endobronchial ultrasound, endobronchial ultrasound-guided transbronchial needle aspiration

## Introduction

Although the definitive clinical management of asymptomatic bronchogenic cysts remains controversial, surgical removal of symptomatic or infected cysts is most likely to be recommended [1-5]. Bronchoscopic aspiration has been used typically for diagnosis and for nonsurgical candidates. We herein report our experience, in which we treated an infected mediastinal bronchogenic cyst with a combination of antibiotics and drainage by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), followed by a resolution of symptoms and no evidence of recurrence after a 12-month follow-up.

## Case Report

A 58-year-old man without a significant medical history presented with dry cough, low-grade fever and chest tightness for 2 weeks. Chest X-ray at the outpatient department (OPD) showed a right mediastinal mass (Figure 1), prompting a chest computed tomography (CT) scan. The CT scan revealed a 5.3 × 4.3 cm cys-

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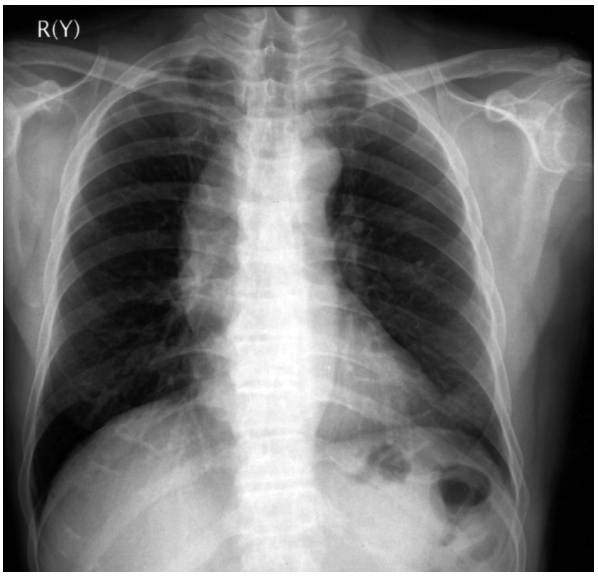


**Fig. 1.** Chest X-ray showed a right mediastinal mass.

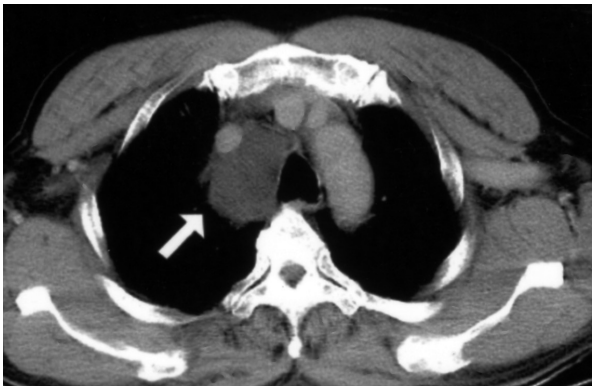

**Fig. 2.** CT of the chest showed a right lower paratracheal rounded lesion, 4.5 cm in diameter, with homogeneous density and soft-tissue attenuation (white arrow).

tic lesion with homogeneous internal density and a thin wall at the right paratracheal region of the mediastinum (Figure 2).

The patient was referred to our hospital for diagnosis and management of a suspected mediastinal mass. He was placed under local anesthesia and sedation, and a flexible bronchoscope was used for the airway examination; no extrinsic compression of the distal trachea was seen.

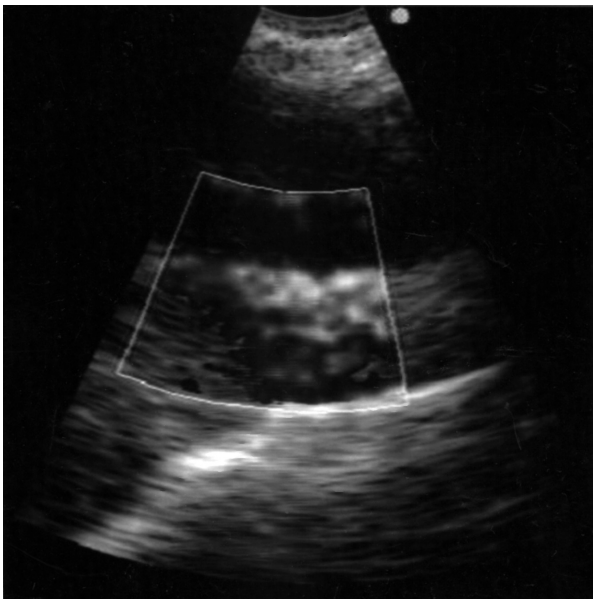

**Fig. 3.** Convex-probe EBUS image showing the same lesion adjacent to the superior vena cava (color Doppler).

This was followed by ultrasound examination of the right lower paratracheal area with a 7.5 MHz convex probe bronchoscope (BF-UC260F; Olympus Ltd., Tokyo, Japan). The lesion was identified as a round hypoechoic structure, 4.0 cm in diameter, and was distinguished from surrounding blood vessels using color Doppler (Figure 3). A dedicated 22-gauge needle (NA-202, Olympus Ltd., Tokyo, Japan) was used to puncture and aspirate the lesion under direct visual guidance, and 140 ml of yellowish fluid was slowly drained. Collapse of the lesion was evident when fluid drainage spontaneously ceased. Fluid cytology then showed histocytes and lymphoid cells, without evidence of malignancy. Gram stain and culture from the fluid subsequently confirmed *Klebsiella pneumonia* and *Streptococcus pneumoniae*.

The patient was treated with a 6-week course of augmentin; his symptoms improved within a few days from the initial procedure. A repeated

chest CT scan subsequent to the 6-week treatment showed a smaller lesion (about 1.5 cm in diameter). The patient remained asymptomatic after the initial procedure and during his 12 months of follow-up.

## Discussion

Bronchogenic cysts are closed and epithelial-lined sacs, and are thought to originate from the anomalous budding of the tracheal diverticulum from the primitive foregut between the 3rd and 6th weeks of gestation [5-7]. Depending on the time of separation from the primary airways, the bronchogenic cyst may be either in the mediastinum or in the lungs, as a result of anomalies occurring during the 5th and 6th weeks of development, respectively [5-6,8]. Bronchogenic cysts of the mediastinum are rare. In a series of 2,163 mediastinal lesions, 72 (3.3%) were found to be due to bronchogenic cysts [8].

Bronchogenic cyst, either intra- or extrathoracic, is usually asymptomatic. Related symptoms, such as cough, dysphagia and dyspnea, could appear if the cyst became larger and compressed adjacent vital structures. Chest X-ray and CT scan both typically reveal a rounded, well-demarcated, noncalcified mass with "water density" (usually less than 20 Hounsfield units by CT). However, infected cysts that contain protein-like material or hemorrhagic cysts can have a more solid appearance (up to 80 to 90 Hounsfield units), thereby increasing the diagnostic uncertainty. The appearance on magnetic resonance imaging (MRI) will also depend on the content of the cyst. Serous fluid will have low signal intensities in T1-weighted images and high signal intensities in T2-weighted images, whereas protein-like fluid will have high signal intensities in T1-weighted images [15]. Histology reveals that bronchogenic cysts are lined by a pseudostratified ciliated columnar epithelium. The cysts walls usually contain cartilage and bronchial mucous glands. The cysts may be filled with secretions [16].

Fever, abscess, sinus drainage or fistula formation could also appear when infected [9]. Therefore, many authors have indicated the necessity of early therapy [1,3,5] and considered complete surgical excision (by VATS or thoracotomy) as the treatment of choice for bronchogenic cyst [1,3,5,10]. Moreover, they believe that simple aspiration can lead to a high recurrence rate because the lining is not completely obliterated [1,5]. Past studies considered the importance of TBNA as a diagnostic procedure, but its therapeutical use was limited to the management of recurrence of bronchogenic cyst [1], and to cases with acute compression [11] and compromised or non-operable candidates [12]. Furthermore, ultrasound facilitates visualization during aspiration and enables complete aspiration of the cyst, which is not always possible when "blind" techniques are utilized. This causes collapse of the cystic space and may facilitate adhesion between the mucosal surfaces lining the cavity, consequently reducing recurrence rates.

In spite of these different and controversial therapeutic approaches, our patient with an infected mediastinal bronchogenic cyst was managed conservatively with EBUS-TBNA, without evidence of recurrence after a long-term follow-up of 12 months.

EBUS is the latest relatively non-invasive procedure, and has widened bronchoscopic vision beyond the bronchial wall [13]. This new diagnostic tool makes it possible to visualize in real-time the cyst's structure, so that we can

perform deep and complete aspiration to obtain a collapse of the lesion and total destruction of the lining (which is the first cause of recurrence of the cyst) under ideal conditions [14]. However, while remaining aware of the coughing and involuntary movement of our patient during the EBUS-TBNA procedure under moderate sedation with propofol, we attempted to aspirate as much as 140 ml of fluid, which resulted in a smaller lesion on chest CT imaging after the 12-month follow-up.

Infected bronchogenic cysts usually adhere densely to adjacent structures, which makes the operation more complicated and risky, and complete removal of the cysts more difficult. Hence, our minimally invasive strategy might provide a useful alternative to surgery as a first step to control the infection and reduce inflammation before resection, and could be an alternative treatment if there is no recurrence after drainage. Since we used EBUS-TBNA as a complementary treatment to later possible surgery in our patient, the diagnosis of bronchogenic cyst was mainly made according to the chest X-ray, CT image and EBUS.

In conclusion, EBUS-TBNA is a less invasive and more accurate procedure in the diagnosis bronchogenic cyst and might provide a useful alternative to surgery as a first step to control the infection before resection.

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# 使用支氣管內視鏡超音波導引細針抽吸術診斷及治療感染性支氣管性囊腫：病例報告

黃國揚 * 陳家弘 *,** 廖偉志 * 涂智彥 *,***,**** 施純明 *,** 徐武輝 *,***

支氣管性囊腫是成人最常見的先天性支氣管肺畸形之一。大多數人皆同意有症狀或感染性支氣管性囊腫需手術移除。我們在此報告一位臨床表現為發燒及縱隔腔腫瘤的 58 歲男性病患；經支氣管內超音波導引經支氣管細針抽吸診斷為感染性支氣管性囊腫及抗生素治療。此病例提議支氣管內超音波導引經支氣管細針抽吸可為感染性支氣管性囊腫除開刀外之有效替代療法。*( 胸腔醫學* ***2013; 28: 278-282)***

關鍵詞：支氣管性囊腫，支氣管內視鏡超音波，支氣管內視鏡超音波導引細針抽吸術

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# Hodgkin's Lymphoma Presenting as Pleural and Chest Wall Invasion: A Case Report

Yen-Ting Lin, Chao-Chi Ho

Hodgkin's lymphoma is not an uncommon cause of mediastinal lymphadenopathy. However, pleural and chest wall invasion are rare. Our patient, a 41-year-old male, presented to our clinic with recurrent right chest pain for 1 month. Physical exam was unremarkable, except a 1.5 cm, non-tender, soft lymph node was found at the left axilla. CXR revealed a faint extrapulmonary lesion at the right upper lung field with rib destruction. CT scan showed wide-based pleural thickening with adjacent right 6th rib destruction, some mediastinal lymphadenopathies, a T9 sclerotic lesion with adjacent enlarged soft tissue and a 1.5 cm left axillary lymphadenopathy. A pleural malignancy was suspected. CT-guided biopsy of the pleural lesion disclosed atypical lymphoid infiltrates, suspicious of Hodgkin's lymphoma. Excision biopsy of the left axillary lymph node revealed foci of large lymphoid cells with hyperchromatic nuclei and condensed cytoplasm. Binucleated Reed-Sternberg cells were present. A Hodgkin's lymphoma, classical-type, was diagnosed. After chemotherapy with an ABVD protocol, the CXR and CT scan both showed significant tumor regression. A PET scan did not disclose a viable hypermetabolic malignancy. Hodgkin's lymphoma usually spreads along with lymph node distribution. Pleural and chest wall involvement are rare. A detailed physical examination and tissue diagnosis are essential with the presence of any suspicious malignancy of pleural origin. ***(Thorac Med 2013; 28: 283-289)***

Key words: Hodgkin's lymphoma, pleural lesion

## Introduction

Pleural thickening is a common radiologic finding in both plain film and computed tomography (CT) scans. Adjacent chest wall and rib destruction imply a malignant disease. The most common malignant pleural disease is metastatic lung carcinoma. Others include metastatic extrapulmonary carcinoma, sarcomas, lymphoproliferative diseases and mesothelioma. Tissue proof is always necessary in these circumstances [1]. Lymphoproliferative diseases such as Hodgkin's lymphoma, non-Hodgkin lymphoma and leukemia can invade the pleura, while primary pleural lymphoma is very rare [2]. Secondary pleural involvement with lymphoma usually results from disseminated or recurrent disease [3]. We report a case that initially pre-

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sented with pleural thickening and adjacent rib destruction, causing chest pain, and that was finally diagnosed as Hodgkin's lymphoma, which is rare.

## Case Report

The patient, a 41-year-old man, was admitted for persistent right chest pain. He had smoked 1 pack of cigarettes per day for more than 20 years. He had no systemic disease, but was an asymptomatic HBV carrier. He had been well until 1 month earlier when an ill-defined right chest pain occurred. It was a pressure-like pain, scoring 2/10, without radiation. It was not aggravated by exercise or limb movement. He denied any history of trauma. Mild shortness of breath and palpitation occurred when he engaged in mild exercise, such as walking for 10 minutes. He had no other discomfort, such as fever, nausea, vomiting, gastrointestinal discomfort, cough, sore throat, hemoptysis, pain at any other site, appetite change, night-sweating or body weight loss in recent months. On examination, he was a well-nourished man with a fair spirit. A non-tender, soft lymph node, about 1.5 cm, was noted at the left axilla. The breath sound was clear. Other examinations were unremarkable. The chest x-ray (CXR) (Figure 1A) revealed several fibrocalcifications at the right upper and left middle lung field. An ill-defined opacity at the right upper lung field was also noted, with destruction of the 6$^{th}$ rib. The mediastinum was widened. Laboratory data revealed hemoglobin 13.1 gm/dL, white blood cell count 9.04 K/μL (segments 64.5% and lymphocytes 24.4%), platelet count 366.0 K/μL, BUN 12.3 mg/dL, creatinine 0.9 mg/dL, albumin 4.5 gm/dL, total protein 8.2 gm/dL, ALT 19 U/L, ALP 401 U/L, LDH 467 U/L, CEA 0.74 ng/mL and CA-199 2.67 U/mL. A CT scan (Figures 1B, 1C, 1D, 1E) showed wide-based pleural thickening and a nodular lesion at the T5/T6 level with adjacent right 6$^{th}$ rib destruction. An enlarged soft tissue lesion at the prevertebral space of T9 and sclerotic change in the T9 vertebral body, suspicious of bone metastasis, were also found. There were both an enlarged left axillary lymph node (1.5 cm) and several mediastinal lymphadenopathies. Some fibrotic and calcified lesions at the bilateral upper lungs were noted, as well. Bronchoscopy did not reveal an endobronchial lesion. Bronchial washing cytology was negative and no acid-fast bacilli were found in the washing specimen. Chest sonography revealed right hypovascular pleural thickening. CT-guided biopsy was performed with a 20G biopsy needle to the T6 paraspinal pleural lesion. Pathology revealed atypical lymphoid infiltrates, suspicious of malignancy (Figure 2A). The left axillary lymph node was then resected surgically. Pathology reported diffuse effacement of the lymphoid structure with infiltration of small lymphocytes and some eosinophils in the background. Foci of large lymphoid cells with hyperchromatic nuclei and condensed cytoplasm were noted. Binucleated Reed-Sternberg cells were also recognized (Figure 2B). The large tumor cells were positive for CD30 and partially positive for CD20 stains. CD45-negative large cells were discerned. CD3 and CD20 highlighted small T-cell and B-cell lymphocytes in the background (Figures 2C, 2D). Focally PAX5-positive small lymphocytes were noted, but tumor cells were negative. The bone marrow study did not reveal lymphoma involvement, and there was no additional evidence of lymphoma in the brain, neck, abdomen and pelvis CT. The patient was diagnosed with a mixed-cellularity classical Hodg-

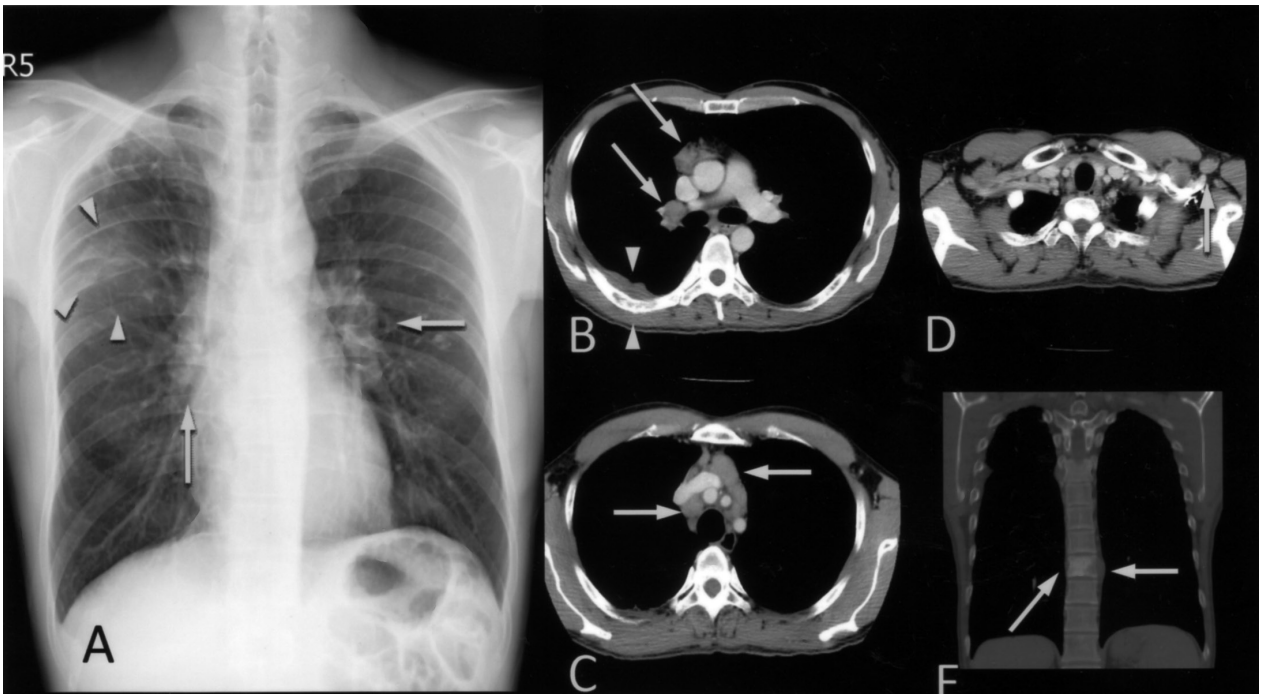


**Fig. 1.** (A) CXR shows an ill-defined opacity at the right upper lung field with destruction of the 6th rib (arrow heads), as well as mediastinal lymphadenopathies (arrows). (Some old fibrocalcified lesions are also seen). (B) CT scan revealed right pleural thickening with nodularity and rib destruction (arrow heads), and mediastinal and right hilar lymphadenopathies (arrows). (C) Mediastinal lymphadenopathies. (D) A 1.5 cm lymphadenopathy at the left axilla. (E) Sclerosing change of the T9 spine and a nearby enlarged soft tissue on the coronal reconstructed CT scan.

kin's lymphoma, with axillary and mediastinal lymphadenopathies and pleura, rib and T spine involvement, stage IV, international prognostic score (IPS) 2.

He was treated with chemotherapy with an ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) protocol. Follow-up CXR and CT scans (Figures 3A, 3B, 3C) showed significant regression of the pleural lesion and mediastinal lymphadenopathies. A whole body fluorodeoxyglucose scan (FDG) 8 months after diagnosis did not reveal a definite hypermetabolic malignancy (Figure 3D).

## Discussion

Mesothelioma clearly dominates any discussion of pleural tumors [1]. However, the most common malignant tumor of the pleura is the result of metastasis from another site, and metastatic lung cancer is the most common (40%) [4]. The mechanism is most often contiguous spread and invasion by the tumor into the pulmonary vasculature and lymphatics. Metastasis from other sites, such as the breast, stomach and ovary, are not uncommon. Sometimes, sarcomas can also metastasize to the pleurae. Lymphoproliferative diseases such as Hodgkin's lymphoma, non-Hodgkin lymphoma and leukemia can also involve the pleura. Primary pleural lymphoma is very rare, and is represented by the famous primary effusion lymphoma, which is associated with HHV-8 and HIV infection.

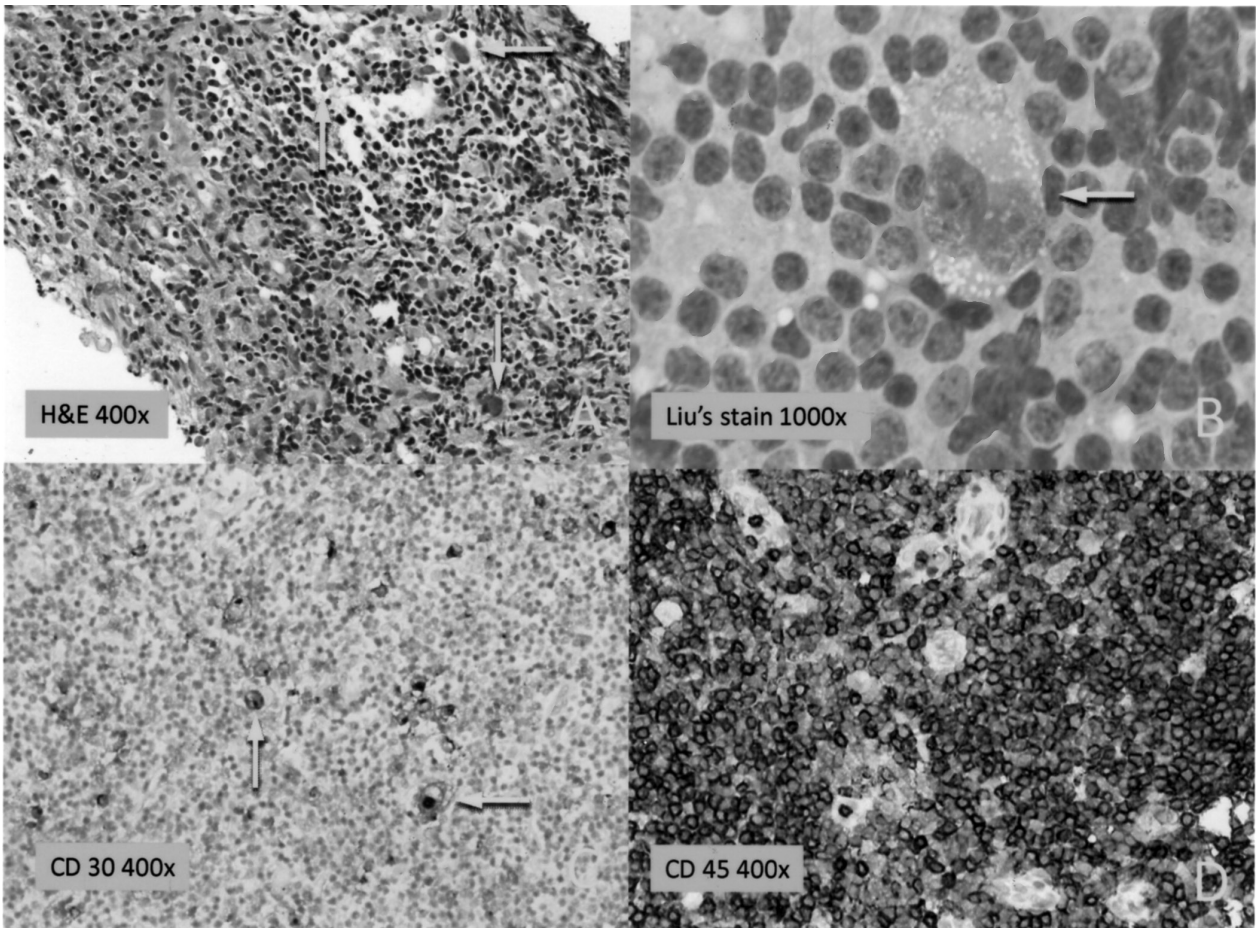


**Fig. 2.** (A) CT-guided biopsy of the right pleural lesion found atypical lymphoid cell infiltrates and some bi-nucleated cells. (B) Imprint cytology of the resected axillary lymph node showed typical Reed-Sternberg cells. (C) (D) Pathology of the axillary lymph node revealed some Reed-Sternberg cells positive for CD30 and numerous lymphoid tumor cells positive for CD45.

Hodgkin's lymphoma typically presents as a painless lymphadenopathy, and is frequently cervical or supraclavicular. The malignant cell is derived from a B lymphocyte, with clonal immunoglobulin gene rearrangements. More than 50% of patients have a mediastinal mass, which can be asymptomatic or present as dyspnea, cough, or obstruction of the superior vena cava [5]. Hodgkin's lymphoma is not an uncommon cause of mediastinal lymphadenopathy. It usually starts in a single lymph node and then spreads to adjacent lymph nodes via lymphatic channels. In a case series of 108 patients with Hodgkin's lymphoma, 77 had intrathoracic abnormalities on chest CT. The pattern seen was that of contiguous spread from the anterior mediastinal/paratracheal area to the other mediastinal nodal groups. Involvement of the pleura, pericardium or chest wall occurred only after the anterior mediastinal/paratracheal mass had enlarged to greater than 30% of the thoracic diameter [6]. Other authors have claimed that pleural involvement is always in conjunction with either mediastinal or parenchymal disease [7]. Distant spread other than contiguous spread to an extranodal site is not common and is al-

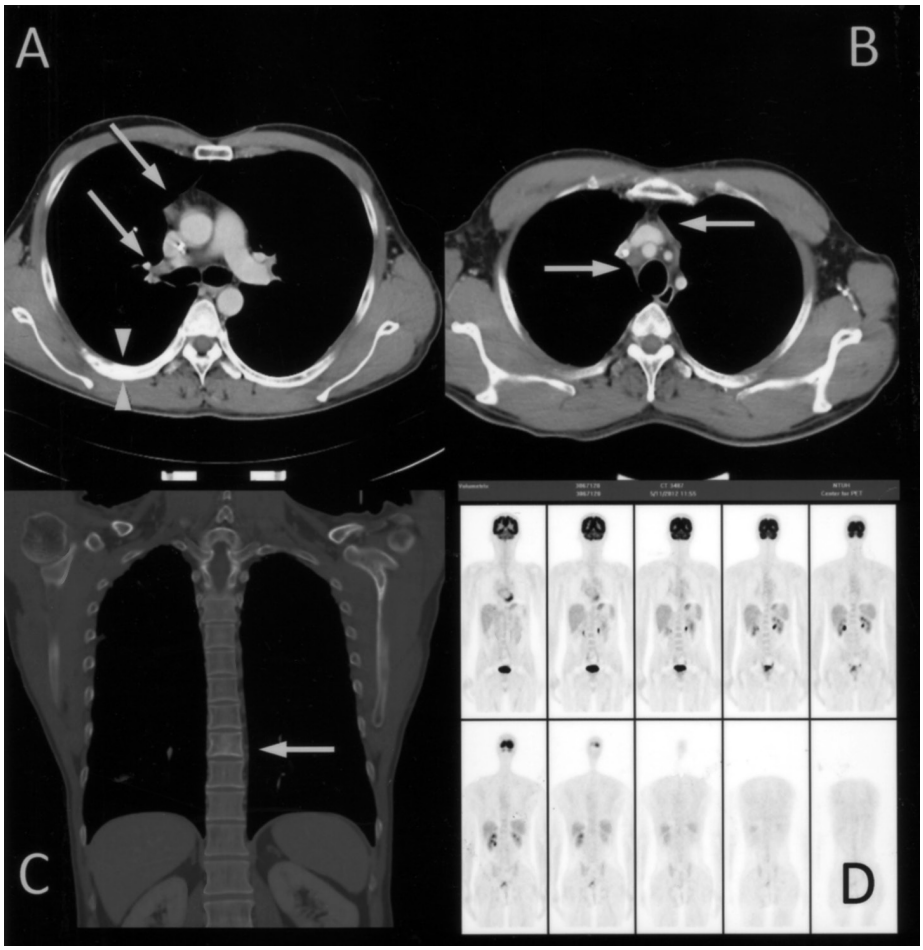


**Fig. 3.** (A) (B) (C) CT scan after treatment showed marked regression of the previous tumors. (D) PET scan 8 months after diagnosis showed no definite hypermetabolic malignancy.

ways preceded by splenic involvement, although the involvement of the spleen may be occult. This type of distant extranodal Hodgkin's lymphoma occurs almost exclusively in 4 organs: the liver, bone marrow, lung, or bone [8].

Hodgkin's lymphoma involves the lung far more frequently than non-Hodgkin lymphoma. It always occurs accompanied with enlarged mediastinal nodes, while non-Hodgkin lymphoma can invade the lung parenchyma alone [9]. The patterns of pleural involvement by lymphoma include single or multiple pleural nodules or masses, or diffuse pleural thickening of more than 1 cm. On CT scan, pleural lymphoma shows contrast enhancement with attenuation similar to muscle [2]. Pleural effusions are more common in non-Hodgkin lymphoma than Hodgkin's lymphoma [2]. This may result from lymphatic obstruction by lymphoma (more frequently) or direct invasion of lymphoma into the pleura [3].

Our patient did have mediastinal lymphadenopathies. However, his mediastinal and hilar lymphadenopathies were far smaller than 30% of the thoracic diameter. Moreover, his pleural lesion and rib destruction were not obviously

contiguous to the mediastinal nodes on CT scan. The T9 spine was also involved. This kind of spreading pattern is rare.

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# 以肋膜和胸壁侵犯爲表現的何杰金氏淋巴瘤：病例報告

林彥廷　何肇基

何杰金氏淋巴瘤（Hodgkin's lymphoma）是縱隔腔淋巴病變的原因之一，其擴散的方式常經由一個個鄰近的淋巴結散布出去。肋膜和胸壁的侵犯多半在縱隔腔淋巴病變已經相當巨大的情況下才會發生。我們報告一位 41 歲男性以胸痛表現求診。胸部 X 光發現一片邊緣不清的肺外病灶伴隨肋骨侵蝕。電腦斷層顯示局部肋膜增厚伴隨右側第 6 肋骨侵蝕、局部縱隔腔淋巴病變及左腋下單一淋巴結腫大。肋膜病理切片顯示非典型淋巴球浸潤，懷疑是何杰金氏淋巴瘤。腋下淋巴結切除後，病理報告確診為典型何杰金氏淋巴瘤。經過化學治療，肋膜病灶和淋巴病變均顯著縮小，正子攝影已看不出任何的惡性變化。在不明原因肋膜增厚的病患，病理學檢查是必須的診斷工具。*( 胸腔醫學 **2013; 28: 283-289**)*

關鍵詞：何杰金氏淋巴瘤，肋膜病變

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# Marantic Endocarditis in a Patient with Lung Cancer: Report of a Case and Review of the Literature

Hsin-Yi Wang, Ping-Hung Kuo

Marantic endocarditis, also known as nonbacterial thrombotic endocarditis (NBTE), is an uncommon complication of advanced malignancy. The disease is characterized by hypercoagulability-related non-infective thrombi on valvular leaflets causing extensive embolization. In this report, we describe a 52-year-old woman with lung adenocarcinoma who developed extensive embolic infarction of the brain and extremities. Nonbacterial thrombotic endocarditis was diagnosed based on the clinical presentation and results from echocardiography. We also review the related literature concerning this rare disease entity. ***(Thorac Med 2013; 28: 290-295)***

Key words: marantic endocarditis, nonbacterial thrombotic endocarditis, infective endocarditis

## Introduction

Marantic endocarditis, also known as nonbacterial thrombotic endocarditis (NBTE), is a well-documented phenomenon but an uncommon diagnosis in clinical practice. Patients with NBTE usually have debilitating systemic disorders, including malignancy and inflammatory and autoimmune diseases, and are associated with a hypercoagulable state [1]. Marantic endocarditis is defined by the deposition of thrombi on previously undamaged valves in the absence of a bloodstream bacterial infection [1]. It is characterized by the increased frequency of arterial embolic events, which may lead to extensive infarction [2]. Malignancy is the most commonly recognized disease entity associated with marantic endocarditis. Cancer-associated thromboembolism has been thoroughly studied since the seminal observation by Armand Trousseau in 1865 [3].

The diagnosis of marantic endocarditis is difficult because no diagnostic "gold standard" for this disease exists. A definite diagnosis can be achieved through autopsy or pathological examination of surgical specimens, which is unrealistic in clinical practice. The differentiation of marantic endocarditis from infective endocarditis (IE) is of paramount importance in terms of therapeutic strategy [4]. Nevertheless, there is some overlap in the clinical presentations of these 2 diseases. Thus, reaching a prompt and confident diagnosis of marantic endocarditis is still a challenge for health-care professionals.

In this report, we describe a 52-year-old woman with lung adenocarcinoma who present-

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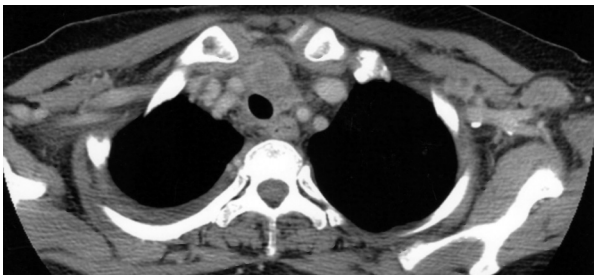
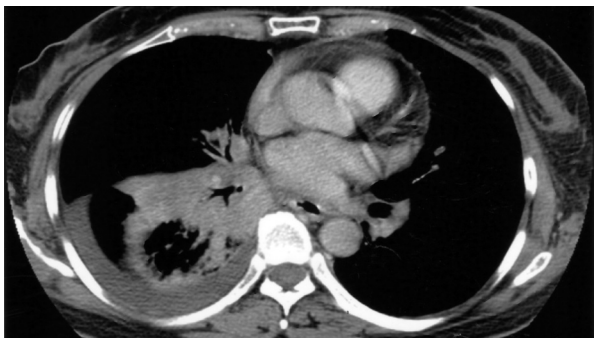


(A)



(B)

**Fig. 1.** Chest CT showing para-tracheal lymphadenopathy (Panel A), a right lower lung tumor with obstructive pneumonitis, and right pleural effusion (Panel B).

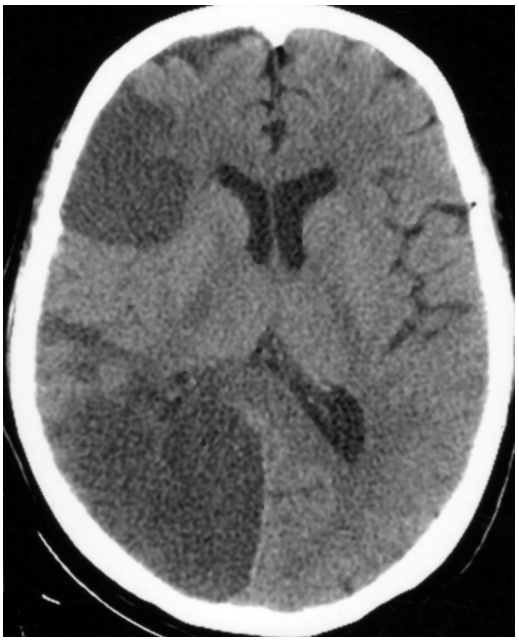


**Fig. 2.** Brain CT revealing 2 large wedge-shaped hypodense areas in the right frontal and parietal-occipital lobes, and another small area in the right parietal lobe consistent with recent right middle and posterior cerebral artery infarctions.

ed with extensively occurring embolic events. NBTE was diagnosed based on the clinical manifestations and echocardiography.

## Case Report

A 52-year-old woman, with stage IV lung adenocarcinoma, presented to our hospital with lymphadenopathy in the axillary and neck region for 7 months prior to this admission. The disease had progressed despite chemotherapy with nedaplatin, pemetrexed and oral gefitinib. Computed tomography (CT) of the chest revealed a right lower lung tumor, right pleural effusion and extensive mediastinal and axillary lymphadenopathy (Figure 1). She developed progressive respiratory distress because of massive malignant pleural effusion and obstructive pneumonitis. Respiratory failure occurred despite antibiotic treatment, aggressive drainage of the pleural effusion and noninvasive ventilation support. She underwent endotracheal intubation for mechanical ventilation and was then transferred to the intensive care unit (ICU).

On examination, her blood pressure and body temperature were normal with a heart rate of 109 beats per minute. Chest auscultation revealed bilateral diffuse crackles and ronchi, with decreased breathing sounds in the right lower lung. There was no cardiac murmur. Fever was detected on the 2$^{nd}$ day of intubation and strong antibiotics, including cefepime, teicoplanin and fluconazole were administered after a septic workup. Consecutive blood cultures did not yield any significant pathogens. She had an episode of sudden-onset consciousness disturbance with left hemiplegia 3 days after extubation. Emergency brain CT showed recent infarction

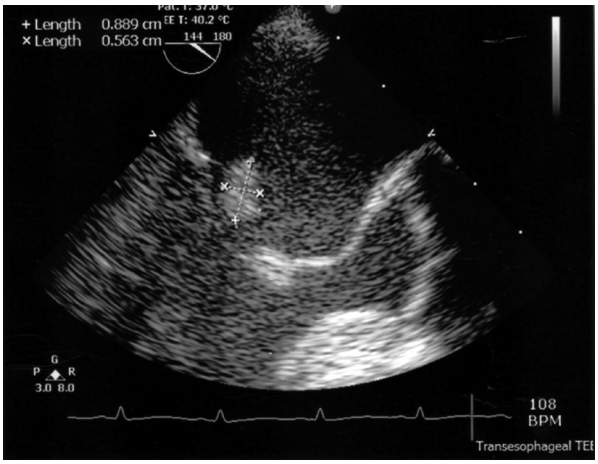
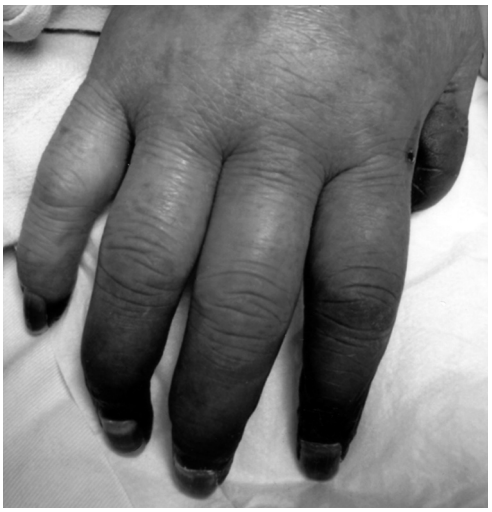
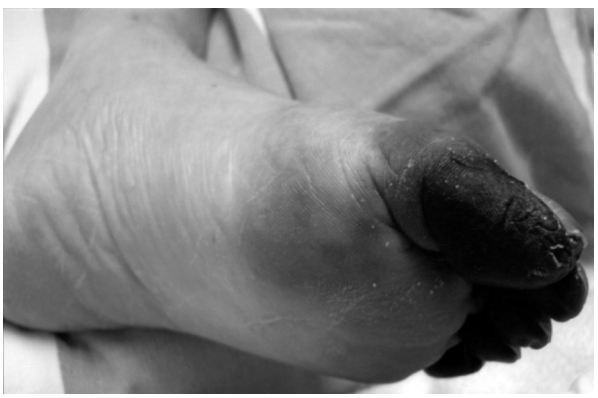



**Fig. 3.** Transesophageal echocardiogram demonstrating oscillating vegetations on anterior and posterior mitral leaflets and mild to moderate mitral regurgitation.

in the area of the right middle and posterior cerebral arteries (Figure 2). Transthoracic echocardiography revealed suspected vegetation at the mitral valve. Transesophageal echocardiography confirmed the presence of 2 oscillating vegetations on the anterior and posterior mitral leaflets, 0.9 × 0.6 and 0.7 × 0.5 cm in size, respectively (Figure 3). There was also a notable ischemic change in bilateral distal extremities, including the fingers and toes, which progressed rapidly to dry gangrene within a few days (Figure 4). Nonbacterial thrombotic endocarditis was suspected, based on the clinical manifestations. The neurologist did not recommend anticoagulation therapy because of the high risk of hemorrhagic transformation. Considering the advanced stage of the malignancy, only supportive care was given in the ICU. Her level of consciousness continued to worsen and the patient finally passed away on the 58th hospital day.



(A)



(B)

**Fig. 4.** Rapid occurrence of dry gangrene at the bilateral distal extremities within a few days.

## Discussion

Marantic endocarditis is a well-documented disease that usually occurs in patients with malignancy-associated hypercoagulability [4]. It has occasionally been reported in lung, pancreatic, and gastric cancers and also in adenocarcinoma of unknown primary origin. There is a tendency toward an association with adenocarcinoma [2].

Microscopic examination showed the lesions of marantic endocarditis are composed of agglutinated blood and platelet thrombi without

evidence of an inflammatory reaction [1]. The vegetations are superficial and the underlying valvular tissue is either entirely normal or shows subtle histological evidence of abnormal collagen and elastic fibers [1]. Because of the superficial structure and the lack of an inflammatory reaction, the vegetations are prone to being dislodged thereby causing extensive embolization [4]. Patients with marantic endocarditis have been shown to have a higher incidence of stroke (33%) than patients with IE (19%) [5].

The vegetations in marantic endocarditis have distinctive characteristics on echocardiography. The valves most often affected are the aortic, mitral and a combination of the 2 [6]. The vegetations are classically observed in areas of high flow or on the contact surfaces (coapting edge) of valvular leaflets [1,7]. Transesophageal echocardiography is superior to transthoracic echocardiography in the identification of a cardiac embolic source [8], probably due to the relatively small size of the vegetations.

The mainstay of treatment is the management of the underlying disease and anticoagulation therapy [2]. The most effective anticoagulation therapy appears to be unfractionated heparin or low molecular weight heparin (LMWH) [3]. In contrast, vitamin K antagonists, such as warfarin, have been shown to have a poor effect on the prevention of thromboembolisms and thus should be avoided [4]. Notwithstanding prompt diagnosis and proper management, the long-term outcomes of patients with marantic endocarditis are still poor, mainly because of the advanced stage of the underlying malignancy [1]. Cardiac surgery is seldom required and should be avoided in patients with terminal malignancies since it may not prevent further embolization [4].

In this case, we encountered some difficulties in establishing the diagnosis of marantic endocarditis, mainly because of the overlapping features of NBTE and IE. The patient had a fever episode before the massive embolic stroke. However, fever is usually a nonspecific phenomenon in patients with advanced malignancies. Our patient met 1 major and 2 minor criteria of the Duke diagnostic schema for IE. However, some of the elements of the Duke criteria overlap with the clinical manifestations of marantic endocarditis. There are some differences between these 2 conditions which can be utilized in clinical practice (Table 1) [9]. In our case, the persistent embolization despite adequate antibiotic therapy indicated a disease entity other than IE. In addition, the massive systemic embolization and discrete cerebral infarctions in the absence of new valvular damage and signs of heart failure were atypical presentations of IE. Moreover, the vegetations in this case developed on the coapting edge of the mitral leaflets, which is 1 of the characteristic echographic features of marantic endocarditis.

There are still some uncertainties regarding the treatment of marantic endocarditis. In patients complicated with a massive embolic stroke, the decision to use anticoagulants is often a dilemma for clinicians. Secondary hemorrhagic transformation of the cerebral infarction may counterbalance the potential benefits of anticoagulant therapy in the prevention of further stroke. To date, little is known about the optimal timing of initiating anticoagulation therapy relative to stroke onset and extent [10]; the management of massive embolic stroke in these patients remains supportive care.

In conclusion, clinicians should keep in mind the possibility of marantic endocarditis

**Table 1.** Comparison between marantic endocarditis and infective endocarditis

| | Infective endocarditis (IE) | Marantic endocarditis (NBTE) |
|---|---|---|
| Risk factors | Predisposing heart condition, intravenous drug user | Malignancy, hypercoagulability |
| Blood culture* | (+) | (-) |
| Infection signs | (+) | (-) |
| Valve damage with heart failure | often | less |
| New onset murmur | often | less |
| Location of Vegetations | Low pressure side | High pressure side/ coapting edge of the leaflets |
| Vegetation size | Could be larger | Smaller |
| Systemic embolization | Less often, limited | Often, extensive |
| Typical picture of embolic stroke** | Multiple, widely distributed, varying sizes | Often single |

* Positive blood culture emphasizing persistently positive blood cultures and typical pathogens for IE

** Patients with NBTE uniformly have multiple, widely distributed, small and large strokes, whereas patients with IE exhibit a panoply of stroke patterns.

in any patient with a malignancy presenting with embolic events. The real incidence of this disease may be underestimated. Differentiating marantic endocarditis from IE can be difficult because of their overlapping features. Nevertheless, the treatment strategies for the 2 diseases are entirely different. Earlier disease recognition and management may improve patient outcomes in the future.

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# 肺癌合併 marantic 心內膜炎：案例報告及文獻回顧

王馨儀　郭炳宏

marantic 心內膜炎，也被稱為非細菌性血栓性心內膜炎，是一種在晚期癌症不常見的併發症。這個疾病主要特徵是在心臟瓣膜上黏附因高凝血功能造成之非感染性血栓，進而造成全身性廣泛的栓塞。在這篇病例報告中，我們描述一位患有非小細胞肺腺癌的 52 歲女性，在腦部與四肢出現廣泛性的缺血性栓塞。根據臨床表徵與心臟超音波結果，最後診斷為非細菌性血栓性心內膜炎。我們同時進行此特殊疾病的文獻回顧。*( 胸腔醫學 **2013; 28: 290-295**)*

關鍵詞：marantic 心內膜炎，非細菌性血栓性心內膜炎，感染性心內膜炎

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# Non-Small Cell Lung Cancer in a Pregnant Woman with Intra-cardiac Metastasis, Superior Vena Cava Syndrome and Right Main Bronchus Compression: A Case Report

Yi-Chun Lai*,**, Shih-Chi Ku**, Chong-Jen Yu**

Lung cancer is often diagnosed at an advanced stage and is inoperable. However, intracardiac metastasis is rare. In addition, the occurrence of lung cancer in pregnant women is not common. Herein, we report the case of a 33-year-old female who presented at 29 weeks of gestation with a 4-week history of gradual shortness of breath and dry cough. Echocardiography and chest computed tomography showed a huge mass involving the anterior mediastinum with multiple lung metastases, compression of the trachea, carina, right main bronchus, and superior vena cava, and intracardiac metastasis. The pathology of a chest ultrasound-guided biopsy revealed non-small cell carcinoma -- poorly differentiated adenocarcinoma of lung origin. The early diagnosis and treatment strategy for such a complex condition with regard to delivery method, the management of the airway and intracardiac metastasis in a pregnant woman are very difficult issues. A healthy baby boy was delivered via emergency cesarean section; however, the patient died of cardiogenic shock due to outflow obstruction by the intracardiac tumor on the 13$^{th}$ day of hospitalization. This case highlights the importance of clinicians being alert to cases of unusual dyspnea in pregnant women that cannot be explained by the course of the pregnancy itself. ***(Thorac Med 2013; 28: 296-303)***

Key words: intracardiac metastasis, lung cancer, pregnancy, superior vena cava syndrome

## Introduction

Cancer develops in 1 of 1000 pregnant women [1]. The leading cause is lung cancer, followed by breast cancer and cervical cancer [2]. The early diagnosis of lung cancer is very difficult because there are no specific related symptoms, and metastases to other sites often have an indolent course. As a result, most lung cancers are diagnosed at an advanced stage and have a poor prognosis [3]. There have been only a few published case reports of non-small cell lung cancer (NSCLC) during pregnancy [4-10].

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Metastatic cardiac tumors originate mainly from melanomas, leukemias/lymphomas, and carcinomas, especially of the lung or breast [11]. About 25% of lung cancer patients are found to have intracardiac metastasis at autopsy [12]. Metastatic tumor involvement of the heart is difficult to manage in clinical settings. Intracavitary metastatic tumors can interrupt ventricular filling, increase pulmonary pressure, and block outflow, resulting in severe life-threatening situations [13]. Herein, we report the case of a 33-year-old pregnant woman who presented at 29 weeks of gestation suffering from a severely compromised airway and unstable hemodynamic condition. She was diagnosed with NSCLC with intracardiac metastasis. The baby was delivered uneventfully after thorough planning by a multidisciplinary team.

## Case Presentation

This 33-year-old Taiwanese woman presented at 29 weeks of gestation with a 4-week history of gradual shortness of breath and dry cough at night. This was her 2$^{nd}$ pregnancy, with 1 previous normal spontaneous delivery and no known medical problems. She did not smoke or drink. Her father previously had NSCLC, but in a stable condition. Although she experienced dyspnea on exertion, she did not pay much attention to it as she assumed it was a symptom related to her pregnancy. There was no chest pain, cold sweats, fever, hemoptysis or radiation pain. Because the dyspnea progressed, even at rest, and was associated with orthopnea and right face swelling, she came to our emergency department for assistance on 4$^{th}$-October 2011. Upon examination, she had a body temperature of 37.1°C, pulse rate 139/min, respiratory rate 24/min, and saturation by pulse oximetry ($SpO_2$) 92% under ambient air. An examination of her head and neck revealed mild right face swelling, and breathing with accessory muscle use. A decreased right upper lung breathing sound was noted. The jugular vein was barely visible and no heart murmur was noted. The fetal heart beat was 120-180 beats/min, and there was no uterine contraction. A hemogram revealed a white blood cell count of 15,070/cumm, hemoglobin 10.6 g/dl, and platelet count of 205,000/cumm. Biochemistry tests revealed BUN/creatinine 5/0.54 mg/dl, total bilirubin 0.76 mg/dl, aspartate aminotransferase and alanine aminotransferase 10 and 11 U/l, respectively, creatine kinase (CK)/CKMB/troponin I < 20/5/0.05, prothrombin time and activated partial thromboplastin time 10.2 and 31.5 seconds, respectively, and an international normalized ratio of 0.9. Arterial blood gas analysis showed pH 7.48, $PaCO_2$ 31.7 mmHg, $PaO_2$ 69.6 mmHg, and $HCO_3^-$ 23.2 meq/l under ambient air. Electrocardiography (ECG) revealed sinus tachycardia without ST-T change. The patient refused any imaging examinations due to concerns over radiation exposure. We arranged a transthoracic echocardiography (TTE) (Figure 1A, B), which revealed multiple masses nearby and within the right ventricle, left atrium and left ventricle. Moderate pulmonary hypertension with tricuspid regurgitation and a pressure gradient (TRPG) of 41.4 mmHg was also found. Heparinization was first prescribed due to the suspicion of pulmonary embolism. Contrast-enhanced chest computed tomography (CT) (Figure 2A, B) showed a huge lobulated mass involving the anterior mediastinum, causing encasement of the superior vena cava, compression of the left brachiocephalic vein, leftward displacement of the brachiocephalic trunk, and posterior displacement and compression of the intrathoracic

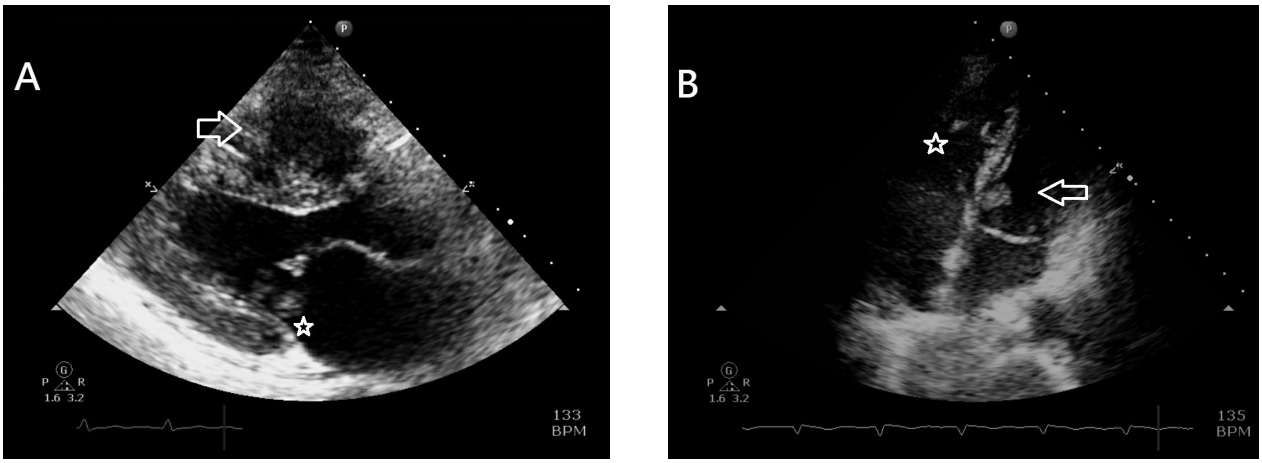
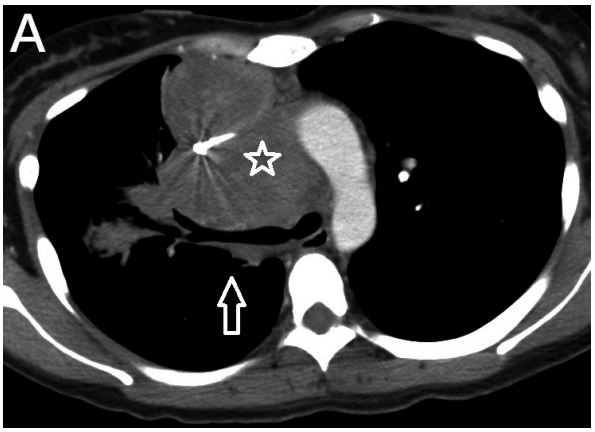


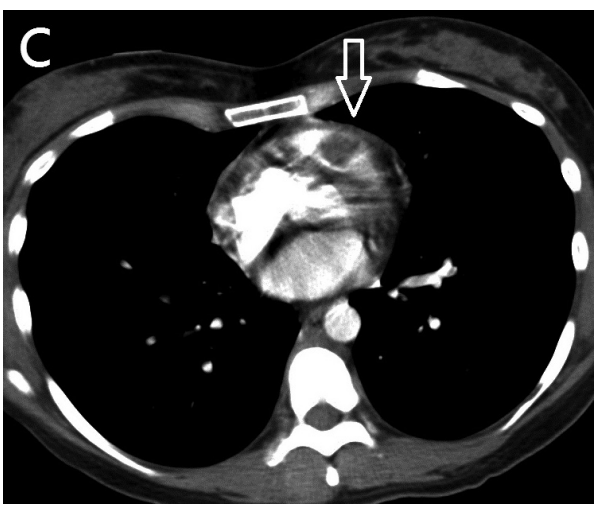

**Fig. 1.** A. Transthoracic echocardiography (TTE) in the parasternal long axis view showed a mass in the right ventricle (white arrow) and left ventricular outflow tract (white star). B. TTE in a 4-chamber view revealed a mass lesion at the mitral valve (white arrow) and right ventricle (white star).

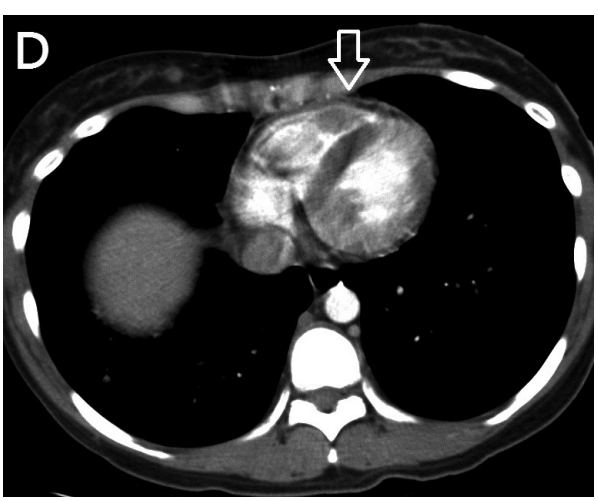
trachea, carina, and right main and right upper bronchus. A nodule lesion at the right ventricle and left atrium (Figure 2C, D), and multiple lung nodules were also found. She was admitted to our medical intensive care unit (ICU) due to her potentially life-threatening cardiopulmonary status. Chest ultrasonography-guided mass aspiration and biopsy were performed after discontinuing heparin. The pathology revealed poorly differentiated adenocarcinoma, of lung origin, with immunohistochemical staining focal-positive for thyroid transcription factor-1 and cytokeratin 7, and negative for CD5, c-kit, synaptophysin, and chromogranin-A.

A multidisciplinary team, including obstetricians, neonatologists, anesthetists, a cardiologist, chest surgeon, cardiovascular surgeon, oncologist, and an intensivist discussed the case and provided therapeutic options to the patient, her husband and parents. Due to the risk of delivery, they planned a delay of elective cesarean section in consideration of fetal lung maturation with betamethasone 12 mg intramuscular injection daily. However, because of worsening dyspnea and increasing chest discomfort the following day, an emergency cesarean section under general anesthesia was performed, with the delivery of a 29 + 4 week-gestation neonate, weighing 1.395 kg (50-75$^{th}$ percentile) and with Apgar scores of 4 and 8 at 1 and 5 minutes, respectively. Refractory hypoxemia developed immediately after delivery in the operating room, and the chest surgeon deployed an Ultraflex tracheal stent (20 × 40 × 25 mm), placed 0.5 cm above the carina via a rigid bronchoscope. Bronchoscopy showed severe external compression of the lower trachea and right main bronchus.

Gefitinib 150 mg per day was administered after the 8$^{th}$ day post-cesarean section (10$^{th}$ ICU day) because of concerns about wound healing after the cesarean section and because the family needed more time to consider further treatment options. The epidermal growth factor receptor (EGFR) mutation was found to be wild-type. A sudden onset of sinus tachycardia and elevated troponin I were noted on the 12$^{th}$ day of the ICU stay. Repeat TTE (Figure 3) showed



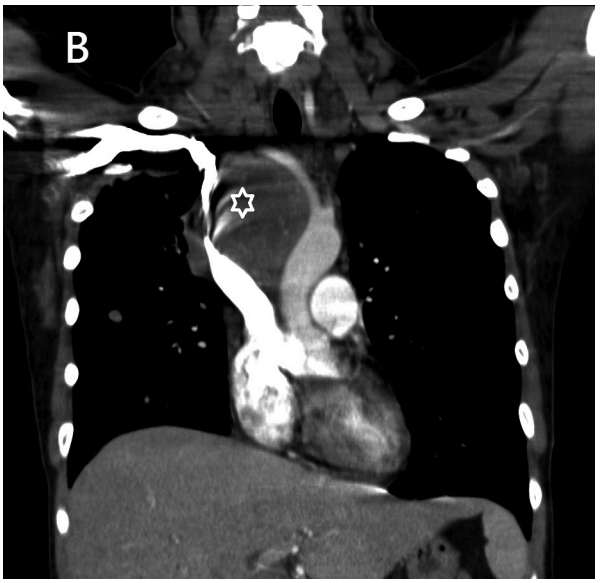




**Fig. 2.** A. Chest computed tomography (CT) revealed a large lobulated mass (white star) involving the superior anterior mediastinum, about 12 cm in size, with central necrosis and right main bronchus compression (white arrow). B. Chest CT in the sagittal view displayed a huge mass (white star) causing encasement of the superior vena cava, compression of the left brachiocephalic vein, leftward displacement of the brachiocephalic trunk, posterior displacement and compression of the intrathoracic trachea, carina, and right main and right upper bronchus. C. Chest CT showed a 1.8-cm nodule lesion in the left atrium (white arrow) with hypodense enhancement in the arterial phase and homogeneous enhancement in the venous phase. D. Chest CT showing a hypodense nodule at the right ventricle (white arrow).

rapidly-growing intracardiac tumors at the right ventricle and mitral valve, resulting in high TRPG of 75.5 mmHg and subpulmonary valvular stenosis. We gave her a high-dose vasopressor and fluid challenge, but in vain. Obstructive shock ensued and the family signed a do-not-resuscitate form. The patient passed away on the 13$^{th}$ day of ICU stay. The baby boy was normal and healthy without any neurological defects.

## Discussion

This case demonstrates the dilemma of a delayed delivery, in terms of imposing a higher risk on the maternal outcome and decreasing fetal complications with increased fetal maturity. Clinical judgment is very difficult and requires a multidisciplinary approach and careful as-

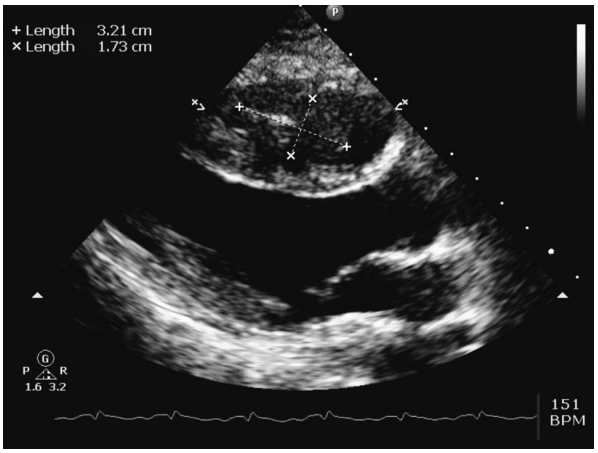



**Fig. 3.** TTE showing rapid-growing intracardiac tumors at the mitral valve, about 1.21 × 1.73 cm in size.

sessment to ensure that these patients and their families understand the complicated nature of these situations and are actively involved in the decision-making. Cancers diagnosed in pregnant women are not common, with an incidence of around 1 of 1000 females [1]. Lung cancer is the most common cause [2]; however, early diagnosis of lung cancer is very difficult due to the subtlety of the symptoms as its progresses. Jackisch C *et al*. [10] reported a series of 15 pregnant women with lung cancer, and all were diagnosed with distant metastasis at an inoperable stage; only 1 fetal involvement was noted [10]. Therefore, we suggest that delivery should be delayed as long as possible in order to advance fetal maturity. Lung cancer is often diagnosed at an advanced stage in pregnant women [3], and mean survival is only 7.7 months. Gurumurthy et al reported [3] a 38-year-old female who was diagnosed with NSCLC, poorly differentiated carcinoma at 24 weeks of gestation. The patient accepted chemotherapy with gemcitabine and carboplatin at 25 weeks of gestation, and the baby was delivered at 29 weeks of gestation with systemic steroid use. The baby was healthy without neuro-developmental sequelae; however, the mother died 2 weeks postpartum. Management of a pregnant woman with a preterm baby and inoperable cancer is a difficult issue. Delivering the baby at the time of tumor diagnosis to allow for early intervention for the mother imposes the risk of increased premature complications for the neonate. However, the situation is reversed if dealt with in the opposite manner. Thus, in these complex situations we organize a multidisciplinary team to discuss, manage and determine an individualized treatment strategy.

EGFR tyrosine kinase inhibitors (TKIs) are the first treatment choice in lung adenocarcinoma with a positive EGFR mutation [14]. However, the safety of EGFR TKIs in pregnant women and fetuses is still unknown. To date, only 2 pregnant women with lung adenocarcinoma and a positive EGFR mutation have had a good response to EGFR TKI therapy [15,16]; 1 was given gefitinib in the 3$^{rd}$ trimester and had a normal fetal outcome [15], and the other was treated with erlotinib in the 1$^{st}$ trimester of unrecognized pregnancy, and had a normal fetal outcome [16].

Metastatic tumors of the heart are rare, and the most common causes are lung cancer, lymphoma, and breast cancer [11,17]. Right-sided heart involvement is more common than left-sided, and the patients are often asymptomatic [18]. The tumors can reach the heart by hematogenous and lymphatic spread, or direct invasion of the vena cava or pulmonary vein [19]. The clinical presentations and severity depend on the metastatic locations and tumor size, and include tachycardia, arrhythmias, heart failure, recurrent emboli and myocardial infarction [19,20]. If the cardiac mass is within the right or left atrium, it increases atrial pressure due

to the effect of valvular stenosis and causes the elevation of pulmonary venous pressure with lung edema [13]. When the cardiac mass occurs in the ventricle, it interrupts ventricular filling and obstructs outflow, causing the symptoms of heart failure and systemic embolization [21,22]. TTE or transesophageal echocardiography are useful diagnostic tools in this situation as they can identify the tumor size, location, heart contractility and valve condition [23]. Contrast-enhanced CT, magnetic resonance imaging (MRI), and angiography have also been used to detect cardiac metastasis [22,24]. Differentiating intracardiac tumor and thrombus is challenging. The thrombus is often located on the atrial appendage and left ventricle apex and is non-movable [25]. However, if the chest CT identifies local invasion of the chamber walls or pericardium, extension to the pulmonary vessels, multiple chamber spread, or mass necrosis, then intracardiac metastases is more likely [25]. MRI is a useful tool because a thrombus will not be enhanced after gadolinium injection [26]. Some reports have highlighted the successful surgical removal of cardiac tumors [27]. However, surgical intervention is always too late in this type of metastatic cardiac tumor at an advanced stage with multiple metastases and unstable hemodynamics, such as that observed in our patient. The remaining treatment choices are local radiotherapy or chemotherapy, but the prognosis remains poor [21].

In summary, we reported a case of NSCLC in a pregnant woman with the symptoms of dyspnea and orthopnea for 1 month. Clinicians often hesitate to use diagnostic imaging tools in pregnant woman because of the risk of radiation exposure, and hence may overlook this disease. When a pregnant patient suffers from unusual progressive dyspnea, non-invasive examinations that do not involve radiation, such as echocardiography or chest ultrasonography should be arranged, and lung cancer should be taken into consideration. Dealing with cases involving a pregnant patient with an advanced stage of cancer, and especially those with a preterm baby, is a significant challenge. As a result, a multidisciplinary approach is needed and careful assessment to plan the treatment in an individualized manner should be conducted.

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# 一位孕婦診斷爲非小細胞肺癌合併心臟轉移、上腔靜脈症候群和右主氣管壓迫：一個病例報告

賴怡君 *,** 古世基 ** 余忠仁 **

肺癌往往在診斷時已經是末期且無法開刀。然而，肺癌發生心臟內轉移是很罕見的。肺癌也不常發生在懷孕的婦女身上。在此，我們要報告的案例是一位懷孕 29 週的 33 歲女性，表現的症狀是一個月以來的乾咳和逐漸變喘。胸腔超音波和胸部電腦斷層發現有巨大腫塊位在前縱隔腔合併多處肺轉移，且壓迫到氣管，和上腔靜脈，並有心臟內轉移。胸部超音波引導下切片病理結果為分化不好的肺腺癌。治療的困難點在於抉擇孕婦該何時引產，用何種方式生產，以及處理被壓迫到的呼吸道和心臟內的轉移。雖然小孩在緊急剖腹產後平安生下來，但病人不幸的在住院第十三天後死亡，死於心臟內腫瘤阻塞住心輸出血流造成的心因性休克。這個病例提醒臨床工作者應好好注意懷孕婦女所發生的無法解釋之呼吸困難，要想到有肺癌的可能性，進而安排後續檢查，如無輻射顧慮的心臟超音波和胸部超音波檢查。*( 胸腔醫學 **2013; 28: 296-303**)*

關鍵詞：心臟內轉移（intracardiac metastasis），肺癌（lung cancer），孕婦（pregnancy），上腔靜脈症候群（superior vena cava syndrome）

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# Acute Pneumonitis and Alveolar Hemorrhage Induced by Illegal Augmentation Mammaplasty – Case Report

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Augmentation mammaplasty with subcutaneous injections of silicone has been proven to be dangerous to the overall health of the patient. Injections of silicone have resulted in migration, granulomatous hepatitis, severe pulmonary reactions and even death. Unlawful silicone injections have led to some very severe reactions within the pulmonary area, and some injections have resulted subsequently in pneumonitis-type illness. We introduce a case of acute pneumonitis and alveolar hemorrhage in a 25-year-old woman who had undergone this procedure twice, 7 and 4 days before admission. The patient initially presented with shortness of breath, massive hemoptysis and hypoxemia. Chest radiograph revealed an alveolar pattern predominantly in the bilateral peripheral zones, and computed tomography scan demonstrated bilateral fluffy air-space infiltrates and intact silicone breast implants. The chest image and symptoms such as dyspnea and hemoptysis all showed improvement within a few days following the administration of oxygen and steroid, and supportive care. ***(Thorac Med 2013; 28: 304-308)***

Key words: silicone, augmentation mammaplasty, acute pneumonitis, alveolar hemorrhage

## Introduction

Silicone (polydimethylsiloxane) is a liquid polymer previously used extensively in cosmetic operations. It has a high degree of thermal stability, undergoes little change in physical properties with aging, and lacks immunogenicity [1]. However, silicone is not completely inert and injections of silicone have resulted in adverse consequences such as migration, granulomatous hepatitis, severe pulmonary reactions and even death [2]. There are only sporadic case reports of pulmonary complications in the literature. We describe a case of acute pneumonitis and alveolar hemorrhage in a 25-year-old woman who had undergone this procedure twice, 7 and 4 days before admission. She had an uneventful recovery after the administration of oxygen, steroid and supportive care.

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## Case Report

A previously healthy 25-year-old woman presented with shortness of breath and massive hemoptysis after receiving an uncertain volume of subcutaneous silicone injections by a medical imposter for augmentation mammaplasty twice in the same areas 7 and 4 days before admission. The patient had a history of smoking 10 to 20 cigarettes per day for 2 years. She denied alcohol abuse or illicit intravenous drug use. She had no history of recent travel, and a review of systems was otherwise unremarkable.

On physical examination, her body temperature was 36.9°C; pulse, 96 beats/min; blood pressure, 97/59 mm Hg; respiration, 22 breaths/min. The patient was comfortable while resting in bed, but became short of breath when she tried to speak in complete sentences. There were diffuse crackles in the lung bases. Arterial blood gas measurements in $FiO_2$ 28% were pH, 7.41; $PaCO_2$, 41 mmHg; $PaO_2$, 64 mmHg; $HCO_3^-$, 26 mmol/L. Complete blood count, including differential, prothrombin time, partial thromboplastin time, serum chemistry and liver function tests, was normal.

Chest radiograph revealed a scattered, patchy, ill-defined alveolar pattern predominantly in the bilateral peripheral zones (Figure 1). Contrast-enhanced computed tomography (CT) scan demonstrated bilateral fluffy airspace infiltrates and intact silicone breast implants (Figure 2). There was no specific finding on sputum examination and the following tests showed results within normal limits: complement levels, anti-extractable nuclear antigens, rheumatoid factor, anti-nuclear antibody, anti-neutrophil cytoplasmic antibodies and anti-glomerular basement membrane antibody.

We reached the diagnosis of silicon pneumonitis and alveolar hemorrhage based on the remarkable history, typical presentations and radiological findings. The dyspnea and hemoptysis showed improvement within a few days after the administration of oxygen and hydrocortisone, and supportive care. The chest radiograph on the 5th admission day also revealed marked resolution of the alveolar pattern (Figure 3).

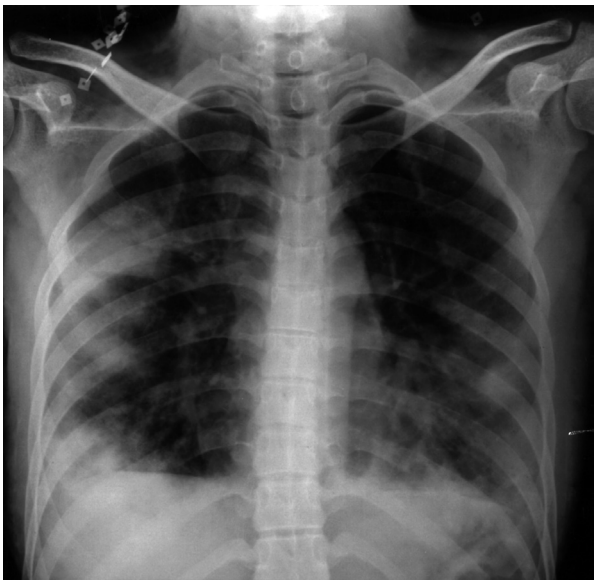

**Fig. 1.** 'Reverse butterfly sign' – alveolar pattern predominantly in the peripheral zones.

## Discussion

Liquid silicone injections can induce silicone emboli and have been implicated as a cause of acute pneumonitis and alveolar hemorrhage. The pathogenesis involves a process of pulmonary embolism following the diffusion of the silicone into the circulatory system, encouraged by high local tissue pressure, massages, migration, or direct injection [3]. In a recent study, 92% of patients with silicone embolism had hypoxemia, 88% had dyspnea, 70% fever,

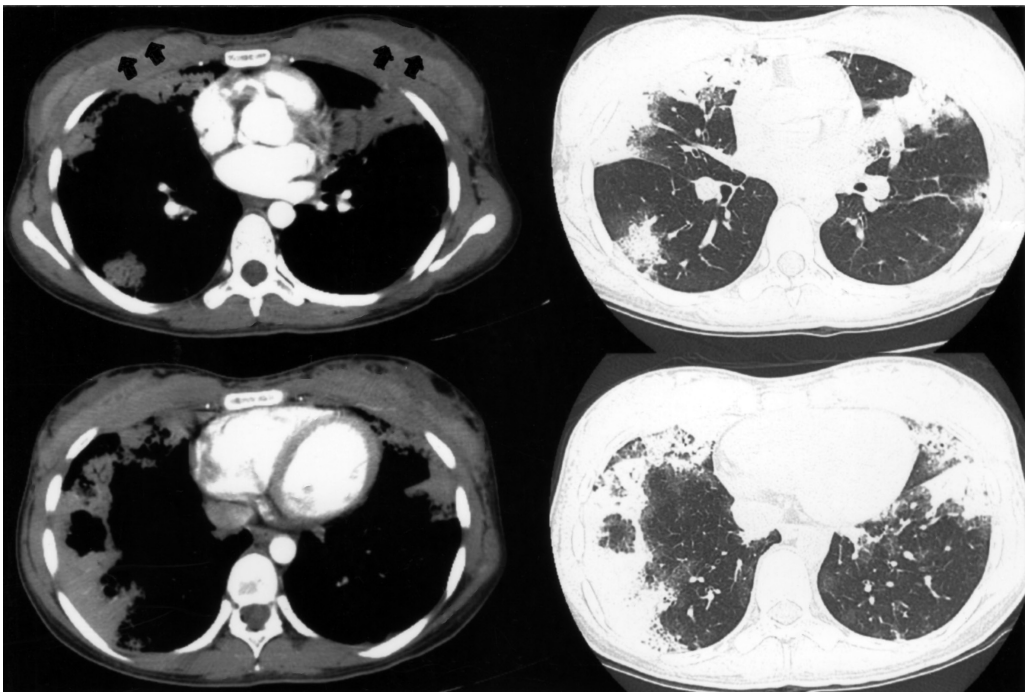

**Fig. 2.** Computed tomography scan demonstrating fluffy air-space infiltrates and intact silicone breast implants (arrows).

and 64% alveolar hemorrhage [4]. In a case series, all patients with silicone pneumonitis presented with dyspnea, chest pain, and an abnormal high-resolution CT; most of the patients had dry cough (60%) and fever (40%). The radiologic appearances all revealed bilateral patchy consolidation and/or ground-glass opacities, predominantly in the peripheral and subpleural lung [5]. As such, the time sequence and clinical course of our patient were compatible with silicone pneumonitis and alveolar hemorrhage.

The diagnosis was confirmed by the finding of embolic vacuoles on a lung biopsy specimen. Sometimes, the finding of macrophages with rounded inclusions on bronchoalveolar lavage can be a clue, especially if there is a history of silicone injections. Despite its diagnostic value, bronchoscopy was deferred in our patient due to the policy of using non-invasive methods to

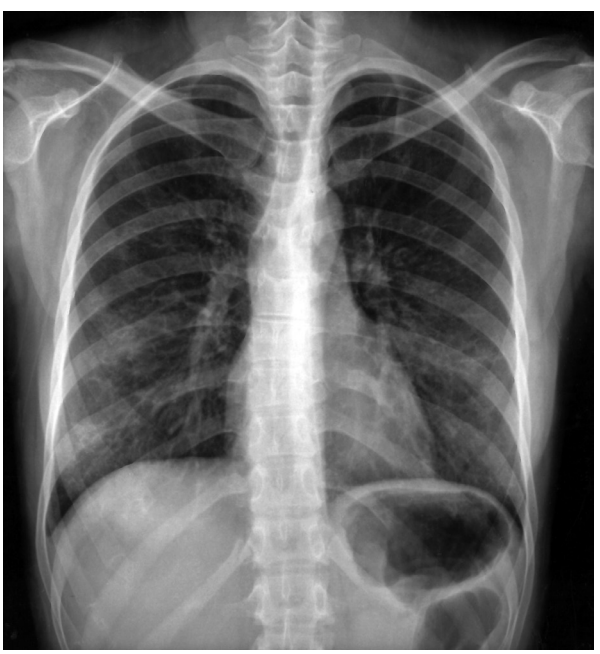

**Fig. 3.** Chest radiograph revealing marked resolution of the alveolar pattern on the 5$^{th}$ admission day.

achieve a rapid course of improvement and realize concomitant economic benefits. Thus the diagnosis was made based on a targeted history, typical presentation and clinical images.

The treatment for silicone pneumonitis and alveolar hemorrhage is usually rest, high-flow oxygen inhalation, and mechanical ventilation [6]. Although there is no clear evidence that corticosteroids influence outcome, the drug is often administered in the setting of unexplained acute respiratory failure, when cultures are negative and serologies for inflammatory etiologies are pending [1]. Patients usually recover without sequelae, but pulmonary fibrosis has been described in patients who survive an acute event. The presence of a change in consciousness is a poor prognostic factor that indicates brain hypoxia [7].

## Conclusion

Illegal subcutaneous injections of silicone have been proven to be dangerous to the overall health of the patient [8]. Silicone pneumonitis should be considered when a patient presents with unexplained hemoptysis, respiratory distress and a remarkable history. It is also important to increase public awareness about the potentially lethal consequences of silicone injections.

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# 違法地使用皮下注射矽膠隆乳術造成急性肺炎及肺泡出血

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違法地使用皮下注射矽膠來進行隆乳術，已經被證實會對人體的健康造成相當程度的危害。大量的矽膠注射會造成矽膠轉移至身體的其他部位、肉芽腫性肝炎、嚴重的肺部反應甚或是死亡。我們報告一位二十五歲的女性，因皮下注射矽膠隆乳而導致急性肺炎及肺泡出血。她的表現為呼吸喘促、大量咳血及動脈低血氧。胸部 X 光呈現以週邊為主的肺泡型病變而電腦斷層則顯示出雙側肺泡浸潤及明顯可見的矽膠植入物。患者的呼吸喘促與咳血情形，在使用氧氣供給搭配類固醇注射及支持性療法之下，明顯在短時間內有效地改善。*( 胸腔醫學 **2013; 28: 304-308**)*

關鍵詞：矽膠，隆乳術，急性肺炎，肺泡出血

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# Early Intracranial Metastases from a Huge Malignant Pleural Mesothelioma – A Case Report

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Malignant pleural mesothelioma is a rare disease and is associated with high mortality. We reported the case of a patient initially presenting with a 15 cm mass in the right posterior pleural space. Pathologic diagnosis of malignant mesothelioma, epithelioid subtype, was made by means of sonography-guided tumor biopsy. No distant metastasis was found in the initial systemic image survey. After receiving 2 courses of chemotherapy, the patient developed significant central nervous system symptoms. The diagnosis of bilateral cerebellar metastases was established by brain magnetic resonance image. The patient underwent brain radiation therapy, but with no response, and died 3 months after the initial diagnosis. Malignant pleural mesothelioma is traditionally regarded as a tumor that occurs through aggressive local invasion rather than distant hematogenous spread. Early and symptomatic brain metastases are a rare event in patients with malignant pleural mesothelioma and a very rare cause of death, as in our case. ***(Thorac Med 2013; 28: 309-314)***

Key words: mesothelioma, pleural, epithelioid, brain metastases

## Introduction

Malignant pleural mesothelioma is a highly aggressive tumor associated with a poor prognosis. Median overall survival has been reported to be between 9 and 17 months [1]. Death is usually caused by complications secondary to extensive local tumor growth rather than by distant metastasis [2-3]. Early and symptomatic brain metastasis from malignant pleural mesothelioma is an uncommon event and a rare cause of death. Herein, we report the case of a patient with malignant pleural mesothelioma that initially presented with a huge right pleural mass. Early brain metastases to the bilateral cerebellum developed 2 months after diagnosis and caused a rapid decline in consciousness and death.

## Case Report

A 46-year-old male presented with a

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2-month history of non-productive cough and chest pain. The chest pain was dull and insidious in onset, and was aggravated by deep breathing and lying down. Marked body weight loss (from 67 kg to 60 kg) was recorded in the most recent 2 months. The patient was an electric appliances repairman, but had no recollection of previous exposure to asbestos.

On physical examination, dullness and decreased breathing sounds in the right lower posterior chest region were noted. Chest radiography showed a huge pleura-based mass in the right lower lung field (Figure 1A). Chest computed tomography (CT) scan revealed a 15 cm solid mass in the right posterior pleural space that had invaded the chest wall, the 7$^{th}$ rib, the diaphragm, and the right hepatic lobe (Figure 1B). Little pleural effusion was found. The position emission tomography (PET) scan demonstrated a high standardized uptake value (SUV), as the maximal SUV was 13.7 of the tumor mass. No distant metastasis was found in the initial systemic survey, including brain CT and PET scan. Histologic examination of the sonography-guided tumor biopsy specimen revealed clusters of large polygonal to round epithelioid neoplastic cells in solid sheets (Figure 2). Immunohistochemical staining was positive for cytokeratin, calretinin, and D2-40, and negative for melanoma monoclonal antibody (HMB-45) and anti-CD56 antibody (MOC-31) stain. The morphology and immunophenotype were in accordance with a diagnosis of malignant mesothelioma with an epithelioid pattern. The patient was started on chemotherapy, receiving pemetrexed and cisplatin every 3 weeks, and tolerated the regimen reasonably well.

Two weeks following the 2$^{nd}$ course of chemotherapy, the patient called on our emergency department with a 3-day history of dizziness, nausea, vomiting, and unsteady gait. The patient was able to comprehend, but was lethargic. No focal weakness was presented. Recorded vital signs were within normal limits. Brain CT revealed a new enhanced mass lesion in the right cerebellar hemisphere suggestive of intracranial metastasis. The brain magnetic resonance image (MRI) after admission revealed 2 enhanced

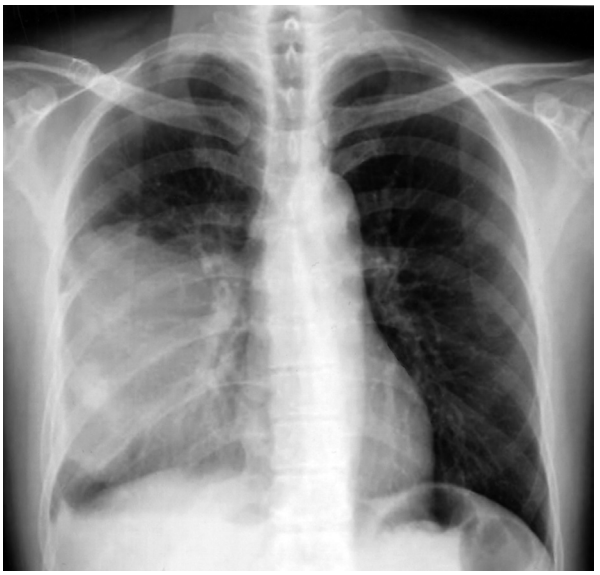

**Fig. 1A.** Chest radiograph showing a huge pleura-based mass at the right lower lung field with mild pleural effusion.

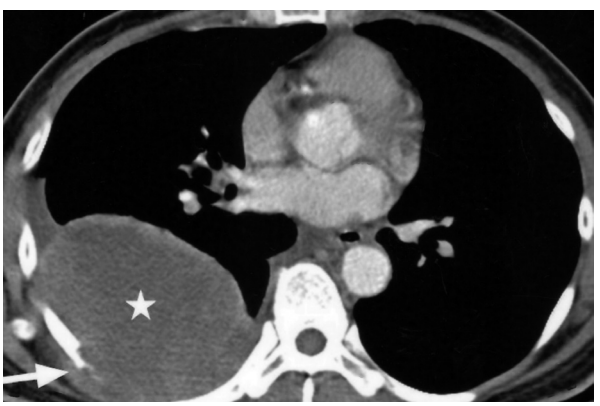

**Fig. 1B.** Chest CT scan revealed a 15 cm solid mass in the right posterior pleural space (star) with chest wall invasion and destruction of the 7$^{th}$ rib (arrow).

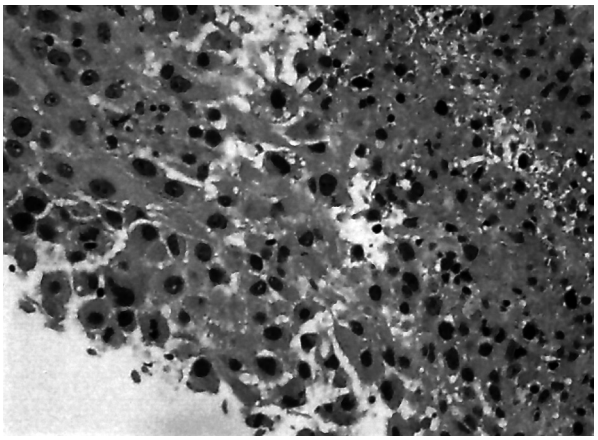

**Fig. 2.** Histology showed clusters of large polygonal to round, epithelioid neoplastic cells in solid sheets, compatible with epithelioid malignant mesothelioma (H&E stain, 200X).

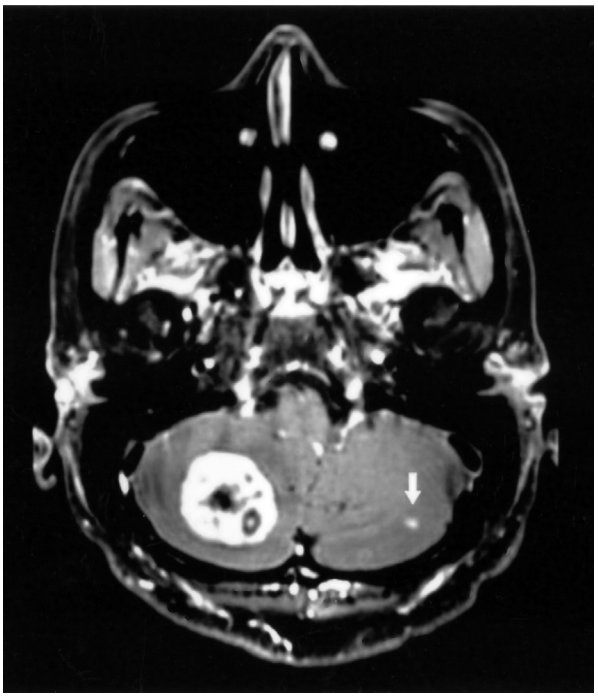

**Fig. 3.** Brain MRI (T1-weighted image, post-gadolinium) revealed a 3 cm enhanced mass lesion with central necrosis involving the right cerebellar hemisphere and with perifocal edema; another 3 mm enhanced nodule in the left cerebellar hemisphere (arrow).

tumors involving bilateral cerebellar hemispheres, 3 cm in the right and 3 mm in the left, causing perifocal edema and mild obstructive hydrocephalus (Figure 3). These image findings were radiologically compatible with brain metastases. Chest CT also showed the right pleural mesothelioma was more enlarged. Intravenous dexamethasone and glycerol were administered. The neurosurgeon advised conservative treatment for the bilateral cerebellar involvement and poor functional status. The patient subsequently underwent palliative whole brain radiation therapy. However, progressive consciousness disturbance proceeded to a comatose state despite the treatment. At that point, the patient's family opted for hospice care and the patient died 1 week later (3 months following the initial diagnosis).

## Discussion

Malignant mesothelioma is a rare tumor arising from serosal surfaces. Over 80% of tumors arise from the pleura, but primary mesothelioma of the peritoneum, pericardium and tunica vaginalis are also reported [4]. There are 3 histologic subtypes of mesothelioma: epithelioid, biphasic, and sarcomatoid tumors. Epithelioid tumors are most common and have a better prognosis than biphasic and sarcomatoid tumors [1]. Asbestos is the principal carcinogen responsible for the development of malignant mesothelioma; only 20% of patients have no history of asbestos exposure [3]. The incidence of malignant mesothelioma has increased worldwide recently as a result of widespread asbestos exposure. The predicted peak annual incidence will occur in year 2020 in Europe and 2025 in Japan, respectively [2].

Malignant pleural mesothelioma is a highly aggressive disease and extremely difficult to treat, with median overall survival ranging between 9 and 17 months, regardless of stage [1].

Poor prognostic factors included male gender, extensive disease, poor performance status, elevated white-cell count, anemia, thrombocytosis, sarcomatoid subtype and high SUV ratios on PET [2]. Death is usually ascribed to tumor invasion of adjacent structures, infection, or respiratory failure secondary to encasement of the lung by the tumor. Distant metastases are extremely rare causes of death [2-3].

Distant metastases of mesothelioma, as opposed to local invasion, are traditionally regarded as an uncommon condition. However, some published studies have revised this long-standing belief. Falconieri *et al*. reviewed 171 cases of malignant mesothelioma at autopsy and discovered that distant metastases could be found at multiple organs. The sites most commonly affected were the liver (56%), adrenals (31%) and kidneys (30%). Metastases to the pancreas, the thyroid gland, the stomach, bones and brain were also noted in a few cases (3-6%) [5]. Wronski and Burt also reviewed post-mortem findings and concluded that the incidence of cerebral metastasis was between 5% and 10% [6]. Autopsy studies clearly document that metastases are not an uncommon feature of malignant mesothelioma late in the course of the disease, but cases of brain metastases are few.

Early, symptomatic metastases remain uncommon in patients with malignant pleural mesothelioma, and symptomatic brain metastases diagnosed ante-mortem is a very rare event [7]. Previous reports have documented that sarcomatoid tumors tend to metastasize more, including brain metastasis in cases of autopsy studies [5-6,8]. Sarcomatoid tumors are also known to be more aggressive and have a worse outcome [1-2]. Despite the subtype of epithelioid tumor, which has a more favorable outcome, and the relatively young age and good performance status of this patient, the tumor had little response to standard chemotherapy with pemetrexed and cisplatin. Early and symptomatic brain metastases developed 2 months after the initial diagnosis and caused rapid consciousness decline and mortality. This is a rare condition in patients with malignant pleural mesothelioma.

There are only 2 cases of patients with brain metastases from malignant pleural mesothelioma of an epithelioid subtype undergoing surgical tumor removal in the literature [9-10]. The metastatic brain lesions in both cases were found to have spindle cell components with an epithelioid background similar to primary lung tumor in the histologic studies. In 1 of the cases, spindle cell elements were also discovered in the primary tumor cells. These findings might imply that spindle cell components play a role in the process of brain metastases in the cases of primary epithelioid subtype tumors.

As malignant pleural mesothelioma is more chemotherapy-resistant than other tumor types, the combination of cisplatin and pemetrexed given every 3 weeks was established as a standard-of-care front-line regimen [11]. The regimen had a 41.3% response rate, median time to progression of 5.7 months, and median overall survival of 12.1 months. Improved therapeutic strategies recently have prolonged the lifespan of patients with unresectable malignant pleural mesothelioma.

In conclusion, symptomatic brain metastases are a rare condition in patients with malignant pleural mesothelioma. However, this type of case is expected to become increasingly more common in the future because of widespread asbestos exposure and the prolonged lifespan of patients due to improved treatment strategies. Brain metastasis should be recognized in patients with malignant pleural mesothelioma

presenting with central nervous system symptoms, even when the initial intracranial survey is negative, and should be considered as a cause of rapid mortality.

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# 一巨大惡性肋膜間皮瘤併早期腦轉移：一病例報告

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惡性肋膜間皮瘤是一個罕見且高致死率的疾病。我們報告一位病例以右後側肋膜腔 15 公分的腫瘤為表現。經由超音波導引腫瘤病理切片，診斷為上皮性的惡性間皮瘤。系統性影像檢查並沒有發現任何遠端轉移。在接受兩個療程的化學治療後，病患出現了明顯的中樞神經症狀。經由腦部核磁共振，診斷了雙側小腦的腫瘤轉移。病患接受了腦部的放射治療但是沒有反應。他在診斷後三個月死亡。惡性間皮瘤在傳統上被認為總是造成腫瘤局部侵犯，而較少有遠端血行性轉移的現象。早期且有症狀的腦部轉移在罹患惡性肋膜間皮瘤的病患中是非常少見的情形，而且也是相當罕見造成死亡的原因。*( 胸腔醫學 **2013; 28: 309-314**)*

關鍵詞：間皮瘤，肋膜，上皮性，腦部轉移

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# Huge Ectopic Posterior Mediastinal Goiter – A Case Report

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Ectopic goiter is rarely seen in the posterior mediastinum. We reported the case of a 54-year-old female who was admitted to our service because of progressive dysphagia, dyspnea on exertion and cough for 3 months. The patient was diagnosed as having a huge posterior mediastinal tumor, which caused tracheal deviation and esophageal compression. The tumor was completely resected through an anterolateral thoracotomy. The final pathological exam confirmed ectopic thyroid tissue. She was discharged with a favorable outcome and relief of symptoms. ***(Thorac Med 2013; 28: 315-320)***

Key words: ectopic goiter, mediastinum, thyroid

## Introduction

Mediastinal extension of primary thyroid tissue, known as substernal or intrathoracic goiter, is a well-defined clinical entity, and not infrequently seen in Taiwan. However, ectopic goiter is rare, and comprised only 1% of all goiters in 1 report [1]. Ectopic goiter in the mediastinum is even rarer, accounting for about 1% of all mediastinal tumors [2]. A review of the literature of ectopic mediastinal goiter showed that most ectopic goiters were found in the anterior or middle mediastinum [3]. To the best of our knowledge, posterior mediastinal localization of thyroid tissue was reported in less than 5 cases in the published English literature. Although ectopic goiter in the posterior mediastinum is rare, it is still considered a diagnostic possibility in the differential diagnoses of posterior mediastinal lesion. We present the case of a patient with a huge ectopic goiter in the posterior mediastinum that caused tracheal deviation and esophageal compression.

## Case Report

A 54-year-old woman complained of dysphagia, dyspnea on exertion, and intermittent dry cough for 3 months. Physical examination showed insignificant findings. A routine chest roentgenogram revealed a widened upper mediastinum, and a subsequent chest computed tomography scan confirmed a huge posterior mediastinal mass, 12.3 × 5.8 cm in size, located posterior to the trachea and anterior to the esophagus, displacing the trachea forward

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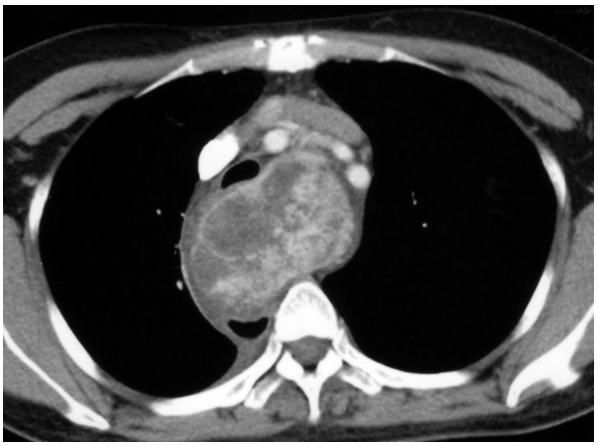

**Fig. 1.** Chest computed tomography shows a huge posterior mediastinal tumor, 12.3 × 5.8 cm in transverse diameter. It was located posterior to the trachea and anterior to the esophagus, surrounded by the azygos vein, spine, and aorta.

with right-side deviation, and causing esophageal compression (Figure 1). The tumor was wrapped by the aortic arch and its major tributaries, the azygos vein, and the pulmonary arteries. The mass was solitary, heterogeneously-enhanced, and had a well-defined border without connection to the thyroid gland and thymic tissue. Barium chest roentgenogram showed a huge soft tissue shadow at the superior mediastinum, and the esophagus was compressed at mid-esophageal level without signs of mucosal filling defect (Figure 2). Upper gastrointestinal endoscopy did not reveal a mucosal lesion, but suggested external compression by the tumor. Flexible bronchoscopy showed a right-side deviation of the trachea, but did not show an endobronchial lesion.

The patient was clinically euthyroid, without a sign or symptom of hyperthyroidism or hypothyroidism. Tumor markers including alpha-fetoprotein, carcinoembryonic antigen, squamous cell carcinoma antigen, and human

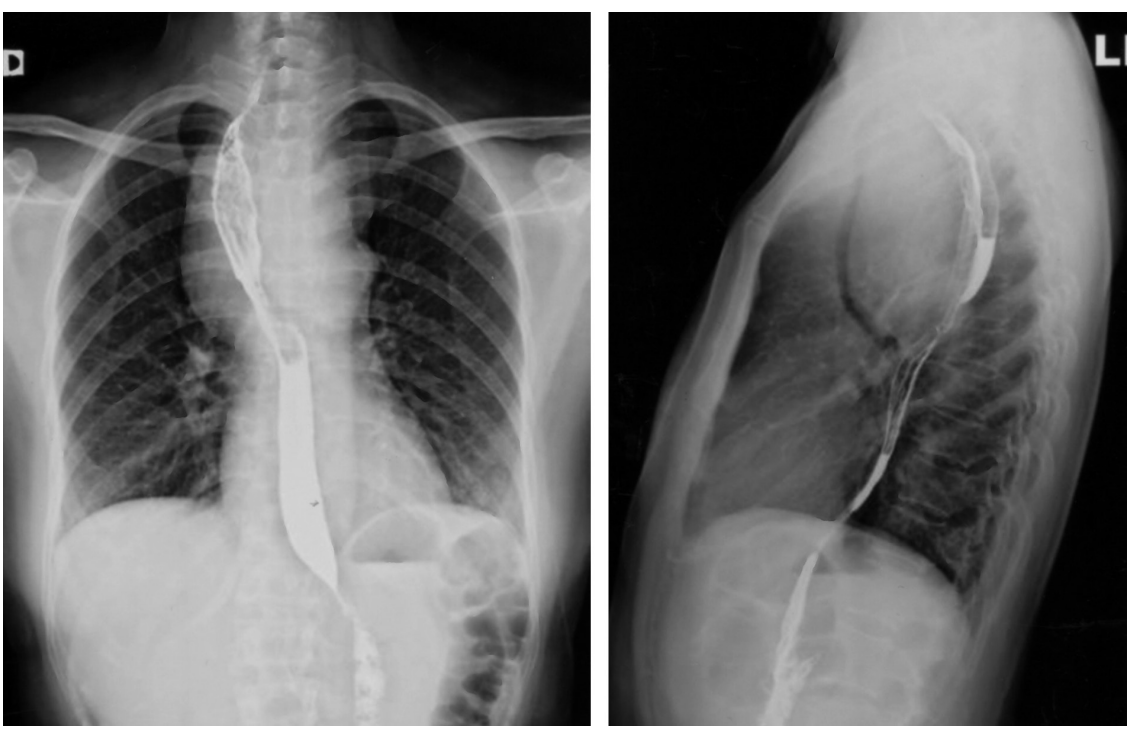

**Fig. 2.** Barium chest roentgenogram showed a huge soft tissue shadow at the superior mediastinum, and the esophagus was compressed at mid-esophageal level without signs of mucosal filling defect.

chorionic gonadotropin were all within normal range. Blood chemistry analysis and thyroid function panel were normal. Needle biopsy for tissue diagnosis had been considered, but we decided against performing it for the following 2 reasons. First, the tumor was surrounded by major vessels and vital organs, so needle biopsy would have presented a potential risk of trauma to these vital structures. Second, the heterogeneously-enhancing nature of the tumor implied a hypervascular entity, which may have led to massive bleeding when biopsy was taken, and subsequent airway compromise would occur due to tumor swelling. Thus, an operation was performed to remove the mass with the intent of diagnosis and symptom relief.

We performed a right-side anterolateral thoracotomy and entered the pleural cavity via the 4$^{th}$ intercostal space. We observed a huge, completely-encapsulated, hypervascular solid mass located at the upper mediastinum. After opening the right upper mediastinal pleura, the azygus vein and vagus nerve were seen to be looped and preserved. A mercury-weighted esophageal bougie was inserted into the esophagus to ease identification during surgery. The adhesions around the tumor were carefully separated, and the intrathoracic vessels supplying the mass were ligated and cauterized. The tumor was mobilized and resected completely. Even with meticulous hemostasis, the estimated blood loss was 1,000 cc after operation because of the tumor's hypervascular nature. The tumor was tan to brown, lobulated, and soft, with focal hemorrhage and necrosis. It weighed 210 gm and was 12.0 × 6.4 × 3.1 cm in size (Figure 3). A biopsy was taken from the mass and sent for frozen section. Histopathological examination revealed thyroid tissue. Postoperative pathological examination confirmed the previous frozen section diagnosis and reported thyroid tissue with nodular hyperplasia (Figure 4). The diagnosis of ectopic thyroid tissue in the posterior mediastinum was confirmed. The patient was discharged home uneventfully on postoperative day 5. She was well 6 months after the surgery.

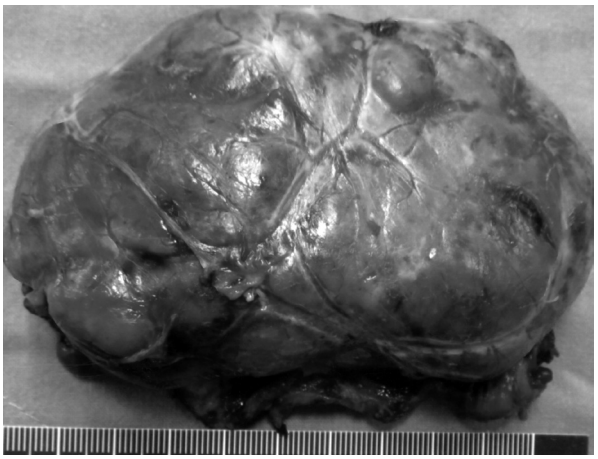

**Fig. 3.** Macroscopic view of the tumor shows a hypervascular and lobulated mass with a well-defined capsule.

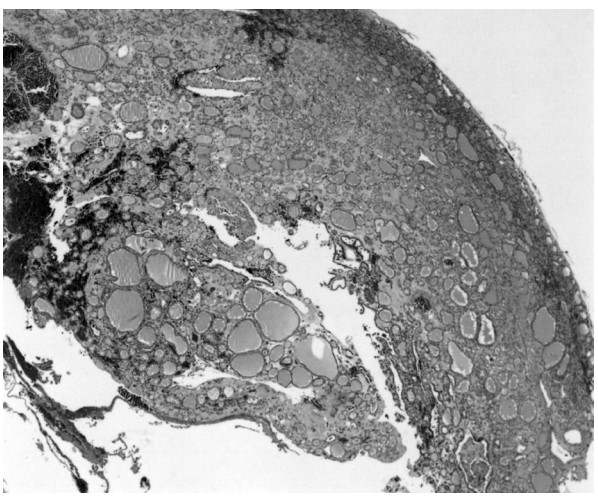

**Fig. 4.** Histopathologic examination of the mass shows colloid cysts of various sizes and nodular hyperplasia.

## Discussion

Most intrathoracic goiters are of a second-

ary type, which is an extension from cervical goiters, and have an incidence rate of 1% to 15% during thyroidectomy [4]. Primary intrathoracic goiter, also called ectopic thyroid goiter, is a rare entity, comprising only 1.7% of all intrathoracic goiters [3]. It has no physical connection to cervical goiter. The major distinction between primary and secondary intrathoracic goiters is the vascular supply. Primary intrathoracic goiter derives its blood supply from local mediastinal vessels such as the internal mammary artery, the innominate artery, or the intrathoracic aorta, while secondary intrathoracic goiter obtains its cervical blood supply from the cervical thyroid [5]. The difference in blood supply would determine the surgical approach to the 2 disease entities. In secondary intrathoracic goiter, a cervical incision to explore the intrathoracic part of the thyroid tissue has been justified. However, this would cause uncontrollable bleeding in the primary intrathoracic goiter because its blood supply is from mediastinal vessels which can only be approached by thoracotomy or sternotomy. Therefore, the preoperative differentiation between primary and secondary intrathoracic goiter is important.

Ectopic thyroid tissue has been found along the midline from the base of the tongue to the mediastinum. Ninety percent of the reported cases are found at the base of the tongue, and termed "lingual thyroid", but are rarely found in the mediastinum [6]. The proposed etiology of primary mediastinal goiter is embryological in nature. It is thought to be an abnormal adhesion between the thyroid anlage and other migrating structures such as the heart and thymus. As the heart or thymus descend into the chest, some of the thyroid tissue is also pulled caudally, resulting in the development of mediastinal thyroid tissue which then derives its blood supply from local mediastinal vessels [3]. However, the rudimental theory of the close association between the descending structures and the thyroid tissues as the cause of primary mediastinal thyroid tissue remains unclear.

Most intrathoracic goiters are incidentally found on image studies, without symptoms or signs. However, in a few reported cases, tumor compression of the trachea, esophagus, or thoracic vasculature may cause dyspnea, dysphagia, cough, chest pain, or superior vena cava syndrome [3]. Most cases are euthyroid with orthotopic thyroid tissue [2].

Chest roentgenogram is usually the first-line diagnostic tool for a mediastinal tumor, as in our presented case. Chest computed tomography and magnetic resonance imaging can provide further information about the location, consistency, and size of the tumor, and its relation to the great vessels and other mediastinal structures. When encountering a posterior mediastinal tumor like the present case, several differential diagnoses, such as lymphoma, Castleman's disease, esophageal tumor, tracheal tumor, and mesenchymal tumors, have been considered. Ectopic thyroid tissue is also a potential possibility. Thyroid nuclear scan with $^{131}$I may be useful in the diagnosis and clinical management. However, a $^{131}$I thyroid scan does not always identify ectopic thyroid tissue. In the intrathoracic tumor, a positive uptake confirms a thoracic goiter, but a negative scan does not exclude the diagnosis [7]. In patients with previous thyroid surgery, a thyroid scan may be helpful to evaluate potential mediastinal recurrence [7]. Upper gastrointestinal endoscopy and esophagography with barium are useful to clarify the association between the tumor and the esophagus. Bronchoscopy is needed to rule out mediastinal tumor of a bronchogenic origin.

In our case, the tumor was huge with tracheal and esophageal compression; therefore, upper gastrointestinal endoscopy and bronchoscopy were performed to rule out transmural esophageal invasion and tracheobronchial invasion.

The management of ectopic intrathoracic goiter is the surgical approach. In a literature review, the majority of authors discussed the need for thoracotomy or sternotomy in order to obtain a complete resection. The cervical approach was reported in a few cases with the mediastinal mass in an upper location [3]. Thoracoscopic excision has also been reported with excellent results in a patient with a small tumor [8]. In the present case, the tumor was relatively large. We performed a thoracotomy to obtain better visualization and vascular control. Malignant transformation in ectopic thyroid tissue is extremely rare because most reported cases of intrathoracic thyroid cancer were actually a secondary extension from the cervical thyroid [9]. However, these ectopic intrathoracic goiters should be resected due to the risk of progressive enlargement or hemorrhage causing respiratory compromise and compression of neighboring mediastinal structures. Surgery has a very low mortality rate (0-2%) and acceptable morbidity. The prognosis following a successful surgical excision is excellent [6].

Ectopic intrathoracic goiters with a posterior mediastinal location are very rare, but have to be considered as a diagnostic possibility in all cases of posterior mediastinal mass. Surgical resection is recommended for both diagnosis and symptomatic relief. In conclusion, we reported a huge ectopic posterior mediastinal goiter successfully resected by means of anterolateral thoracotomy with complete excision and relief of symptoms.

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# 巨大異位性後縱隔腔甲狀腺腫：一病例報告

劉昭宇　林志鴻 *　楊伊凡 *　徐中平 *

異位性甲狀腺腫罕見於後縱隔腔。我們報導一位 54 歲女性因為吞嚥困難、運動時呼吸困難，及咳嗽持續三個月，來本院就診。此病患被診斷患有一巨大的後縱隔腔腫瘤，造成氣管位移及食道壓迫。此腫瘤經由前側位開胸手術完全切除。最後病理報告確認為異位性甲狀腺組織。她後來順利出院，症狀改善且結果良好。*( 胸腔醫學 **2013; 28: 315-320**)*

關鍵詞：異位性甲狀腺腫，縱隔腔，甲狀腺

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