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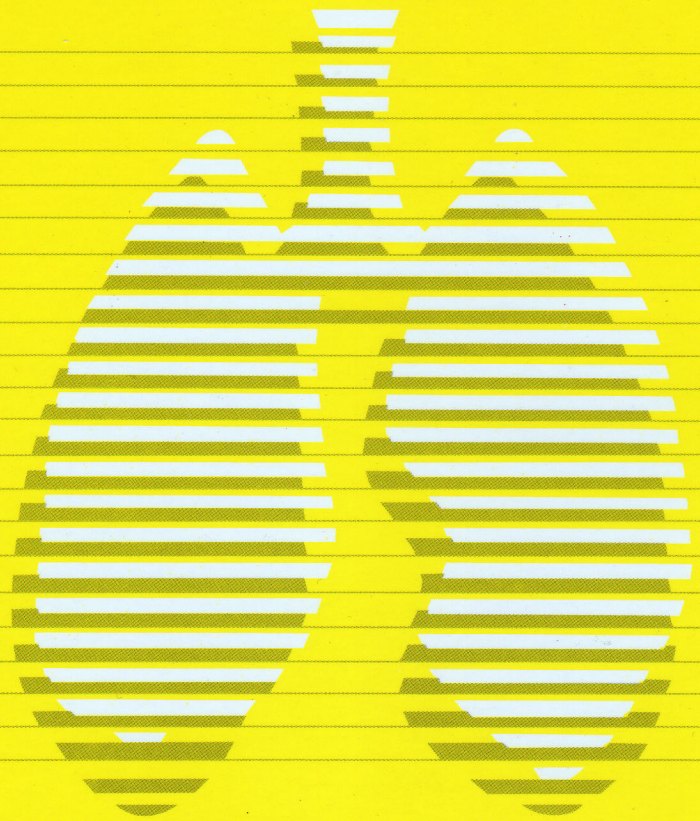

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原著

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Orginial Articles

Case Reports

胸腔醫學投稿聲明書

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特此聲明

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Outcomes of Mechanically Ventilated Non-Small Cell Lung Cancer Patients Receiving Tyrosine Kinase Inhibitors in Intensive Care Units

Shao-Yu Wang, Chih-Hao Chang, Hang-Chung Hu, Kuo-Chin Kao, Po-Hao Feng*, Ping-Chih Hsu, Li-Chung Chiu, Chen-Yiu Hung, Ning-Hung Chen, Chung-Chi Huang, Cheng-Ta Yang, Ying-Huang Tsai**

Background: The clinical response to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) of critically ill non-small cell lung cancer (NSCLC) patients has not been well addressed. The purpose of this study was to investigate the outcome of mechanically-ventilated (MV) NSCLC patients under EGFR-TKI treatment.

Methods: A retrospective study of NSCLC patients in medical intensive care units (ICUs) between January 1, 2004 and July 1, 2010.

Results: Thirty-three (36%) of the 91 NSCLC patients with MV taking EGFR-TKIs were successfully weaned from MV, including 13 (14%) who were responsive to EGFR-TKI treatment. Age, gender, performance status, Acute Physiology and Chronic Health Evaluation II score, cancer cell type and stage did not affect the outcome of MV weaning. Patients with controlled disease before ICU admission and those with EGFR-TKI response in the ICU achieved a significantly higher rate of successful weaning (39% and 52%, respectively).

Conclusions: NSCLC patients with controlled disease or EGFR-TKI response may need more aggressive management, even if they are under MV. ***(Thorac Med 2015; 30: 125-133)***

Key words: non-small cell lung cancer, tyrosine kinase inhibitors, mechanical ventilation, intensive care units

Introduction

Lung cancer is the leading cause of cancer-related death in Taiwan. The 5-year survival rate of metastatic non-small cell lung cancer (NSCLC) patients was only 5% before epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) proved to be an effective treatment [1]. The effects of EGFR-TKI treatment for NSCLC are remarkable and

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have resulted in a dramatic improvement in progression-free survival and quality of life for advanced patients, especially those with an EGFR mutation [2-5]. With the improvement in treatment, an increasing number of advanced lung cancer patients require admission to intensive care units (ICUs) [6]. However, the mortality rate of critically ill NSCLC patients remains high, ranging from 50% to 70% [7-9].

Many risk factors for the increased mortality rate of patients with lung cancer admitted to ICUs have been studied. These factors include high Acute Physiology and Chronic Health Evaluation (APACHE) II score, low albumin level, increased number of organ failures, presence of disseminated intravascular coagulation, use of a vasopressor, and duration of mechanical ventilation (MV) [10-16]. Use of MV does not imply terminal illness, but prolonged MV support is an unfavorable prognostic indicator. Therefore, weaning from MV should be treated as an immediate outcome, with mortality as the final outcome. Previous studies have revealed that the successful MV weaning rate of NSCLC patients admitted to the ICU ranges from 15% to 27% [13,17]. Identifying the predictors of successful weaning from MV will help clinicians decide whether to treat aggressively or use palliative care with these patients. Furthermore, this could also avoid ineffective treatment and prolonged dying.

Immunosuppression induced by cytotoxic chemotherapy greatly limits use of chemotherapy for cancer patients admitted to the ICU. However, EGFR-TKIs have a great safety profile. An increasing body of evidence shows that EGFR-TKIs are safe and effective for elderly patients with advanced NSCLC and for those with a poor performance status (PS) [18-19]. In critically ill NSCLC patients requiring MV, EGFR-TKIs may be considered as salvage therapy, yet there are few data addressing the role of EGFR-TKIs in these patients. The purpose of this study was to investigate the effect of EGFR-TKIs on NSCLC patients requiring MV in the ICU.

Patients and Methods

Patients

This study included a total of 56 beds in 3 medical ICUs in Linkou Chang Gung Memorial Hospital, which is a university-affiliated tertiary-care teaching hospital and a comprehensive cancer center in northern Taiwan. The hospital's Institutional Review Board Ethics Committee approved the study protocol, and informed consent was deemed not to be required.

A retrospective analysis of lung cancer patients who were admitted to medical ICUs between January 1, 2004 and July 1, 2010 was performed. Inclusion criteria were as follows: (1) cytological or pathological proof of advanced stage NSCLC; (2) respiratory failure with invasive MV support; and (3) patients who had received EGFR-TKI therapy longer than or equal to 2 weeks, so as to evaluate treatment response. Patients who stayed in the ICU less than 24 hours or for post-surgery care were excluded.

Data collection

Demographic, physiological and clinical data, including age, sex, race, smoking history, comorbidities, histological type, stage, and treatment of lung cancer before admission to the ICU were collected. "Early-stage NSCLC" was defined as stages I and II, and "advanced stage" was defined as stages III and IV, according to the American Joint Committee on Cancer

(AJCC) 6th edition [20]. Smokers were defined as patients who had smoked more than 100 cigarettes in their lifetime [3]. PS was evaluated according to World Health Organization criteria.

Clinical response to EGFR-TKIs was evaluated by a physician and radiologist based on chest roentgenogram or computed tomography scans after 1 month of EGFR-TKI therapy. For patients who received EGFR-TKIs less than 4 weeks, responsiveness was evaluated via a review of medical records and radiology reports. Response to cancer treatment before ICU admission was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, and was categorized as progressive disease or controlled disease, the latter including partial response and stable disease [21]. To evaluate response to EGFR-TKI treatment in the ICU, the initial chest plain film taken on admission to the ICU was set as a baseline image. Then, we took another chest plain film around day 14 to compare with the initial one. Controlled disease was defined as a partial response to treatment or stable disease according to the RECIST guidelines. Patients who died in the ICU were defined as having progressive disease. Successful weaning was defined as being independent from MV for 3 consecutive days after being taken off MV.

The reasons for ICU admission were categorized as cancer-related and non-cancer-related. Laboratory and clinical data obtained within 24 hours of ICU admission were collected. Organ failure count was recorded within 24 hours of ICU admission and was defined according to the consensus committee of the American College of Chest Physicians and Society of Critical Care Medicine criteria [22]. Patients with dysfunction in more than 2 organs were defined as having multi-organ dysfunction syndrome (MODS).

Statistical analysis

Data of successful and unsuccessful weaning were compared. Categorical variables were compared using the chi-square test or Fisher's exact test. The *t*-test was used to compare continuous variables with a normal distribution, and the Mann-Whitney test was used for continuous variables not distributed normally. A p value less than 0.05 was considered statistically significant. Univariate analyses were primarily used in selecting variables, based on p values of less than 0.1. The selected variables were entered into a multinomial logistic regression analysis to identify the net effect of each individual factor. Odds ratios (OR) and their 95% confidence intervals (CI) were used to assess the independent contribution of significant factors. All of the analyses were performed using SPSS software version 16.0 (Chicago, IL, USA).

Results

Between January 1, 2004 and July 1, 2010, 127 NSCLC patients took EGFR-TKIs in the ICU, and 91 were enrolled (Table 1). Eighteen patients did not require MV, and 18 took EGFR-TKIs for less than 2 weeks. The mean age was 61 years, 60% of the patients had a PS score of 1 at the time of diagnosis of lung cancer, and 75% of them had cancer in a progressive disease status before entering the ICU.

In all, 38% of patients had cancer-related conditions—such as pulmonary, neurologic and cardiac complications, compromised airways and lymphangitic carcinomatosis—as reasons for ICU admission (Table 2). Non-cancer-relat-

Table 1. Baseline Characteristics of the Study Population (n = 91)

Gender	
Male	53 (58)
Female	38 (42)
Age	61.8 ± 12.5
Smoking status	
Non-smoker	49 (54)
Former or current smoker	42 (46)
Initial Stage	
Stage I-II	11 (12)
Stage III-IV	80 (88)
Pathology	
Adenocarcinoma	56 (62)
Non-adenocarcinoma	35 (38)
Performance status at diagnosis of lung cancer	
1	55 (60)
≥2	36 (40)
Cancer treatment prior to ICU admission	
Treatment-naïve	23 (25)
Chemotherapy-naïve	33 (36)
Platinum-based chemotherapy	51 (56)
EGFR-TKIs treatment	
1st line	34 (37)
≥2nd line	57 (63)
EGFR-TKIs in the ICU	
Gefitinib	51 (56)
Erlotinib	40 (44)
Cancer status before ICU admission	
Controlled disease	23 (25)
Progressive disease	68 (75)

All values are expressed as n (%) or mean ± SD.

ICU: intensive care unit, EGFR-TKIs: epidermal growth factor receptor-tyrosine kinase inhibitor

ed conditions, such as pneumonia and sepsis, were present in 62% of patients. Thirty-three (36%) patients were successfully weaned from MV, and 58 (64%) patients failed weaning. There were no differences in baseline epidemiology between these 2 groups, including gender, age, smoking status, lung cancer staging and cell type, PS, and cancer treatment prior to ICU admission. Before ICU admission, there were more patients with controlled disease in the successful weaning group than in the unsuccessful weaning group (39% vs. 17%, p=0.025).

As expected, ICU mortality was much higher in the unsuccessful weaning group than in the successful group (93% vs. 21%, p<0.0001). Regarding EGFR-TKI response in the ICU, the successful weaning group had more controlled disease patients than the unsuccessful weaning

Table 2. Clinical Data of Successfully and Unsuccessfully Weaned Patients on Admission to the ICU

Variables	Successful weaning (n = 33, 36%)	Unsuccessful weaning (n = 58, 64%)	*p* value
Gender			
Male	19 (58)	34 (59)	1.000
Female	14 (42)	24 (41)	
Age	61.9 ± 12.9	62.3 ± 13.0	0.760
Smoking status			
Non-smoker	17 (52)	32 (55)	0.828
Former or current smoker	16 (48)	26 (45)	
Stage			
Early stage	3 (9)	8 (14)	0.740
Advanced stage	30 (91)	50 (86)	
Pathology			
Adenocarcinoma	24 (77)	32 (55)	0.120
Non-adenocarcinoma	9 (23)	26 (45)	
Performance status at diagnosis of lung cancer			
1	22 (67)	33 (57)	0.383
≥2	11 (23)	25 (43)	
Cancer treatment prior to ICU admission			
Treatment-naïve	7 (21)	16 (28)	0.619
Chemotherapy-naïve	10 (30)	23 (40)	0.497
Platinum-based chemotherapy	21 (64)	30 (52)	0.380
EGFR-TKIs treatment			
1st line	11 (33)	23 (40)	0.654
≥2nd line	22 (67)	35 (60)	
EGFR-TKIs in ICU			
Gefitinib	18 (55)	33 (57)	0.830
Erlotinib	15 (45)	25 (43)	
Cancer status before ICU admission			
Controlled disease	13 (39)	10 (17)	0.025*
Progressive disease	20 (61)	48 (83)	
Causes of admission			
Cancer-related	10(11)	25(27)	0.227
Non-cancer-related	23(25)	33(37)	
APACHE II score	17.3 ± 5.3	18.7 ± 5.4	0.283
MODS score	3 (9)	6 (10)	1.000
Platelet (1000/uL)	246 ± 158	214 ± 146	0.265
Calcium (mg/dL)	8.2 ± 0.9	8.2 ± 1.0	0.649
Albumin (g/dl)	2.8 ± 0.7	2.8 ± 1.1	0.769
Arterial blood gas			
pH	7.39 ± 0.15	7.34 ± 0.13	0.051
CO_2 (mmHg)	46 ± 21	51 ± 24	0.307
O_2 (mmHg)	94 ± 67	102 ± 79	0.847
HCO_3 (mm/L)	26.6 ± 8.6	25.7 ± 8.0	0.713

*P-value < 0.05

All values are expressed as n (%) or mean ± SD.

ICU: intensive care unit, APACHE: acute physiology and chronic health evaluation, MODS: multi-organ dysfunction syndrome, EGFR-TKIs: epidermal growth factor receptor-tyrosine kinase inhibitor

Table 3. Associated Outcome of Successfully and Unsuccessfully Weaned Patients

Variables	All	Successful weaning (n = 33)	Unsuccessful weaning (n = 58)	*p* value
EGFR-TKIs response in ICU				
Controlled disease	25 (27)	17 (52)	8 (14)	0.000*
Progressive disease	66 (73)	16 (48)	50 (86)	
MV duration (days)	12.6 ± 14.4	6.8 ± 5.1	17.9 ± 17.1	0.000*
ICU LOS, mean (days)	15.0 ± 17.0	14.0 ± 15.2	18.1 ± 18.6	0.232
ICU mortality	61 (67)	7 (21)	54 (93)	0.000*

*P-value < 0.05

All values are expressed as n (%) or mean ± SD.

ICU: intensive care unit, MV: mechanical ventilation, LOS: length of stay, EGFR-TKIs: epidermal

group (52% vs. 14%, p<0.0001), and this remained a significant difference after multivariate logistic regression analysis (OR: 5.31, 95% CI: 0.06-0.83, p=0.021) (Table 3).

Discussion

This study was designed to evaluate the effect of EGFR-TKI treatment on NSCLC patients under MV in the ICU. Our results demonstrated that patients in a controlled status before entering the ICU and with a response to EGFR-TKI treatment in the ICU have a better chance of successfully weaning from MV.

To the best of our knowledge, there have been few reports discussing the treatment response to EGFR-TKIs of NSCLC patients under MV. The immediate outcome of successful weaning from MV of NSCLC patients with respiratory failure is of more concern to intensivists, the families, and even the patients themselves than mortality. During the more than 5 years of this study period, following the introduction of EGFR-TKIs as a treatment for NSCLC in our institute, the weaning rate from MV in the ICU was 36%. Before EGFR-TKIs were used as a standard treatment, the weaning rate was 27%, as shown in our previous study [13]. Although these 2 studies are not directly comparable, NSCLC treatment seems to have had different outcomes before and after EGFR-TKIs were introduced.

The response to EGFR-TKIs of NSCLC patients with a poor PS and unknown EGFR mutation status was low, from 6% to 28% [18-19,23-24], In a pooled meta-analysis study, EGFR-TKIs still had a 40% disease control rate in unselected patients [18]. In our study, the average rate of response to EGFR-TKIs in unselected, patients under MV and with a poor PS was 14%, with an average disease control rate of 27%.

The outcomes of NSCLC patients in ICUs are poor, with an overall mortality rate of approximately 40%, and as high as 73% in patients under MV [7,9,13-14]. In this study, the APACHE II and MODS scores were not significantly different between the successful and unsuccessful weaning groups. The APACHE II and MODS scores may underestimate the mortality outcome in these high mortality patient groups. Several studies have tried to identify clinical predictors of mortality, and most authors agree that an increased number of organ

failures was an independent risk factor [7,9,13]. Uncontrolled cancer status was also an independent risk factor for mortality in 2 studies [7,14]. The major difference between our study and previous studies is that we focused on NSCLC patients under MV, whereas previous studies included all lung cancer patients with or without MV in the ICU. Therefore, risk factors in previous studies may not be completely reflected in our patients.

There were some limitations in this study. First, the relatively small sample size of this retrospective study could result in selection bias and a possible lack of evaluation of potential predictors for weaning from MV. Second, this was a single hospital study conducted in a tertiary academic medical center, and the severity of disease and indication for MV use may differ from other hospitals. Finally, we did not have EGFR mutation data in this retrospective study, since EGFR mutation status was not a routine examination during the period of this study. We could not perform EGFR mutation tests with these patients because most of them had died and it is difficult to obtain tissue samples in a retrospective study. However, our study still can provide scientific evidence for physicians who care for MV NSCLC patients, to aid in their decision-making. Further large-scale prospective controlled studies should be undertaken to investigate the benefit of EGFR-TKIs in NSCLC patients under MV in the ICU.

Conclusion

The effects of EGFR-TKI treatment for NSCLC are remarkable, but the prognosis of critically ill NSCLC patients remains poor. Among NSCLC patients with respiratory failure requiring MV, those with a controlled status before ICU admission and a response to EGFR-TKI treatment in the ICU have a better chance of successfully weaning from MV.

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非小細胞肺癌病人在加護病房接受標靶藥物的成果

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黃崇旂　楊政達　蔡熒煌 **

前言：標靶藥物—表皮生長因子接受器 - 酪胺酸激酶抑制劑（epidermal growth factor receptor-tyrosine kinase inhibitors, EGFR-TKIs）在非小細胞肺癌併呼吸器支持的病人上，其臨床療效尚不明確。本篇研究旨在探討呼吸器支持下的非小細胞肺癌病人接受標靶藥物治療的成果。

方法：自 2004 年 1 月 1 號至 2010 年 7 月 1 號加護病房中的回溯性分析。

結果：91 位非小細胞肺癌併呼吸器支持的病人使用標靶藥物 EGFR-TKIs，33 人（36%）成功脫離呼吸器，其中有 13 人（14%）對標靶治療有反應。年齡、性別、日常體能狀態（performance status）、APACHE II score、腫瘤分型和期別不影響呼吸器的脫離。進入加護病房前腫瘤在穩定狀態（controlled disease）或在加護病房中對標靶藥物治療有反應的病人有較高的比例成功脫離呼吸器（分別為 39% 和 52%）。

結論：原腫瘤在穩定狀態或對標靶治療有反應的非小細胞肺癌患者，即使在接受呼吸器支持下，仍值得更積極的治療。*(胸腔醫學* ***2015; 30: 125-133)***

關鍵詞：非小細胞肺癌，酪胺酸激酶抑制劑，呼吸器，加護病房

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Successful Resuscitation of Patients with Acute Massive Pulmonary Embolism Using Endovascular or Surgical Embolectomy and ECMO Support

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Purpose: Acute massive pulmonary embolism (PE) is frequently a desperate situation, but rapid diagnosis and aggressive therapy with endovascular or surgical embolectomy supported by extracorporeal membrane oxygenation (ECMO) may be lifesaving. However, the management is not standardized. This report detailed our experience with rapid diagnosis of massive PE patients and early ECMO support in severely compromised patients.

Methods: Between June 2011 and September 2012, 6 female patients (aged from 23 to 76 years, with a mean of 53.3 years) were diagnosed as having massive PE with either acute irreversible oxygenation failure (n=6) or cardiac arrest (n=5). All patients required ECMO support. They were treated with surgical embolectomy (n=1), Angiojet aspiration (n=1), and endovascular embolectomy (n=4). All patients were evaluated as high risk using the simplified Pulmonary Embolism Severity Index (sPESI),[1] and were classified and diagnosed with the aid of chest CT, echocardiogram, and pulmonary angiography.

Results: One patient died from an ECMO cannula insertion complication of massive retroperitoneal hematoma and bleeding, and 2 patients expired due to multi-organ failure. Three were weaned from ECMO and were discharged; they were in good condition at follow-up.

Conclusion: Aggressive endovascular or surgical pulmonary embolectomy with ECMO support appears to be beneficial for massive PE with acute cardiopulmonary failure. ***(Thorac Med 2015; 30: 134-141)***

Key words: acute massive pulmonary embolism, embolectomy, ECMO

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Introduction

Acute massive pulmonary embolism (PE) can result in a critical condition with unstable hemodynamic status, and may induce pulmonary hypertension, hypoxemia or cardiogenic shock [1-4]. Acute massive PE can cause right heart ventricle failure with reduced cardiac output or dramatic decrease in gas exchange. In order to decrease mortality, rapid diagnosis and immediate hemodynamic stabilization are important before intervention [5]. The estimated prevalence of acute PE was about 1% [6], and the mortality in severe patients was above 60% [7]. There are no definite accepted guidelines in current treatment for acute massive PE. Biomarkers such as cTnT (cardiac Troponin T) and NT-BNP may be used to evaluate the outcome in hemodynamically stable patients, but not in unstable patients [8]. Patients with acute PE and a severely compromised situation are too unstable to receive conventional treatment with systemic anticoagulation that lacks the ability to lyse massive thrombus and maintain patients' hemodynamic status. Therefore, early extracorporeal membrane oxygenation (ECMO) support is an essential rescue therapy for these patients [9]. Catheter-based thrombolytic therapy, catheter-based fragmentation, catheter embolectomy, and surgical embolectomy are commonly used methods in treating massive PE patients. However, management with catheter-based thrombolytic therapy, catheter embolectomy and catheter fragmentation have not been proven to decrease mortality in randomized controlled trials [10-11]. In this report, we reviewed our current therapy with ECMO support to determine whether an aggressive surgical approach is the best alternative.

Patients and Methods

Six female patients (pts) were diagnosed with acute massive PE from June 2011 to September 2012. Ages ranged from 23 to 76 years, with a mean of 53.3 years. The simplified Pulmonary Embolism Severity Index (sPESI) evaluation revealed the patients were at a high risk, with a sPESI score more than 3 (Table 1). Rapid diagnosis of acute massive PE was reached by echocardiography (n=3), transesophageal echocardiogram (n=1), chest CT (n=3) and pulmonary angiography (n=1). Five patients required cardiopulmonary resuscitation (CPR) before intervention. Systemic thrombolysis therapies with heparin, tissue-plasminogen activator (t-PA) or urokinase were given as soon as acute massive PE was diagnosed in the CathLab (Catheterization Laboratory). ECMO support was placed at bedside during resuscitation. Four patients underwent endovascular embolectomy, 1 received AngioJet aspiration and 1 received surgical embolectomy (Table 2). The durations for ECMO survivors were 2, 96, and 158 hours, respectively. All survivors received warfarin anticoagulation to resolve the residual emboli.

Results

There were 3 survivors. Five patients with cardiac arrest (patients 1, 2, 4, 5 and 6) underwent CPR before interventions. Thrombolysis with tissue-plasminogen activator (t-PA) was used with 3 patients and urokinase with 2; continuous heparin infusion was given to all patients as soon as massive PE was diagnosed. Four patients were cannulated via femoral VA-mode ECMO, and 1 patient was cannulated via femoral AA-mode ECMO (patient 4) because of failure to approach the femoral vein. One

Table 1. Patients' Characteristics.

Patient	Age/Sex	Clinical settings	Symptoms	sPESI
1	23/F	Brain tumor s/p left frontal craniotomy AT-III deficiency	SOB, chest tightness	3 High risk
2	37/F	S/P cesarean section	Dyspnea and cardiac arrest	3 High risk
3	58/F	Acute pulmonary embolism s/p medical treatment Congestive heart failure	Dyspnea and chest tightness for 3 months	3 High risk
4	70/F	Hyperglycemic hyperosmolar status DVT history	SOB, consciousness disturbance	2 High risk
5	76/F	Hemorrhagic cystitis Cervical cancer s/p radiotherapy and chemotherapy	Dyspnea	3 High risk
6	56/F	History of sub-massive PE under aspirin control Diabetes mellitus	SOB and cardiac arrest	3 High risk

Table 2. Evaluation and Management.

Patient	Evaluation Study	Indication for ECMO	Duration of ECMO Mode/ hrs	Intervention	Outcome	Follow-Up (mos)	Hemodialysis (H/D)	Drug
1	Echocardiogram Pulmonary angiography	Oxygenation failure + CPR	VA mode / 48	Endovascular embolectomy t-PA	Deceased MOF	-	H/D (-)	
2	Echocardiogram Chest CT	Oxygenation failure + CPR	VA mode / 158	Catheter-based fragmentation	Weaned	20	H/D (-)	Coumadin
3	Echocardiogram Chest CT	Oxygenation failure	VA mode / 2	Surgical embolectomy	Weaned	15	H/D (-)	Coumadin
4	TEE	Oxygenation failure + CPR	AA mode / 1.5	Endovascular embolectomy t-PA+ Heparin	Deceased MOF	-	H/D (-)	
5	Echocardiogram Chest CT	Oxygenation failure + CPR	VA mode / 21	Endovascular embolectomy t-PA+ Heparin	Deceased Internal bleeding	-	H/D (-)	
6	Echocardiogram Chest CT	Oxygenation failure + CPR	VA mode / 96	Endovascular embolectomy Urokinase + Heparin	Weaned	4	H/D (+) (5 wks)	Coumadin + Aspirin

patient received surgical embolectomy (patient 3), 1 received endovascular catheter-based fragmentation (patient 2), and 4 patients received endovascular embolectomy because of unstable situations (patients 1, 4, 5, 6). Three of the 6 patients (patients 2, 3, 6) survived to hospital discharge. Two patients died of multi-organ failure while on ECMO support and the third had a massive retroperitoneal hematoma (Table 1).

Patients 1, 4, 5 were poor candidates for any further invasive intervention. Their hemodynamic instability persisted despite the vasopressor, fluid resuscitation and ECMO support. Patient 6 was the only survivor of endovascular embolectomy, but had the complication of acute renal failure and required hemodialysis. Patient 3 was a candidate for surgical embolectomy because of a history of deep vein thrombosis (DVT), and chest CT showed total occlusion of the right pulmonary trunk and left inferior pulmonary artery after medical treatment had failed. The patient had a cardiopulmonary collapse on the 13th day of hospitalization and ECMO support was begun at bedside. She was discharged 13 days after surgery. Patient 2 collapsed with cardiac arrest 2 days after caesarean section and required CPR. After successful CPR, chest CT showed bilateral pulmonary artery occlusion (95%) by a massive thrombus (Figure 1). She underwent AngioJet rheolytic thrombolysis, and most of the embolisms were removed (Figures 2, 3). At the 1-year follow-up, the pulmonary perfusion test showed normal pulmonary function (Figure 4).

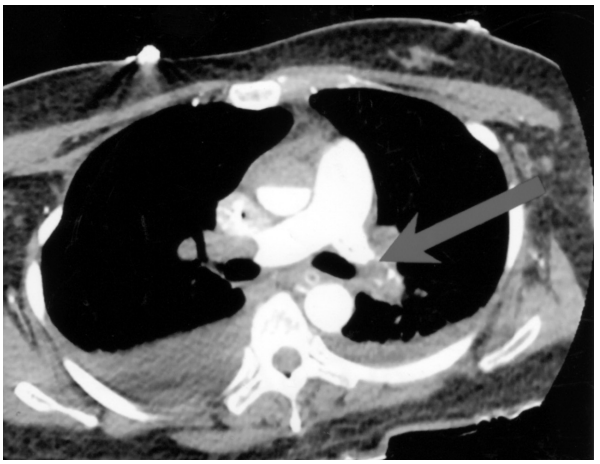
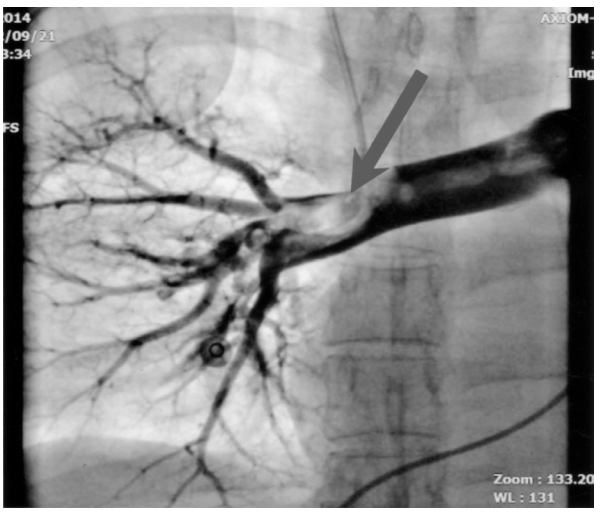


Fig. 1. CT angiography.



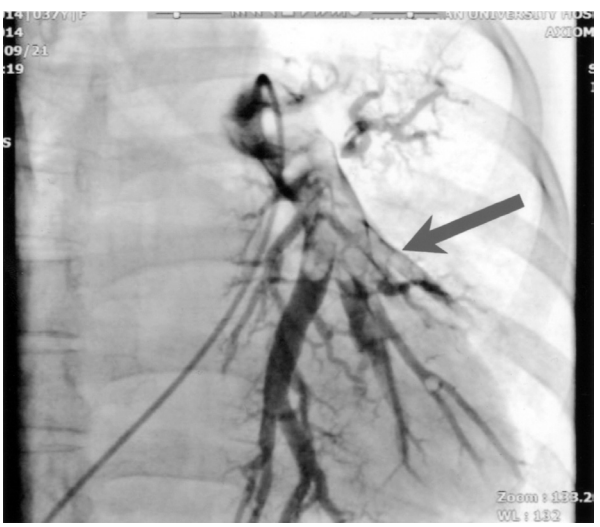
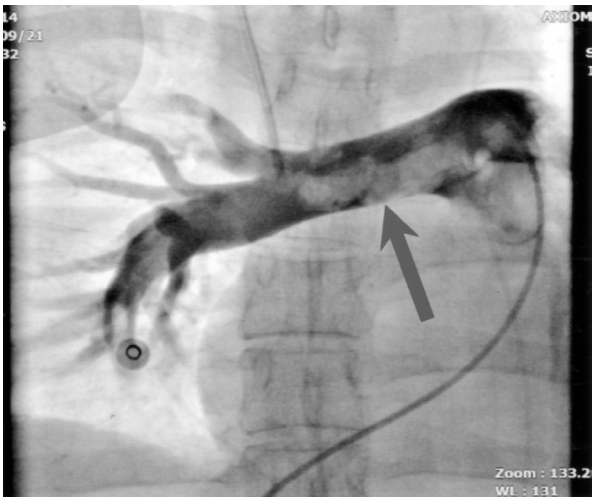


Fig. 2-1, 2-2. Pulmonary angiography.

Discussion

Acute massive PE is frequently lethal because of acute irreversible cardiopulmonary collapse. Unstable hemodynamic status has



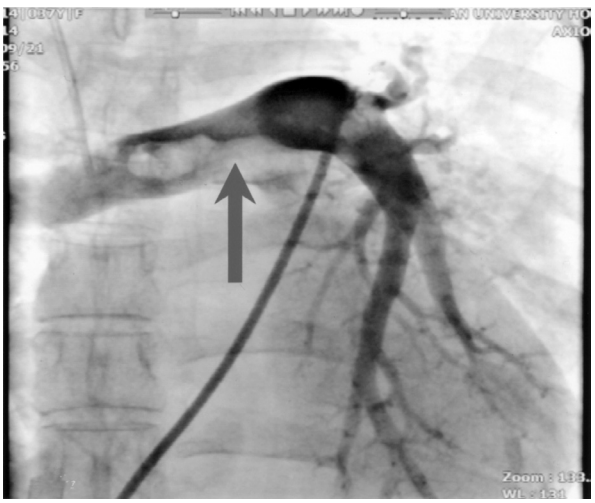


Fig. 3-1, 3-2. Status post-percutaneous transluminal angioplasty (PTA with AngioJet).

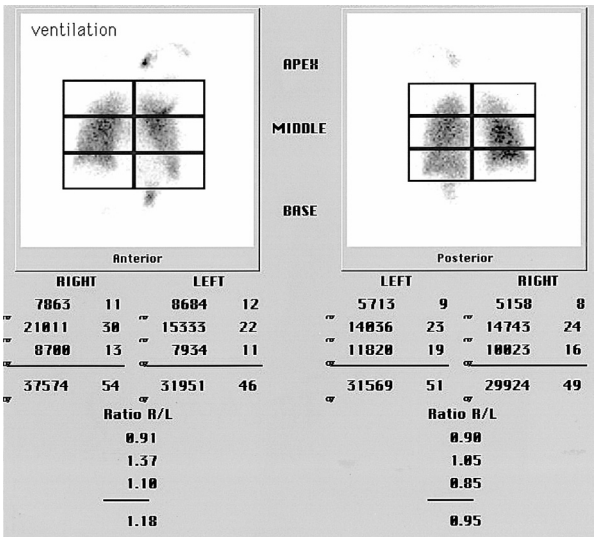


Fig. 4. Lung ventilation/perfusion scans showed homogenous distribution v/p in both lungs. No significant segmental perfusion defect.

presented in about 20% of patients with acute massive PE [12]. The mortality rates of patients with the symptoms of right ventricular (RV) dysfunction, hypotension, cardiogenic shock, and those who need CPR were 8.1%, 15.2%, 24.5%, and 64.8%, respectively [7]. In this case series report, we found that patients who experienced severe cardiorespiratory compromise after acute massive PE and required CPR could be benefit from extracorporeal life support.

The main cause of death among our patients, multi-organ failure, was similar to that in Berman's report [9]. Systemic fibrinolysis is recommended as standard first-line treatment for acute massive PE patients, and may reduce the risk of mortality by 55% [13]. A previous report, a meta-analysis overview of 11 randomized controlled trials involving 748 patients, showed systemic fibrinolysis increased major bleeding more than heparin only (9.1% versus 6.1%; OR 1.42, 95% CI 0.81 to 2.46) [13]. However, the recent Pulmonary Embolism International Thrombolysis (PEITHO) trial showed that among intermediate-risk normotensive acute PE patients, thrombolysis with bolus of tenecteplase significantly reduced 7-day mortality. However, the benefit of thrombolysis came at the cost of the increased major bleeding risk that led to the death of 1 of our patients.

In general, the mortality rate of surgical embolectomy varies from 4% to 24% in chronic PE patients [14-15]. Proper indications for the patient, intensive care after surgery and the experience of the surgical team have reduced the surgical mortality rate [16]. But surgical

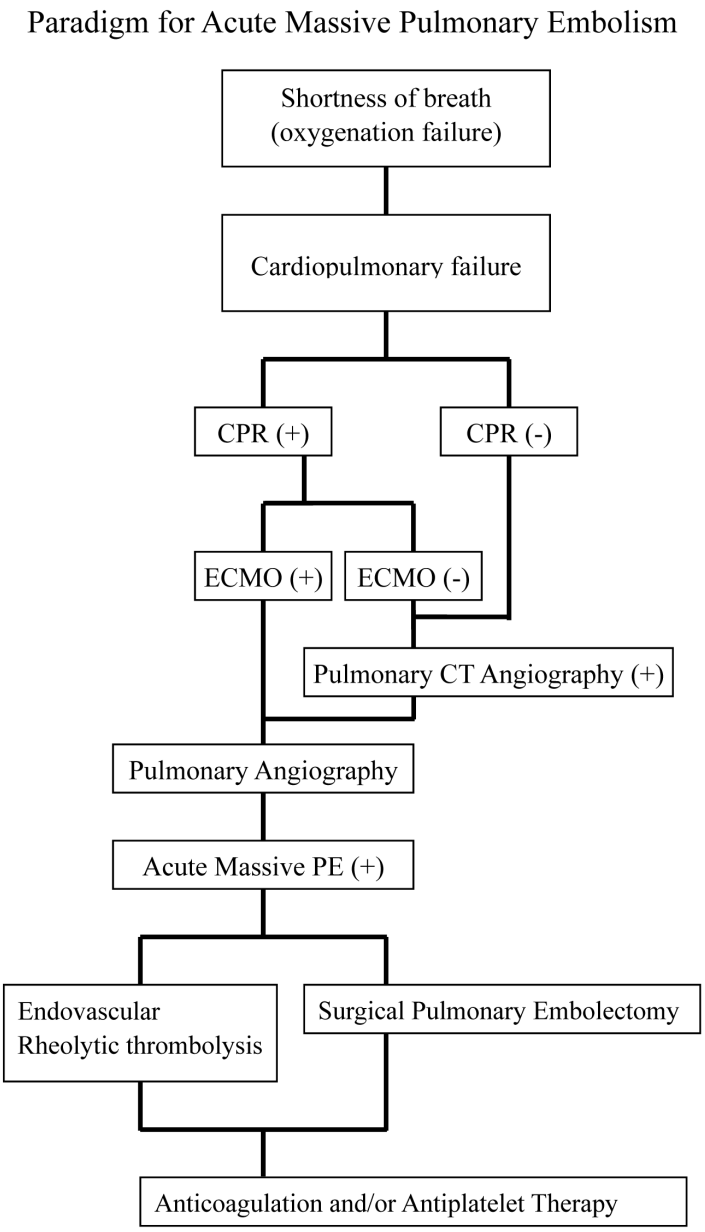


Table 3. Paradigm of Acute Massive PE Management.

embolectomy is rarely used with patients with acute massive PE. Catheter-based intervention is now more common in the treatment of acute massive PE patients with contraindications to thrombolysis and at a high risk with surgery. The AngioJet system removed large emboli effectively, and the patient made a rapid recovery (Figure 3). A success rate of up to 90% using the endovascular approach with AngioJet rheolytic thrombolysis in the treatment of massive PE patients has been reported [17-19]. The AngioJet and Angiovac systems will become novel techniques in treating acute massive PE in the near future.

In conclusion, percutaneous ECMO may provide quick and excellent cardiopulmonary support before beginning treatment for acute massive PE. Accurate and rapid diagnosis is a key factor in acute massive PE treatment. Hemolytic therapy with an endovascular approach and catheter-based hemolysis and catheter thrombectomy, or even open surgical embolectomy in severe patients, can remove the emboli rapidly and safely (Table 3). We believe that endovascular or surgical embolectomy with ECMO support has beneficial effects for acute massive PE [20].

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使用葉克膜置入術合併血管腔內導管血栓清除術或外科肺動脈血栓切除術，救治急性大量肺栓塞合併心肺衰竭

賀業宏 *,*** 林佑璉 *,*** 余榮敏 **,**** 曹素琴 *,***** 陳永福 ***,******
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前言：急性大量肺栓塞合併心肺衰竭是死亡率極高的急重症疾病，若能及時診斷與積極治療，使用葉克膜置入術，合併血管腔內導管血栓清除術或外科肺動脈血栓切除術，可以提高存活率，但此治療方式並未有一致的標準。本篇提出我們的經驗，使用葉克膜置入術合併血管腔內導管血栓清除術或外科肺動脈血栓切除術，救治急性大量肺栓塞合併心肺衰竭。

方法：自 2011 年 6 月至 2012 年 9 月，共有 6 位女性病患（23-76 歲，平均 53.3 歲），診斷為急性大量肺栓塞，合併呼吸衰竭；低血氧（n=6）或心臟停止（n=5）。所有病患皆接受葉克膜置入術。另外接受外科肺動脈血栓切除術（n=1），或血管腔內導管血栓清除術（n=5）。所有病患皆接受肺栓塞指標評估（simplified pulmonary embolism severity index, sPESI）、電腦斷層與心臟超音波診斷。

結果：一位病患死於葉克膜置入術的合併症，大量後腹腔出血及血腫。二位病患死於多重器官衰竭。三位病患成功脫離葉克膜，復原良好出院，門診追蹤。

結論：及時診斷治療且積極的使用葉克膜置入術，並合併血管腔內導管血栓清除術或外科肺動脈血栓切除術，可以拯救急性大量肺栓塞合併心肺衰竭的危急病患，提高存活率。*(胸腔醫學 **2015; 30: 134-141**)*

關鍵詞：急性肺栓塞，血栓切除術，葉克膜

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Pulmonary Alveolar Proteinosis Complicated with Cryptococcal Pneumonia – A Case Report

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Pulmonary alveolar proteinosis (PAP) is a diffuse lung disease characterized by the accumulation of periodic acid-schiff (PAS)-positive lipoproteinaceous material in the distal air spaces. There is little or no lung inflammation, and the underlying lung architecture is preserved. PAP is occasionally complicated with infections caused by unusual organisms, such as Nocardia, though cryptococcosis has seldom been reported. We reported a patient with PAP superimposed with cryptococcal pneumonia that initially presented with bilateral lung opacities, intermittent fever and dry cough for several months. The patient failed to respond to standard treatment for community acquired pneumonia. Chest computed tomography (CT) revealed multifocal patchy ground-glass opacities and interlobular septal thickening, with a crazy-paving appearance scattered in both lungs. The video-assisted thoracic surgery (VATS) pathology report suggested PAP with cryptococcal pneumonia. Fluconazole was given and the cryptococcal antigen decreased from 1024X to 128X after 15 months of treatment. ***(Thorac Med 2015; 30: 142-149)***

Key words: pulmonary alveolar proteinosis, Cryptococcus, cryptococcal pneumonia

Introduction

Pulmonary alveolar proteinosis (PAP), first described by Rosen *et al*. in 1958, is a rare lung disease characterized by the accumulation of periodic acid-schiff (PAS)-positive lipoproteinaceous material in the distal air spaces [1]. The prevalence of acquired PAP has been estimated to be 0.37 per 100,000 people [1]. PAP is classified into 3 types [2]: The congenital type often presenting in the neonatal period is related to mutations in genes of surfactants [3]. The secondary type is related to hematogenic malignancy, pneumoconiosis or allogeneic bone marrow transplantation. The acquired type is the most common form and accounts for about 90% of all PAP cases [4]. It is associated with a high level of anti-granulocyte macrophage-colony stimulating factor (GM-CSF) antibodies that are believed to contribute to macrophage dysfunction. That patients with PAP are at risk of secondary infections with a variety of organisms, such as Nocardia and mycobacteria, has long been recognized, but cases of PAP compli-

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cated with cryptococcal pneumonia have rarely been reported [5-7].

Case Report

A 38-year-old male visited the emergency room due to dry cough for 10 days. There was mild shortness of breath (SOB) with no daily activity limitation, and no fever or hemoptysis. The patient, who worked at a factory for polishing cars and rarely wore a mask during work, had a smoking history of 1 pack per day for 2 decades. Chest X-ray (CXR) displayed bilateral patchy opacity (Figure 1). Lab data showed hemoglobin: 14.2 g/dl, white blood cell (WBC) count: 11800/cumm with neutrophils: 71%, monocytes: 12%, lymphocytes: 17%, platelets: 442 k/cumm and C-reactive protein: 6.97 mg/dl. The serum blood urea nitrogen, creatinine, sodium and potassium levels were within normal limits. Mycoplasma IgG, IgM and urine Legionella antigen were negative. The patient was treated for community-acquired pneumonia (CAP) with moxifloxacin 400 mg for 12 days, and discharged when the cough, WBC count and CXR improved.

The patient returned to the outpatient department 1 month later due to dry cough and mild SOB. CXR revealed that the patchy consolidation at the bilateral lower lobes had progressed. The pneumonic patch partially resolved after 7 days of augmentin and azithromycin treatment.

After that, the patient had regular outpatient follow-up visits and experienced mild dry cough with nasal obstruction, but no fever, sputum production or chest pain. Follow-up CXR 1 month later showed improvement of the previous patchy consolidation, but newly developed nodular lesions were observed at the right middle and left upper lung fields (Figure 2). The patient visited another hospital, where a CT-guided percutaneous needle biopsy was per-

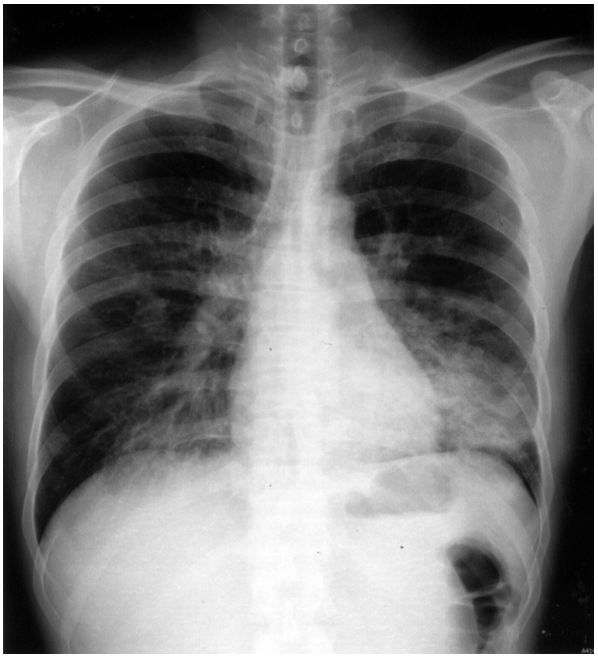

Fig. 1. Initial chest X-ray revealed infiltrates at bilateral lower lung fields.

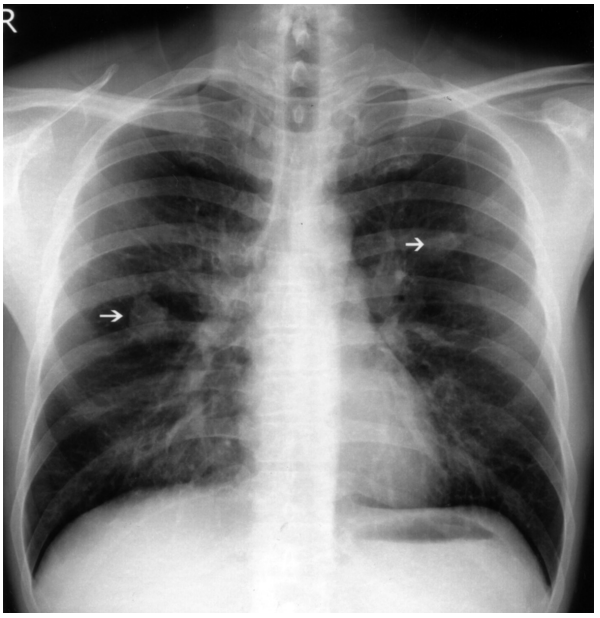

Fig. 2. At the second month, the bilateral alveolar process had improved, but newly developed nodular lesions (arrow) were found at the right middle and left upper lung fields.

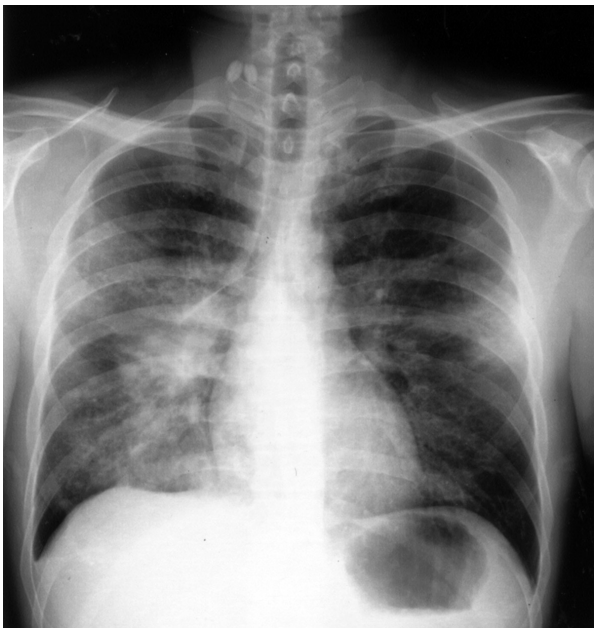

Fig. 3. At the fourth month, the nodular lesions had enlarged with more extensive infiltrates at both lung fields.

formed. Pathology report indicated focal fibrosis and amorphous material of a ring structure with concentric lamination.

Two months later, the patient visited the emergency department due to recurrent fever and SOB. CXR displayed large areas of patchy consolidation (Figure 3). Chest CT revealed multifocal patchy opacities with ground-glass density and consolidation in both lungs, while more extensive consolidation was present in the left upper and right lower lobes. Open lung biopsy was performed and the pathology report suggested PAP and crytoccocal pneumonia. In the microscopic exam, the lung tissue showed focal airspace-filling, and an active fibrosing process that involved distal bronchioles and peribronchiolar alveoli. Proteinaceous exudate and foamy macrophages were prominent within the alveolar spaces. PAS stain was positive. In addition, mucicarmine stain indicated crytoccocal yeasts in the alveolar spaces (Figure 4). Blood test revealed crytococcal antigen 1024X.

The patient received oral fluconazole 300-400 mg daily for 9 months. Follow-up blood cryptococcal antigen decreased to 512X. Arterial oxygen partial pressure improved from 71.8 mmHg with nasal cannula at 2 L/min to 92.1 mmHg when breathing ambient air. Follow-up CXR showed partial regression of the nodular lesions, so the use of fluconazole was continued. The cryptococcal antigen decreased to 128X after 15 months of fluconazole treatment. However, progressive SOB and desaturation developed. CXR revealed that the nodular lesions had improved, but the bilateral ground-glass opacity had progressed (Figure 5). Chest CT showed multifocal ground-glass opacity with interlobular septal thickening and a crazy-paving appearance scattered in the bilateral lung fields (Figure 6). For progression of PAP with SOB, the patient received whole lung lavage, which yielded a copious amount of milky PAS stain-positive fluid. SOB and desaturation improved after whole lung lavage.

Discussion

Pulmonary alveolar proteinosis (PAP) itself is a disease with little or no lung inflammation. PAP complicated with secondary infection is commonly associated with *Nocardia asteroides*, but PAP complicated with *Mycobacterium avium-intracellulare* and *Pneumocystis carinii* infection has also been noted [8]. Although rare, PAP has been reported with pulmonary and meningeal cryptococcosis [7,9]. Studies have shown that diminished GM-CSF protein or its function plays a key role in PAP. Dranoff and co-workers reported that genetically engineered mice lacking the gene for GM-CSF had an accumulation of surfactant and surfactant apopro-

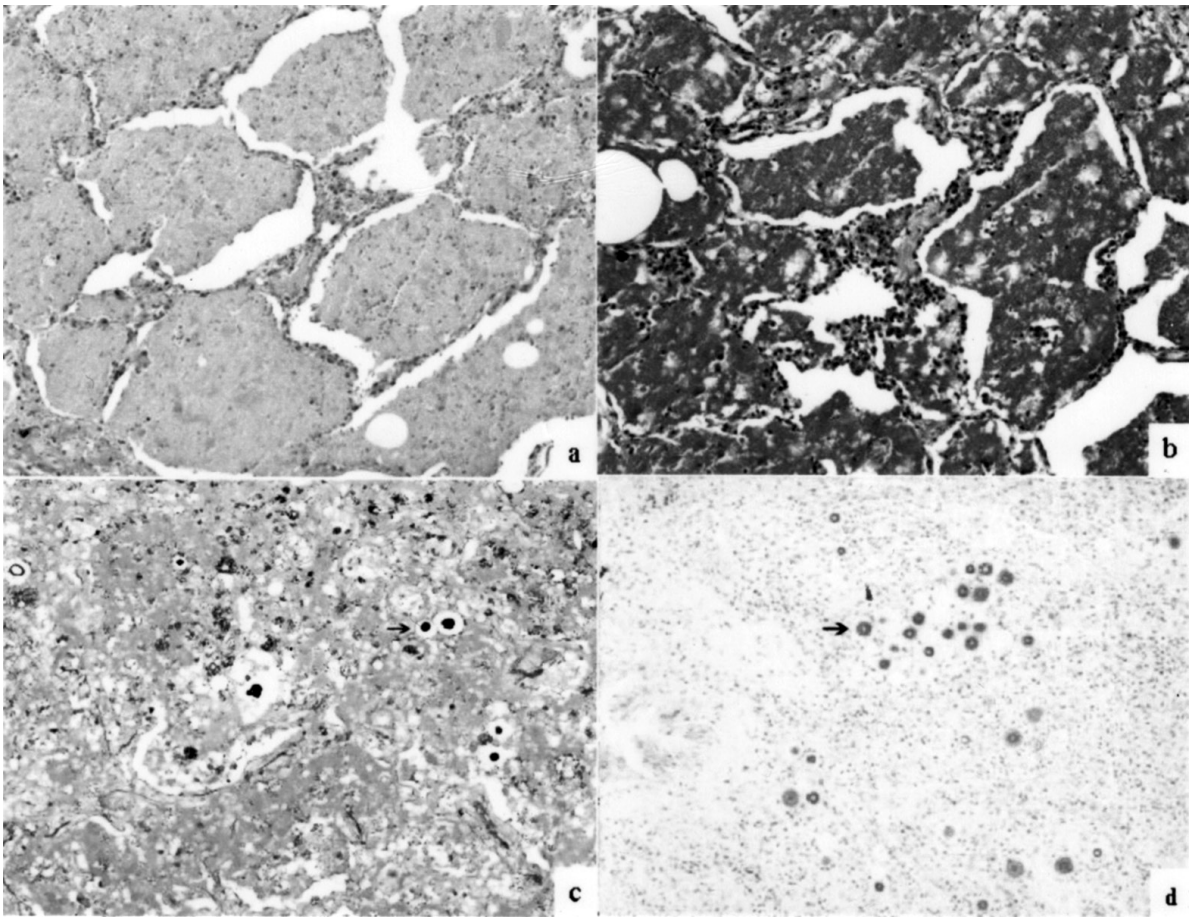

Fig. 4. a: H&E stain 200X. b: PAS stain 100X. Proteinaceous exudate and foamy macrophages were prominent within the alveolar spaces. The PAS stain was positive. c: GMS stain 100X. d: mucicarmine stain 100X revealed crytoccocal yeasts (arrow) in the alveolar spaces.

tein in the alveolar space similar to that seen in patients with PAP [10]. Reconstruction with the GM-CSF gene completely corrected the alveolar proteinosis in these mice, as did treatment with aerosolized GM-CSF [11-12]. The accumulation of surfactant and surfactant apoprotein further impairs alveolar macrophage function. Alveolar macrophages and the type II cell clearance mechanism are progressively overwhelmed by the accumulation of the surfactant-rich material, resulting in impaired phagocytosis and phagolysosome fusion. Alveolar macrophages themselves, upon dying, may further contribute to the amorphous material [13]. The pathophysiology of impaired GM-CSF and macrophage function may explain why PAP patients are prone to secondary infection.

Humans become infected with Cryptococcus by inhaling the basidiospore form of the fungus. A large proportion of the population has been exposed to Cryptococcus, with primary infections being common and mostly asymptomatic. The most important determinant of the subsequent course of the infection is the immune status [14]. A coincidental relationship between PAP and cryptococcal pneumonia in our patient was possible, but PAP was likely a predisposing factor for the development of

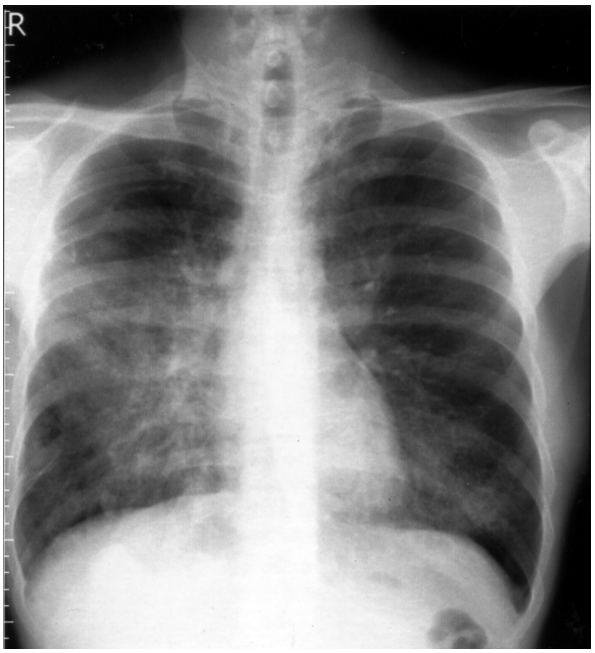

Fig. 5. After 15 months of fluconazole treatment, the nodular lesions had regressed, but the bilateral ground-glass appearance had progressed.

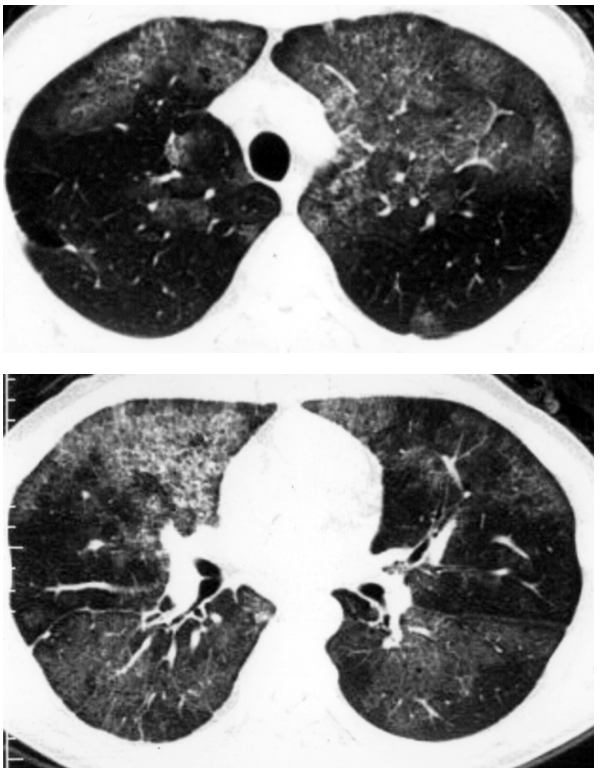

Fig. 6. After 15 months of fluconazole treatment, chest CT revealed multifocal ground-glass opacity with interlobular septal thickening and a crazy-paving appearance scattered in bilateral lung fields. The finding was consistent with the CT appearance of PAP.

cryptococcal pneumonia in this case.

The 2010 Infectious Diseases Society of America guideline suggested using fluconazole 6 mg/kg/day for 6-12 months for pulmonary cryptococcal infection with mild symptoms [15]. The patient exhibited mild symptoms and thus was treated with fluconazole 6 mg/kg/day, after which improvement was observed. However, the rate of Cryptococcus antigen decrease and nodular lesions resolution as shown by CXR was somewhat slower than usual. This may be related to the impaired GM-CSF and macrophage function in PAP patients, as discussed previously.

Since impaired macrophage function is anticipated in PAP patients, it might be better to treat the patient as an immunocompromised case. The treatment would consist of induction therapy with amphotericin B 3-4 mg/kg/day plus flucytosine 100 mg/kg/day for at least 4 weeks, followed by consolidation therapy with fluconazole 400 mg-800 mg/day for 8 weeks and maintenance therapy with fluconazole 200 mg/day for 6-12 months [15]. The optimal treatment regimen for this patient remained a question, since no specific treatment for PAP-related cryptococcal infection has been suggested in the literature.

The typical radiographic finding for PAP is a bilateral patchy, diffuse, or peri-hilar ill-defined nodular or confluent airspace pattern, which is usually most severe in the lung bases. High-resolution CT findings include bilateral areas of ground-glass opacity, smooth interlobular septal thickening in lung regions showing ground-glass opacity, consolidation and a

patchy or geographic distribution [1]. The typical image finding is an important clue for diagnosing PAP.

The patient first appeared with a typical presentation of CAP, which improved after the use of antibiotics. In this case, it could have been bacterial pneumonia that was treated with antibiotics or PAP with spontaneous remission, as some PAP cases have remitted spontaneously [1]. Nodular lesions later developed in the lung, and were more likely caused by Cryptococcus because nodular lesions are rare in pure PAP. The fact that the nodular lesion regressed after using fluconazole further confirmed that the lesions resulted from Cryptococcus infection. Nevertheless, ground-glass opacity increased, likely due to PAP progression, and only then was the typical image presentation of PAP observed. As seen in this patient, when PAP is complicated with Cryptococcus, the presentation is atypical and puzzling, making the diagnosis difficult.

Conclusion

With diminished GM-CSF and macrophage function, patients with PAP are prone to secondary infections caused by organisms such as Nocardia, *Mycobacterium avium-intracellulare* and *Pneumocystis carinii*. PAP superimposed with Cryptoccocus infection has seldom been reported, but when they do occur together, with an atypical presentation, the diagnosis may be difficult and delayed. Since PAP patients are prone to secondary infection and cryptococcal infection may be asymptomatic or present with only mild symptoms, the possibility of concurrent PAP and cryptococcal infection should be acknowledged when treating PAP patients. A prompt exam to rule out cryptococcal infection should be considered so as not to delay or miss the diagnosis. However, after the diagnosis is made, the optimal treatment regimen for concurrent PAP and cryptococcal pneumonia with impaired macrophage function is still unclear.

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肺泡蛋白質沉積症合併隱球菌肺炎－病例報告

顏嘉德　彭明仁　曾岐元 *

肺泡蛋白質沉積症是廣泛性的肺部疾病，特徵為在末端肺泡有呈現 PAS 染色陽型的脂蛋白物質沉積。肺部僅有輕微的發炎或無發炎現象而肺部本身的結構沒有受到破壞。肺泡蛋白質沉積症常併發一些平常少見的感染，特別是奴卡氏菌。但肺泡蛋白質沉積症合併隱球菌感染則較少有報告。我們報告一個罕見的肺泡蛋白質沉積症合併隱球菌感染病例。患者胸部先表現出 X 光上雙側肺野的陰影，並有數個月的間歇性的發燒及乾咳症狀。經過針對一般肺炎的標準治療之後無明顯的改善。胸部電腦斷層顯示出兩側肺野多處的毛玻璃狀病灶，肺小葉中隔增厚及碎石路狀徵候（crazy paving appearance）。病理切片顯示為肺泡蛋白質沉積症合併隱球菌感染。在給予 15 個月的 Fluconazole 治療後，患者隱球菌血清抗原指數由 1024X 下降至 128X。*(胸腔醫學 **2015; 30: 142-149**)*

關鍵詞：肺泡蛋白質沉積症，隱球菌，隱球菌肺炎

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Pulmonary Mucoepidermoid Carcinoma Mimicking Catamenial Hemoptysis – A Case Report

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Chee-Yin Chai****,******, Jhi-Jhu Huang*,*****, Inn-Wen Chong*,*****

Pulmonary mucoepidermoid carcinoma is a rare disease with a common presentation as an intraluminal mass leading to airway obstruction. We reported a 26-year-old woman who suffered from hemoptysis during or a few days before every menstrual period, and spontaneous pneumothorax. The initial clinical impression was thoracic endometriosis syndrome due to the presence of catamenial hemoptysis. However, computed tomography revealed a suspicious mass-like lesion in the left main bronchus and bronchoscopy confirmed the presence of an endobronchial tumor. She underwent sleeve bronchial resection of the tumor and pathological examination revealed low-grade mucoepidermoid carcinoma. She had an uneventful recovery and was continuously followed in our clinic. For patients presenting with catamenial hemoptysis, endobronchial tumor should be considered, in addition to thoracic endometriosis syndrome. ***(Thorac Med 2015; 30: 150-156)***

Key words: mucoepidermoid carcinoma, lung cancer, hemoptysis

Introduction

Catamenial hemoptysis is hemoptysis concurrent with the menstrual period. Since this uncommon clinical sign is almost always related to ectopic endometrium in the respiratory tract, the diagnosis is usually established clinically. Herein, we report a patient with an endobronchial tumor presenting with catamenial hemoptysis.

Case Report

This 26-year-old otherwise healthy woman had been diagnosed as having asthma because of exertional dyspnea for 2 years. About 1 year ago, she began suffering from hemoptysis during or a few days before every menstrual period. During regular follow-up in the chest clinic for 6 months, the chest radiograph showed migrating focal opacity and partial atelectasis with

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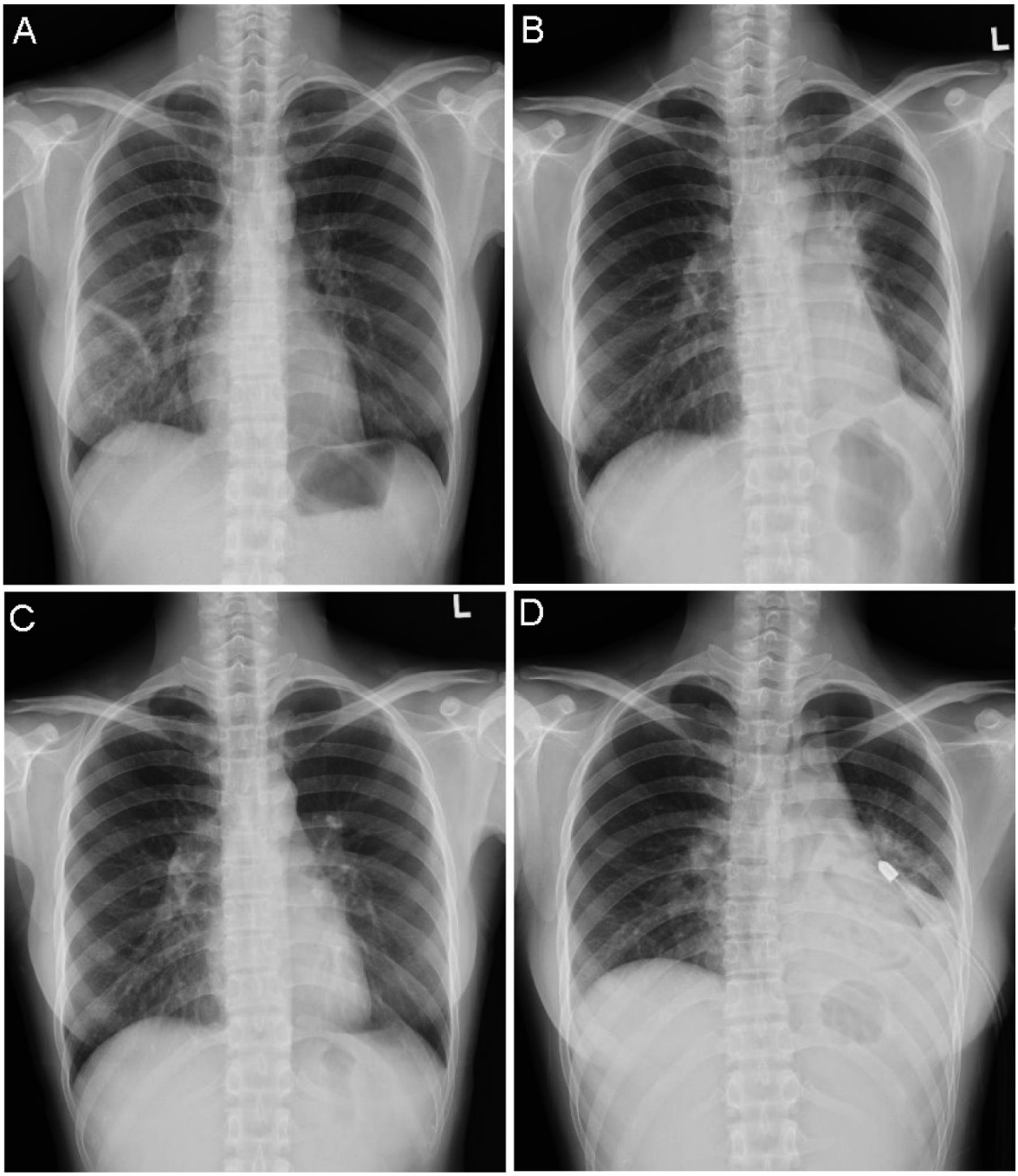
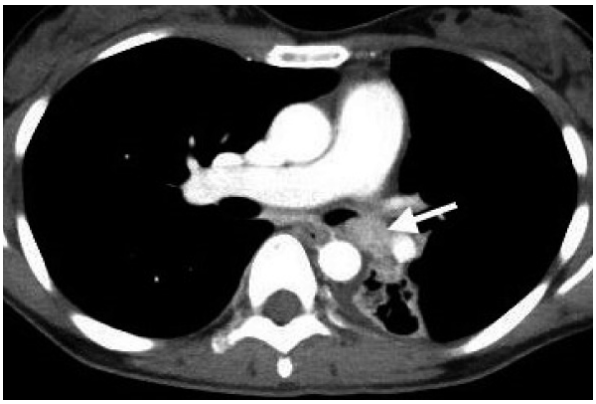


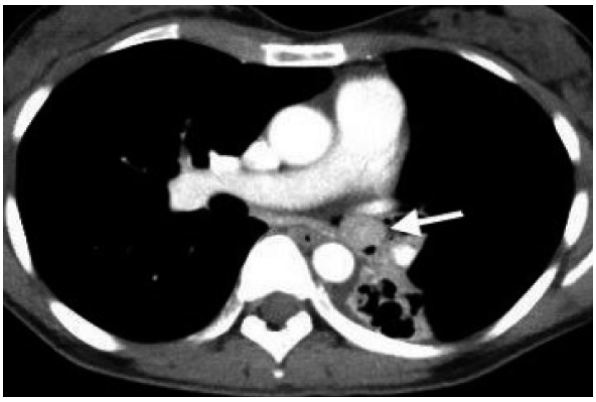
Fig. 1. (A) Chest radiograph on initial presentation showed a linear opacity in the right lower lung field. (B) Chest radiograph 4 months later showed partial atelectasis of the left upper lung. (C) Chest radiograph 6 months later showed spontaneous resolution of the pulmonary opacity. (D) Chest radiograph 9 months later showed pneumothorax status post-tubal thoracostomy.

spontaneous resolution (Figure 1A-C). She was initially diagnosed as having thoracic endometriosis syndrome based on the clinical history of catamenial hemoptysis.

Nine months after the initial presentation, she was admitted for left pneumothorax, and



(A)



(B)

Fig. 2. Computed tomography of the chest showed a suspicious mass-like lesion in the left main bronchus, near the left secondary carina.

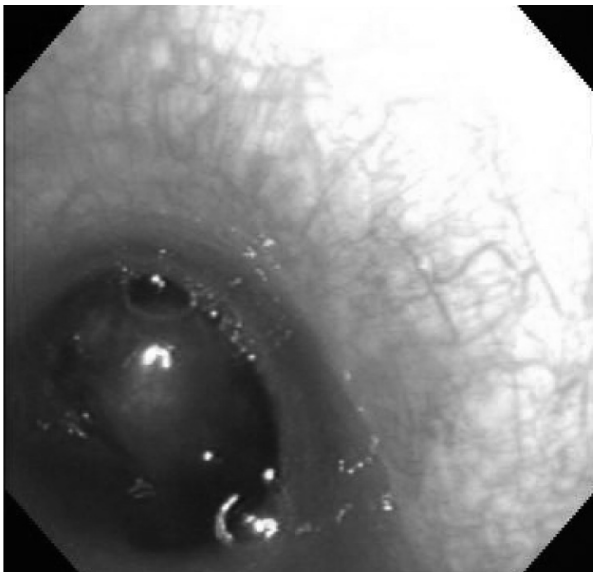


Fig. 3. Bronchoscopy showed a hyperemic tumor in the left main bronchus.

received tubal thoracostomy (Figure 1D). Although catamenial hemoptysis with pneumothorax was suspected, computed tomography (CT) performed after resolution of the pneumothorax revealed a suspicious mass-like lesion in the left main bronchus, near the left secondary carina (Figure 2). Bronchoscopy revealed an ovoid and hyperemic tumor with nearly total occlusion of the left main bronchus (Figure 3). She underwent sleeve bronchial resection of the tumor and lymph node dissection. Pathological examination showed a combination of clear cells, squamoid cells and intermediate polyglonal cells interspersed in an area with mucus-secreting glandular cells (Figure 4A, 4B). The immunohistochemical staining of the tumor cells was positive for cytokeratin 7 (CK7), and the mucin contents in the tumor cells were highlighted with mucicarmine staining (Figure 4C, 4D); Ki-67 expression was 15%. The lymph nodes were all negative for metastasis. These pathological findings suggested the diagnosis of a low-grade mucoepidermoid carcinoma. Because of the tumor staging of T2N0M0 (stage Ib), no further adjuvant therapy was arranged. The follow-up bronchoscopy revealed no residual tumor. She had an uneventful recovery and was continuously followed in our clinic; no hemoptysis was noted.

Discussion

Catamenial hemoptysis is an uncommon disease and the diagnosis is usually based on clinical findings when the periodic hemoptysis synchronizes with the menstrual period. It is

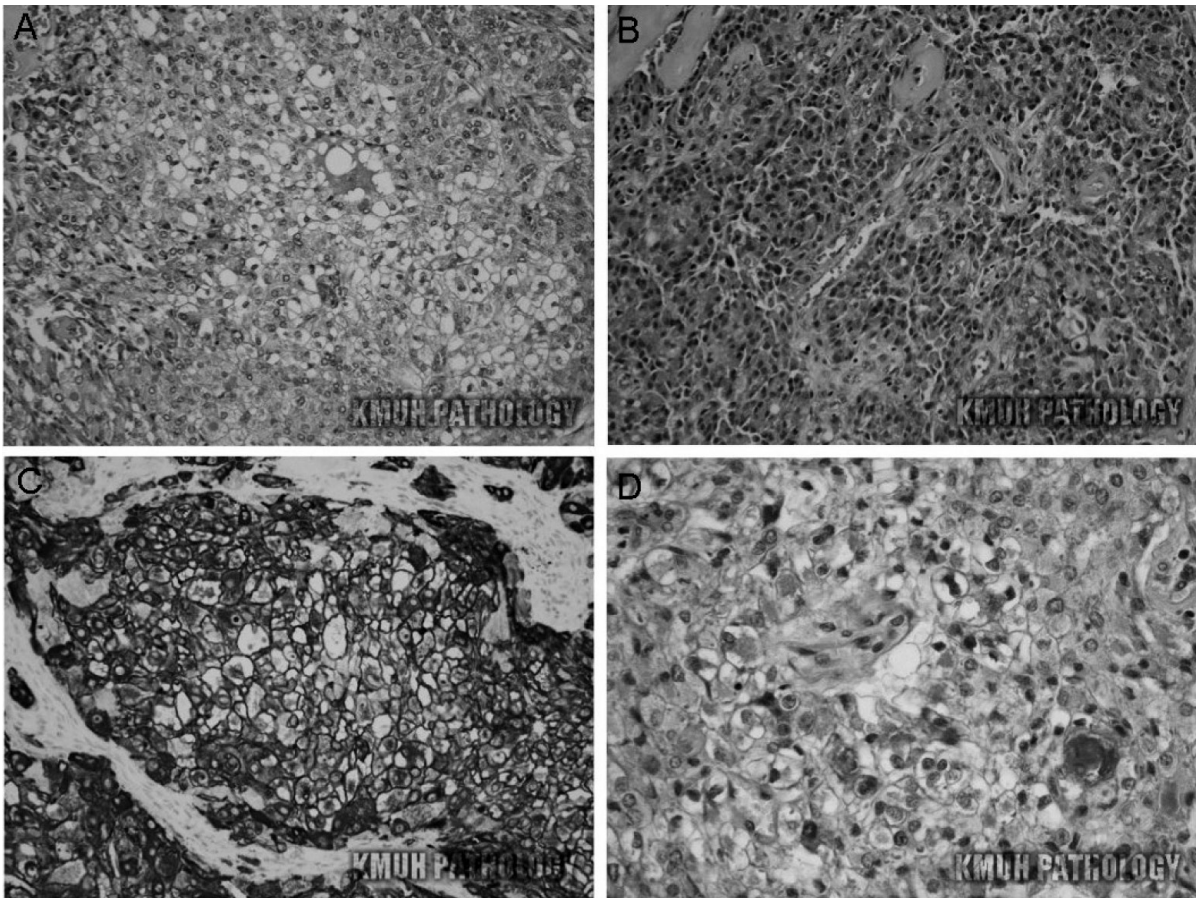


Fig. 4. Pathological examination showed a combination of clear cells, squamoid cells and intermediate polyglonal cells interspersed in an area with mucus-secreting glandular cells (A and B; hematoxylin-eosin stain, original magnification: 200×). The immunohistochemical staining of the tumor cells was positive for cytokeratin 7 (C; original magnification: 200×) and the mucin contents in the tumor cells were highlighted with mucicarmine staining (D; original magnification: 200×).

a presentation of thoracic endometriosis syndrome and occurs with a frequency of 7-12% [1]. The other symptoms and complications of thoracic endometriosis syndrome include chest pain, dyspnea, catamenial pneumothorax, and catamenial hemothorax [2]. The mechanism includes microembolization through pelvic veins and peritoneal-pleural movement of endometrial tissue through diaphragmatic defects [3]. Patients with endometrial tissue in the bronchus or lung parenchyma usually present with catamenial hemoptysis [4]. In this patient, thoracic endometriosis syndrome was the first impression, based on the catamenial hemoptysis and pneumothorax. However endobronchial pulmonary mucoepidermoid carcinoma was confirmed by CT and pathology. In the literature review, no report on pulmonary mucoepidermoid carcinoma with catamenial hemoptysis was found, and there was only 1 report with pneumothorax. The pathologic examination did not show endometrial tissue in our case, so thoracic endometriosis was excluded. The patient's pneumothorax might be related to a pulmonary infectious process or airway obstruction with a ball-valve effect [5].

Pulmonary mucoepidermoid carcinoma is a rare disease and accounts for 0.1-0.2% of lung cancers [6]. It is usually found as an ovoid or lobulated intraluminal mass, whereas other appearances, including cavitation, spiculation and diffuse thickening of the airway wall, are occasionally encountered [7]. The clinical presentations include cough, hemoptysis, wheezes and recurrent pneumonia relating to airway obstruction. The differential diagnoses include pneumonia, asthma, atelectasis and right middle lobe syndrome [8]. In our patient, the symptoms of asthma were not well controlled with asthma treatment until the tumor was resected. Therefore, for patients with persistently poorly controlled asthma, an endobronchial lesion should be considered.

Radical tumor resection is the main treatment for mucoepidermoid carcinoma. The prognosis is correlated with age and grade and stage of the tumor. Vadasz *et al*. reported 34 patients that underwent limited resection, lobectomy or pneumonectomy; the 5-year-survival rate was about 80% in the low-grade tumor group, but only 31% in the high-grade tumor group [9]. Chin *et al*. reported that patients with early-stage (stage IA, IB, IIB) tumors had better outcomes (10-year survival rate of 87.5%) than those with late-stage (stage IIIB and IV) tumors (1-year and 2-year survival rates of 28.6% and 0%, respectively) [10]. Age and lymph node metastasis were also associated with overall survival and progression-free survival in 1 study [11]. In our patient, low-grade mucoepidermoid carcinoma was confirmed by pathologic findings, and after sleeve bronchial resection for the tumor, she recovered well without recurrence.

Advanced tumors are generally treated as non-small cell lung cancers (NSCLC), but the response to chemotherapy is generally poor. Because high-grade and late-stage tumors are quite rare, no consensus has been reached with regard to adjuvant chemotherapy or radiotherapy. In advanced NSCLC, mutations in epidermal growth factor receptor (EGFR) predict the response to EGFR tyrosine kinase inhibitors (TKIs). Macarenco *et al*. found that pulmonary mucoepidermoid carcinoma also expressed EGFR, but no mutation in the EGFR gene was detected [12]. However, Han *et al*. reported that a patient with recurrent metastatic mucoepidermoid carcinoma that was negative for EGFR mutation had a partial response to treatment with gefitinib [13]. Lee *et al*. also reported a patient with metastatic mucoepidermoid carcinoma that received erlotinib, and had a radiographic response [14]. Mucoepidermoid carcinoma may harbor a t (11;19) translocation with an associated fusion oncogene (CRTC1-MAML2) [15]. In recent studies, mucoepidermoid carcinoma cell lines with a t (11;19) translocation were sensitive to gefitinib. This may be related to the up-regulation of the EGFR ligand amphiregulin, mediated by CRTC1-MAML2. These findings support the role of CRTC1-MAML2 oncogen as a possible target for treatment with gefitinib, even in the absence of EGFR mutations [16].

Conclusion

Catamenial hemoptysis is a manifestation of thoracic endometriosis syndrome, which is found mostly in patients with endobronchial or pulmonary parenchymal endometriosis. This is the first report in the literature of endobronchial pulmonary mucoepidermoid carcinoma presenting with catamenial hemoptysis. In conclusion, in a patient with catamenial hemoptysis, endobronchial tumor should also be taken into con-

sideration.

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肺部黏液表皮樣癌以類似月經性咳血表現－病例報告

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黃吉志 *,*****　鍾飲文 *,*****

肺部黏液表皮樣癌是一少見疾病，常以呼吸道管腔內的腫瘤表現並導致呼吸道阻塞。我們報告一位26歲女性於月經週期或月經週期數天前咳血並有自發性氣胸，根據月經性咳血的病史初診斷為胸部子宮內膜異位症候群，但經由電腦斷層發現疑似氣管內腫瘤並經由支氣管鏡於左側主支氣管內確認腫瘤。她接受支氣管袖狀切除腫瘤且病理切片報告診斷為低惡性度黏液表皮樣癌，術後恢復良好並持續於門診追蹤。病患以月經性咳血表現時，除考慮胸部子宮內膜異位症候群外，臨床醫師應亦考慮支氣管內腫瘤的可能性。*(胸腔醫學* ***2015; 30: 150-156)***

關鍵詞：黏液表皮樣癌，肺癌，咳血

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Pulmonary Squamous Cell Carcinoma Harboring EGFR Exon 19 Mutation Responded Dramatically to EGFR-TKI – A Case Report

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Epidermal growth factor receptor (EGFR) gene mutations are common in non-small cell lung cancer (NSCLC) patients characterized by female gender, a history of never smoking and an adenocarcinoma histology. These mutations usually predict favorable EGFR-tyrosine kinase inhibitors (TKIs) treatment efficacy and outcome. We report a non-smoking female with synchronous brain metastasis from pulmonary squamous cell carcinoma (SCC), which uncommonly harbored an EGFR exon 19 mutation and dramatically responded to EGFR TKI treatment. This case highlights that EGFR mutational analysis may be performed for pulmonary SCC patients that are East Asian females without a smoking history. The identification of EGFR mutations in pulmonary SCC may provide a treatment option using EGFR-TKIs. ***(Thorac Med 2015; 30: 157-163)***

Key words: epidermal growth factor receptor (EGFR) mutation, EGFR tyrosine kinase inhibitor (TKI), pulmonary squamous cell carcinoma

Introduction

The importance of epidermal growth factor receptor (EGFR) gene mutations has been widely demonstrated in non-small cell lung carcinoma (NSCLC). EGFR mutations are more frequent in NSCLC patients of East Asian ethnicity who are female, nonsmokers, and with an adenocarcinoma histology [1-3]. The aforementioned clinicopathological features are predictors of EGFR mutant NSCLC, which is known to have a better response to EGFR-tyrosine kinase inhibitors (TKIs) [4-6]. EGFR mutations in true pulmonary squamous cell carcinoma (SCC) have a reported incidence of around 0 to 3.4% [7-8], EGFR mutational testing is not routinely recommended in this subset of NSCLC patients. Pulmonary SCC harboring an EGFR mutation treated with EGFR-TKIs as first-line therapy is rarely reported. We present a patient with primary SCC harboring an EGFR exon 19 deletion and brain metastasis (BM) who responded dra-

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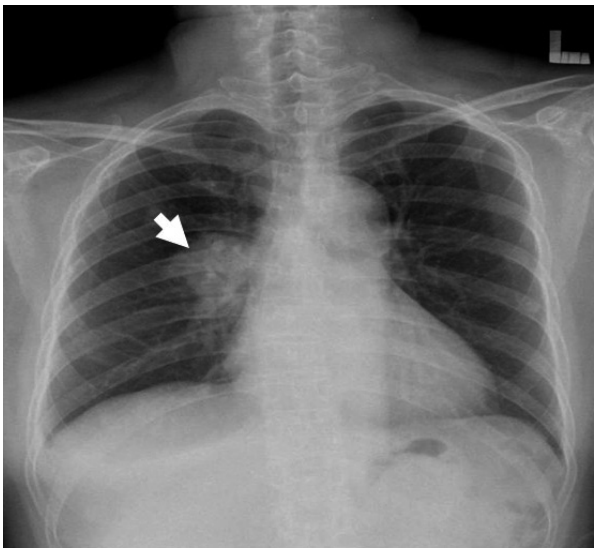

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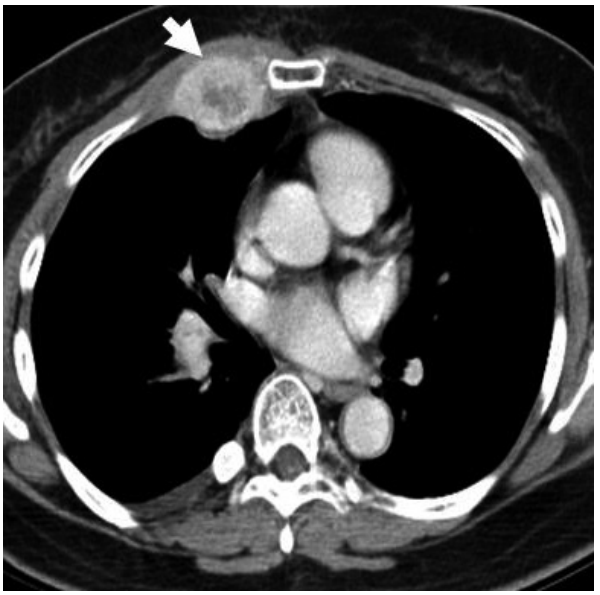

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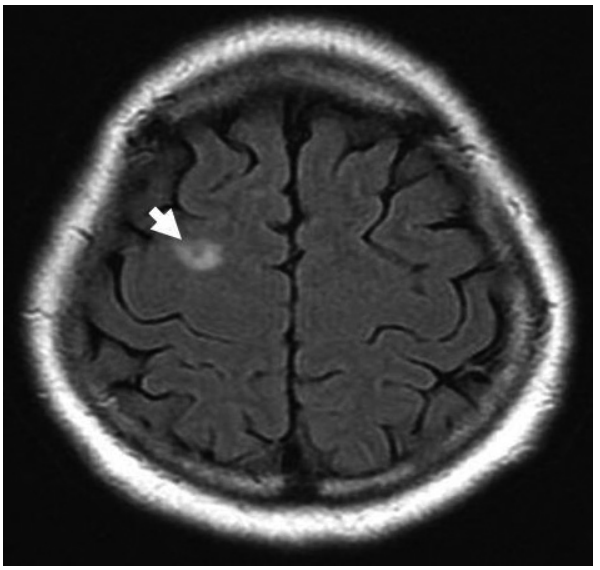

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Fig. 1. Chest radiograph, chest CT and brain MRI showed pulmonary squamous cell carcinoma and metastatic lesions. A (arrow), primary lung cancer mass at the right hilum. B (arrow), metastatic lesion at the right anterior chest wall. C (arrow), right parietal metastatic nodule.

matically to EGFR-TKI treatment.

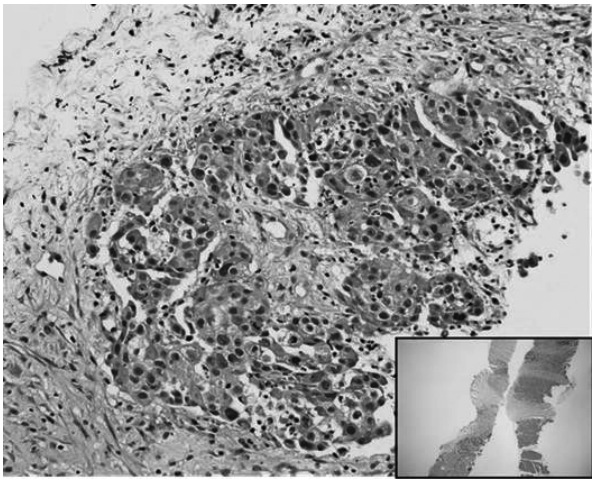
Case Report

A 53-year-old female, a never-smoker and with no underlying comorbidities, presented with right anteromedial chest pain for 1 month. There were no associated symptoms. Physical examination revealed mild tenderness when palpated on the right anteromedial chest wall, without visible mass protrusion. Chest radiograph showed a 4.7×3.6 cm mass located at the right hilum (Figure 1A). The computed tomography (CT) scan of the chest revealed a right hilar infiltrative tumor, mediastinal lymphoadenopathy, a small amount of right pleural effusion, and a right anterior chest wall space-occupying lesion (Figures 1B). Furthermore, brain magnetic resonance imaging (MRI) showed an ill-defined mass in the right parietal lobe (Figure 1C).

The pathology of the tissue specimen obtained from the metastatic site at the chest wall revealed poorly differentiated SCC (Figure 2A); immunohistochemical (IHC) staining showed the tumor cells were positive for p40

and CK5/6, and negative for thyroid transcription factor 1 (TTF-1) (not shown here). In addition, DNA extracted from the metastatic tumor specimen was submitted for EGFR mutational testing, and the result showed a gene deletion of EGFR exon 19 (del Leu747-Ala750insPro) (Figure 2B). As a result, this patient, who had bone and brain metastases, was diagnosed as having lung SCC with an EGFR exon 19 deletion, cT4N2M1b, stage IV.

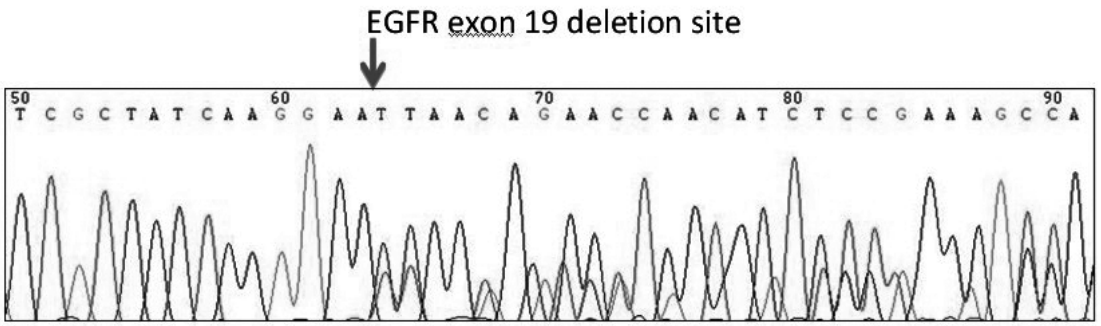
Taking into account the potential toxicities and efficacies of the various treatment modalities, including platinum-based doublet chemotherapy, target therapy and radiotherapy, and the patient's preferences, we suggested EGFR-TKI alone as the front-line treatment for this patient. Her chest pain improved within 2 weeks after taking gefitinib 250 mg daily, beginning on November 16, 2011. Follow-up CT scan of the chest (December 26, 2011) and brain MRI (February 21, 2012) also demonstrated that the primary and metastatic tumors in the thorax, as well as the BM, had responded well to EGFR-TKI (not shown here). She continued gefitinib treatment till disease progression. The overall progression-free survival (PFS) was 20 months.



(A)

Discussion

We herein reported a rare presentation of pulmonary SCC with a remarkable response to EGFR-TKI. However, the tumor specimens were small and obtained from the metastatic lesion, which inevitably raises some concerns about the diagnosis of SCC with an EGFR mutation. Several critical issues are further addressed below, including the incidence of EGFR mutations in SCC, the suitability of successfully



(B)

Fig. 2. Histological diagnosis of squamous cell carcinoma and epidermal growth factor receptor (EGFR) mutational testing for specimen obtained from the metastatic tumor at the right anterior chest wall of this female patient. A, poorly differentiated squamous cell carcinoma. B, EGFR molecular analysis showed a gene 19 deletion (del Leu747-Ala750insPro) in exon 19 of EGFR.

subtyping NSCLC in small biopsied specimens, the treatment efficacy of EGFR-TKIs in pulmonary SCC harboring EGFR mutations, and the role of EGFR-TKIs in the treatment of BM from NSCLC.

First, we agree that lung tumor is heterogeneous, which implies that 1 tumor may consist of squamous cancer cells or adenocarcinoma cells or both, and diagnosis of SCC based on small biopsied tumor specimens may not represent the reality of the whole tumor. Some studies have shown that the diagnosis of SCC could be a result of incomplete sampling of adenosquamous carcinoma or difficult pathologic discrimination from poorly differentiated adenocarcinoma [8]. However, approximately 80% of lung cancers are diagnosed at an advanced stage, indicating that large resected tumor samples are not available and diagnoses are made on small biopsied specimens in most of the lung cancer population. In addition, adenosquamous carcinoma is known to harbor a spectrum of EGFR/KRAS mutations that is similar to adenocarcinoma [9]. In this case, IHC staining, including TTF-1, p40, and CK5/6 biomarkers, was used to verify whether the tumor was adenosquamous carcinoma or SCC; the staining was negative for TTF-1 and positive for p40 and CK5/6, leading to the diagnosis of SCC.

EGFR mutations are commonly observed in NSCLC specimens from patients characterized by female gender, adenocarcinoma histology, and a history of never smoking. EGFR mutational testing is routinely recommended for patients with advanced adenocarcinoma [10], but not for those with SCC, largely based on the fact that the incidence of EGFR mutations in SCC is very low (0 to 3.4%) [7-8]. However, histological subtype cannot preclude the possibility that an EGFR mutation can be detected in SCC. In our case, EGFR mutational analysis showed a gene deletion in exon 19 of EGFR, which highlighted the significance of EGFR mutation testing not only for patients with adenocarcinoma, but also for females with SCC and who have a history of never smoking. Another concern before administration of EGFR-TKI for a patient would be whether the EGFR mutation status was the same in both the primary and metastatic tumors in an individual. Some studies suggested that there is a discordance of EGFR mutation status between primary and corresponding metastatic tumors [11-12]. However, a well-designed study reported that the heterogeneous distribution of EGFR mutations is extremely rare in NSCLC [13], which implies that NSCLC patients could be treated based on the result of EGFR mutational testing, no matter whether the tumor specimen is obtained from the primary or metastatic tumor.

EGFR-TKIs are widely used currently as a front-line therapy for lung adenocarcinoma with EGFR mutations, but are not routinely recommended for SCC with EGFR mutations due to unsatisfactory treatment efficacy. One pooled analysis showed the response rate of SCC with EGFR mutations to gefitinib was only 30% (8 out of 27) [14]. After weighing the concerns mentioned above and the safety and efficacy of a standard platinum-based doublet, our patient decided to take gefitinib 250 mg per day beginning November 16th 2011. Serial images of the chest demonstrated that both the primary lung tumor and the metastatic bone lesions responded well to EGFR-TKI, which indicated the EGFR exon 19 mutation underlying the tumorigenesis of SCC in our case.

BM commonly develops in cancer patients, and usually leads to an unfavorable prognosis [15]. Interventional management of BM, includ-

ing surgery, radiosurgery and whole brain radiotherapy, generally provides modest treatment efficacy [16-17] at the cost of neurological adverse effects. However, case series have found that EGFR-TKIs may work in patients with BM from NSCLC with EGFR mutations [18-21]. In our case, the synchronous BM shrank remarkably after administration of EGFR-TKI, with a 20-month PFS in the brain. A recent phase II clinical trial found that patients with BM from NSCLC with sensitizing EGFR mutations benefited from front-line EGFR-TKI treatment, with an 87.8% response rate and 14.5-month PFS in the brain [22]. Together, these findings suggest that EGFR-TKIs can be used as a front-line treatment option for TKI-naive BM from NSCLC with sensitizing EGFR mutations.

Conclusion

We suggest that EGFR mutational testing may be performed in patients with pulmonary SCC, in particular, those with relevant clinical features such as Asian female and non-smoker. We also suggest EGFR-TKIs may be considered as a front-line treatment for TKI-naïve patients with BM from SCC harboring sensitizing EGFR mutations.

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具表皮細胞生長因子接受器突變之肺鱗狀細胞癌病患使用上皮細胞生長因子接收器－酪胺酸酶抑制劑呈顯著治療效果：病例報告

李凱靈 * 林賜恩 ** 鍾政錦 *** 蕭世欣 * 鍾啟禮 *,****

表皮細胞生長因子接受器（Epidermal growth factor receptor，簡稱 EGFR）的基因突變常見於非小細胞肺癌病患，尤其是從不抽菸、女性和肺腺癌患者。擁有此突變之病患有較好的 EGFR 酪胺酸酶抑制劑（Tyrosine kinase inhibitor，簡稱 TKI）治療效果和預後。我們提出的個案為一個不抽菸女性患有肺鱗狀細胞癌併發腦部遠處轉移，卻罕見地擁有 EGFR exon 19 突變，並對 EGFR TKI 治療有顯著的療效。此篇病例報告指出 EGFR 基因突變分析應可實行於肺鱗狀細胞癌的病患，尤其是具有亞裔、女性和從不抽菸的特徵者，而且可為此類病人提供使用標靶治療的機會。*(胸腔醫學 **2015; 30: 157-163**)*

關鍵詞：表皮細胞生長因子接受器突變，上皮細胞生長因素接收器－酪胺酸酶抑制劑，肺鱗狀細胞癌

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Mucormycosis-Related Mycotic Pulmonary Artery Pseudoaneurysm: A Case Report

Chiung-Yu Lin*, An-Shen Lin*, Meng-Chih Lin*,**, Sum-Yee Leung*

Mucormycosis is an uncommon infectious fungal disease that mostly affects immuno-compromised patients or those with diabetes mellitus. Rhino-orbital-cerebral, pulmonary, or cutaneous invasion is often seen; however, mucormycosis-related mycotic aneurysm and pseudoaneurysm are relatively rare. Few cases have been reported in the past decade. In this report, we share a case of mucormycosis-related mycotic pulmonary artery pseudoaneurysm complicated by chest wall fasciitis. Mucormycosis is usually accompanied with a poor prognostic outcome, but early diagnosis and appropriate management may reduce the rate of mortality. ***(Thorac Med 2015; 30: 164-170)***

Key words: mucormycosis, pulmonary artery pseudoaneurysm, fungal infection, hemoptysis, aneurysm

Introduction

We present a rare case of mucormycosis-related mycotic pulmonary artery pseudoaneurysm (PAP). The case was characterized by a rapid-growing mass in the right lower chest field in the plain film, and PAP was confirmed by computerized tomography (CT) angiography. We made the diagnosis of mucormycosis after observing many blunt-angled fungal hyphae and spores in the postoperative resected necrotic tissue. Although amphotericin B was given after the diagnosis was made, the patient ultimately died. This result may highlight the importance of early diagnosis and early appropriate management.

Case Report

A 75-year-old female patient had a history of hypertension, chronic kidney disease stage 4 (creatine: 1.72 mg/dL; creatinine clearance rate: 1.26, calculated using the Cockcroft-Gault equation), and diabetes mellitus for over 10 years. She was prescribed 3 kinds of oral anti-diabetic drugs in the local medical department, but poor glycosylated hemoglobin profiles (HbA1c: 8.8~9.7) were still observed for 1 year prior to this hospitalization. In addition, she had suffered from *Klebsiella pneumoniae*-induced liver abscess on 2 separate occasions 3 and 6 years ago. The patient was a housewife and had no recent contact or cluster history. She came

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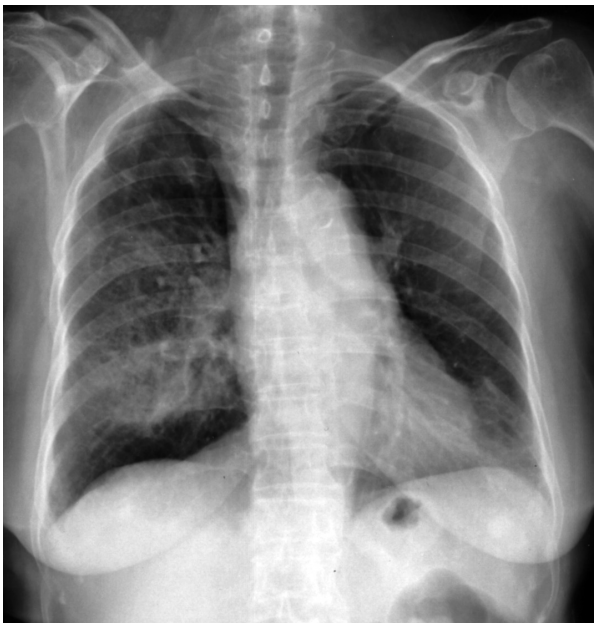

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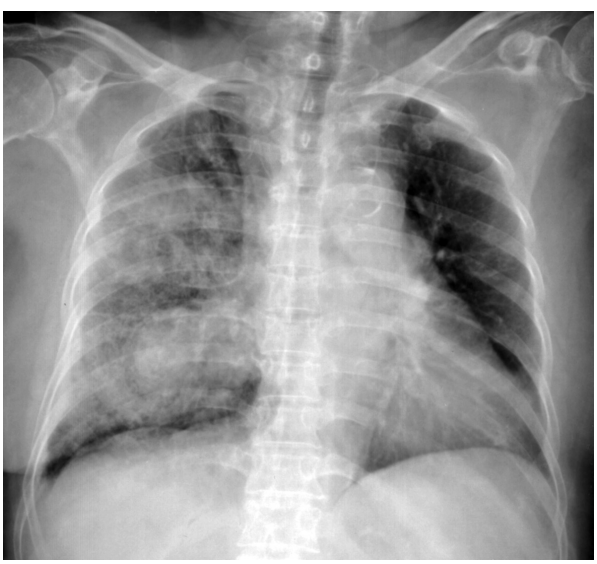

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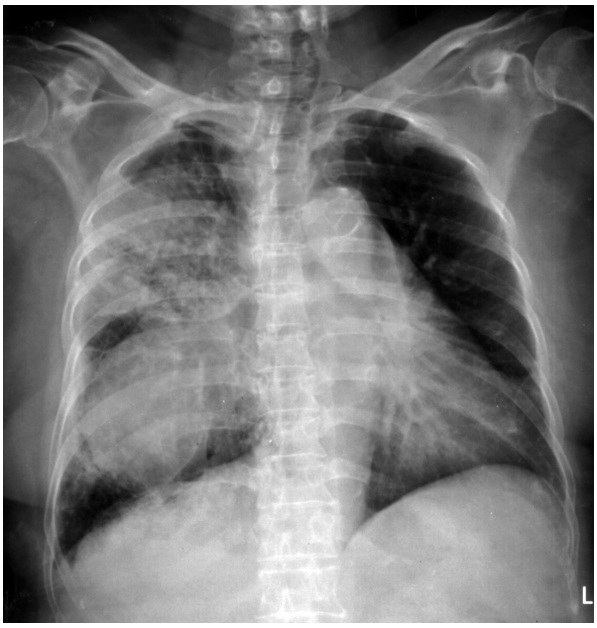


(C)

Fig. 1A-C. These 3 pictures illustrate an ongoing disease process. A rapidly growing mass lesion was found in the RLL field; these pictures were taken on July 28 (Fig. 1A), August 1 (Fig. 1B) and August 6, 2012 (Fig. 1C), respectively. The interval between the first and last chest roentgenogram images was 9 days.

to our hospital on July 28, 2012 with the initial presentation of cough and right lateral chest wall pain for 1 week. Her chest pain was discribed as obtuse pain aggravated by respiration; intermittent hemoptysis developed after hospitalization as well.

Her laboratory studies revealed leukocytosis with a left shift (white blood cell count: 25500/mm^3; segments: 90.5%), and her chest X-ray plain film showed right lower lung (RLL) consolidation (Figure 1A). The patient was treated for RLL pneumonia at first; however, a rapid-growing mass emerged in her RLL field 3 days later (Figure 1B, 1C). We arranged a CT scan for her lung mass, and the image suggested an 11-cm heterogeneous hematoma (Figure 2). Right upper, middle and lower lobe orifice narrowing was found through bronchoscopy; a protruding lesion was noted at the distal truncus intermedius favoring external compression. We performed right upper lobe bronchial washing, but the culture was negative.

Her hemoptysis persisted and we looked at surgical assistance or embolization. However, the patient refused surgery, citing her age; she

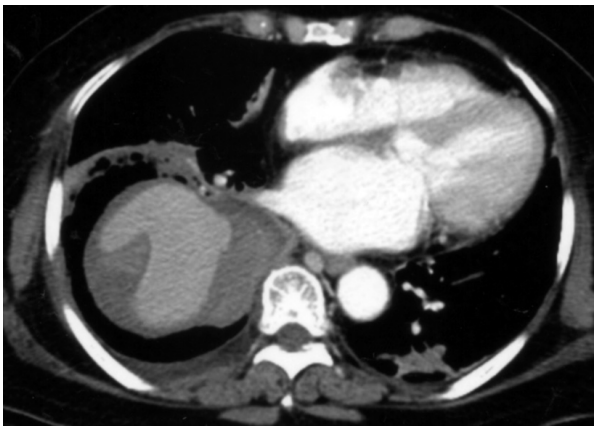


Fig. 2. CT image of the patient (date: August 8, 2012). A giant heterogeneous hematoma was noted in the RLL, 11.0-cm in size at its largest diameter. Loculated pneumothorax was also seen in the images.

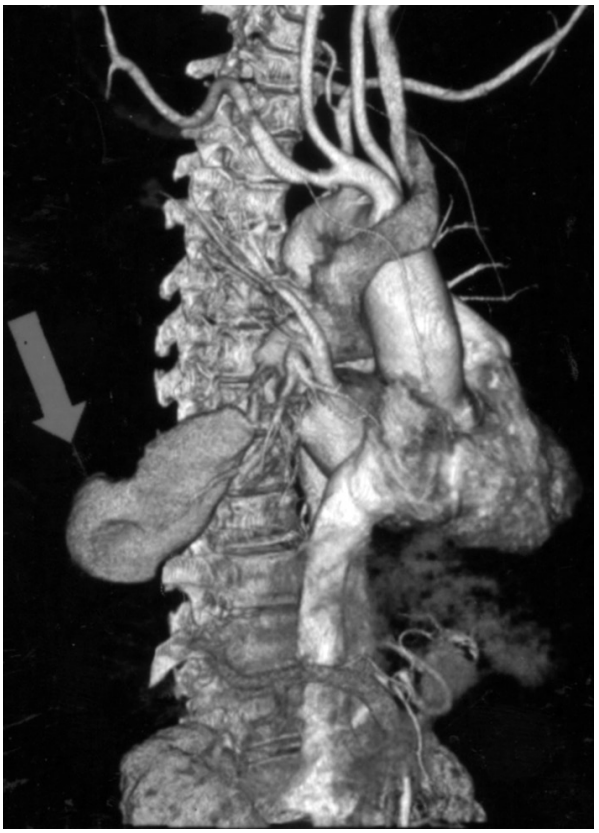
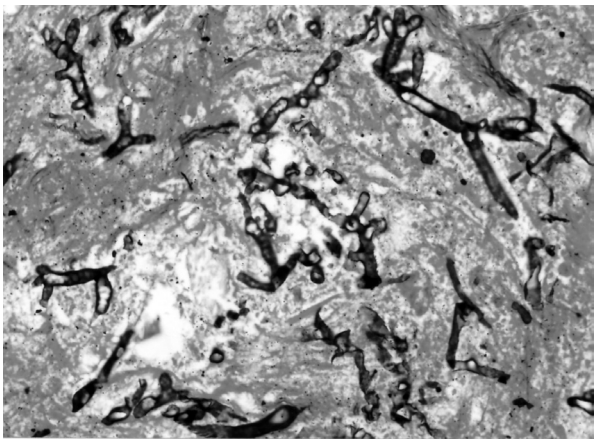


Fig. 3. Three-dimensional combination image reconstructed via CT angiography. A large pulmonary pseudoaneurysm is indicated by an arrow in the RLL field.

requested conservative treatment with antibiotics first. In the following days, we studied autoimmune and tumor markers to exclude vasculitis and neoplasm, and arranged cardiac sonography to exclude any possible valvular heart diseases. All these studies provided non-specific results. Rapidly progressive subcutaneous emphysema developed on September 5, 2012, and as a result, the patient soon accepted surgical intervention. CT angiography was done prior to her surgery, and a large pulmonary pseudoaneurysm was found in her RLL (Figure 3).

Right middle and lower lung lobectomy, wedge resection of the right upper lung, and debridement of necrotizing chest wall muscle were done on September 6, 2012. Mucormycosis-related PAP was later diagnosed via histopathology examination, which revealed many blunt-angled fungal hyphae and spores in the necrotic tissue (Figure 4A, 4B). Amphotericin B was given after the diagnosis was made. However, wound infection and hypercapnic respiratory failure were repeatedly observed after surgery. The patient received chest wall debridement again on September 18 and on September 29, 2012, as well as right upper lung lobectomy on the latter date. Her infection status did not improve after those interventions, and repeated wound culture revealed a heavy amount of *Klebsiella pneumoniae*, coagulase-negative Staphylococcus and Candida. The patient died on October 1, 2012; all the blood culture examinations during this hospitalization were negative. The cause of her death was suspected to be wound infection-related sepsis and a new ongoing ventilator-associated pneumonia in her left residual lung.



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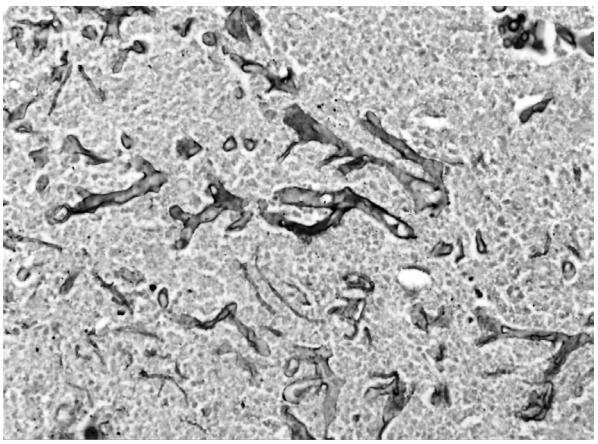

(B)

Fig. 4A-B. Multiple blunt-angled fungal hyphae and spores were observed in the necrotic tissue with Grocott methenamine-silver stain (Fig. 4A) and periodic acid-Schiff staining (Fig. 4B) separately, compatible with the diagnosis of mucormycosis.

Discussion

Pulmonary artery aneurysm (PAA) is a term used to describe dilatation of the pulmonary artery trunk or major branches with associated cystic necrosis of the media of the vessel wall; similarly, PAP indicates the enlargement of the pulmonary artery due to entire vessel wall destruction [1]. PAAs and PAPs may cause similar symptoms, such as hemoptysis, dyspnea, cough, and chest pain. Hemoptysis may occur when the integrity of the pulmonary artery is compromised, and the same mechanism sometimes leads to pulmonary hypertension and right heart failure in patients with PAAs and/or PAPs [1]. Attention should therefore also be paid to hemoptysis, as it may become massive and fatal in some cases. In addition, should the aneurysm rupture, a very high mortality rate of 54% to 100% has been reported [2-3].

Congenital abnormalities, such as cardiac septal defects or Marfan syndrome, may result in PAA. Both PAA and PAP can be caused by inflammatory processes or an infectious etiology, but PAPs are more commonly associated with trauma, such as the complications from Swan-Ganz catheterization [4-6]. With regard to the infectious etiology, either direct extension of pneumonia or seeding via the blood stream can cause vessel wall damage. The destruction of 1 or all layers will conduce to the formation of PAA or PAP [3-4]. In the past, mycotic PAAs were usually associated with cavitary tuberculosis or syphilis; however, infective endocarditis secondary to congenital heart disease or intravenous drug use is gradually becoming the most common etiology [1]. The term mucormycosis is defined as the infectious disease caused by the order Mucorales. It generally affects immunocompromised patients, including those with diabetes, organ transplantation, neutropenia, or malignancy [7-8]. The most common pathogens causing mucormycosis include Rhizopus and Rhizomucor; rhino-orbital-cerebral, pulmonary, gastrointestinal tract or cutaneous invasion is often seen. The rhinocerebral and pulmonary systems are the 2 most commonly infected systems [8].

The diagnosis can be confirmed by fungal culture, histopathology, or polymerase chain reaction. Histopathological examination may

provide additional assistance since fungal cultures often reveal negative findings. The typical histopathological characteristic of mucormycosis is thick hyphae and cell walls; the mucor shows an absence of compartmentation with irregular straight or blunt-angled branches from the cell body [9]. Silver methenamine stains are superior to hematoxylin-eosin stains in visualizing the fungal elements, and the presence of hyphae should be looked for, as they can easily be overlooked unless multiple sections are scrutinized [10].

Bronchoscopy is a less complicated choice to obtain biopsy tissue than open lung biopsy or surgical resection. However, post-bronchoscopy fatal endobronchial hemorrhage was reported in a rare case of diffuse pulmonary mucormycosis [11]. Surgical management may be life-saving, but postoperative complications are encountered in approximately 50% of these patients. A fatal outcome occurs in 20% of patients, even when surgery is performed within the first 24 hours after hemoptysis [12-13]. Use of polyene antibiotics is suggested when the diagnosis is made, either as a single treatment or in a combination therapy, such as amphotericin B deoxycholate or caspofungin plus lipid polyene [8]. Pulmonary fungal infection-related pseudoaneurysm should be treated regardless of size, due to its high risk of rupture [14]. Benvenieste *et al*. recommended early embolization or surgery in a study of collected mycotic PAA cases [3]. Embolization for mycotic PAA or PAP is now widely accepted; however, few articles focusing on embolization of mucormycosis-related PAA or PAP have been published. A patient with lung apex mucormycosis-related subclavian artery occlusion and pseudoaneurysm was reported to be successfully treated with transcatheter embolization [15]. Surgical revascularization was not performed in that patient because of an increased risk of post-surgery bacterial contamination. As an alternative, an 11-month course of antifungal therapy with liposomal amphotericin B and prosaconazole was given [15].

In our case, the patient died after surgery and antibiotics therapy. There may be 2 main reasons for this outcome. First, we failed to confirm the causative organism cultured from the recovered bronchial washing fluid, and this, in combination with the patient refusing to receive surgical management initially, postponed the histopathological examination. The above resulted in the late diagnosis and late initiation of appropriate anti-fungal therapy, which may account for the rapid progression of her disease and eventually the necrotizing fasciitis in the chest wall. Second, the patient's advanced age, comorbidities and compromised immunity conduced to a difficulty in post-surgical care and increased susceptibility to secondary infections, despite surgical interventions to remove the primary infected sources and necrotic chest wall tissues. Due to the highly invasive nature of mucormycosis, with its documented high postoperative complication and mortality rates, poor wound healing and a refractory infection status were observed. As a result, the patient's poor prognosis did not reverse despite repeated lobectomy and debridement.

Conclusion

In this case, we found that mucormycosis is a highly invasive disease. For those with an uncertain diagnosis of mucormycosis-related pulmonary aneurysm or pseudoaneurysm, multi-detector row CT angiography could provide more accurate information for surgical or embolization management. There is not cur-

rently a standard therapy guideline, and the optimum time to commence antifungal therapy is perhaps controversial due to the small number of existing case reports. However, we feel that appropriate anti-fungal therapy should be given as soon as a confirmed diagnosis is made. As documented in case reports, early application of polyene antibiotics is highly recommended in cases of mucormycosis infection. Surgical procedures may be life-saving, but a high complication and mortality rate has been reported post-surgery. Although we were unable to save our patient, her case has highlighted to us important points in the management of this condition.

Acknowledgments

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白黴菌病併發肺動脈假性動脈瘤－病例報告與文獻回顧

林炯佑 * 林安伸 * 林孟志 *,** 梁深怡 *

白黴菌病主要發生在糖尿病病患或免疫不良的病患，影響的部位包括鼻眼腦區域、肺部、皮膚等處。我們在此報告一位 75 歲曾經罹患肝膿氯及糖尿病病史的女性，該病患因咳血入院，住院期間持續咳血及併發皮下氣腫，同時在胸部 X 光影像出現快速增大之腫塊。透過肺部電腦斷層影像，我們診斷出該病患罹患肺動脈假性動脈瘤；該病患接受右中肺葉暨右下肺葉切除術，並藉由病理學檢察，診斷出白黴菌病肺部感染導致肺動脈假性動脈瘤。雖然給予適當的抗生素藥物治療，最終仍無法控制病患肺部的感染，並且導致死亡。在此個案報告中，我們了解到了白黴菌病的高度侵犯性；臨床醫師宜早期診斷，並且給予適當的抗生素藥物治療。*(胸腔醫學 **2015; 30: 164-170**)*

關鍵詞：白黴菌病，肺動脈假性動脈瘤，咳血，黴菌感染

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Primary Pulmonary Lymphoepithelioma-like Carcinoma – Experience with Five Cases at MacKay Memorial Hospital

Hsin-Pei Chung, Ming-Jen Peng, Wei-Chin Chang*, Pei-Jan Chen, Chien-Liang Wu, Rong-Luh Lin

Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare subtype of non-small-cell lung cancer (NSCLC) and is mostly reported in Southeast Asia. It was first reported by Begin in 1987; it has pathological features similar to nasopharyngeal carcinoma and was associated with Epstein-Barr virus infections in Asia.

We reported 5 cases of primary pulmonary LELC from Jan 1991 to Dec 2013, 3 of them were incidentally found as asymptomatic tumors or nodules on chest radiographs. Four patients were non-smokers and none of them was diagnosed as having advanced disease (2 stage IA, 2 stage IIA, 1 stage IIIA, respectively). The typical CT radiographs show single, centrally located tumors of various sizes. The typical pathologic features revealed sheet growth of tumor cells surrounded by lymphoplasmacytic cells; 4 of the specimens were positive for EBV stain. The 5 patients responded well to multi-modality treatment without progression during a follow-up of 10 to 93 months.

Primary pulmonary LELC often affects asymptomatic and younger non-smokers without gender predilection. Patients diagnosed with early, resectable disease respond well to chemotherapy or radiotherapy. ***(Thorac Med 2015; 30: 171-177)***

Key words: lymphoepithelioma-like carcinoma, Epstein-Barr virus

Introduction

Lung cancer remains the leading cause of cancer-related death nowadays. Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare subtype of non-small cell lung cancer (NSCLC), but presents with a morphology similar to undifferentiated nasopharyngeal carcinoma (NPC). It was first reported in 1987 by Begin [1]. Primary pulmonary LELC is considered to be closely associated with Epstein-Barr virus (EBV) infections, and shares the same endemic area in Southeast Asia [2-3]. In previous reports of pulmonary LELC, most patients were young non-smokers, and were in an early, resectable stage with a better prognosis [4].

We report 5 patients diagnosed as having primary pulmonary LELC in our center. We

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analyze the clinical characteristics, histopathology, immunohistochemical profile, and outcomes.

Materials and Methods

From January 1991 to December 2013, there were 6739 cases of lung cancer at MacKay Memorial Hospital (MMH), and a total of 7 patients were diagnosed with pulmonary LELC. The demographic data, radiologic studies, pathological findings, and clinical course were reviewed in the medical records. Nasopharyngeal examinations were performed for most patients to exclude metastatic LELC. Two of the patients had a history of treated NPC (5 and 3 years before, respectively), although there was no evidence of local recurrence. The 2 cases were excluded. The thoracic lesions in the CT imagery were evaluated in terms of tumor sites (peripheral or central), size (defined as the product of the 2 maximum diameters), tumor borders (well-defined, spiculated, ill-defined), and the presence of pleural, vascular, and pericardial involvement. Tumors were considered "central" if they were within the inner 2/3 of the lung, and close to the mediastinum and main bronchi [5]. The diagnosis was confirmed by an experienced pathologist (C.-W.C.). The presence of EBV in all the specimens was examined by latent membrane protein 1 (LMP1) immunohistochemical stains. Antigen availability was enhanced by pretreatment for 5 minutes with Proteinase K (DAKO) at room temperature.

Results

Demographic and Radiographic Characteristics

Two of the patients in our series were male, and 3 were female; only 1 had a history of smoking. Three of the patients were incidentally found to have asymptomatic tumors or nodules on the chest radiograph. The mean age was 59.6 years (range, 54-69 years), and the median follow-up was 2.8 years. Four patients were diagnosed as having early-stage disease and 1 with locally advanced disease (2 stage IA, 2 stage IIA, 1 stage IIIA, respectively); all had a disease-free status during follow-up (Table 1).

The CT features of the 5 patients revealed that 3 had a centrally located tumor, 1.8-6.6 cm in size (Table 2). The border of the primary tumor was well-defined or irregular (Figure 1A-C). One of the centrally located tumors had central necrosis with vascular encasement (Figure 1C), and another had pericardial invasion (Figure 1B). Two of the patients had well-defined peripheral nodules measuring less than 2 cm (Figure 2).

Pathologic features

The typical pathological characteristic of LELC is undifferentiated carcinoma with diffuse lymphocytes infiltration (Figure 3A-B). The immunohistochemical profile showed all specimens were positive for p63, 4 were positive for cytokeratin AE1/AE3, and 3 were positive for cytokeratin 5/6 (Figure 3C-E). LMP1 immunohistochemical stain for EBV was performed for all the patients, and 4 had a positive result (Figure 4).

Treatment Modality and Clinical Outcomes

Two patients with stage IA underwent surgery and remained disease-free during a mean period of 5.5 years. The other 3 patients with more advanced disease received chemotherapy; all the patients received cisplatin-based chemotherapy. The patient with stage IIIA refused

Table 1. Primary Pulmonary LELC at Our Institution

Pt No.	Age, Y	Sex	Stage	Clinical presentation	Treatment	Follow-up (mo)
1	54	F	IA (T1aN0M0)	Cough for 3 months	Sug	Alive/93
2	58	F	IA (T1aN0M0)	Incidental finding	Sug	Alive/38
3	58	F	IIA (T1N1M0)	Incidental finding	Sug + Chem	Alive/33
4	59	M	IIIA (T4N0M0)	Incidental finding	Sug + Rad	Alive/12
5	69	M	IIA (T2bN0M0)	Cough for 6 months	Sug + Chem	Alive/10

Abbreviation: LELC=lymphoepithelioma-like carcinoma; F=female; M=male; LLL=left lower lung; LUL=left upper lung; RML= right middle lung; RLL= right lower lung; Sug=surgery; Rad=radiotherapy; mo=month.

Table 2. Radiologic Features of Patients with Primary LELC

Patient No.	Location	Size	CT characteristics
1	LLL	2.0 cm	Peripheral, well-defined
2	LLL	1.8 cm	Central, well-defined
3	LUL	1.2 cm	Peripheral, well-defined
4	RML	6.6 cm	Central, irregular, with pericardial invasion
5	RLL	6.5 cm	Central, lobulated, with vascular encasement and central necrosis

CT=computed tomography

chemotherapy, therefore we administered a dose of 5900 cGy of radiotherapy. All patients were in a disease-free status during follow-up.

Discussion

Over the past 2 decades, less than 300 cases of LELC have been reported in the published literature [6-8]. In our study, 2 patients were male, and 3 were female. This was consistent with published results in which there was no gender predilection in primary pulmonary LELC [2,6]. Only 1 patient (20%) had a smoking history, more than half of our patients were asymptomatic, and the mean age at diagnosis was 59.6 years, similar to previous studies [2,4,6] which showed that the median age was 51 years and only 25% of patients were former or current smokers.

All of our patients were diagnosed as having early-stage and locally advanced disease, and all were in a disease-free status after a median follow-up of 33 months. In the latest and largest cohort study, nearly 33% of the patients were asymptomatic and most had early, resectable disease with a high response rate (>75%) [6]. Thus, primary pulmonary LELC has distinctive features that differ from those of other histological types of lung cancer.

The distinct CT features of advanced primary pulmonary LELC, first observed by Ooi *et al*, reveal a large, well-defined tumor closely associated with the mediastinum, and peribronchovascular lymph node metastasis and vascular encasement [5]. In our study, more than half of the cases were centrally-located and of various sizes, and were not associated with lymphadenopathy, which was consistent with a previous study [7].

The diagnosis of primary pulmonary LELC

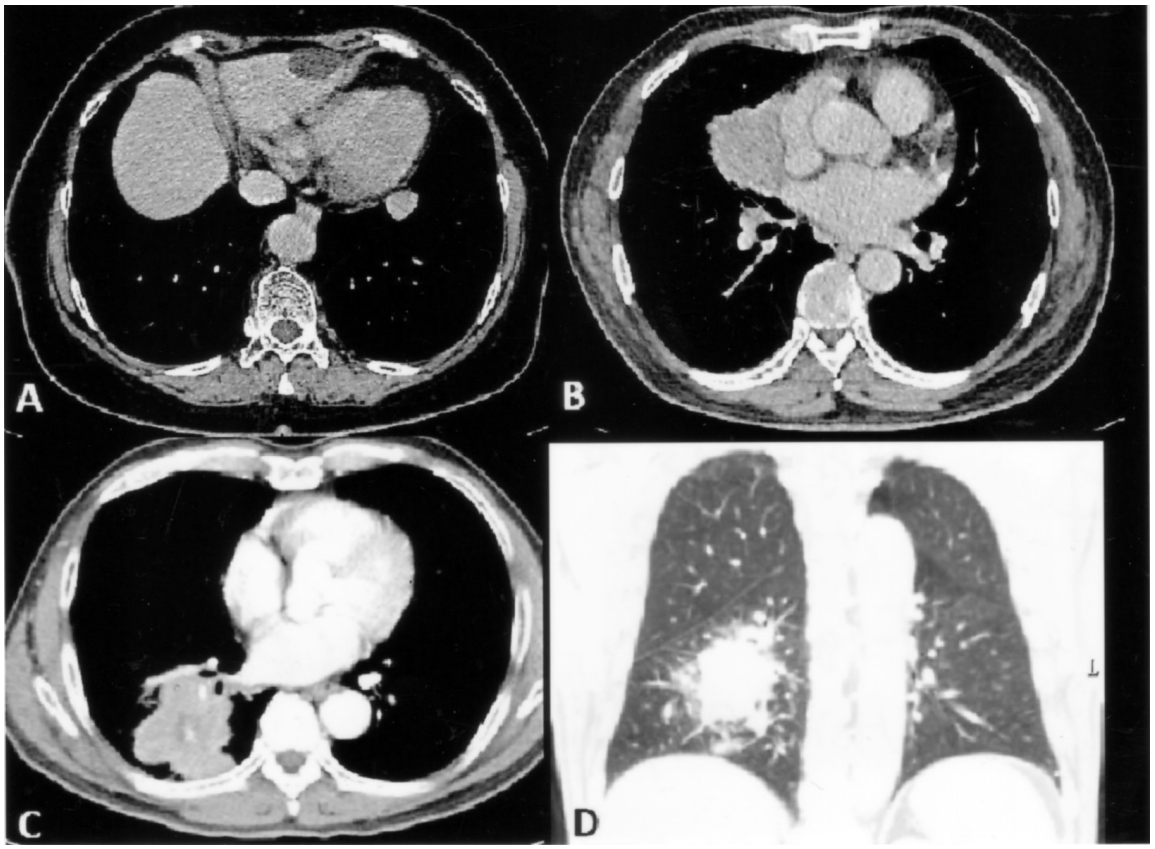

Fig. 1. The typical CT characteristics of primary pulmonary LELC are a centrally located tumor, 1.8-6.6 cm in size (Figure 1A-C). (A) Small, well-defined, centrally located nodule in the left lower lung, without pericardial invasion. (B) Centrally located tumor with irregular border and obvious pericardium invasion. (C, D) One of the centrally located tumors had central necrosis with vascular encasement.

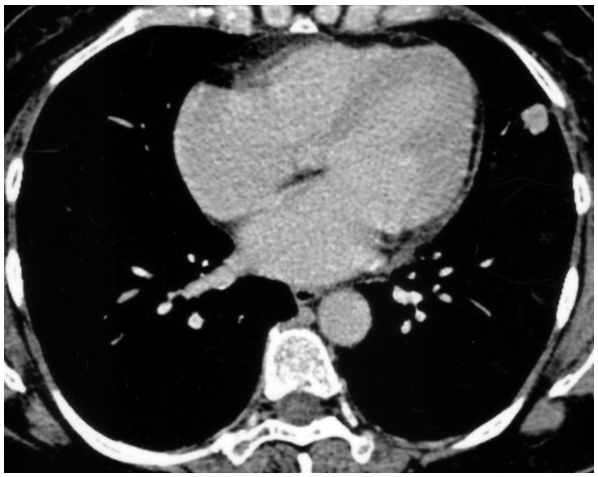

Fig. 2. A 1.2 cm, well-defined peripheral pulmonary nodule noted in the in patient No 3.

depends on the specific histopathology and absence of a primary lesion in the nasopharynx; the pathology of LELC is identical to that of NPC. Therefore nasopharyngeal examinations or radiographic studies should be performed to exclude metastatic LELC from the nasopharynx. In our study, LMP1 immunohistochemical stain for EBV infection was positive in 4 of our patients. EBV can be detected by polymerase chain reaction for EBV DNA, ISH for EBV DNA and RNA, and immunohistochemistry for EBV-associated protein; detection of EBV-encoded small RNA (EBER) is considered to be the standard method of late [3,6,9]. In a previous study, almost all EBV-positive cases oc-

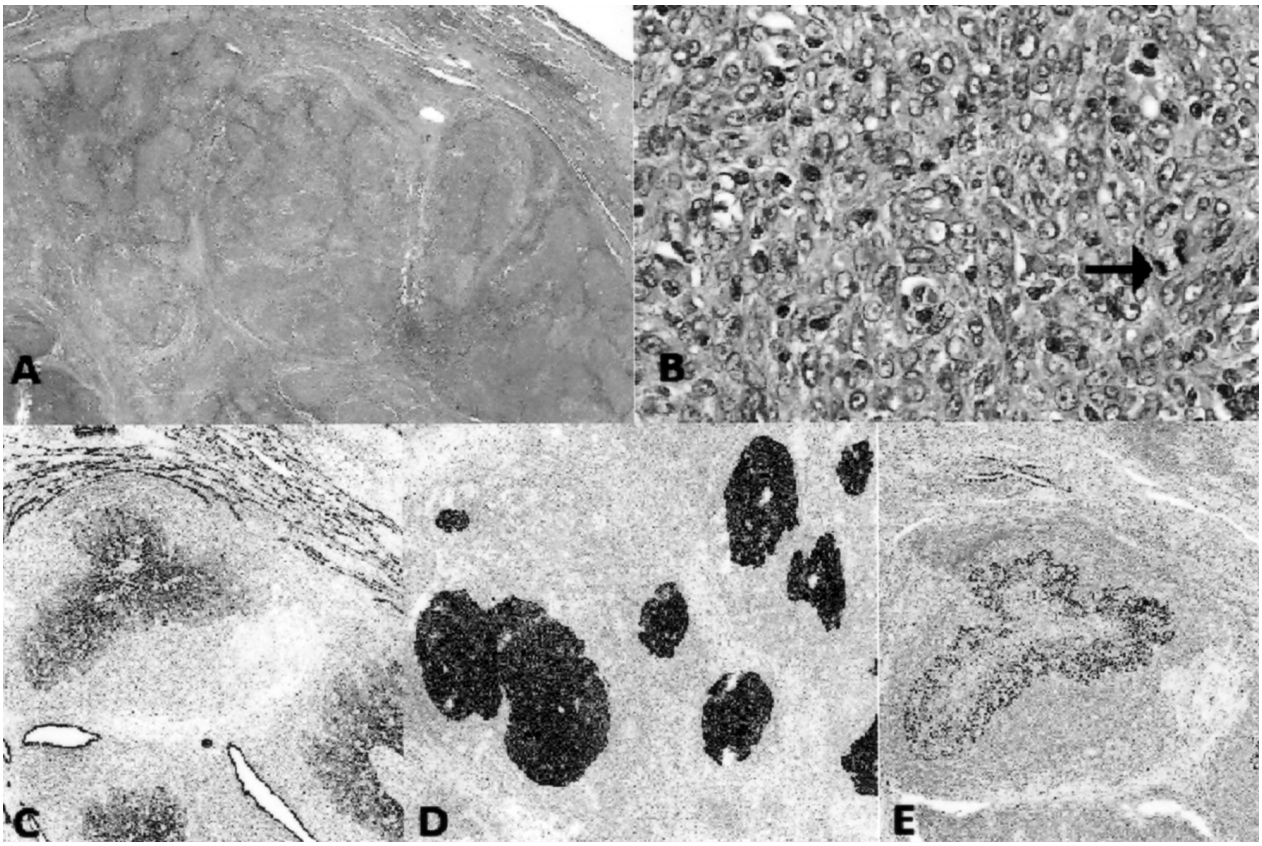

Fig. 3. The typical pathologic features of LELC presented in patient No. 4. (A) Low-power (10x) photomicrograph of H&E stain showed undifferentiated tumor nests surrounded by diffuse lymphoid infiltration. (B) The large tumor cells showed prominent vesicular nuclei. The typical characteristics of malignant cells, including mitosis (arrow) are shown in a high power field (200x). (C-E) The tumor cells showed positive immunoreactivity for (C) cytokeratin (AE1/AE3), (D) cytokeratin 5/6 and (E) p63.

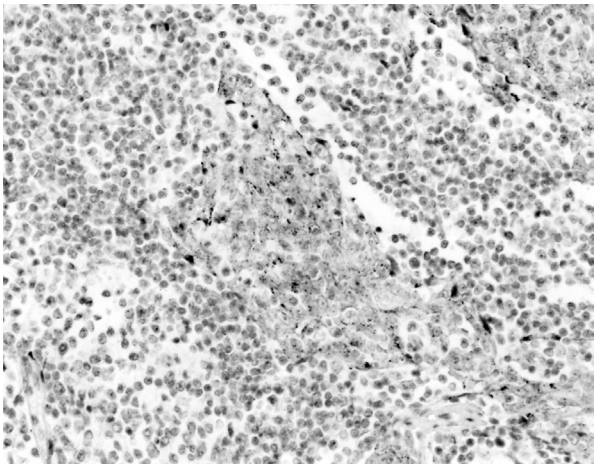

Fig. 4. The EBV LMP1 immunohistochemical stain was positive in patient No 2.

curred in Asian patients and all negative cases occurred in patients of other races [3]. EBV detection in tumor cells may offer information to confirm the diagnosis of LELC in Asian patients. Thyroid transcription factor-1 (TTF-1) is not a good diagnostic marker to differentiate primary or metastatic LELC, since the positive rate in primary pulmonary LELC was 20% in a previous study [6].

The prognosis of primary pulmonary LELC is much better than that of NSCLC. In our study, 2 patients with stage IA received surgery and remained disease-free during a mean period of 5.5 years. Chemotherapy or radiotherapy

was administered to the patients with stage IIA or IIIA disease and all were in a disease-free status during follow-up. Although the exact regimen of chemotherapy to be used in primary pulmonary LELC is still controversial, tumor behavior is relatively more chemosensitive and radiosensitive, as in previous results [4].

Conclusion

Primary pulmonary LELC is a distinct clinicopathological entity in NSCLC. It is often diagnosed in asymptomatic and younger non-smokers without gender predilection. Primary pulmonary LELC has histologic characteristics and EBV infection similar to NPC; it is usually diagnosed as early disease and has a good response to chemotherapy and radiotherapy, with a better prognosis.

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原發性類淋巴上皮細胞肺癌－五個馬偕醫院案例經驗

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原發性類淋巴上皮細胞肺癌屬於一種非常罕見的非小細胞肺癌，且大部分發生在南亞地區。Begin 在 1987 年首次發表這種疾病，原發性類淋巴上皮細胞肺癌與鼻咽癌有相似的病理特徵，且在亞洲地區是和 EB 病毒的感染相關。

從 1991 年 1 月至 2013 年 12 月期間，馬偕醫院總共診斷 5 個原發性類淋巴上皮細胞肺癌的個案。其中 3 名個案沒有症狀為影像學上的意外發現，其中 4 名為非吸菸者，沒有個案診斷時為晚期肺癌（2 名個案是 IA 期、2 名為 IIA 期、1 名為 IIIA 期）。典型的電腦斷層影像為單個大小不一、靠近中央的腫瘤；而典型的病理表現為層狀生長的腫瘤細胞，外圍環繞淋巴漿細胞，其中 4 名個案的病理檢體的 EB 病毒染色呈陽性反應。5 名個案皆對於多種治療效果良好，在追蹤 10 到 93 個月後無惡化。

原發性類淋巴上皮細胞肺癌大部分發生在無症狀、較年輕的非吸菸者，且無性別相關性。這個疾病和 EB 病毒有關聯性，且與分化不全型鼻咽癌在臨床上和生物特性上相類似。案例皆診斷於早期、可手術切除，且對於化學或放射治療反應良好。*(胸腔醫學* ***2015; 30: 171-177)***

關鍵詞：原發性類淋巴上皮細胞肺癌，EB 病毒

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Spontaneous Hemothorax Caused by Ruptured Right Subclavian Artery in a Patient with Neurofibromatosis Type 1

Shun-Ying Yin, Tzu-Ping Chen*, Chi-Hsiao Yeh*

Spontaneous hemothorax is a rare but life-threatening condition. Vascular manifestations of neurofibromatosis type 1 (NF1), or Von Recklinghausen disease, are rare, but may be fatal if they are disrupted. We report the case of a 37-year-old woman with NF1 who developed a spontaneous right massive hemothorax caused by a branch of the right subclavian artery. We successfully performed direct surgical ligation of the bleeding vessel, and the patient's recovery was uneventful. Spontaneous hemothorax in patients with NF1 is a life-threatening condition and may require emergency surgery or endovascular embolization/stenting, depending on the hemodynamic status. ***(Thorac Med 2015; 30: 178-182)***

Key words: spontaneous hemothorax, neurofibromatosis

Introduction

Spontaneous hemothorax is a rare but life-threatening condition. Neurofibromatosis type 1 (NF1), or Von Recklinghausen disease, is an autosomal-dominant disorder caused by an abnormality of the long arm of chromosome 17. The common clinical features include cafe-au-lait spots, plexiform neurofibroma and other forms of neurofibroma, Lisch nodules, fleckling, optic nerve glioma, and abnormal bony lesions. This disease is associated with multi-organ involvement, primarily central nervous system involvement. However, vascular involvement, such as stenosis, occlusion, aneurysm, pseudoaneurysm, and rupture or fistula formation in small, medium, and large arteries is rare. We report a case of spontaneous hemothorax caused by rupture of a branch of the right subclavian artery

Case Report

A 37-year-old woman with a medical history of NF1 was awakened from sleep by severe chest pain and dyspnea. She was sent to our emergency department. On arrival, GCS was E2V1M4, and blood pressure was 75/54 mm Hg with a tachycardia of 117 beats per minute. Respiratory rate was 22 breaths per minute and oxygen saturation was not recordable. Chest

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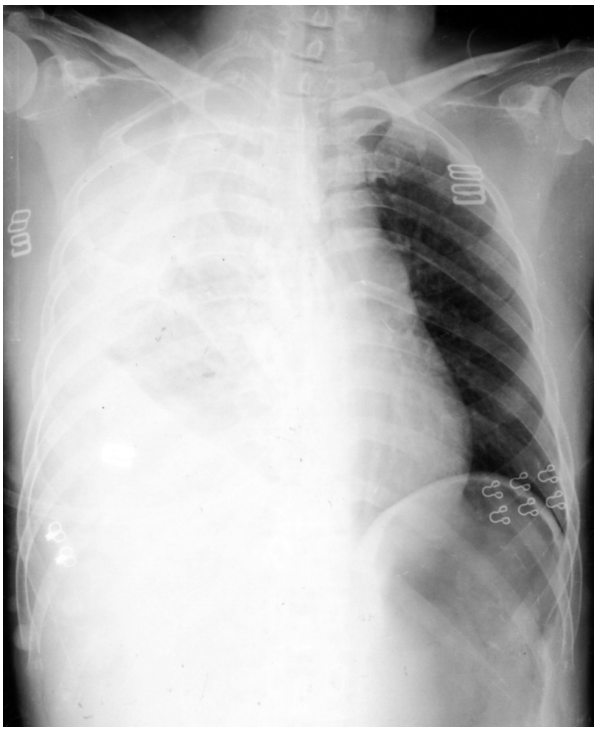

Fig. 1. Right hemithorax opacification, consistent with hemothorax.

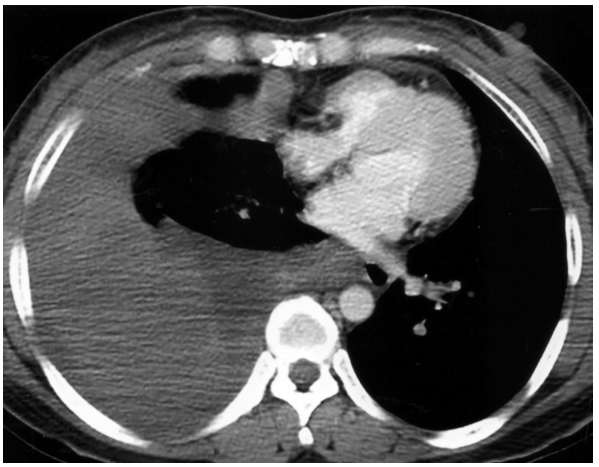

Fig. 2. Tension hemothorax, pulmonary hemorrhage was favored.

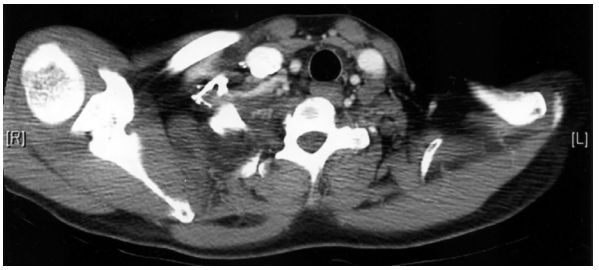

Fig. 3. Injury to the right subclavian artery was highly suspected.

expansion was asymmetrical. Initial blood tests revealed hemoglobin of 8.6 g/dl, platelets of $346\times10^3/\mu L$, and normal coagulation. Arterial blood gas analysis showed metabolic acidosis. Chest roentgenogram revealed right hemithorax opacification, consistent with a hemothorax (Figure 1). A chest tube thoracostomy was done and bright red blood was drained. The appearance on an initial computed tomography (CT) scan was interpreted as tension hemothorax, so pulmonary hemorrhage was favored (Figure 2). The mediastinal vessels were intact. No source of bleeding was identified. After ongoing losses, the patient deteriorated, requiring intubation and resuscitation. The chest tube was clamped, and continuous blood transfusion and fluid resuscitation were required to maintain adequate blood pressure. Angiography was considered, but further hemodynamic deterioration necessitated transfer to the operating room for thoracotomy and exploration. Emergency exploratory right thoracotomy was indicated because of persistent bleeding and clinical instability. After thoracotomy, a massive 3 liter blood clot was evacuated. There was persistent oozing from the apex of the right hemithorax, but no obvious bleeder was identified. The CT was re-read and injury to the right subclavian artery was highly suspected (Figure 3). Right lower neck exploratory was performed, and the bleeding site was identified as a disruption of a branch of the right subclavian artery. Multiple attempts at primary suture repair were made, but due to its extreme friability and brittleness, the artery was divided and ligated. The postoperative course was unremarkable and the patient was discharged 1 week later. On pathologic examination, dissec-

tion of the arterial wall was noted.

Discussion

Vascular involvement in the setting of NF1 is well described. An incidence of 3.6% has been reported, and case reports indicate both large and small vessel involvement, including the abdominal aorta, brachial, and most commonly, renal arteries [1]. Two main pathologies of vascular weakness in NF1 have been advanced, including mesodermal dysplasia and direct vascular invasion from adjacent tumors such as schwannoma, neurofibroma, or neurofibrosarcoma as the reasons for the loss of vascular integrity and rupture [2]. For large vessels, the aneurysm formation is secondary to the direct invasion of the vessel wall by neurofibroma tissue, compressing the vasovasorum with resultant wall weakness, leading to ischemia [3]. In small vessels, dysplasia in the wall with fibrohyaline thickening of the intima and muscularis causes stenosis and subsequent significant weakening and friability of the arterial wall [2]. Only 27 cases of spontaneous hemothorax or hemomediastinum have been reported in the literature [4-15]. The most common sites of bleeding are the intercostal and subclavian arteries; the thyrocervical trunk, internal thoracic artery, phrenic artery and left vertebral artery have also been documented as bleeding sites.

Spontaneous massive hemothorax is a life-threatening condition. In the past, emergency thoracotomy was the treatment of choice. In recent times, success with percutaneous embolization [7-9,11,13,15] and endovascular stenting [14] has been reported. These treatments are gaining in popularity because they are less invasive. One study reported that 7 patients were successfully treated with coil embolization, and only 1 patient died from re-bleeding [11]. However, another study [8] indicated that the overall mortality rate of NF1 patients with thoracotomy was 45%. Percutaneous embolization seems to yield a better prognosis than thoracotomy.

The treatment options for spontaneous hemothorax are dependent on hemodynamic stability. Instability mandates urgent surgical control of the intrathoracic hemorrhage after initial resuscitation. However, the vessels associated with NF1 are friable, making surgical control extremely difficult. In the present case, the hemodynamics of the patient were unstable on arrival, so percutaneous embolization or endovascular stenting was not favored as a first-line treatment of choice. Whenever a patient demonstrates reasonable stability, urgent angiography with percutaneous embolization or endovascular stenting presents a potential primary option for management, and thus far has demonstrated an outcome superior to surgery. Consideration must be given to prevention of this presentation given the likelihood of mortality. With improving CT angiogram capabilities, it is reasonable to consider surveillance for this group of patients, as vessels as small as intercostals are easily visualized. Any evidence of aneurysmal disease in the vessels of the thorax should be aggressively managed percutaneously by coil embolization or stenting to prevent future rupture.

In conclusion, spontaneous massive hemothorax in an NF1 patient is rare, but potentially life-threatening; in patients with stable hemodynamics, percutaneous embolization or endovascular stenting is an alternative treatment to surgery, due to its being less invasive and more effective. However, surgery should remain the first-line treatment in patients with unstable he-

modynamics or when percutaneous treatment is not successful.

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神經性纖維瘤病人因右側鎖骨下動脈破裂所引起的自發性血胸－病例報告

尹順盈　陳子平 *　葉集孝 *

自發性血胸是相當罕見但卻對生命造成危急的情況，在臨床上除了胸主動脈瘤破裂或是自發性氣胸因增生迷路血管斷裂會造成自發性血胸外，神經性纖維瘤第一型所引起的血管病變也有可能引起自發性血胸。本文提出一位患有神經性纖維瘤第一型的 37 歲女性，因右側鎖骨下動脈破裂造成的自發性血胸。我們直接利用手術的方式成功地將血管綁紮止血，而且病人術後恢復良好。現今的治療方式除了手術外還包括了血管栓塞以及血管支架置放；至於哪種方式較好還是要視病人當時的生命徵象來決定。*(胸腔醫學 **2015; 30: 178-182**)*

關鍵詞：自發性血胸，神經性纖維瘤

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Huge Posterior Mediastinum Liposarcoma – A Rare Case Report

Hung-Ling Huang*, Tai-Huang Lee*, Yi-Ting Chen**, Jen-Yu Hung*,***, Inn-Wen Chong*,****

We describe a 73-year-old women who presented with dyspnea and dry cough for 6 months. The chest radiograph showed a “water-bag” silhouette with widened mediastinum. The computed tomography (CT) of the chest revealed a huge posterior mediastinal mass with mixed soft tissue and fatty components, suggestive of liposarcoma. Biopsy of the lesion revealed spindle cell tumor composed of connective tissue with marked hyalinization. The patient agreed to surgery from the posterior mediastinum for complete resection. The pathological and immunohistochemical analysis confirmed the diagnosis of dedifferentiated liposarcoma. After complete resection, she had an uneventful recovery. Liposarcoma is the most common sarcoma in adults, but primary liposarcoma of the mediastinum is very rare. Mediastinal liposarcoma is often localized in the anterior mediastinum, and posterior invasion is extremely rare. The patient may present with subtle clinical symptoms until the mass reaches a giant size. Complete surgical resection remains the main treatment strategy for mediastinal liposarcoma. ***(Thorac Med 2015; 30: 183-189)***

Key words: mediastinal tumor, liposarcoma

Introduction

Liposarcoma is the most common malignant soft tissue cancer in adults, and accounts for approximately 15-20% of mesenchymal neoplasms [1]. It arises from adipocytes in deep soft tissue, from areas including the retroperitoneum, lower extremities, abdomen, vulva and buttocks. Primary mediastinal liposarcomas are rare, and account for less than 1% of mediastinal tumors. Most of them are found in the anterior mediastinum, and are usually derived from thymus-related fatty tissue [2-3]. Liposarcoma is a slow-growing tumor, and the symptoms are always subtle until it assumes a large size. It is classified into 5 subtypes histologically [4]. Dedifferentiated liposarcoma (DDL) has a mixture of well-differentiated liposarcoma (WDL) components and high-grade, non-lipogenic sarcoma components, and is most commonly seen

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in large tumors, particularly in the retroperitoneum. Herein, we present a rare case of primary DDL in the posterior mediastinum and review the current literature.

Case Presentation

A 73-year-old female non-smoker presented to our hospital with progressive dyspnea and nonproductive cough for 6 months. She reported a weight loss of about 10 kg during a period of 3 months, but denied having fever, chest pain, hemoptysis or gastrointestinal symptoms. She had a medical history of congestive heart failure and hypertension. She had no obvious history of respiratory disease, nor had she had a remarkable operation, occupation or travel history. Physical examination of the chest revealed symmetric expansion with inspiration, and dullness on percussion of the right hemithorax. Pulmonary auscultation revealed diminished breathing sounds in the right middle-to-lower thorax, and decreased fremitus and bronchophony in the right lung field up to the mid-scapular area. The remainder of the examinations were normal.

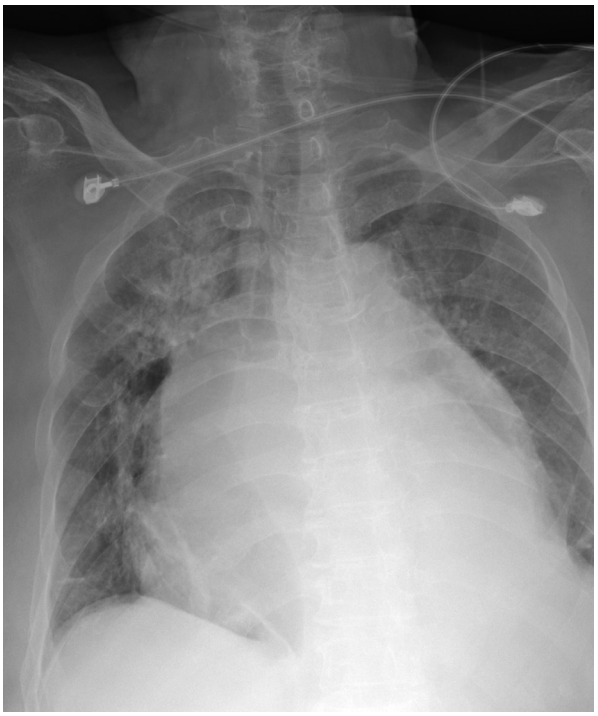
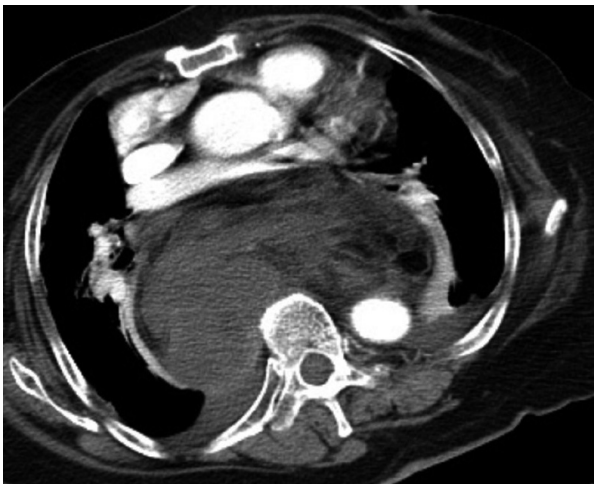


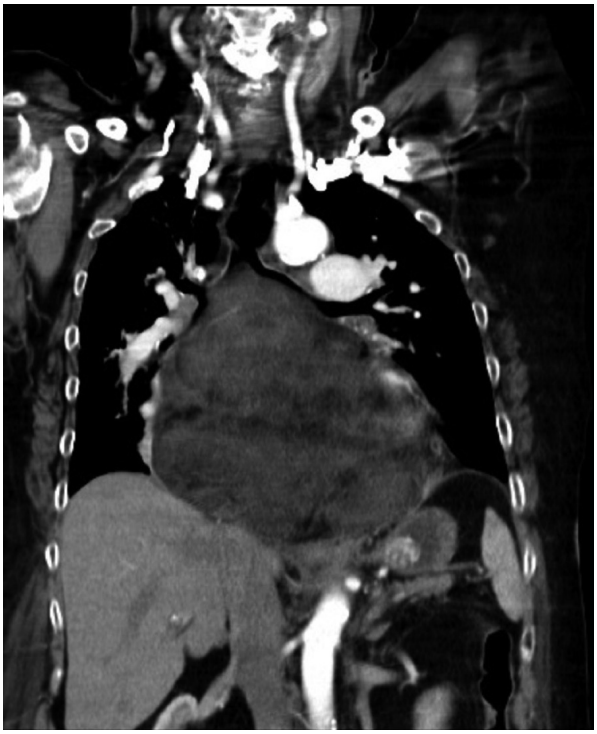
Fig. 1. Chest radiograph revealed an opaque lesion occupying 2/3 of the right hemithorax with positive silhouette signs against bilateral cardiac borders and hila, resulting in a water-bottle-like silhouette with a widened mediastinal shadow. Passive atelectasis in adjacent portions of bilateral lungs was also seen. There was no mediastinal shift or tracheal deviation; the right costophrenic angle was spared and the right hemi-diaphragm was normal. These findings indicated a huge, homogenous mass in the mediastinum.

The chest radiograph (Figure 1) showed a huge, homogenous mass in the mediastinum. The tumor markers, including carcinoembryonic antigen, squamous cell carcinoma antigen, tissue polypeptide antigen, α-fetoprotein, and human chorionic β-gonadotropin, were all within normal range. Contrast-enhanced computed tomography (CT) (Figure 2) revealed a huge posterior mediastinal mass with mixed soft tissue and fatty components, suggestive of liposarcoma; displacement of the heart and esophagus was also noted. A CT-guided fine needle aspiration was performed, but the biopsy specimen obtained from the mass revealed spindle cell tumor composed of connective tissue with marked hyalinization. Neither hypercellularity, nuclear atypia, nor necrosis was identified.

She underwent further tumor resection from the posterior mediastinum through a median sternotomy and intercostal incision. A huge yellowish encapsulated lobulated tumor, measuring 15×15×9 cm and 930 grams in weight, was noted. The cut section of the mass was yellow to tan-gray in gross appearance (Figure 3A and 3B). In the microscopic examination, sections showed combined WDL and non-lipogenic high-grade sarcoma. Presence of adipocytic nuclear atypia and hyperchormasia was identified in the WDL area (Figure 4A and 4B). Hyper-

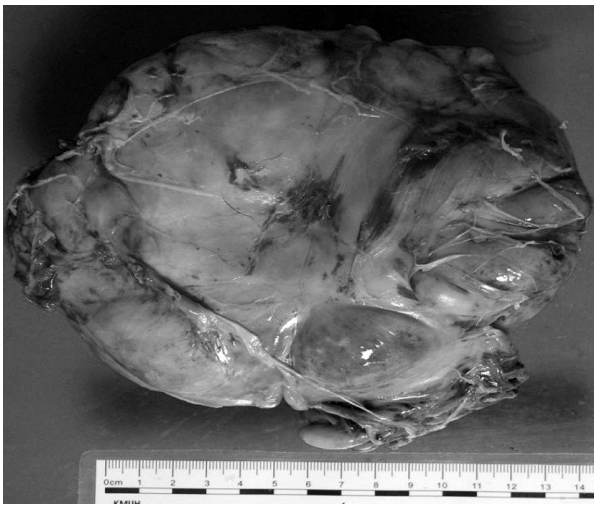


(A)

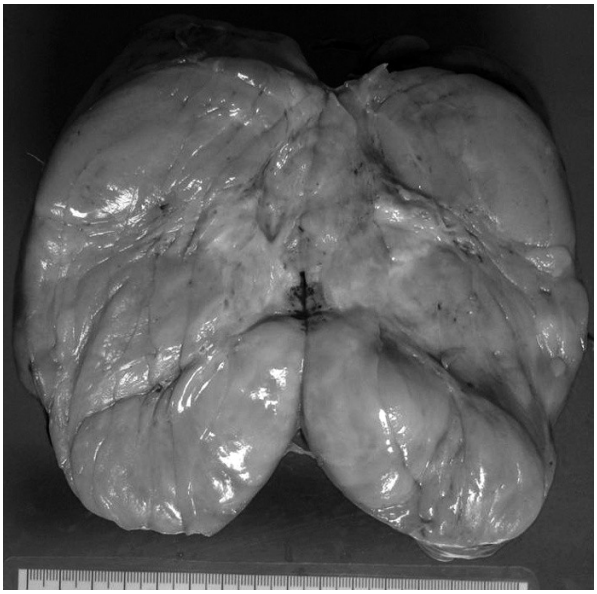


(B)

Fig. 2. (A) Computed tomography (CT) revealed a huge inhomogeneous low attenuation (average CT number of about -80 HU) mass in the posterior mediastinum, composed of mixed soft tissue and fatty components. The huge tumor compressed and distorted the heart, bilateral lung, trachea and esophagus. Lymphadenopathy in the paratracheal region and bilateral axillae was also noted (not shown). (B) Coronal reformation showed the extent of the huge mass occupying the entire posterior mediastinum and parts of both hemithoraxes.



(A)



(B)

Fig. 3. Gross pictures of the tumor obtained from wide excision. (A) A huge encapsulated lobulated tumor measuring 15×15×9 cm and 930 grams in weight was excised. (B) The cut surface of the mass showed a lobulated pattern, yellow to tan-gray in color.

cellularity of undifferentiated spindle or pleomorphic cells was also revealed focally (Figure 4C and 4D). The tumor cells were immunoreactive for p16 and MDM2 immunostains (Figure 4E and 4F). The final diagnosis was DDL, histologic grade 2 (French Fédération Nationale

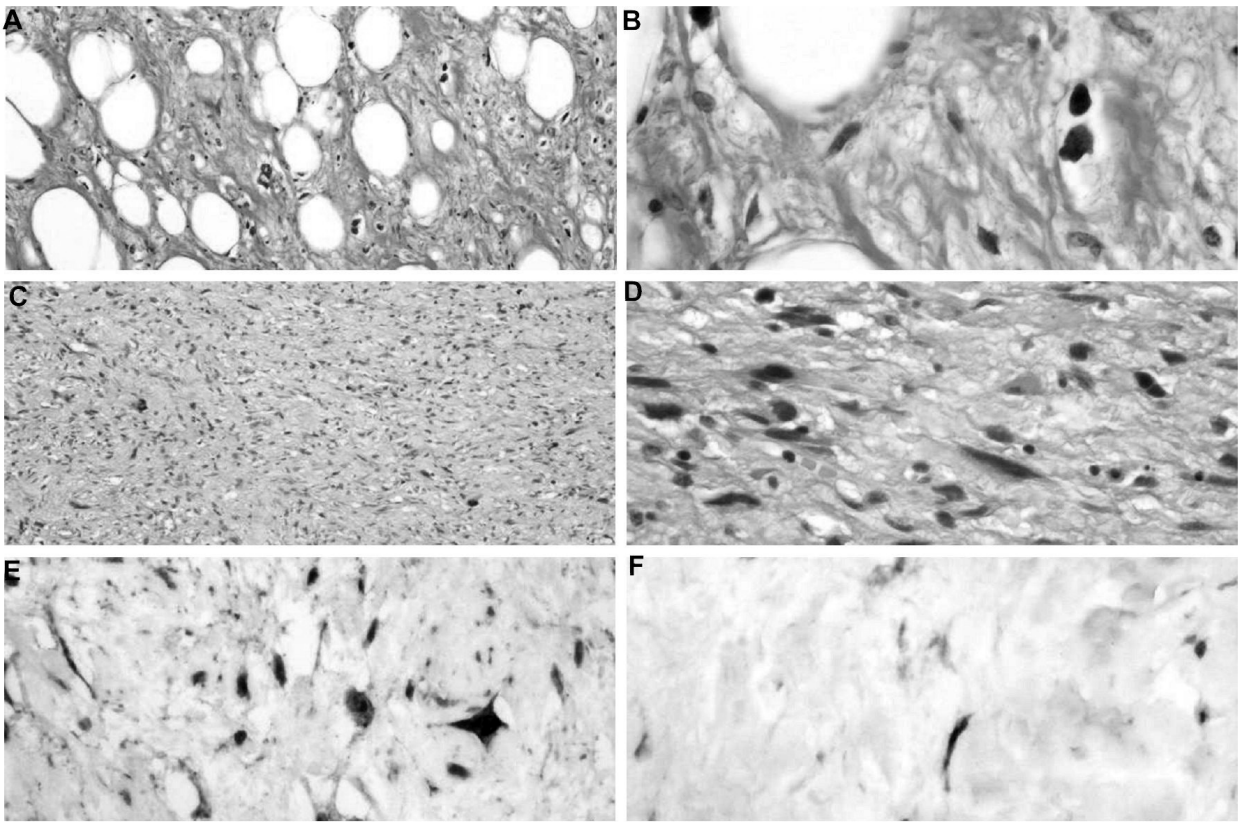


Fig. 4. Microscopic findings of tumor wide excision. (A) Showing variable-sized adipocytic proliferation with focal cellular atypia. (200×) (B) Presence of atypical and hyperchromatic cells was identified. (400×) (C) Hypercellular non-lipogenic area was seen. (100×) (D) Foci revealed undifferentiated hyperchromatic spindle or pleomorphic cells. (400×) The tumor cells were immunoreactive for p16 (E) and MDM2 (F) immunostains. (400×)

des Centres de Lutte Contre le Cancer (FNCLCC system). The patient's postoperative course was uneventful with no evidence of recurrence.

Discussion

Liposarcoma, first described by Virchow in the 1860s, is a rare malignancy of mesenchymal origin, arising from adipocytes. It is the most common soft tissue sarcoma in adults, accounting for up to 18% of all soft tissue sarcomas. It normally appears as a slowly enlarging, painless, non-ulcerated sub-mucosal mass, and has a peak incidence from age 50 to 70, with equal gender distribution.

The World Health Organization classifies liposarcomas into 5 subtypes based on their different histopathological characteristics: (1) well-differentiated (lipoma-like), which includes the adipocytic, sclerosing, and inflammatory subtypes; (2) dedifferentiated; (3) myxoid; (4) round cell; and (5) pleomorphic. Different subtypes have different prognoses. DDL is the most aggressive subtype, with higher local recurrence rates, potential metastases to the liver or lung and higher mortality rates [4-5].

Liposarcoma has a wide anatomical distribution, and is encountered mostly in deep

muscle tissues of the extremities and retroperitoneum [6]. Primary mediastinal liposarcoma is very rare, and accounts for only 0.13-0.75% of all mediastinal tumors [1,7]. They always present as insidiously growing tumors. Mediastinal liposarcomas are often in the anterior mediastinum, and most are reported to originate from thymus-related fatty tissue [2-3,8-9]; a posterior mediastinal origin is relatively rare.

As an insidiously growing tumor, mediastinal liposarcoma may extend into the pleural space and achieve a large size before detection. Some might be asymptomatic and be discovered accidentally by radiological imaging. Others may be symptomatic, depending on the size and extent of direct invasion to contiguous structures, such as the pericardium and superior vena cava. Commonly presenting symptoms include dyspnea, wheezing, cough, chest pain and weight loss [1,5,7-8].

Plain films usually show nonspecific findings, whereas CT and magnetic resonance imaging (MRI) may be more informative. CT is important to evaluate the size and content of liposarcoma. CT also contributes to clarifying surgical options by detecting the involvement of surrounding organs and vasculature. The CT appearance of lipomatous tumors depends on the adipose components. Normal fat shows low attenuation with a CT number of -70 to -130 HU. DDL has relatively higher attenuation, similar to solid tumors, due to its abundant non-adipose component and occasional calcified content [10-11]. Imaging characteristics, enhancement patterns and demographics can provide the differential diagnosis of soft tissue tumor only to a certain extent, rather than identify the tumor type.

Distinguishing between normal fat, lipoma, WDL and DDL is a diagnostic challenge, due to the marked histological similarities. A histopathological examination is required to confirm the definite pre-operative diagnosis. The immunohistochemical trio of p16, MDM2, and CDK4 has been determined to be a useful ancillary diagnostic tool to distinguish liposarcoma from other adipocytic neoplasms [12-13].

The clinical behavior and prognosis of liposarcoma correlates with its histological pattern. Those that are poorly differentiated are often highly aggressive in behavior, which accounts for the high incidence of local recurrence and distal metastases [1-2,8].

Due to the rarity of these tumors and the complexity of treatment, no treatment guidelines are available to date. Surgery with complete excision of the tumor is considered as the only potentially curative treatment for mediastinal liposarcoma; however, some surgery is performed to alleviate complications secondary to displacement and invasion of adjacent vital structures. The role of chemotherapy and radiotherapy is controversial. Adjunctive radiation therapy is generally reserved for poorly differentiated, unresectable and recurrent tumors. For patients with retroperitoneal liposarcoma, radiotherapy reduces the risk of local recurrence but does not improve overall survival; however, its role in mediastinal liposarcoma is unclear [14-15]. The benefit of adjuvant chemotherapy following surgical resection of a soft tissue sarcoma at any site is controversial [16].

The recurrence rate mainly depends on the histological subtype and the safety margin of the surgical resection. Recurrence is seen in approximately 40% of cases, and some recurrence has been reported 10 years after the initial surgical treatment. Local recurrence is much more than distant metastases [2-3,8,17]. Complete surgical resection at the initial diagnosis

was considered the most important prognostic factor for survival [2-3] However, Hejin *et al*. reported a high local recurrence rate in all DDL and pleomorphic liposarcoma, whether they had positive or negative margins; none of the WDL recurred within the follow-up period, even those with positive margins. Therefore, the histological subtype might predict the prognosis better than a clear surgical margin does [8].

In conclusion, we reported a rare case of giant primary liposarcoma arising from the posterior mediastinum. Although histological subtype may predict the prognosis, a timely diagnosis and complete surgical resection remain factors that contribute to a better outcome.

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巨大的後縱膈腔脂肪肉瘤－一個罕見病例報告

黃虹綾 * 李岱晃 * 陳怡庭 ** 洪仁宇 *,*** 鍾飲文 *,****

我們在此報告一個病例：七十三歲女性，主訴喘及乾咳長達六個月，胸部 X 光片發現疑似心包膜積水，但經胸部電腦斷層檢查後發現一巨大腫瘤位於後縱膈腔中，判斷由脂肪成分組成，手術切片檢查發現此腫瘤為一 dedifferentiated liposarcoma。經手術治療後腫瘤完全緩解，並已在門診追蹤超過一年。縱膈腔之脂肪肉瘤為非常罕見之病例，目前已發表的案例報告大多數發生於前縱膈腔，此病例則發生於後縱膈腔中。此外，回顧這些文獻報告，大多數病人一開始並無明顯特異之臨床症狀，待檢查發現時之縱膈腔脂肪肉瘤大多非常巨大。手術治療是目前認為最適合之方法，大部分經過手術切除後的預後大致上都不錯，化學治療及放射線治療的角色目前並不顯著。*(胸腔醫學 **2015; 30: 183-189**)*

關鍵詞：縱膈腔腫瘤，脂肪肉瘤

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致讀者：

發表於本刊 2015 年 4 月三十卷第二期 (Vol.30 No.2) 之文章“Disseminated *Mycobacterium avium* complex Disease in an Immunocompetent Patient: A Case Report”一文，內文中 Discussion 第一段第二行 MAC 更正為 *Mycobacterium tuberculosis* complex，特此說明。

胸腔醫學投稿需知

1.本雜誌以提升胸腔醫學為主要宗旨，有關胸腔醫學之教育性文稿與活動報導均為刊登對象，但以未曾刊登於其他學術雜誌者為限。
2.來稿經審查委員審查通過後刊登，內容及撰寫方式若不合要求，本刊有權修改或拒絕刊登。來稿一經刊載，著作權即為本刊所有，未經本刊編輯委員會之書面同意，不得以任何方式轉載於其他出版刊物。
3.文稿之性質分原著、病例報告、綜覽、簡報、其他。
4.原稿以英文撰寫。文中（包括表）行距應為兩倍行高。論文題目、Running Title以及圖（Figure）、表（Table）標題除介詞和定冠詞外之第一字母以大寫打字。另須附中文簡錄（需含中文題目、中文著者姓名、中文摘要、中文關鍵字以及中文通訊作者之聯絡資料），其中英文及括弧內之英文對照，除專有名詞外一律小寫。
5.原著應按下列順序書寫：第一部分包括題目、作者、研究單位、通訊作者之聯絡資料、簡略題目（Running Title)。第二部分為摘要、關鍵字（Key word）。若投稿為原著，摘要部分須簡略呈現包括：Introduction、Methods、Results、Conclusion。第三部分為本文（前言、材料、方法、結果、討論、結論）、誌謝、文獻、圖表、及中文摘要。論文內容以Times New Roman 12號字體撰寫。中文摘要的寫法亦依照：前言、方法、結果、結論等分段繕打。
6.數字除英文句首外，請以阿拉伯數字書寫，度量衡單位應使用國際單位系統符號，即cm, mm, ml, dl, g, mg, mm^3等。PO_2請用mmHg為單位。其他符號縮寫應參考IUPAC-IUB Document No. 1 (Arch Biophys 1966; 155: 1-12)。
7.圖片的格式請以JPG、JPEG為主，且解析度需300dpi以上。
8.表（Table）：請分別繕打於各別的稿紙，每張表附以簡短標題，以註腳在表下方解釋表中資料，註腳所用符號須按下列順序：*，$^{+}$，$^{\mp}$，II，π，**，$^{\mp\mp}$，……。表內不要有直線。
9.術語用法：縮寫及簡稱應在第一次使用時先用全文，後加簡寫如：nasopharyngeal cancer（NPC），然後才直接使用於其後之正文中。草藥名稱及草藥辭彙須為慣用語、藥學名、植物學名或漢方學名（若為處方則字首須大寫）。漢方醫學名詞須於文中定義或加附說明，針灸術相關名詞則須以世界衛生組織（WHO）所認可之標準針灸術語（Standard Acupuncture Nomenclature）為撰寫依據。
10.投稿需附「胸腔醫學投稿聲明書」，說明所有著者均詳細閱讀並簽名同意投稿刊登。
11.依據行政院農業委員會實驗動物倫理委員會九十一年度第一次委員會議決議，本雜誌擬刊登之論文，其中如涉及使用脊椎動物進行科學應用計劃者，撰稿者於投稿時應檢附該計劃（自九十二年度開始實施之計劃）業經所屬機構動物實驗管理小組審議認可之文件，以落實實驗動物之人道管理。
12.參考文獻按引用的先後順序排列，在本文引用時，以阿拉伯數字括號〔 〕表示於引用之後方，原著參考文獻不宜超過30個。其撰寫方法如下：
    (1) 期刊請依「作者姓名：篇名。期刊名稱，出版年代；卷數：起訖頁數」。
    (2) 書籍請依「作者姓名：篇名，編者姓名，書名，版次，出版地，出版商，出版年代；起訖頁數」。
    (3) 作者在3人以上時，僅列3名作者姓名，其餘以*et al*表示。
    (4) 期刊名稱之縮寫：請參考Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Steering Committee, Ann Intern Med 1979; 90: 95-99。

範例：

(1) 楊思標、林吉崇、吳敏鑑等：台灣肺癌之盛行調查。台灣醫誌1976; 75: 429-39。
(2) Barach AL The adaptive function of hypercapnia. In: Petty TL ed. Chronic Obstructive Pulmonary Disease. New York; Marcel Dekker, 1978: 151-62。（引用有編輯者之單行本）
(3) Anonymous. Neurovirulence of enterovirus 70 [Editorial]. Lancet 1982; 1: 373-4。（引用文獻之作者無記名時之例子）。
(4) I to S, Senda Y, Torii Y, *et al*. Clinical study of aspiration pneumonia. Respir Res 1987; 6: 1247-53. [In Japanese English abstract]（引用文獻本文非英文，但有英文摘要）
(5) Tsai CM, Perng RP, Huang WL, *et al*. Lung cancer in young adults [Abstract]。3rd World Conference on Lung Cancer. Tokyo, 1982: 31（引用學會摘要專集中摘要）

★自104年二月份起，線上投稿系統正式啟用。相關訊息請參閱學會網頁(http://www.tspccm.org.tw/)或與編輯部聯絡(06-2353535轉5401余小姐)，謝謝。

★自104年六月份起，紙本期刊將改為電子期刊，論文一經接受刊載，請自行登入投稿系統下載該篇電子檔；若有論文下載需求者，亦可至學會網站(http://www.tspccm.org.tw/)搜尋。