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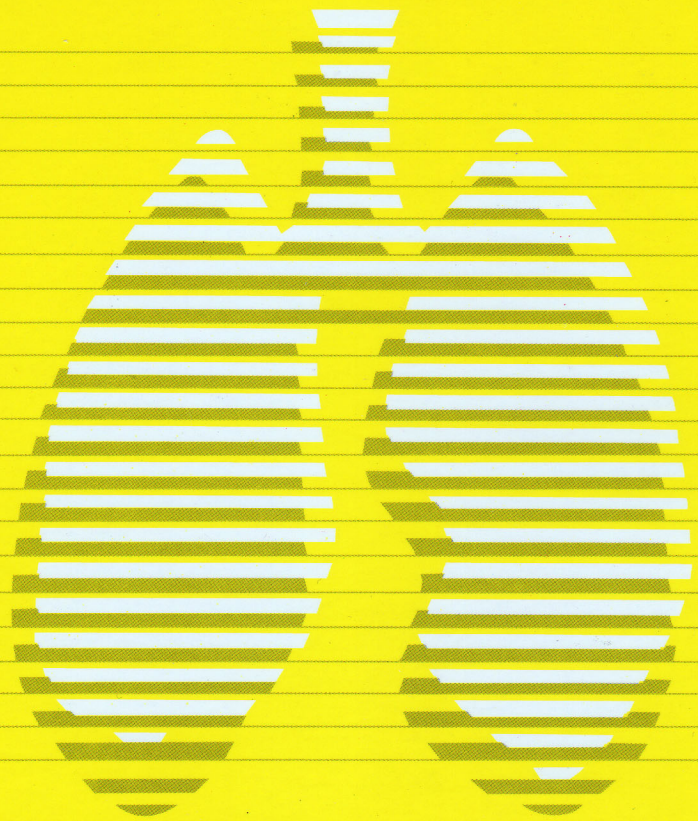

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Orginial Articles

Case Reports

Effects of Mishandling of Inhalers on the Management of Asthmatic Patients

Ying-Hao Huang, Yu Sophie Wang*, Jeng-Shing Wang**, Shih-Min Chen

Introduction: Incorrect usage of inhaler devices might have a major influence on the clinical effectiveness of the delivered drug. The objectives of this study were to assess the effect on patients with asthma of using an incorrect technique with established inhalers, to highlight the common errors observed in inhalation techniques and to discuss implications for clinical efficacy.

Methods: First, recruited patients completed a standardized questionnaire; each questionnaire consisted of a general section and specific parts, each related to a specific inhaler. Then, each patient demonstrated for the investigator their inhalation technique with all devices in a quiet area, using a placebo device.

Results: We collected 100 records of the inhaler usage technique of asthmatic patients. At least 1 critical mistake was made by users of each of the inhalers, ranging from 19% for Evohaler®, 19% for Accuhaler®, and 29% for Turbuhaler®. There were significant differences between inhaler misuse and older age (p=0.01), few years of education (p=0.01) and lack of instruction or checking up on inhaler technique by healthcare professionals (p=0.03). Inhaler misuse was associated with increased risk of hospitalization (p<0.001), emergency room visits (p<0.001), courses of oral steroids (p<0.001) and antimicrobials (p<0.001) and poor disease control as evaluated by the Asthma Control Test (ACT) score for asthma (p<0.001).

Conclusion: Inhaler mishandling continues to be common among experienced outpatients referred to chest clinics and is associated with increased unscheduled healthcare resource use and poor clinical control. Instruction by healthcare professionals may be a modifiable factor useful in reducing inhaler mishandling. ***(Thorac Med 2015; 30: 1-8)***

Key words: asthma control test, asthma, inhaler

Introduction

Inhalation of drugs is the major therapy for obstructive lung disease [1-2]. Inhalation is the principle route for effective administration of medication for asthma. Pressurized metered

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dose inhalers (pMDIs) and dry powder inhalers (DPIs) are the devices most commonly used for treatment of asthma. DPIs have been developed without the need to coordinate inhalation and actuation [3-4], but they require loading before inhalation as they are breath-actuated [1,3].

The effectiveness of inhaled drugs can be influenced by many factors, including age, sex and educational level of the patient, duration of disease, type of inhaler used, correct inhalation technique or the use of several inhalers [5-9]. Many elderly people have a poor inhalation technique because of arthritis, weakness or impaired dexterity or vision [10]. A correct inhalation technique plays a vital role in effective asthma therapy [11]. Incorrect usage of inhalers is a significant problem for asthma management because it may result in a diminished therapeutic effect, poor control of symptoms and insufficient disease management [5-7,12-13].

It has been shown that up to 85% of patients do not use their inhalers correctly [9,14-15]. Both pMDIs and DPIs are complicated to use, some requiring up to 8 steps for a correctly performed inhalation maneuver [16]. To acquire the skills, healthcare professionals and patients must be adequately educated and trained [17-18]. Management of asthma might improve with devices that are easy to use correctly and have feedback mechanisms confirming correct inhalation and assured drug delivery [11].

The objectives of this study were to evaluate the inhalation technique of outpatients referred to chest clinics, to investigate the factors associated with inhaler misuse, and to assess the relationship between inhalation technique and some clinical outcomes.

Materials and Methods

This retrospective study of asthma patients aged more than 20 years was performed from August 2012 to July 2013 in a rural teaching hospital. Patients with inhaler therapy use at least once daily for 4 weeks in the 3 months before enrollment were included. Medical records were reviewed when all inhaler devices of interest were available. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the ethics committee of the participating hospital.

Patients completed a standardized questionnaire; each question consisted of a general section and specific parts, each related to a specific inhaler (a medium resistance DPI (Accuhaler), a medium/high resistance DPI (Turbuhaler), and a pMDI (Evohaler)). The general and specific sections each included a self-reported and an investigator-reported part. The self-reported general section included questions, which, after gathering some demographic information, investigated clinical data related mostly to respiratory disease control. Since asthma is a fluctuating respiratory disease, we included the Asthma Control Test (ACT) in the last month [19]. Patients were also asked about unscheduled medical interventions, such as visits to an emergency room, hospital admissions, antimicrobial treatments, and corticosteroid use, due to their respiratory disease in the last year. Each specific self-reported part included queries about the use of inhaled treatment, and the source and the modalities of education regarding the inhalation technique used. The physician-reported part evaluated the primary respiratory diagnosis, the baseline oxyhemoglobin saturation while breathing air at rest, the prescribed inhaler devices and the drugs used. Subjects underwent spirometry, performed and reported according

to accepted guidelines [20].

Each patient demonstrated to the investigator their inhalation technique with all devices in a quiet area, using a placebo device. Patients were asked to use their aerosol just as they would at home. Investigators were blinded to the results of the self-administered questionnaire when recording the mode of inhalation. All observations of inhaler use were reported in accordance to a standardized device checklist described in the questionnaire. We chose to focus the analysis of results on critical errors (Table 1) that were likely to render aerosol therapy useless, according to previous literature [21].

Analysis of the data was done using Microsoft® Office Excel 2007 (Microsoft, Santa Rosa, CA, 2007) and a Statistical Package SPSS18 (SPSS, Chicago, IL, 2009) with a personal computer. The Student's *t*-test was used for 2-group comparisons. The Chi-saquare test was performed to assess differences in categorical variables. A p value <0.05 was considered to be statistically significant. Continuous variables were expressed as mean±SD unless otherwise specified.

Results

We recruited 100 patients, and there were no significant differences in their clinical characteristics (Table 2). Mistakes were widely distributed among users of all the inhalers (Table 1). At least 1 critical error in the use of the Evohaler®, Accuhaler®, and Turbuhaler® respectively, was observed for 19%, 19%, and 29% of users. There were significant differences between patients with at least 1 critical error and those without an error in term of age, schooling, instruction, and check-ups (55±14 vs. 50±14 with p=0.01, 9±3 vs. 13±3 with p=0.01, 3±1 vs. 4±1 with p=0.03, and 1±1 vs. 2±1 with p=0.03). The patients with at least 1 critical error were older, and had few years of education, less instruction and fewer check-ups.

There was a significant difference between patients with at least 1 critical error and those without an error in their ACT score (p<0.001) (Figure 1), and the patients with at least 1 criti-

Table 1. Checklist of Proper Inhalation Technique and Errors Recorded (%)

Steps in inhaler use	Accuhaler (n=31)	Evohaler (n=48)	Turbuhaler (n=21)
Remove or turn cover#	0	0	5
[Load dose]	6	na	19
(Shake inhaler)	na	8	na
Hold inhaler upright	na	10	24
Breathe out the device	23	23	33
Inhale by mouth#	0	2	5
Place mouthpiece between lips#	3	2	10
[Forceful and rapid inhalation]#	19	na	29
(Actuation in inhalation)#	na	19	na
(Slow and deep inhalation)#	na	19	na
Breath-hold	23	21	33

[]: Dry Powder Inhalers - related step; (): Pressurised Metered Dose Inhalers - related step; #: critical error.

Table 2. Clinical Characteristics of Enrolled Patients According to Inhalers Used

Characteristics	Accuhaler (n=31)	Evohaler (n=48)	Turbuhaler (n=21)
Male, %	52	54	53
Age, years	51±14	50±15	52±13
School, years	12±4	12±3	12±3
Instruction, times	3±1	3±1	3±1
Check-up, times	2±1	2±1	2±1
BMI, kg/m^2	25.3±6.6	25.1±6.8	25.5±6.3
FEV_1/FVC, %	72±20	71±18	73±17
FEV_1, %	80±23	82±21	79±22

BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; FVC= forced vital capacity.

cal error had worse life quality. There were also significant differences in ACT scores among patients with at least 1 critical error and those without an error using each of the different inhalers. There was a significant difference between patients with at least 1 critical error and those without an error in unscheduled resource use (Figure 2); and the patients with at least 1 critical error had more unscheduled resource use. Inhaler misuse was associated with increased risk of hospitalization (p<0.001), emergency room visits (p<0.001), and courses of oral steroids (p<0.001) and antimicrobials (p<0.001). There were also significant differences in unscheduled resource use between patients with at least 1 critical error and those without an error using each of the different inhalers.

Discussion

Inhalation is the preferred method for administering drugs to asthma patients. Our study results indicate that inhaler mishandling remains a serious issue with currently available inhalers. Many patients did not receive proper training on inhaler use and the lack of this training by healthcare professionals increased the risk of misuse. The current busy clinical practice and the introduction of newer devices may possibly reduce the rates of inhaler education in real life.

The failure to achieve an ideal inspiratory flow through a device was the most common result of critical mishandling of inhalers in our series (Table 1), and the higher mishandling rate with the Turbuhaler® may be due to its position-sensitive loading. In this study, we observed associations between inhaler misuse and age, level of education and amount of instruction and checking-up on inhaler technique. We would like to stress the role of healthcare professionals in reducing inhaler mishandling, as it may be a modifiable factor. Training devices to optimize patients' breathing are easy to use and can measure the patient's inspiratory flow, so the inhalation technique can be learned quickly and be checked by a doctor or practicing nurse. Although these training devices are useful for training patients how to inhale through a device, they obviously do not teach patients how to hold, prime and position their inhaler

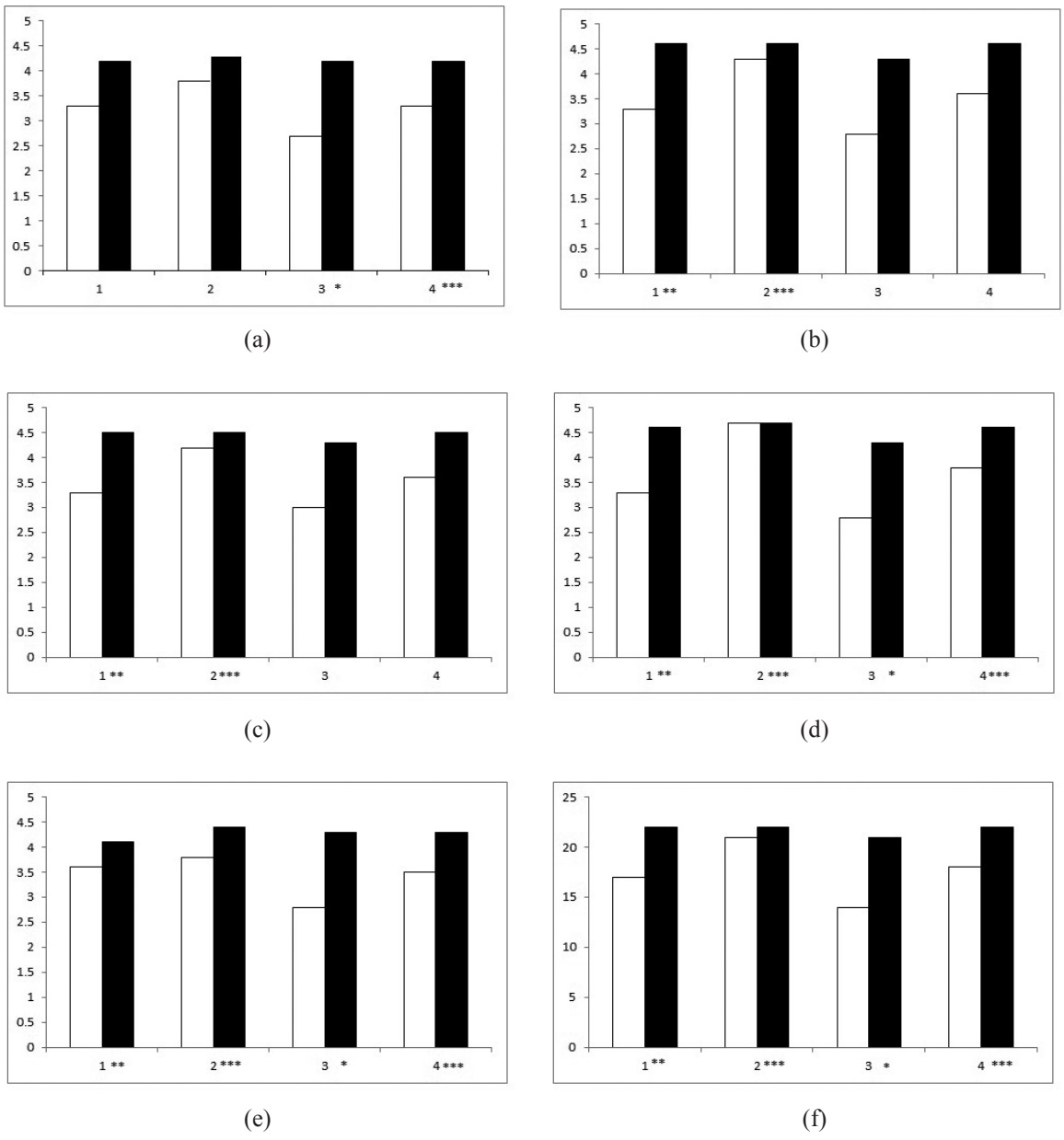

Fig. 1. Inhaler technique according to the Asthma Control Test. a, limited activity in everyday life; b, sleep disturbance; c, frequency of shortness of breath; d, use of rescue inhaler; e, rate respiratory disease control; f, Asthma Control Test. white bar = with at least 1 critical inhaler error; black bar = without a critical inhaler error; 1 = Accuhaler; 2 = Evohaler; 3 = Turbuhaler; 4 = Total inhaler; * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$.

for optimal benefit. To ensure correct advice is provided to patients, healthcare professionals should be well versed in how to operate the various devices used by their patients and they should have access to demonstration devices. Education for healthcare professionals significantly improves their inhaler technique [22]. In addition, regular ongoing training should be

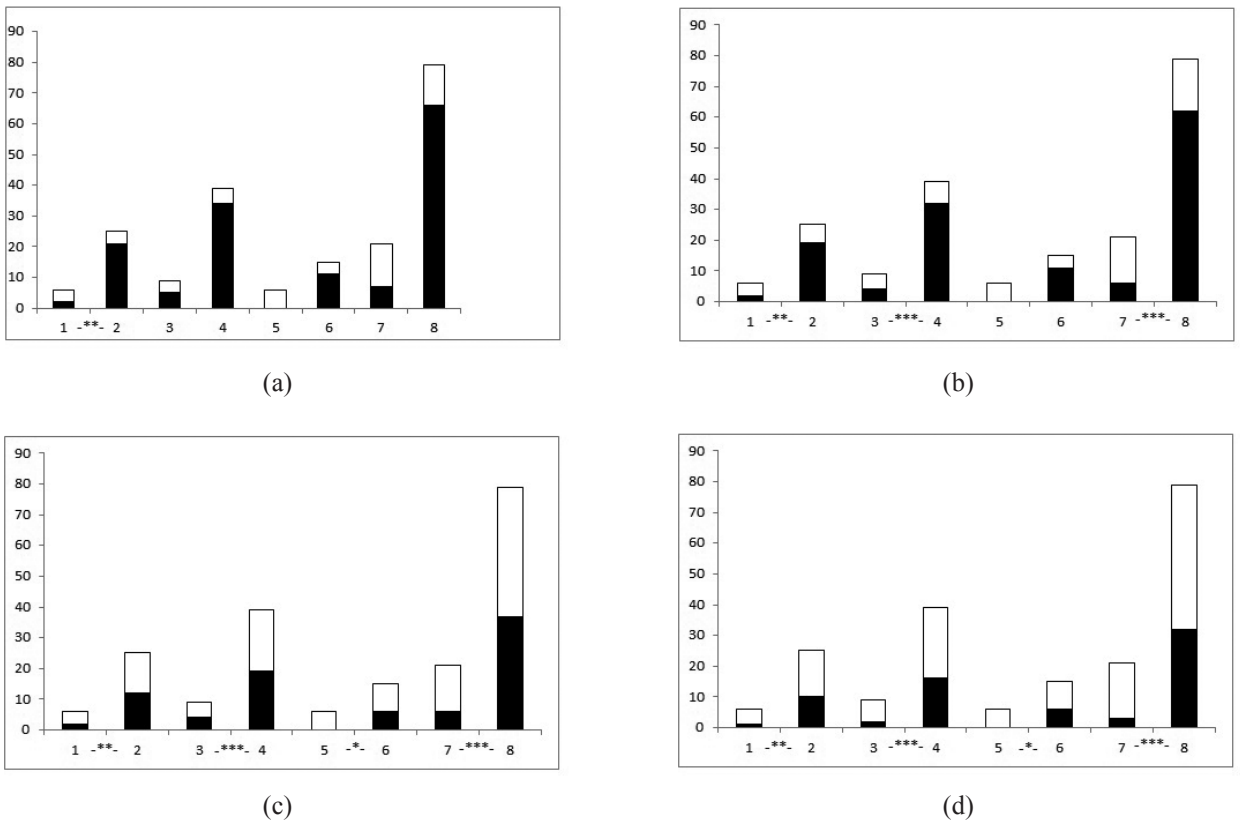

Fig. 2. Inhaler technique according to unscheduled resource use. a, hospital admissions; b, emergency department visits; c, antimicrobic courses; d, corticosteroid courses. black bar = 0; white bar = ≥1; 1 & 2 = Accuhaler; 3 & 4 = Evohaler; 5 & 6 = Turbuhaler; 7 & 8 = Total inhaler; odd number = with at least 1 critical inhaler error; even number = without a critical inhaler error; * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$.

provided to ensure that clinicians retain these skills.

Mishandling errors may lead to insufficient drug delivery, which adversely influences drug efficacy and may contribute to inadequate control of and unscheduled resource use for asthma and COPD (Figures 1 & 2). Our study, however, has some limitations. First, our findings on inhalation technique may be biased by the choice of criteria to define the mishandling. Second, our findings were based on the investigator's judgment and may have a subjective bias. The recruiting of more patients would yield more confident results.

Our findings confirm that inhaler mishandling is not only wasteful, but may have related clinical consequences in terms of unscheduled health-care resource use and poor disease control. The association between unscheduled resource use or poor disease control and critical errors with inhaler use do not mean that a better inhalation technique would improve resource use or disease control. Other factors such as smoking cessation, environmental modification, and medication non-adherence may result in unscheduled healthcare resource use and poor disease control.

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吸入器的處理不當對哮喘患者的效果

黃英豪　王貞云 *　王正信 **　陳世民

目的：吸入裝置的不正確使用可能對藥物的臨床效果產生重大影響。本研究的目的是評估哮喘患者不正確的吸入技術，要突顯吸入技術觀察到的常見錯誤，並討論對臨床療效的影響。

方法：首先，招募患者完成一個標準化的問卷，每份問卷包括一個常規部分和特殊部分，每部分涉及一個特定的吸入器。然後，在一個安靜的區域，每個病人使用安慰劑裝置對研究者示範吸入技術。

結果：我們已經收集了 100 條記錄吸入器技術。至少一個關鍵的錯誤分佈在吸入器的患者，從 Evohaler®19%，Accuhaler®19%，到 Turbuhale®29%。吸入器使用不當和年齡大（p=0.01），受教育低（p=0.01），缺乏健康照護者提供的吸入器技術教學或檢查（p=0.03）有顯著差異。吸入器使用不當是與住院（p<0.001），急診（p<0.001），口服類固醇課程（p<0.001）和抗菌劑（p<0.001）的風險增加，和疾病控制不佳（p<0.001）有關。

結論：吸入器處理不當仍是轉介到胸腔科門診經驗豐富的患者常見，並與計劃外增加的醫療保健資源的使用和不良臨床控制相關。由健康照護者教學或檢查也許是有利於減少吸入器處理不當的因素。*(胸腔醫學* ***2015; 30: 1-8)***

關鍵詞：哮喘控制測試，哮喘，吸入器

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Indicators of Successful Weaning from Prolonged Mechanical Ventilation in a Sub-acute Respiratory Care Ward in Northern Taiwan

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Introduction: Prolonged mechanical ventilation may lead to a higher incidence of nosocomial complications and increased healthcare costs. Early and successful weaning of patients from prolonged use of mechanical ventilation has become an important task for medical professionals in the sub-acute respiratory care ward (RCC). The purpose of this study is to identify successful weaning parameters associated with the care of patients, using the new clinical performance indicators for the RCC released by the Taiwan Joint Commission of Hospital Accreditation in July 2013.

Methods: We recorded demographic data, biochemical markers, and weaning parameters through a retrospective observational study of 315 patients from July 2011 to June 2013 transferred from the intensive care unit (ICU) for further weaning from the ventilator.

Results: The average age of the 315 patients was 71.59±15.38 years; 154 (42.53%) were successfully weaned from the ventilator. The mean length of RCC stay was 24.96 days. The successful weaning rate was 52.20%. The ICU transfer rate was 6.49%, and the chronic respiratory care ward (RCW) or home care transfer rate was 15.45%. The tracheostomy rate was 58.99%. The mean ventilator period in the RCC was 22.23 days. The mortality rate was 22.98%. In the stepwise multivariate logistic regression analysis, blood urea nitrogen (BUN) levels (odds ratio (OR)=0.985, p<0.002), metabolic alkalosis (OR=2.100, p<0.02), length of RCC stay (OR=1.074, p<0.001), and number of mechanical ventilation days during RCC stay (OR=0.951, p<0.001) were found to be significant predictors of successful weaning.

Conclusion: High rates of liberation from the ventilator can be achieved in a RCC setting as an alternative to ICU care. Factors associated with successful weaning included BUN levels, metabolic alkalosis, length of RCC stay, and number of ventilator days during RCC stay. ***(Thorac Med 2015; 30: 9-17)***

Key words: prolonged mechanical ventilation, clinical performance indicator, sub-acute respiratory care ward

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Introduction

Prolonged mechanical ventilation (MV) is defined as the need for MV for more than 21 days [1]. In Taiwan, an integrated delivery system, including intensive care unit (ICU), subacute respiratory care ward (RCC), chronic respiratory care ward (RCW), and home care, has been developed by the Bureau of National Health Insurance for patients who need longer ventilator support. The RCC, previously known as the respiratory care center, is a step-down specialized respiratory care unit that can provide more gradual support reduction strategies for the care of patients transferred from an ICU in stable clinical condition but with difficulty in weaning from MV. Many physiological variables associated with weaning from the ventilator have been measured to predict weaning outcome, but there is still no agreement about the major respiratory parameters related to successful weaning [2-4].

Prolonged use of MV can increase the risk of laryngeal edema, respiratory infections, and lung fibrosis with restrictive pulmonary function, which not only cause physical, psychological, and spiritual suffering but also affect quality of life and increase the financial burden on patients and their families [5-6]. The ratio of ventilator-dependent patients to total objects with health insurance is between 0.04-0.05%; however, the medical care expenses of ventilator-dependent patients are between 4.3-5.1% of the overall healthcare cost [7]. The high consumption of medical resources of patients requiring prolonged MV is a critical issue. Therefore, assisting ventilator-dependent patients in early weaning from ventilators has become an important objective for medical professionals in the RCC.

Using the Taiwan Clinical Performance Indicators (TCPI) published by the Taiwan Joint Commission of Hospital Accreditation in July 2013 [8], we conducted a study to identify the factors that can be used to predict weaning outcome with great sensitivity in the RCC. Our findings may provide useful indicators in the care of patients with recurrent respiratory failure.

Materials and Methods

Design

We conducted a retrospective observational study to analyze the clinical performance indicators for the RCC in the TCPI and also to identify factors associated with successful weaning from the ventilator. This study was approved by the Institutional Review Board for Human Studies in our institute (permit number: 102-5873B).

Patients and Methods

The RCC at Linkou Chang Gung Memorial Hospital is a 24-bed unit designed to care for patients with prolonged MV that are hemodynamically and metabolically stable. All patients transferred to the RCC between July 2011 and June 2013 were identified and eligible for inclusion in this study. Demographic data including age, gender, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and Glasgow Coma Score (GCS) were recorded after the patients were transferred to the RCC. Medical records were retrospectively reviewed. Recorded data included congestive heart failure history, active cancer history, lung fibrosis history, tracheostomy, hemodialysis, duration of RCC stay, number of MV days in the RCC and total MV days. Patients received medical care

in the RCC, where weaning parameters were measured twice a week and laboratory tests were measured once a week. Physician-directed weaning was performed according to weaning parameters and clinical conditions. Weaning parameters included maximal inspiratory pressure (PImax) and rapid shallow breathing index (RSBI). Laboratory tests included blood urea nitrogen (BUN), serum creatinine (Cr), serum calcium (Ca), serum phosphate, serum magnesium (Mg), albumin, cholesterol, triglyceride, free T4, thyroid stimulating hormone (TSH), cortisol, and arterial blood gas data. Patients were transferred to an ordinary ward after they had undergone successful weaning if no ventilator support was required for 5 consecutive days. The new clinical performance indicators for the RCC were calculated according to the definition, which was released by the Taiwan Joint Commission of Hospital Accreditation in July 2013 [8].

Statistical Analysis

Continuous data are expressed as mean ± standard deviation (SD), while categorical data are expressed as frequencies and percentage. Demographic and clinical characteristics were compared using Student's *t*-test or the Chi-Square test. Univariate logistic regression analysis was performed to determine the factors associated with unsuccessful weaning. Multivariate stepwise logistic regression analysis was performed to determine the factors predictive of unsuccessful weaning, while controlling for confounding factors. A model to predict unsuccessful weaning was then constructed using these factors. Data were analyzed using the Statistical Package for the Social Sciences (version 17.0; SPSS Inc., Chicago, IL, USA) and a p value <0.05 was considered statistically significant.

Results

Between July 2011 and June 2013, 315 patients (male: 56%), with an average age of 71.59±15.38 years, were eligible for inclusion. A total of 154 patients (42.53%) were successfully weaned from the ventilator. The mean length of RCC stay was 24.96 days; the successful weaning rate was 52.20%; the ICU transfer rate was 6.49%; the RCW or home care transfer rate was 15.45%; and the tracheostomy rate was 58.99%. The mean ventilator period in the RCC was 22.23 days, and the mortality rate was 22.98% (Table 1).

Patients were grouped with respect to weaning status (successful or unsuccessful) and comparisons were made. Successfully weaned patients had significantly higher GCS scores (p<0.001) and higher rates of metabolic alkalosis, but lower APACHE II scores, BUN levels, Cr levels, and serum phosphate levels, shorter RCC stay, fewer MV days during RCC stay, fewer total MV days, and less body weight loss during RCC compared to unsuccessfully weaned patients. There were no significant differences in age, Ca, Mg, albumin, cholesterol, triglycerol, free T4, TSH, cortisol, history of congestive heart failure, lung fibrosis, tracheostomy, PImax, and RSBI between these 2 groups (Table 2).

We observed that gender, APACHE II scores, GCS scores, BUN levels, Cr levels, phosphate levels, metabolic alkalosis, active cancer history, requirement of hemodialysis, length of ICU stay, length of RCC stay, number of MV days during RCC stay and total MV days were significantly associated with successful weaning (p<0.05) (Table 3).

Table 1. New Clinical Performance Indicators for the Sub-acute Respiratory Care Ward (RCC) in the Most Recent 2 Years

Clinical performance indicator	%
RCC -Integ 01 successful weaning rate	52.20
RCC -Integ 02 ICU transfer rate	6.49
RCC -Integ 03 RCW or home care transfer rate	15.45
RCC -Integ 04 tracheostomy rate	58.99
RCC -Integ 05 mean length of RCC stay	24.96
RCC -Integ 06 mean ventilator period in the RCC	22.23
RCC -Integ 07 mortality rate	22.98

Variables with significant differences between successful and failed weaning were chosen. After controlling for confounding factors, BUN levels, metabolic alkalosis, length of RCC stay, and number of MV days during RCC stay were found to be significant predictors of successful weaning ($p<0.05$) (Table 4).

Discussion

Prolonged MV use may increase the risks of subglottic injury, ventilator-associated pneumonia, and chronic lung disease [5]. Nevertheless, premature liberation from the ventilator can cause respiratory muscle dysfunction, gas exchange failure, loss of airway protection, and an increase in patient mortality [9]. The RCC provides a gradual weaning strategy for patients who require specialized respiratory care but no longer need ICU monitoring. However, previous studies reported that successful weaning rates were nearly 50% depending on the heterogeneous clinical conditions of the patients within each study category [2,10-12]. Therefore, it is crucial to identify effective clinical parameters to improve the predictive performance of weaning patients from long-term ventilator use. Using the TCPI, we observed that BUN level, metabolic alkalosis, length of stay in the RCC, and number of ventilator days in the RCC, among the various clinical parameters, were correlated with successful withdrawal of MV.

Modawal and coworkers have previously reported that a lower BUN level was identified as a significant predictor of weaning success [13]. Consistent with their findings, we observed that a high BUN level was associated with weaning failure. An elevated BUN level is an indicator of impaired renal function, reduced kidney blood flow and excessive protein catabolism. In addition to BUN levels, we also found that patients requiring hemodialysis were associated with unsuccessful weaning [2-3]. This may be due to the disturbed blood gas homeostasis and poor responsiveness of chronic renal failure patients to a ventilator control system [14]. Univariate analysis showed that the Cr level was associated with successful weaning, but multivariate analysis did not confirm its role as a weaning predictor [2-3]. This suggested that both BUN and Cr levels were correlated with weaning, but the level of Cr played a less significant role in the multivariate analysis.

Prolonged MV can lead to ventilator-induced lung injury characterized by diffuse inflammation, enhanced alveolar-capillary

Table 2. Characteristics of Patients who were Successfully Versus Unsuccessfully Weaned from Prolonged Mechanical Ventilation (n=314)

Characteristic	All patients	Successful (n=134)	Unsuccessful[a] (n=181)	*p* value
Age (years)	71.59 ± 15.38	70.28 ± 16.00	72.56 ± 14.87	0.192
Male	172 (54.6%)	59	113	0.001*
GCS	8.72 ± 3.45	9.74 ± 3.00	7.97 ± 3.56	0.001*
APACHE II	20.24	19.20 ± 5.66	21.02 ± 6.08	0.008*
BUN (mg/dL)	55.52 ± 45.45	38.15 ± 33.24	68.37 ± 48.94	0.001*
Cr (mg/dL)	2.05 ± 5.22	1.30 ± 1.91	2.59 ± 6.63	0.030*
Ca (mg/dL)	8.49 ± 1.06	8.62 ± 0. 93	8.38 ± 1.13	0.052
P (mg/dL)	4.04 ± 1.96	3.74 ± 1.31	4.24 ± 2.30	0.019*
Mg (mg/dLl)	1.90 ± 1.04	1.82 ± 0.37	1.94 ± 1.30	0.364
Albumin (mg/dL)	2.86 ± 1.44	2.98 ± 0.48	2.76 ± 1.85	0.194
Cholesterol (mg/dL)	129.50 ± 43.50	130.71 ± 44.98	128.61 ± 42.51	0.716
Triglyceride (mg/dL)	128.30 ± 106.11	130.43 ± 102.43	126.65 ± 109.17	0.773
Free T4 (ng/dL)	1.10 ± 0.62	1.16 ± 0.86	1.05 ± 0.34	0.144
TSH (uIU/mL)	2.93 ± 5.92	3.04 ± 7.13	2.83 ± 4.82	0.769
Cortisol (μg/dL)	26.26 ± 31.22	26.07 ± 30.35	26.40 ± 31.93	0.931
Metabolic alkalosis	143 (45.4%)	85 (63.4%)	58 (32.6%)	0.001*
Severe CHF	69 (21.9%)	23 (17.2%)	46 (25.4%)	0.080
Active cancer	50 (15.9%)	14 (10.4%)	36 (19.9%)	0.023*
Lung fibrosis	10 (3.2%)	3 (2.2%)	7 (3.9%)	0.415
Tracheostomy	157 (49.8%)	69 (51.5%)	88 (48.6%)	0.614
Hemodialysis	92 (29.2%)	22 (16.4%)	70 (38.7%)	0.001*
Length of sub-acute respiratory ward stay (day)	24.52 ± 17.85	19.22 ± 9.74	28.44 ± 21.20	0.001*
Total MV days	51.73 ± 24.08	43.58 ± 14.13	57.77 ± 27.89	0.001*
Ventilator days during sub-acute respiratory ward stay	21.10 ± 18.75	13.46 ± 9.47	26.77 ± 21.70	0.001*
PImax (cm H_2O)	-35.36 ± 14.26	-35.24 ± 12.99	-35.47 ± 15.28	0.895
RSBI	118.87 ± 65.96	111.53 ± 58.12	125.04 ± 71.49	0.084
Decreased body weight	203 (64.4%)	100 (74.6%)	103 (56.9%)	0.001*
Diuretics	188 (59.7%)	66 (49.3%)	122 (67.4%)	0.001*

Continuous data are expressed as mean ± SD, and categorical data are expressed as number (%). *Indicates a statistically significant between-group difference ($p<0.05$).

[a] The unsuccessful weaning group included patients who died and those who were ventilator-dependent. APACHE II = Acute Physiology and Chronic Health Evaluation II; BUN = blood urea nitrogen; Ca = serum calcium; CHF = congestive heart failure; Cr = serum creatinine; GCS = Glasgow Coma Score; Mg = serum magnesium; P = serum phosphate; PImax = maximal inspiratory pressure; RSBI = rapid shallow breathing index; Total MV days = number of mechanical ventilation days in the intensive care unit and in the sub-acute respiratory care ward; TSH = thyroid stimulating hormone.

Table 3. Summary of Univariate Analysis Revealing the Factors Possibly Associated with Unsuccessful Weaning[a] from Prolonged Mechanical Ventilation

Factor	OR	95%CI	*p* value
Male	0.473	0.300-0.746	0.001*
GCS	1.173	1.092-1.259	0.001*
APACHE II	0.949	0.912-0.987	0.008*
BUN	0.980	0.973-0.988	0.001*
Cr	0.749	0.640-0.876	0.001*
P	0.869	0.764-0. 989	0.033*
Metabolic alkalosis	3.619	2.260-5.794	0.001*
Active cancer	2.128	1.097-4.130	0.026*
Hemodialysis	0.311	0.180-0.538	0.001*
Length of sub-acute respiratory ward stay	0.959	0.942-0.977	0.001*
Total MV days	0.966	0.953-0.980	0.001*
Number of MV days during sub-acute respiratory ward admission	0.936	0.916-0.956	0.001*
Decreased body weight	2.227	1.368-3.628	0.001*
Diuretics	0.469	0.296-0.743	0.001*

Data were tested by univariate logistic regression analysis and are presented as the odds ratio (OR) and 95% confidence interval (CI). *Indicates a statistically significant predictor ($p<0.05$).

[a] The unsuccessful weaning group included patients who died and those who were ventilator-dependent.

Table 4. Summary of Multivariate Analysis Revealing the Factors Possibly Associated with Unsuccessful Weaning[a] from Prolonged Mechanical Ventilation

Factor	OR	95% CI	*p* value
BUN	0.985	0.977-0.993	0.002*
Metabolic alkalosis	2.100	1.166-3.781	0.020*
Sub-acute respiratory ward length of stay	1.074	1.018-1.133	0.001*
Number of MV days during sub-acute respiratory ward admission	0.951	0.927-0.976	0.001*

Data were tested by stepwise logistic regression analysis and are presented as odds ratio (OR) and 95% confidence interval (CI). *Indicates a statistically significant predictor ($p<0.05$).

[a] The unsuccessful weaning group included patients who died and those who were ventilator-dependent.

membrane permeability, and accumulation of protein-rich pulmonary edema, and ultimately lead to impaired gas exchange [15]. Moreover, previous studies have shown that management of patients with severe lung injury by means of a fluid-restrictive strategy may benefit both hydrostatic and oncotic pressures, and has been demonstrated to improve the weaning outcome and reduce extravascular lung water while shortening the RCC length of stay and decreasing mortality [12,16-18]. Our study also demonstrated that patients in the successful wean-

ing group had a higher incidence of metabolic alkalosis than those in the unsuccessful weaning group, indicating the decrease in interstitial pulmonary edema associated with the decrease in body weight [19].

Long duration of hospital stay has been shown to increase the incidence of nosocomial infection [20]. Consistent with the findings of previous studies, we observed that the length of RCC stay and mean ventilator days in the RCC were crucial indicators of weaning success [2,5]. Patients who failed ventilation weaning spent an average of 9 more days and 13 more MV days in the RCC. Since many risk factors may affect the duration of RCC stay, the clinical significance of hospital stay is greater in the control of underlying diseases contributing to difficult weaning.

Weaning predictors such as RSBI and PImax are routinely measured in the weaning of patients. However, there has been some controversy about the impact of RSBI and PImax on successful weaning in various studies, depending on the research protocol, patient number, and patient categories [2,19,21-22]. We observed that RSBI was a marginally better determinant (p=0.084), but did not find PImax to be significantly associated with successful weaning. To minimize both delayed weaning and premature extubation in clinical practice, measurements of weaning predictors followed by a T-tube trial are necessary for the physician to make a better decision before extubation.

Tracheostomy is a common procedure for patients who are anticipated to undergo MV for more than 21 days. It has several advantages over endotracheal intubation, including lower airway resistance, easier airway management, improved patient comfort and communication, and earlier transition to oral feeding [10,23]. Previous studies demonstrated that tracheostomy after 3 weeks of intubation was associated with a higher rate of weaning failure [23]. We did not find a difference between the successful and unsuccessful weaning groups relative to tracheostomy, because all patients were routinely encouraged to undergo the procedure after admission to the RCC.

Our study has some limitations. Previous studies have revealed that APACHE II scores were promising indicators of successful weaning, especially for patients with pneumonia, cardiovascular disease, and cancer [2-3]. However, another study and ours did not find high APACHE II scores to be substantially associated with weaning success [4]. The inconsistency might be that the APACHE II score is an acute-phase indicator that was originally designed for use in the ICU setting. Furthermore, this study was a retrospective review of all patients transferred to a single hospital-based unit over a 2-year period; therefore, the size and staff may be different from those of non-hospital-based units.

Conclusion

We have demonstrated that high MV weaning rates can be achieved in a RCC setting through continuous monitoring of clinical performance indicators. This supports the notion that RCC care is a good alternative to ICU care for ventilator-dependent patients. The factors associated with successful weaning outcome included BUN level, metabolic alkalosis, length of RCC stay, and number of MV days during the RCC stay. Improvement of these factors may enhance the management of patients requiring long-term dependence on a ventilator.

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北台灣亞急性呼吸照護病房成功脫離呼吸器的預測指標

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背景：延長使用呼吸器常導致較高的院內併發症及增加醫療資源的支出。早期且有效的協助病人脫離呼吸器是亞急性呼吸照護病房醫療人員的重要任務。本研究目的乃藉由使用財團法人醫院評鑑暨醫療品質策進會於2013年7月公布的新版台灣臨床成效指標來找出有利於照顧病人成功脫離呼吸器的預測指標。

方法：自 2011 年 6 月至 2013 年 7 月，我們藉由回顧病歷收集 315 位由加護病房轉至亞急性呼吸照護病房嘗試脫離呼吸器病人的人口統計資料、生化指標及脫離呼吸器相關參數。

結果：315 例病人平均年齡 71.59±15.38 歲，315 例中有 134 例（42.53%）成功脫離呼吸器。亞急性呼吸照護病房平均住院天數 24.96 天，呼吸器脫離成功率 52.20%，回轉加護病房比率 6.49%，未脫離呼吸器下轉至慢性呼吸照護病房或居家照護比率 15.45%，氣切比率 58.99%，平均呼吸器使用天數 22.23 天，死亡率 22.98%。以多變項邏輯迴歸分析發現，成功脫離呼吸器的預測指標包括尿素氮（相對危險比：0.985，p<0.002），代謝性鹼中毒（相對危險比：2.100，p<0.02），亞急性呼吸照護病房住院天數（相對危險比：1.074，p<0.001），亞急性呼吸照護病房呼吸器使用天數（相對危險比：0.951，p<0.001）。

結論：在亞急性呼吸照護病房可達到高呼吸器脫離率。成功脫離呼吸器的相關因子包括尿素氮、代謝性鹼中毒、亞急性呼吸照護病房住院天數、及亞急性呼吸照護病房呼吸器使用天數。*(胸腔醫學* ***2015; 30: 9-17)***

關鍵詞：延長使用呼吸器，臨床成效指標，亞急性呼吸照護病房

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Central Airway Obstruction-Related Acute Respiratory Failure Due to Ovarian Carcinoma with Thyroid Metastasis – A Case Report and Literature Review

Yen-Liang Kuo, Wei-Chih Chen

Central airway obstruction (CAO) results from a variety of diseases and causes significant morbidity and mortality. We present a case of ovarian cancer with thyroid metastasis-related CAO and acute respiratory failure. After concurrent chemoradiation therapy, the patient was extubated successfully. This case reveals that patients with CAO-related respiratory insufficiency resulting from a malignancy with extrinsic compression may still have a chance to be successfully weaned from mechanical ventilation without tracheostomy, if the operation is deemed to be too risky and the patient responds to anticancer treatment. ***(Thorac Med 2015; 30: 18-23)***

Key words: central airway obstruction, ovarian cancer, respiratory insufficiency, thyroid metastasis, wean

Introduction

Central airway obstruction (CAO) is a consequence of a variety of diseases and contributes to significant morbidity and mortality [1]. The most common cause of malignant CAO is direct extension from an adjacent tumor, notably bronchogenic carcinoma, followed by esophageal and thyroid carcinoma; metastatic cancer from a distant site or primary tumors of the airway is relatively uncommon.

Herein, we report a rare case of ovarian cancer with thyroid metastasis and CAO resulting in acute respiratory failure. Extubation was performed smoothly after the metastatic tumor had regressed following a series of chemo- and radiotherapy treatments. No recurrent respiratory failure was noted during a close follow-up for 1 year.

Case Report

A 76-year-old woman presented to the emergency room with dyspnea and respiratory distress for 3 days. There was no fever, cough or sputum production. Physical examinations showed tachycardia, a palpable neck mass and obvious stridor. Lab data revealed acceptable complete blood count, biochemistry and arterial blood gas exams. A nasopharyngoscopy found a smooth bulging mass at the subglottic area with partial airway obstruction. A computed

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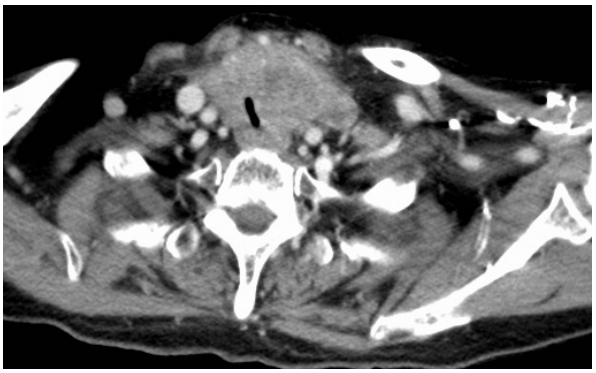

Fig. 1. Computed tomography of the larynx disclosed a diffuse low density mass lesion in bilateral thyroid glands, more obviously on the left. Tracheal compression and tracheal deviation to the right side were also noted.

tomography (CT) scan of the larynx (Figure 1) disclosed bilateral thyroid tumors around 3 centimeters in length with tracheal deviation and more than 70% narrowing of the lumen. Nasoendotracheal intubation with mechanical ventilation was performed due to CAO with impending acute respiratory failure and she was admitted to the intensive care unit.

Tracing back her clinical history, she was diagnosed with stage IIC bilateral ovarian carcinoma of a clear cell type 7 years previous to this admission. She initially underwent debulking surgery with abdominal total hysterectomy, bilateral salpingo-oophorectomy, paraaortic and bilateral pelvic lymph nodes lymphadenectomy, appendectomy, and total omentectomy with adjuvant chemotherapy. Subsequent exams including tumor markers such as carcinoma antigen 125, carcinoma antigen 199 and abdominal CT scan around every 3 months showed no evidence of tumor recurrence until about 4 years before admission. Lung metastases and a mass lesion at the right paratracheal zone were noted in the chest CT. A CT-guided biopsy of the right paratracheal mass confirmed metastatic cancer from the ovaries; chemotherapy with paclitaxel and cisplatin was then given for 4 cycles. Thereafter, disease progression was seen with an increasing size of the right paratracheal mass and increasing numbers of metastatic nodules at the bilateral lungs. Thus, the regimen was shifted to topotecan for 3 cycles with subsequent liposomal doxorubicin for 2 cycles. However, the disease continued to progress in spite of treatment. Radiotherapy was given for palliation and symptomatic control with a total dose of 50 gray in 25 fractions from 19 July 2010 to 20 August 2010. Then, the chemotherapy regimen was shifted to gemcitabine and paclitaxel. A partial response of the metastatic cancer was seen in a series of chest CT exams. Nonetheless, the tumor recurred with metastasis to the isthmus of the thyroid 2 years before admission. Therefore, another course of chemotherapy with melphalan was prescribed, but the metastatic tumor of the thyroid isthmus still progressed.

Based on the detailed history review and physical examination, metastatic tumor-related CAO and acute respiratory failure was highly suspected. We arranged an ultrasound-guided biopsy of the subglottic tumor after admission. The pathology revealed thyroid tissue with infiltrating adenocarcinoma composed of pleomorphic cells arranged in an irregular glandular pattern that was immunoreactive for cytokeratin 7 and non-immunoreactive for thyroid transcription factor-1 and cytokeratin 20 (Figure 2). Metastatic adenocarcinoma from the ovaries was suspected. Urgent concurrent chemoradiation therapy (CCRT) with gemcitabine, paclitaxel and a total radiation dose of 40 gray in 18 fractions was arranged from 27 April 2012 to 23 May 2012. A thoracic surgeon was also consulted for tracheostomy. However, tracheostomy was not suggested by the surgeon due to the high operative risks, including a high fraction

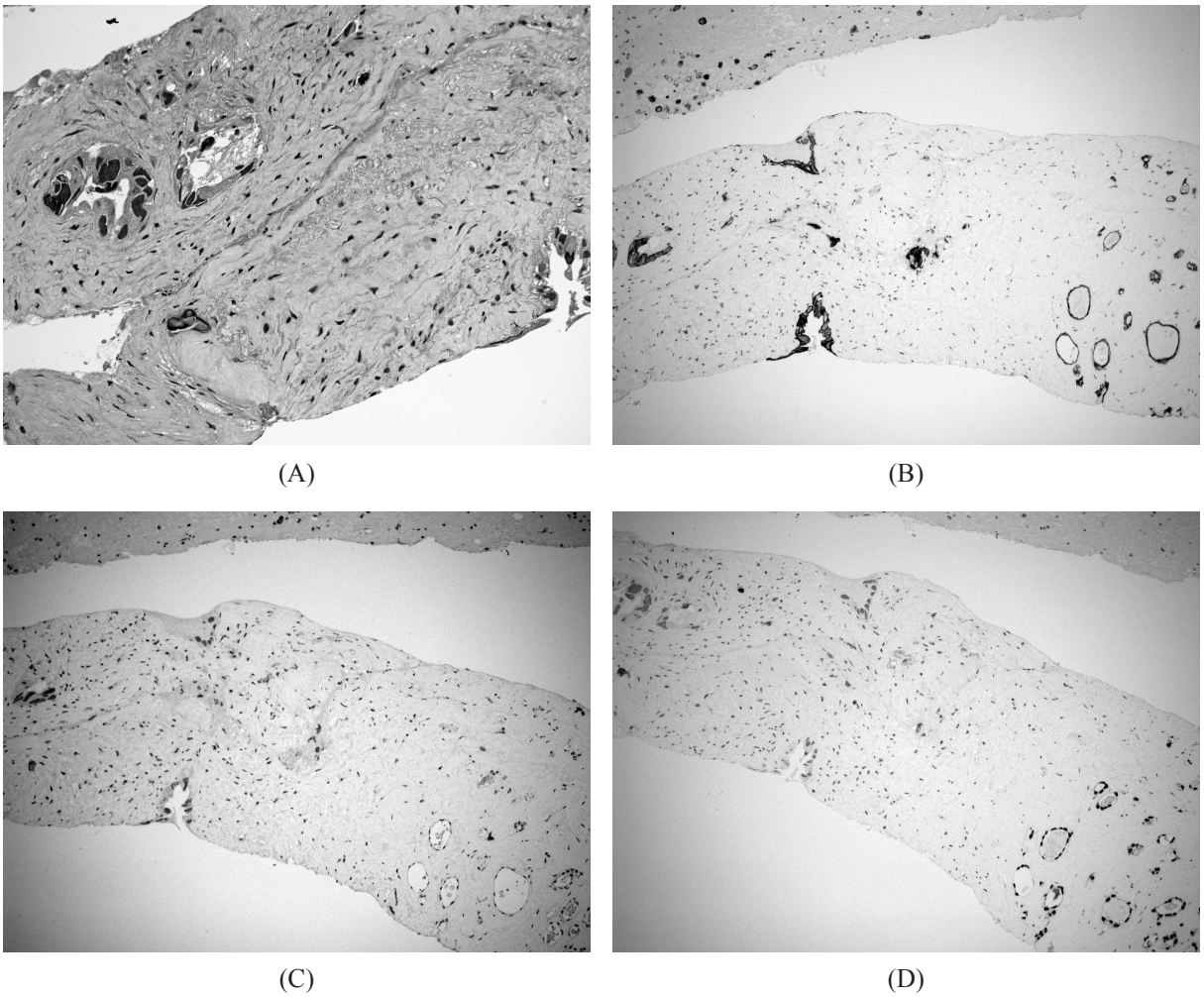

Fig. 2. Pathology of the thyroid tumor via a needle biopsy, 200X. (A) With hematoxylin and eosin staining, sections showed thyroid tissue with infiltrating adenocarcinoma, composed of pleomorphic cells arranged in an irregular glandular pattern. (B) The tumor cells were immunoreactive for cytokeratin 7. (C) The tumor cells were non-reactive for cytokeratin 20. (D) The tumor cells were non-reactive for thyroid transcription factor-1.

of inspired oxygen and a lack of enough surgical space to approach the trachea due to the huge lesion occupying the neck. After her condition had stabilized, assessment of readiness to wean from mechanical ventilation revealed an acceptable weaning profile. However, a cuff leak test showed no air leakage. We changed the chemotherapy medications to topotecan and dacarbazine due to a poor response to the previous therapy. Repeated neck CT showed regression of the tumor and the cuff leak test improved to 253 milliliters. Extubation was performed smoothly after 66 days of invasive mechanical ventilation. Non-invasive ventilation was administered for 4 days after extubation to ensure the weaning process. No recurrent respiratory failure was noted by close observation of the respiratory rate, breathing pattern and oxygen saturation during hospitalization. She remained in stable condition during a 1-year outpatient

follow-up after discharge.

Discussion

The mechanism of CAO is derived from several different processes, including endobronchial tumor growth, extrinsic compression of the airway, or a combination of these processes [2]. The diagnosis and treatment of intrinsic versus extrinsic obstruction generally can be made only through interventional bronchoscopy for further management of airway obstruction with laser, rigid bronchoscopy, or stent placement if intraluminal disease is present, although CT scan of the neck and chest can demonstrate invasion of the tracheal wall by a tumor [3]. The choice of treatment depends on patient factors, the underlying process, equipment availability and operator training. To date, there is a paucity of prospective randomized studies comparing the effectiveness of 1 approach to the other [4]. The urgency of the clinical scenario dictates the approach to the disease [3].

The most life-threatening airway complication is tracheal obstruction causing asphyxia [2]. Managements of CAO are initial resuscitation and airway interventions. Endotracheal intubation is indicated to ensure adequate ventilation and oxygenation for the unstable patient. Tracheotomy may be the stabilizing procedure of choice in patients with severe proximal upper airway obstruction, but will not alleviate more distal airway obstruction. Interventional options for CAO are subject to the availability of experienced personnel and equipment.

Epithelial ovarian cancers can spread intraperitoneally via lymphatic channels or hematogenously. Lymphatic dissemination to the pelvic and paraaortic lymph nodes is common in clinically advanced disease [5]. Hematogenous dissemination is rare, but can involve any organ, although the liver is more frequently involved [6]. Overall, distant metastases, especially those above the diaphragm, are unusual at presentation and during the course of ovarian carcinoma [7].

Surgery is the standard initial management of ovarian cancer, and debulking operation is thus recommended for maximum tumor removal [8]. Recent trials have shown that platinum-based adjuvant chemotherapy improved survival and recurrence-free survival in early-stage ovarian cancer [9]. Chemotherapy is currently the standard of care after surgery. The role of radiotherapy still has to be elucidated due to the lack of large prospective randomized trials. However, the effectiveness of radiation therapy in certain stages and extents of ovarian cancer has been reported in several trials [8]. Radiotherapy may also be utilized for salvage [10], consolidative [11-12], or palliative purposes [13]. For patients with advanced disease that is unresectable and chemoresistant, radiotherapy has an especially important palliative role in reducing symptoms, such as controlling vaginal or rectal bleeding, controlling pulmonary metastasis, and pain control.

To the best of our knowledge, only 1 similar case with endobronchial CAO due to metastatic ovarian cancer has been reported [14]. Our patient presented with typical symptoms and signs of central airway obstruction and was diagnosed correctly by nasopharyngoscopy and image study. Based on previous experience with tumor response to anti-tumor agents and radiotherapy, the most feasible treatment for the underlying disease was also administered immediately. The current case reveals that patients with CAO-related respiratory insufficiency resulting from extrinsic compression by ovarian cancer who

had difficulties undergoing tracheostomy may still have a chance to be successfully weaned from mechanical ventilation without operation if the patient responds to anticancer treatment. Further large-scale prospective clinical studies are needed to determine the role of anticancer treatment for CAO caused by metastatic ovarian cancer.

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因卵巢癌併甲狀腺轉移導致之中央氣道阻塞併急性呼吸衰竭—病例報告及文獻回顧

郭彥良　陳威志

中央氣道阻塞可以因為很多不同的疾病導致並且造成很嚴重的病況甚至死亡。我們報告一位因卵巢癌併甲狀腺轉移導致中央氣道阻塞併急性呼吸衰竭的病人，在經過同步化學治療及放射治療後成功拔管。此病例報告顯示因惡性腫瘤之外部壓迫產生中央氣道阻塞併急性呼吸衰竭的病人，如果氣切手術風險過高，而且病人在抗腫瘤治療有反應的情況，仍可能有機會不做氣切手術而成功脫離呼吸器。*(胸腔醫學* ***2015; 30: 18-23)***

關鍵詞：中央氣道阻塞，卵巢癌，呼吸衰竭，甲狀腺轉移，呼吸器脫離

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An Unusual Presentation of Pleural Effusion Caused by Mediastinal Angiomyolipoma: A Case Report and Literature Review

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Angiomyolipomas (AMLs) are benign tumors composed of various tissues, including fat, abnormal blood vessels and smooth muscle cells. Renal AMLs are often associated with tuberous sclerosis complex (TSC) or pulmonary lymphangio- leiomyomatosis (LAM). However, mediastinal AMLs are less reported and the association with pleural effusion are less frequently reported. We present a case of middle-aged woman with left pleural effusion. The analysis of pleural effusion shows exudate with macrophage/monocyte-predominant exduate. Chest computed tomography (CT) reveals mediastinal mass (about 6.0cm). Mediastinal tumor was excised through video-assisted thoracoscopic surgery (VATS) and pathology revealed angiomyolipoma. After tumor excision, pleural effusion didn't recur. We reported this unusual presentation of pleural effusion caused by mediastinal angiomyolipoma, and review the related articles. ***(Thorac Med 2015; 30: 24-29)***

Key words: angiomyolipoma, mediastinum, pleural effusion

Introduction

Angiomyolipomas (AMLs) are benign tumors with the composition of blood vessels, smooth muscle cells and fat cells. AMLs mainly are located at kidney and highly associated with the genetic disease - tuberous sclerosis comple. Most individuals with tuberous sclerosis complex have several angiomyolipomas affecting both kidneys. AMLs are also commonly found in women with the rare lung disease, lymphangioleiomyomatosis (LAM).

Other than kidney, AMLs are less commonly found in other organ, especially at mediastinum. The association with pleural effusion is even rarely reported. Thus, we report a case of middle-aged woman who has left pleural effusion caused by mediastinal angiomyolipoma.

Case Report

This 51-year-old female patient complained about dyspnea on exertion for about 3 months. Physical examination showed decreased breath

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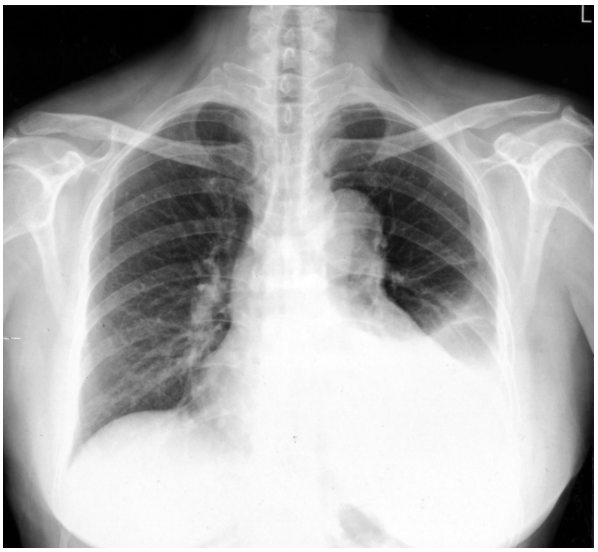

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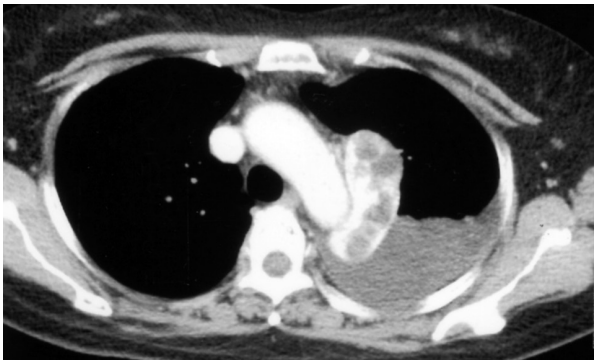

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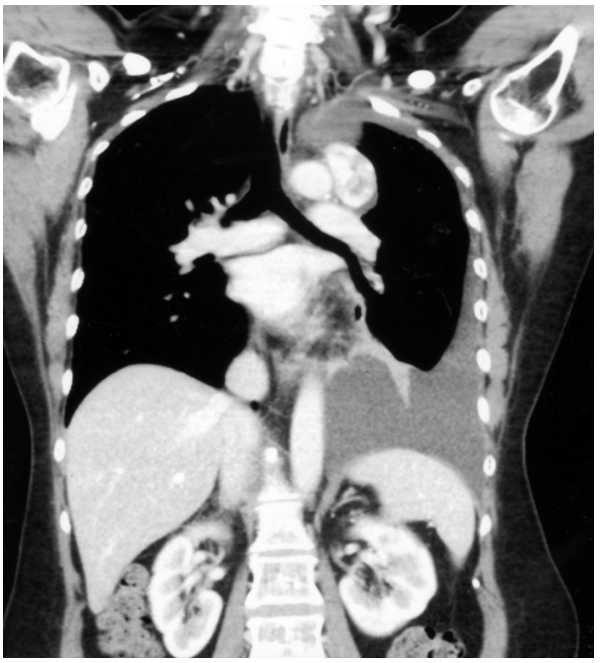

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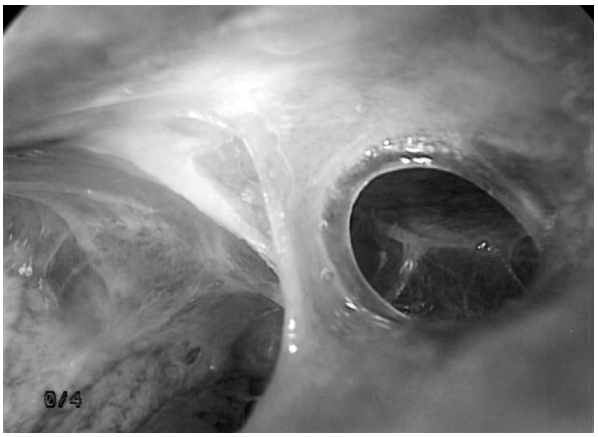
Fig. 1. Image findings of the mediastinal Angiomyolipoma. (A) Chest radiography showed a left mediastinal mass near aorta and left pleural effusion, (B) & (C) The transverse and coronal sections of contrast-enhanced chest CT revealed a mediastinal mass (about 6 cm) at posterior mediastinum near aorta and left pleural effusion

sound at left side lung field and plain film roentgenogram revealed left pleural effusion. Thoracocentesis was done and yellowish pleural effusion was noted. Pleural effusion study showed exudate with predominant macrophage/monocytes (pleural effusion total protein: 5.1 g/dL, lactic dehydrogenase: 121 U/L; serum total protein: 8.3 g/dL, lactic dehydrogenase: 179 U/L; macrophage/monocytes: 50%). Under the suspicion of mycobacterium tuberculosis infection, anti-tuberculosis medication was prescribed for two months. However, the pleural effusion did not resolve. Chest computed tomography (CT) was arranged which revealed one mediastinal mass beside the aorta (about 6.0 cm) (Figure 1). No focal nodular lesion was noted in the visible portions of the kidneys, adrenal glands, liver, gallbladder, spleen, and pancreas. Pleural biopsy was arranged first, but pathology showed chronic inflammation only. Therefore, tumor excision through video-assisted thoracoscopic surgery (VATS) was done (Figure 2). Final pathology revealed angiomyolipoma. The tumor was composed of a mixture of mature fat cells and proliferative narrow vascular channels with occasional microthrombi. Immunohisto-



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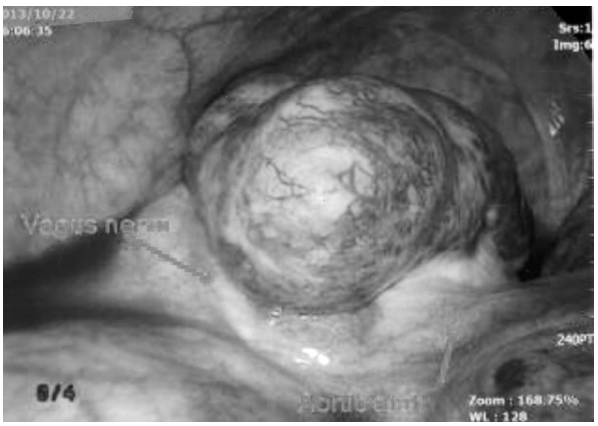

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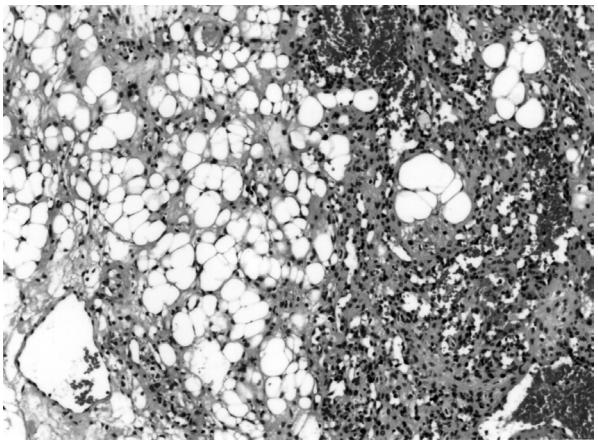
Fig. 2. VATS findings of the mediastinal Angiomyolipoma. (A) pleural effusion with fibropurulent peel loculated over left C-P angle, lung surface, and interlobar fissure (B) Meidastinal tumor, about 6×2.5×2.5 cm, over paraaortic area

chemistry showed positive stain for desmin, but negative for HMB45. Desmin highlights hyperplastic smooth muscle cells, while HMB-45 is negative for the mediastinum tumor (Figure 3). Pleural pathology revealed chronic pleurisy with eosinophilia. No evidence of malignancy was noted. After tumor excision, the pleural effusion doesn't recur.



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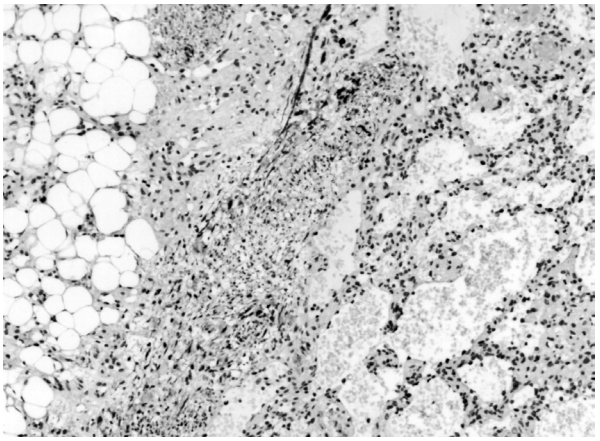

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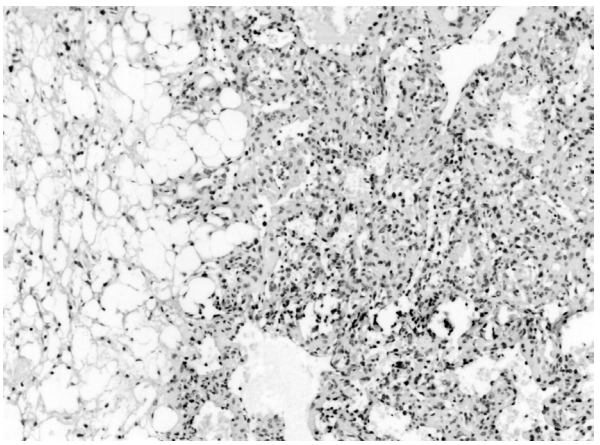

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Fig. 3. Microscopic findings of the mediastinal Angiomyolipoma. (A) Hematoxylin & Eosin staining (X100) demonstrating the tumor characteristics, including fat, abnormal blood vessels and smooth muscle components. (B) & (C) The immune- histochemical staining showed positive for desmin (B) and negative for HMB-45 (c) (X100).

Table 1. Summary of All Reported Mediastinal Angiomyolipomas

No.	Authors	Year	Age	gender	Location	Size (cm)	Symptoms
1	Bertrand *et al* [3]	1984	57	M	Central	4.0×2.0×2.0	Non
2	Fukuzawa *et al* [4]	1992	63	F	Posterior	2.0×2.3×3.7	Non
3	Hayashi *et al* [5]	1994	22	F	Anterior	7.0×7.0×1.0	Non
4	Watanabe *et al* [6]	1997	53	F	MI-posterior	8.0	Non
5	Kim *et al* [7]	2001	62	F	Posterior	4.0×3.0×3.0	Dyspnea
6	Torigian *et al* [8]	2002	35	F	Posterior	6.8×10.0×4.5	Dysrhythemia
7	Amir *et al* [9]	2004	22	M	Anterior	19.0×15.0×9.0	Dyspnea
8	Qu *et al* [10]	2005	63	F	Central	20.0×14.0×8.0	Dyspnea
9	Watts *et al* [11]	2007	57	F	Anterior	5.7	Non
10	Warth *et al* [2]	2008	32	M	Anterior	15.0×8.0×3.0	Dyspnea Pleural effusion
11	Knight *et al* [12]	2008	57	F	Anterior	4.4×2.5	Non
12	HAN *et al* [1]	2012	50	M	posterior	23.0×10.8×5.3	Dyspnea Pleural effusion

Discussion

Angiomyolipomas are benign, solitary, non-invasive lesions that most often arise in the kidney. Extrarenal sites of these tumors include the skin, oropharynx, the abdominal wall, retroperitoneum, gastrointestinal tract, heart, lung, liver, uterus, penis, and spinal cord. Renal AMLs are often associated with tuberous sclerosis complex (TSC) or pulmonary lymphangioleiomyomatosis (LAM).

Mediastinal AMLs are less frequently commonly reported. According to our review, there are only 12 cases of mediastinal AMLs (Table 1). Among the 12 reported cases, only 2 cases of mediastinal AMLs are associated with pleural effusion [1,2]. Both reports showed chylous pleural effusions. In these cases, the finding of massive tumor growth around mediastinal lymph nodes may explain chylous pleural effusions. Warth *et al* mentioned a male patient affected by TSC with intermittent, massive chylous pleural effusions, who developed recurrent mediastinal angiomyolipomas [2]. Chylous pleural effusions in TSC patients are uncommon and raise suspicions about LAM. In the present case, the pleural effusion revealed macrophage/ monocyte predominant exudate, not chylous pleural effusion. The mediastinal tumor in our case showed negative for HMB-45. HMB-45 is a monoclonal antibody that reacts against an antigen present in melanocytic tumors such as melanomas. HMB-45 is non-reactive with almost all non-melanoma human malignancies, with the exception of rare tumors showing evidence of melanogenesis (e.g., pigmented schwannoma, clear cell sarcoma) or tumors associated with tuberous sclerosis complex (angiomyolipoma) [13]. Therefore, the solitary mediastinal tumor in our case seems unlikely related to TSC or LAM. Moreover, no other systemic involvement including kidneys is noted according to our stury.

In our care, the association between the me-

diastinal AML and pleural effusion is not clear. However, the pleural effusion disappeared after tumor excision. Hsieh *et al* reported a case of 46-year-old female has both primary AML and an adenocarcinoma was incidentally found during surgery [14]. No tuberous sclerosis or renal angiomyolipoma was noted. No pleural effusion is noted at that case. In our case, pleural pathology showed chronic inflammation with eosinophilia (no evidence of malignancy), we proposed the pleural effusion is due to chronic irritation of pleura by the benign tumor and resolved after tumor excision.

Benign mediastinal AMLs related refractory exduative pleural effusion is rare but possible.

Conclusion

We reviewed a middle-aged woman who presented with left exudative pleural effusion was diagnosed to have a posterior mediastinal angiomyolipoma. After tumor excision, the pleural effusion resolved. There is no evidence of TSC or LAM. To our knowledge, this is the first case reported on a mediastinal AML associated with exudative pleural effusion.

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縱膈腔血管肌脂瘤併發肋膜積液爲不尋常之表現：病例報告及文獻回顧

陳逸燕　韓孟志　陳盈妊 *　張孔昭 *　顏亦廷 **　張漢煜

血管肌脂瘤為良性腫瘤且大多好發在腎臟，在過去文獻中有被報告過發生於肝臟、後腹腔、口腔、皮膚、脊椎，但僅有極少數案例發現於縱膈腔內，至於跟肋膜積水的相關性就更少提及。本篇案例報告介紹了一名五十一歲女性一開始表現為肋膜積液引起喘的症狀，電腦斷層顯示有一縱膈腔腫瘤（約六公分），經外科手術切片後病理報告顯示為血管肌脂瘤，術後患者順利出院，並無惡性腫瘤之跡象。據文獻指出血管肌脂瘤所引起的肋膜積液皆為乳糜胸，在此，我們報告一位縱膈腔血管肌脂瘤引起肋膜滲出液之罕見病例。*(胸腔醫學 **2015; 30: 24-29**)*

關鍵詞：血管肌脂瘤，縱膈腔，肋膜積液

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Pulmonary Nocardiosis in a Non-HIV Patient: A Case Report

Chia-Hao Chang, Ping-Huai Wang, Hou-Tai Chang

The occurrence of pulmonary nocardiosis (PN) among patients with community-acquired pneumonia is quite uncommon. The diagnosis is usually delayed and as a result the mortality rate is high. Furthermore, the incidence of *Nocardia beijingensis* is low in Taiwan. We report a 67-year-old man with chronic obstructive pulmonary disease (COPD) who was admitted under a diagnosis of community-acquired pneumonia. Chest radiography showed multiple nodular infiltrates in bilateral lungs. The sputum Gram stain revealed Gram-positive branched filaments. *Nocardia beijingensis* was subsequently confirmed by 16S ribosomal RNA gene sequencing analysis. The patient's clinical condition improved after receiving trimethoprim/sulfamethoxazole treatment. The non-specific clinical manifestations of PN render the correct diagnosis challenging. Therefore, a high degree of clinical suspicion is the key when making a diagnosis, even in patients with a non-human immunodeficiency virus (HIV) status. ***(Thorac Med 2015; 30: 30-35)***

Key words: chronic obstructive pulmonary disease, nocardiosis

Introduction

Pulmonary nocardiosis (PN) infection in patients with community-acquired pneumonia is very rare and is a well-known opportunistic pathogen that predisposes to impairment of cell-mediated immunity. Therefore, patients with a history of diabetes, human immunodeficiency virus (HIV), malignancy, connective tissue disease, alcoholism, bone marrow or solid organ transplantation and those taking high-dose corticosteroids are at high risk of PN infection. Because of the nonspecific clinical-radiological presentations and the difficulties in cultivating the pathogen, the diagnosis of this infection is usually delayed, resulting in a high rate of mortality. The average duration from symptoms to diagnosis of PN ranges from 42 days to 12 months.

The most common Nocardia species in Taiwan is *Nocardia asteroides*. The prevalence of *Nocardia beijingensis* in Taiwan is relatively low. Herein, we report the case of a 67-year-old man with chronic obstructive pulmonary disease (COPD) who was receiving an inhaled corticosteroid/long-acting beta agonist only,

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and had no long-term regular systemic steroid use. No overt causes of immunocompromise existed. *Nocardia beijingensis* was confirmed subsequently by 16S ribosomal RNA gene sequencing analysis.

Case Report

A 67-year-old man who was an ex-smoker was diagnosed with COPD GOLD stage II with forced expiratory volume in 1 second of 72% of predicted value. He underwent treatment with fluticasone 250 mcg plus salmeterol 25 mcg (seretide evohaler). He had previously experienced acute exacerbation on 2 separate occasions and had received a short-course of systemic steroids. This time, he suffered from progressive dyspnea, productive cough and fever for several days. He visited a regional hospital, where community acquired pneumonia and acute exacerbation of COPD was diagnosed. After receiving an initial therapy that included antibiotics and bronchodilators, his condition deteriorated. Thereafter, he was referred to our hospital for further management.

Upon admission, intermittent fever and coarse breathing sounds were detected. His white blood cell count was 44550/μl with predominately polymorphonuclear leukocytes, and C-reactive protein was 20.6 mg/dl. His chest radiography displayed multifocal patchy consolidation (Figure 1A) and chest computed tomography exhibited bilateral lung masses of varied size and multifocal peribronchial and centrilobular infiltrates with thickened bronchial walls (Figure 1B). Piperacillin/tazobactam was administered empirically.

No specific microorganism was identified in sputum and blood cultures. Ultrasonography-guided lung aspiration and biopsy were thus arranged, and also revealed negative findings for bacteria and malignant cells. Acid-fast staining of sputum and lung aspiration specimens also revealed negative findings. Although several antibiotics (piperacillin/tazobactam, levofloxacin, teicoplanin, and amikacin) were administered, the patient's clinical condition worsened with progressive dyspnea and increased oxygen demand. Chest radiography revealed progres-

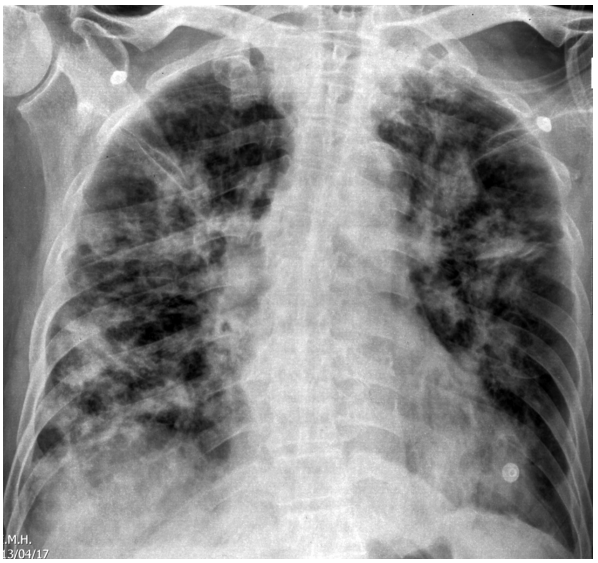

Fig. 1A. Chest radiography displays a multifocal consolidation patch in the bilateral lung field.

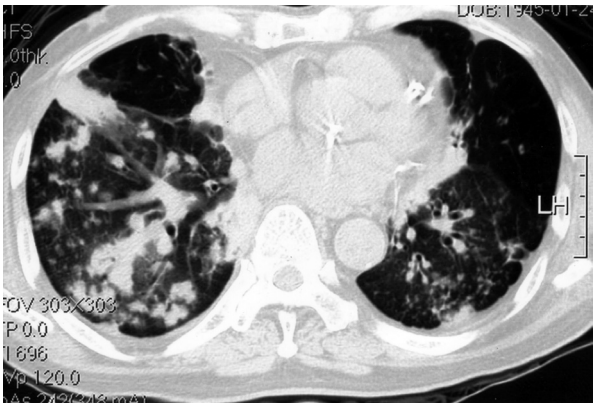

Fig. 1B. Chest computed tomography shows increased bilateral infiltrates with bilateral lung masses and multifocal peribronchial and centrilobular infiltrates with thickened bronchial walls.

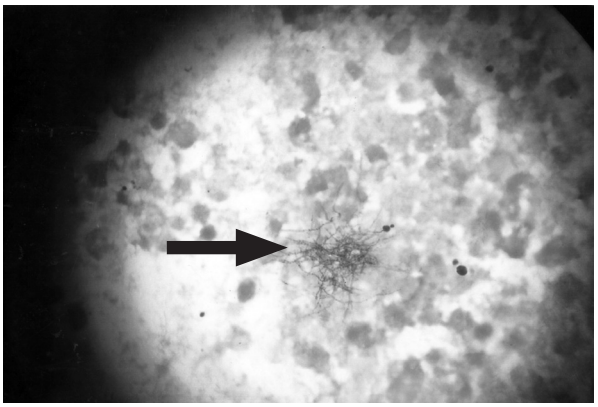

Fig. 2. *Nocardia spp.* Photomicrograph (original magnification, ×1000; Gram stain) sputum Gram stain shows Gram-positive branched filaments with fragmentation (arrows).

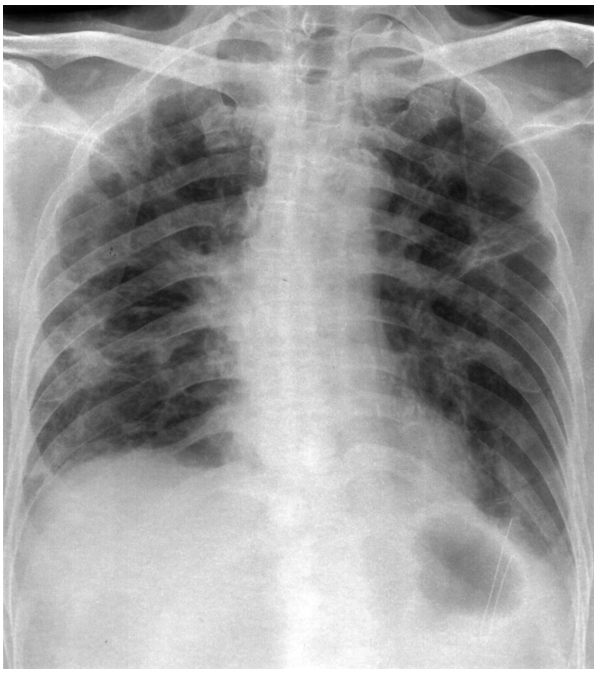

Fig. 3. Two weeks after treatment, chest radiography reveals improvement in the bilateral multifocal consolidation patch.

sive bilateral infiltrates. Successive thorough examinations, including autoimmune profile, Cryptococcus antigen, Aspergillus antigen, HIV antibody and tumor markers all had normal findings. Gram staining of the sputum culture was repeated, and showed Gram-positive branched filaments with fragmentation (Figure 2); however, modified acid-fast staining yielded negative findings.

Due to the Gram-positive branched filaments, Actinomyces and Nocardia species were suspected. Ampicillin/sulbactam and sulfonamides/trimethoprim were administrated. We discontinued ampicillin/sulbactam after finally receiving confirmation of *Nocardia beijingensis* using 16S ribosomal RNA gene sequencing analysis. Regression of bilateral lung infiltrates was observed on chest radiography after 14 days of sulfonamides/trimethoprim use (Figure 3). After confirming the diagnosis of pulmonary nocardiosis, the patient's history of soil exposure was inquired about. He was interested in gardening and owned a small yard at his house. He was later discharged with oral sulfonamides/trimethoprim and was prohibited from gardening.

Discussion

Immunocompromised patients are commonly infected with Nocardia species; at least 30 species of Nocardia can lead to human infections [1]. Pulmonary infection is usually caused by *Nocardia asteroides* (85%) [2]; infection by *Nocardia beijingensis* is very rare (0.7%) [3]. The prevalence of *Nocardia beijingensis* in Taiwan is also low (around 1.2% to 5.9%) [4-6]. It was first found in the soil of China in 2001. Since it may also exist in the soil of Taiwan, the patient had a risk of *Nocardia beijingensis* exposure even though he had never been to China. The risk factors for Nocardia species infection include COPD, bronchiectasis, neoplastic disease, HIV infection, long-term high-dose cor-

ticosteroid therapy and alcoholism [2,5]. The insidious onset and slow progression of symptoms of nocardiosis include fever, cough, dyspnea, and chest pain, and all of the above mimic bacteria pneumonia. Chest image findings vary, and include focal nodules, mass or focal areas of consolidation, or multi-focal areas of consolidation with or without cavitation. However, none of these findings are specific to pulmonary nocardiosis. Therefore, the diagnosis is often delayed, except when pulmonary manifestations are accompanied by skin nodular lesions or chest wall involvement. In disseminated nocardiosis, central nervous system diseases, especially those in immunocompromised patients, account for a higher mortality rate (28%) [5].

Nocardia species are intracellular pathogens, and the pathogenesis of nocardiosis is complicated. Patients may be predisposed to Nocardia species infection due to an impaired T cell-mediated immune response [7]. Nocardia can also infect immunocompetent hosts, due to local impairment of bronchial defenses and bronchial structural remodeling. This most commonly occurs in the presence of COPD and bronchiectasis, which have both been reported to be important risk factors for respiratory colonization by Nocardia species [9].

Takabatake *et al*. also suggested that patients with COPD have impaired systemic cell-mediated immunity and increased susceptibility to acute respiratory tract infections due to the higher circulating levels of soluble interleukin-2 receptor (sIL-2R), neopterin, and soluble intercellular adhesion molecule-1 (sICAM-1), compared to controls [8].

Similar to the therapy for other Nocardia species, *Nocardia beijingensis* was sensitive to sulfonamides/trimethoprim in an *in vitro* study [4], but the duration required for this therapy is not always clear. Nevertheless, the average duration of treatment is 6-12 months [10]. The duration of therapy also depends on the use of immunosuppressive agents and other underlying conditions (e.g., COPD, HIV infection and solid organ transplantation).

In conclusion, we described a rare etiology of pulmonary infection caused by *Nocardia beijingensis* in a non-HIV patient with COPD in Taiwan. Due to clinical symptoms that initially mimic bacterial infection, the diagnosis of pulmonary nocardiosis is challenging, and is frequently delayed in immunocompetent hosts. When a patient has slow progression to a clinical condition after receiving several types antibiotic therapy and has typical image findings, especially chest wall involvement, a high degree of suspicion is mandatory for the diagnosis of nocardiosis.

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非人類免疫缺陷病毒帶原者併發北京諾卡氏菌感染：病例報告

張家豪　王秉槐　張厚台

社區型肺炎的病患中，因為肺諾卡菌感染是非常罕見的。診斷上通常延遲，並且有很高的死亡率。在 85 種肺諾卡菌中，北京諾卡氏菌在台灣的發生率是很低的（約 1.2% 至 5.9%）。我們報告一位 67 歲本身有慢性阻塞性肺疾病的男性病患，病人因為社區型肺炎住院，住院時的胸部 X 光片顯示雙肺為多發結節狀浸潤。病患的痰液的革蘭氏染色顯示革蘭氏陽性分枝絲狀體。16S ribsomal RNA 基因序列分析證實為北京諾卡氏菌感染。病人的臨床狀況在使用 trimethoprim/sulfamethoxazole 後有明顯改善。肺諾卡菌的感染臨床表現並無明顯的特異性，這使得診斷更加困難。即使在免疫正常的病人肺諾卡菌感染也需要保持高度的警覺性。*(胸腔醫學 **2015; 30: 30-35**)*

關鍵詞：慢性阻塞性肺病，肺諾卡菌

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Reduction of Lobar Torsion after Thoracoscopic Lobectomy: Report of a Case

Cheng-Hung How*,**, Wei-Ling Hsiao**, Jang-Ming Lee**

Lobar torsion after thoracic surgery is a rare but life-threatening complication with reported high morbidity and mortality. Recognition of this complication may be difficult, especially if signs of infarction, such as shock, sepsis and interstitial pulmonary edema are lacking. Herein, we present the case of an 83-year-old male with lung cancer who underwent video-assisted thoracoscopic surgery (VATS) for a left upper lobectomy and mediastinal lymphadenectomy. Since postoperative serial chest roentgenogram showed progressive opacity of the left lung field, chest computed tomography (CT) and bronchoscopy were arranged on postoperative day (POD) 2, and revealed total obstruction of the left lower bronchus. Under the impression of lobar torsion, we performed emergency thoracoscopic reduction surgery immediately thereafter, and successfully rescued the affected lobe. ***(Thorac Med 2015; 30: 36-41)***

Key words: lung, torsion, postoperative complications, video-assisted thoracoscopic surgery

Introduction

Pulmonary torsion is defined as parenchymal torsion of the bronchovascular pedicle with resultant airway obstruction and vascular compromise. This condition may involve the entire lung or an individual lobe and occur spontaneously, after trauma, or after cardiac or thoracic surgery [1]. Lobar torsion, a rare but life-threatening complication, could lead to gangrene or necrotizing pneumonitis of the affected lobe [1-2]. The incidence of lobar torsion is estimated to be between 0.089% and 0.4%, and mortality of 12% to 16% has been reported for complicated torsion [3-4]. Recognition of this complication may be more challenging, especially if signs of infarction, such as shock, sepsis and interstitial pulmonary edema are lacking. We encountered a case of lobar torsion following video-assisted thoracoscopic left upper lobectomy. In these cases, conventional chest radiography may show atelectasis, but chest computed tomography (CT) and bronchoscopy are more helpful in confirming the diagnosis.

Case Report

An 83-year-old man had a past history of

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hypertension under medical control. In a routine health examination, chest roentgenogram, revealed opacity at the left hemithorax. Contrasted chest CT revealed no definite hilar or mediastinal lymphadenopathy, but a 4-cm sized spiculated tumor at the left upper lobe (LUL) was seen. The tumor was confirmed as an adenocarcinoma, using percutaneous needle aspiration biopsy. Brain CT and bone scan revealed no evidence of distant metastasis. The patient was diagnosed as having primary lung cancer in the LUL, adenocarcinoma, cT2aN0M0, stage Ib, and was admitted for scheduled lobectomy and mediastinal lymph node dissection.

The patient underwent video-assisted thoracoscopic surgery (VATS) for a left upper lobectomy with mediastinal lymph node dissection. Three incisions were made: a 1-cm sized thoracoscopic port at the 7th intercostal space on the middle axillary line, a 4-cm sized working port at the 5th intercostal space on the anterior axillary line and a 1-cm sized working port at the 7th intercostal space on the posterior axillary line.

Postoperative, extubation was performed smoothly at the Operation Theater. On postoperative days (POD) 1 and 2, the patient presented with an afebrile and stable status, but serial chest radiographs showed progressively increased infiltration and opacity in the lower field of the left hemithorax, with abnormal air lucency in the upper zone (Figure 1). An elevated C-reactive protein (CRP) level, up to 30 mg/dl, was also noted. On POD 2, an emergency flexible bronchoscopy examination was performed. After aspiration of mucus plugs, bronchoscopy revealed a swollen left lower lobe (LLL) bronchial orifice, which the bronchoscope could not pass through (Figure 2). The LUL bronchial stump was intact. Contrast-enhanced CT showed abrupt termination and complete obstruction of the LLL bronchus at its origin (Figure 3). Emergency VATS LLL reduction surgery was performed immediately on

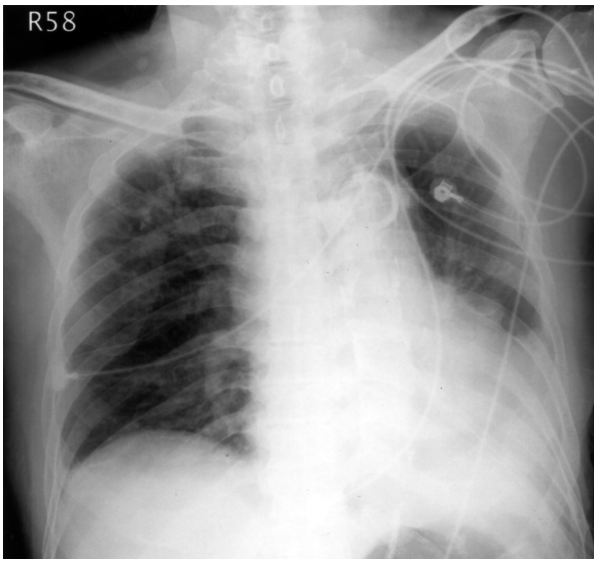

Fig. 1A. Chest radiograph on POD 1 showed an opacified left hemithorax with abnormal air lucency in the upper zone.

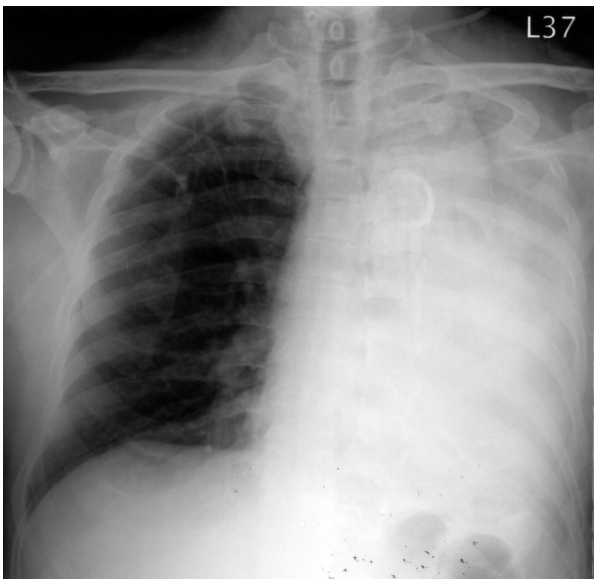

Fig. 1B. Chest radiography on POD 2 showed total opacification of the left lung field with mediastinal deviation to the left side and mildly increased infiltration in the right perihilar region.

POD 2, under the impression of LLL torsion. Direct visualization revealed the LLL had a 180º counterclockwise torsion along the pedicle axis. After surgery, the patient was admitted to the intensive care unit for postoperative care. Extubation was performed 3 days later. The patient was discharged 20 days after the operation.

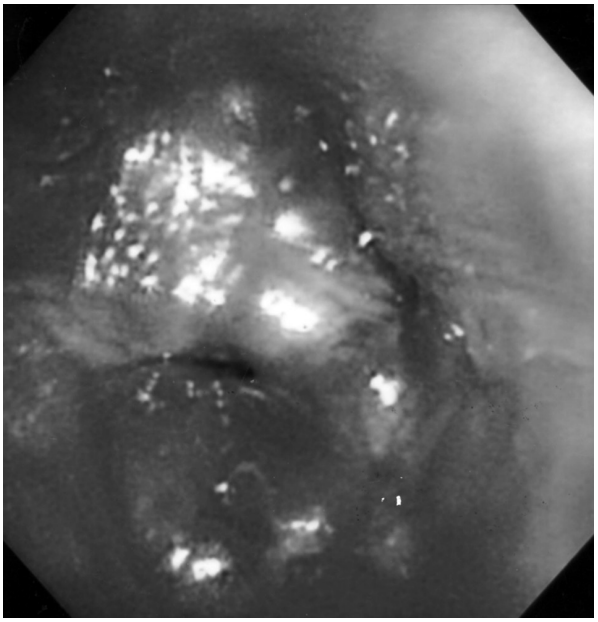

Fig. 2. Flexible bronchoscopy revealed left lower lobe lumen stenosis with the appearance of a fish mouth.

Discussion

Pulmonary torsion is defined as parenchymal torsion of the bronchovascular pedicle with resultant airway obstruction and vascular compromise. This condition may manifest within the entire lung or in an individual lobe and occurs spontaneously, after trauma, or after cardiac or thoracic surgery [1]. The degree of rotation in pulmonary torsion is generally 180 degrees, although 90 or 360-degree torsions have been reported and can occur in both directions [5-6]. Lobar torsion, a rare but life-threatening complication, could lead to gangrene or necrotizing pneumonitis of the affected lobe [1-2,7]. Lobar torsion after lobectomy occurs in 0.089% to 0.40% of patients [3,7-8]; 70% of all lobar torsions developed following a right up-

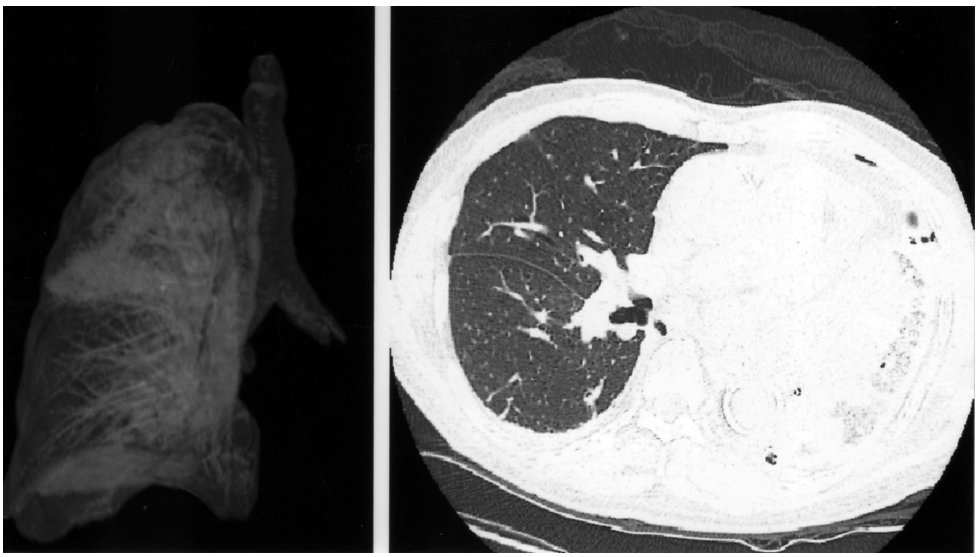

Fig. 3. Chest CT showed abrupt termination and complete obstruction of the left lower lobe bronchus at its origin.

per lobe (RUL) resection and 15% after a LUL resection [3]. The most vulnerable of all is the right middle lobe after resection of the RUL [9-10]. The exact pathophysiology of lobar torsion remains unclear, but some predisposing factors such as the presence of a complete interlobar fissure, absence of adhesions, a heavy compact lobe, pneumothorax, pleural effusion, a narrow middle lobe hilum, or extensive mobilization at surgical dissection of intrathoracic attachments and the inferior pulmonary ligament may contribute to lobar torsion [5,8]. Duan *et al*. [11] proposed that VATS lobectomy may contribute to the development of lung torsion because vessel dissection, lymphadenectomy, and thorax hemostasis all move and rotate the residuary lobe repeatedly during VATS lobectomy.

The clinical presentation of lobar torsion varies, and includes sudden and unexplained dyspnea refractory to oxygen supplementation, persistent fever, tachypnea, hemoptysis, productive cough, abruptly ceasing air leak, elevated white blood cell count, dullness to percussion and reduced breathing sounds on examination [3,12]. The arterial blood gas analysis and oxygen saturation are usually normal, secondary to complete shunting of blood from the twisted lobe or segments [12].

Chest roentgenograms play a crucial role in the initial diagnosis [6]. Routine serial chest roentgenograms taken after surgery may show different abnormalities: a collapsed or consolidated lobe in an unusual position, hilar displacement, unusual pulmonary vasculature position, rapid opacification, an opacified lobar position change, bronchial cut-off or distortion, lobar air trapping and pneumothorax [6]. Chest CT findings of lung torsion included bronchial obstruction, distortion and abnormal arterial and venous relationships in the torsive lung or lobe [13]. Bronchoscopy may show partial or complete obstruction of the bronchus to the affected lobe, caused by edema or distortion (fish-mouth sign) [14]. However, non-specific findings in chest radiographs, CT and bronchoscopy and incorrect interpretation of these findings may lead to a delay in diagnosis and treatment. The median time to diagnosis is 10 days after surgery [3]. Failure to recognize lobar torsion postoperatively will result in death caused by lobar infarction, pulmonary hemorrhage or fatal gangrene [1-2].

The conventional treatment of lung torsion is resection of the affected lobe, especially if it is clearly necrotic [1,14]. Although there are some reports of successfully preserving the twisted lobe by repositioning [1,15], most had to be resected later. The major argument against detorsion is the risk of significant influx of inflammatory mediators and necrotic tissue into the systemic circulation, which could potentially provoke a systemic inflammatory response resulting in multi-organ failure and death [16]. Thromboembolic or vascular complications are another concern [3,14]. As minimally invasive thoracic surgery becomes more readily available, VATS may offer a second option with a possible benefit over open thoracotomy [17-18]. The successful repositioning in our case was due to immediately performing an emergency VATS once a possible diagnosis of lobar torsion was suspected.

The best prophylaxis against lobar torsion is to keep in mind that it may appear both during the surgical procedure and in the postoperative period [14,18]. Pneumopexy during surgery is a key procedure to prevent torsion in patients with a high risk of lobar torsion after pulmonary resection. The position of the remaining lobes should be noted, and they should be fixed

together if they are unusually mobile [19]. Use of a double lumen endotracheal tube, and lung infiltration under direct observation before the closure of the thorax are other measures to prevent torsion [4].

In conclusion, careful postoperative observation with routine chest roentgenograms for early diagnosis of lobar torsion and prompt surgical intervention are crucial to prevent the disastrous consequence of lobar torsion. Pneumonectomy or lobectomy for the affected lobe should be considered first if diagnosis of lobar torsion has been delayed for days.

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經胸腔鏡復位之左上肺葉切除後肺扭轉：案例報告

郝政鴻 *,** 蕭偉伶 ** 李章銘 **

胸腔鏡手術後肺葉扭轉是一種罕見但有高死亡率風險的致命性術後併發症。對於胸腔手術的術後照護，如何迅速且正確地辨識肺葉扭轉的徵象相當重要。然而，當病患生命徵象穩定，無明顯休克、敗血症或肺水腫表現的情況下，要適切的診斷出肺扭轉在臨床上仍極具挑戰性。在此，我們要報告的案例是一位83歲男性，因健檢發現左上肺野陰影，經切片確診為非小細胞肺癌，入院施行胸腔鏡左上肺葉切除與淋巴結廓清。術後胸部放射線序列檢查表現逐漸擴大的肺葉塌陷。在術後第二日的斷層掃描以及支氣管鏡檢查，直接觀察到肺血管與支氣管的扭轉，確診為左下肺扭轉。經緊急胸腔鏡復位手術後，恢復良好順利出院。*(胸腔醫學 **2015; 30: 36-41**)*

關鍵詞：肺，扭轉，術後併發症，胸腔鏡手術

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Unilateral Absence of Right Pulmonary Artery in an Asymptomatic Adolescent: A Case Report and Literature Review

Kuan-Li Wu*, Yi-Hsuan Tsai*, Ming-Ju Tsai*, Inn-Wen Chong*,**

Unilateral absence of pulmonary artery (UAPA) is a rare congenital malformation. Some cases cause deadly complications during childhood, others are usually diagnosed incidentally in asymptomatic patients in adulthood by chest plain film. The image feature on plain film is often a hypoplastic lung on the affected side. Confirmatory CT angiography or magnetic resonance angiography may be needed. The common symptoms of UAPA are hemoptysis, dyspnea, and recurrent pulmonary infections. However, high-altitude pulmonary edema has been thought to be a possible complication recently. Herein, we present an asymptomatic 15-year-old adolescent with absence of a right pulmonary artery. Magnetic resonance angiography confirmed this diagnosis and revealed associated left inferior pulmonary vein stenosis, which has not been reported previously. ***(Thorac Med 2015; 30: 42-47)***

Key words: unilateral absence of pulmonary artery, pulmonary hypoplasia, pulmonary vein stenosis

Introduction

Unilateral absence of pulmonary artery (UAPA) is a very rare congenital malformation with a prevalence of about 1 in 200,000 adults [1]. Some patients remain asymptomatic and are usually diagnosed incidentally in adulthood by chest plain film. Herein, we report the case of a healthy 15-year-old adolescent who presented with an abnormal chest radiograph, and was eventually diagnosed as having absence of a right pulmonary artery and stenosis of the left inferior pulmonary vein by magnetic resonance angiography (MRA).

Case Report

A 15-year-old male presented to the chest clinic of our hospital due to an abnormal chest radiograph on his regular health examination. He denied any respiratory symptoms or past medical illness. He was a student and had never smoked. He had normal daily activities and had no discomfort during strenuous exercise. The oxygen saturation was 99% while breathing ambient air. Physical examination revealed an

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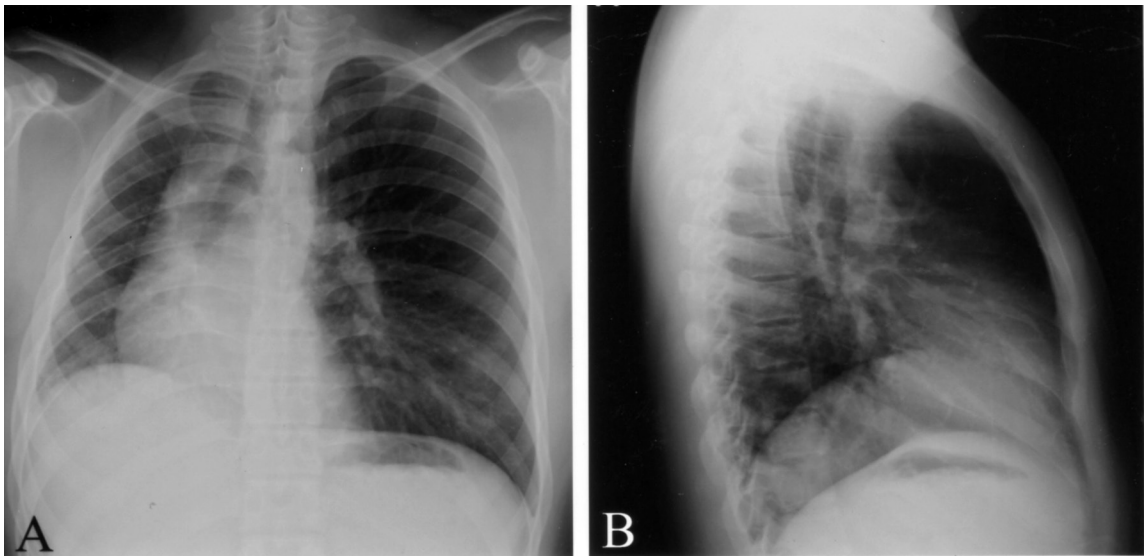


Fig. 1. (A) Postero-anterior chest radiograph reveals a small right hemithorax with rightward shifting of the mediastinum. (B) Lateral view reveals an elevated right hemidiaphragm without evidence of lobar collapse.

asymmetric thoracic cage on inspiration with smaller expansion on the right side. Decreased breathing sounds without an adventitious sound was noticed in the right-side chest. Other examinations were unremarkable.

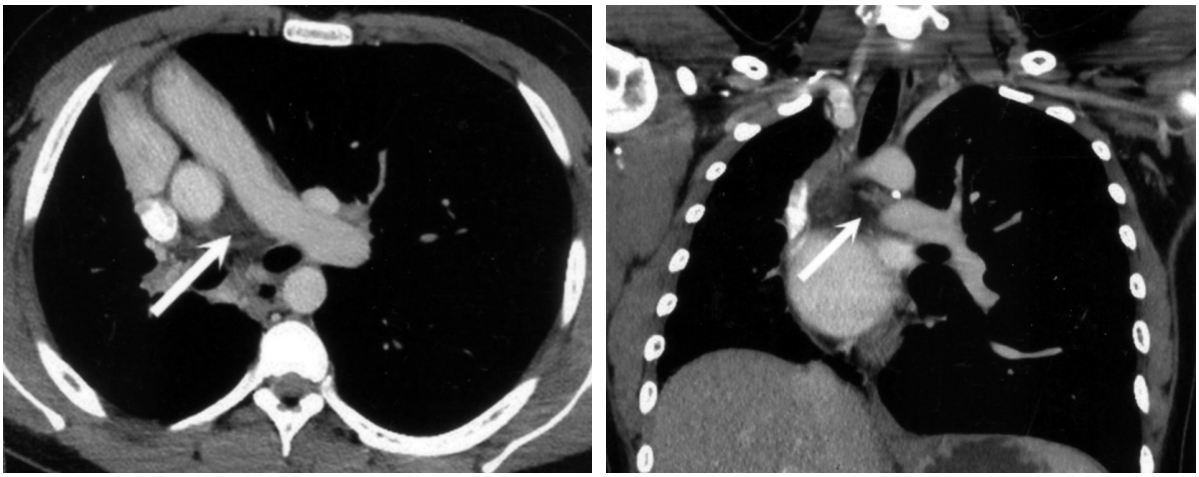
The postero-anterior chest radiograph showed decreased volume of the right hemithorax with rightward shifting of the mediastinum (Figure 1A); the lateral view showed no evidence of lobar atelectasis (Figure 1B). Computed tomography (CT) showed absence of a right pulmonary artery with hypoplastic right lung and compensating hyperinflation of the left lung (Figure 2). The pulmonary function test revealed no obstructive or restrictive ventilatory defect (FEV_1/FVC of 83.67%; total lung capacity of 4.18 L, 81.9% predicted) and normal diffusing capacity of the lung for carbon monoxide (DLCO) (7.15 L/min/mmHg, 82.3% predicted; KCO of 1.78).

Transthoracic echocardiography, arranged to exclude any accompanying congenital heart disease, showed normal left ventricular systolic function, mild tricuspid regurgitation with pulmonary hypertension, and estimated right ventricular systolic pressure of 39.31 mmHg. The cardiovascular MRA showed agenesis of the right pulmonary artery with collateral circulation from the right bronchial artery, right internal mammary artery, and right inferior phrenic artery; stenosis of the left inferior pulmonary vein was also found (Figure 3).

The patient and his parents refused any further invasive survey. He remained asymptomatic and was regularly followed in the chest clinic.

Discussion

Unilateral absence of pulmonary artery (UAPA), also known as pulmonary artery agenesis, is a very rare congenital cardiovascular malformation. Frentzel was the first to describe this anomaly in 1868. The estimated prevalence of UAPA ranged from 1 in 200,000 to 1 in 300,000 adults, with no sex predilection in dif-



(A) (B)

Fig. 2. (A) Computed tomography of the chest shows absence of a right pulmonary artery from the main pulmonary trunk (arrow). (B) Coronal reconstruction reveals hypoplasia of the right lung and hyperinflation of the left lung. The left pulmonary artery is noted, whereas the right pulmonary artery is not found at the expected site (arrow).

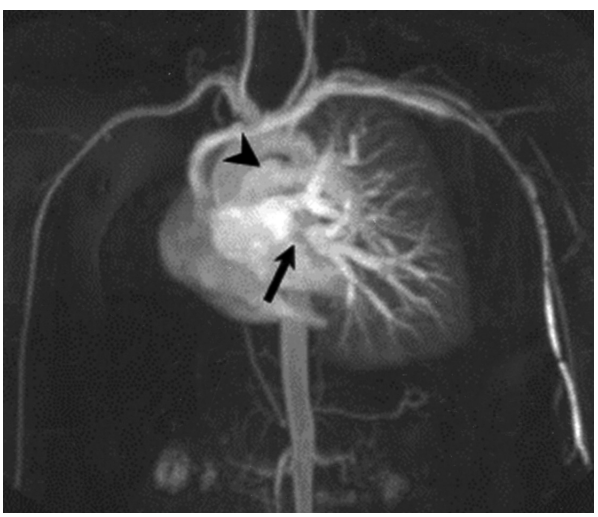


Fig. 3. Magnetic resonance angiography shows absence of a right pulmonary artery (arrowhead) with left interior pulmonary vein stenosis (arrow).

ferent reports [1].

The cause of an absent pulmonary artery is thought to be malformation of the sixth aortic arch during embryonic development. Lacking normal blood supply from the pulmonary arteries, the collaterals commonly arise from the bronchial arteries, but supplies from the intercostal arteries, subdiaphragmatic arteries, subclavian arteries and even the coronary arteries have also been reported [2]. UAPA is more common with the right pulmonary artery, with a 60% greater occurrence rate than on the left side in affected patients [3].

UAPA is usually accompanied with other congenital cardiovascular anomalies, including tetralogy of Fallot, atrial septal defect, coarctation of the aorta, right aortic arch, truncus arteriosus, patent ductus arteriosus and pulmonary atresia. About 80% of reported cases with the above anomalies involved the left pulmonary artery [4].

Associated anomalies of the pulmonary vein are seldom mentioned in the literature. One report found abnormal communication between the left upper pulmonary vein and the superior vena cava with a concurrent absence of the right pulmonary artery [6]. Pulmonary vein stenosis, as in our case, has not been reported previously.

Two types of clinical presentations have been described. One is seen mostly in infants, who often present with pulmonary hypertension and congestive heart failure. The other is in older patients, who are usually asymptomatic. Some adult patients have exercise intolerance (18-40%), hemoptysis (20%), pulmonary hypertension (44%), or recurrent pulmonary infection (37%), but most cases are detected incidentally during chest radiography [4].

Because patients, especially adults, may be asymptomatic, the history and physical examination are usually non-diagnostic. Examinations may show an asymmetrical chest wall with decreased breathing sounds on the affected side [7]. The electrocardiogram may reveal, less commonly, right ventricular dominance in cases with pulmonary hypertension [4].

Typical chest radiographic features are asymmetric lung fields, with a small hemithorax and hyperlucent lung on the affected side. Shifted mediastinum and diminished hilar vasculature are observed. The contralateral lung may compensate with hyperinflation on the image [5]. The absence of blood flow results in hypoplastic lung, which usually presents as a small hemithorax on the chest radiograph. The possible differential diagnoses of similar imaging patterns include many primary and secondary conditions [8]. In adults, Swyer-James Syndrome, Poland syndrome, and Scimitar syndrome are common etiologies of similar imaging findings and should be carefully excluded [9-11]. CT and magnetic resonance imaging (MRI) are useful tools to reach a definitive diagnosis of UAPA. CT and MRI may identify the intact peripheral branches of the pulmonary arteries, variable collateral circulation, mosaic parenchymal changes and bronchiectasis resulting from recurrent infection [5].

Transthoracic echocardiography is also important to exclude any other concomitant cardiovascular abnormalities or pulmonary hypertension. Angiography is the “gold standard” for diagnosis of UAPA. However, due to the feasibility of CT and MRI, angiography is seldom performed nowadays. Angiography is reserved mostly for therapeutic purposes, such as embolization for massive hemoptysis [12].

No treatment is needed for UAPA patients without cardiopulmonary symptoms. The therapeutic plan may be initiated whenever the patient is symptomatic, especially in those with hemoptysis, recurrent infection, or pulmonary hypertension [1]. Treatment options include partial or total pneumonectomy, closure of selected collateral arteries or a primary or staged pulmonary artery anastomosis [13].

The overall mortality rate is about 7%. A poor outcome is often due to pulmonary hypertension and pulmonary hemorrhage. Causes of death may include right heart failure, massive pulmonary hemorrhage, respiratory failure and high-altitude pulmonary edema [4].

Conclusion

UAPA is a rare disease, and is often diagnosed early in symptomatic children. Since most adult patients are asymptomatic, a high index of suspicion while reading a chest radiograph remains the key to diagnosis. In addition, the clinician should carefully exclude any possible associated congenital cardiovascular anomalies and be aware of possible complications such as pulmonary hemorrhage and heart failure.

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一名無症狀青少年的單側右肺動脈先天性缺失－病例報告與文獻回顧

吳寬澧 * 蔡怡萱 * 蔡明儒 * 鍾飲文 *,**

單側肺動脈缺失是一種罕見的先天性異常。部分患者在幼兒時期就產生致命性的併發症，然而也有部分的病人持續無症狀至成人階段。因此通常是在例行的胸腔 X 光或電腦斷層檢查時意外發現。可能的症狀包含咳血、呼吸困難、反覆性下呼吸道感染等。此外高海拔肺水腫也在此類病人中被報導過。影像學上的特徵為單側發育不全的肺合併有縱膈腔偏移。在此，我們報告一位十五歲的健康男性經由核磁共振血管造影診斷為右側肺動脈缺失且有左下肺靜脈狹窄，確認並無合併先天性心臟病。而合併肺靜脈狹窄目前在文獻上未曾提及。由於病人拒絕進一步侵入性檢查，仍持續在門診追蹤當中。*(胸腔醫學 **2015; 30: 42-47)***

關鍵詞：單側肺動脈缺失，肺發育不全，肺靜脈狹窄

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Tracheal Bronchus in a Lung Cancer Patient – Demonstrated with Reconstructed CT Images and Virtual Bronchoscopy

Wen-Shuo Wu*, Yuh-Min Chen*,***, Li-An Wu**, Shi-Chuan Chang*,***,****, Yu-Chin Lee*,***, Kun-Ta Chou*,***

Tracheal bronchus is a rare congenital malformation. It is defined as an abnormal bronchus that originates from the lateral wall of the trachea and progresses toward the upper lobe territory of the lung. In most cases, it is incidentally found by bronchoscopy or computed tomography. It is rarely symptomatic, but some patients may present with recurrent upper airway symptoms that may require surgical intervention. We described an 81-year-old man who was found incidentally to have tracheal bronchus while undergoing bronchoscopy for suspected lung cancer. We reconstructed the chest computed tomography images to clearly visualize the origin and surroundings of the tracheal bronchus. ***(Thorac Med 2015; 30: 48-54)***

Key words: tracheal bronchus, congenital malformation, reconstruction computed tomography

Introduction

Tracheal bronchus is an abnormal bronchus originating from the trachea or main bronchus. In most cases, it is incidentally found by bronchoscopy or computed tomography (CT). Although it is usually asymptomatic, some patients may present with recurrent upper airway symptoms that may require surgical intervention. Herein, we reported an 81-year-old man who was incidentally found to have tracheal bronchus while receiving bronchoscopy for suspected lung cancer. We reconstructed the chest CT images, which further helped us to clearly visualize the origin and surroundings of the tracheal bronchus.

Case Report

An 81-year-old male patient, who had a past medical history positive for type 2 diabetes mellitus and chronic obstructive pulmonary disease, presented to our clinic with chest pain after a falling accident. He was a past and current cigarette smoker, consuming 1 pack of cigarettes per day for more than 60 years. No spe-

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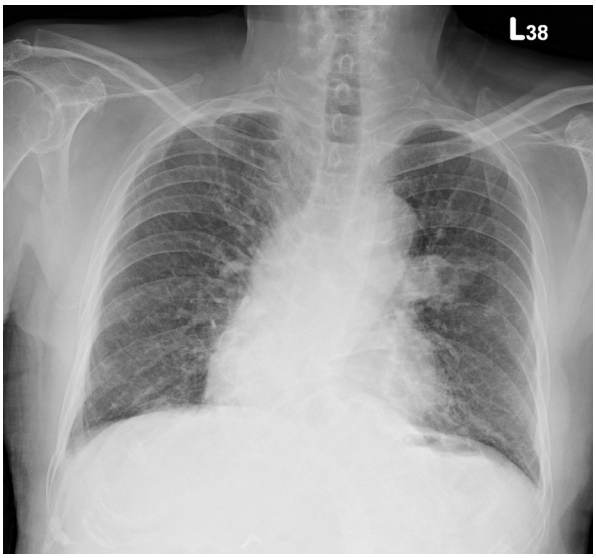

Fig. 1. Chest radiography shows a mass lesion at the left lung field and increased density at the RUL.

cific finding was observed on physical examination. Chest radiography disclosed a mass lesion in the left lung field (Figure 1). Chest computed tomography (CT) was performed and showed a large mass at the left upper lobe (LUL), about 5.6×3.9×2.8 cm in size (Figure 2) and abutting the left upper mediastinal pleura. Two enlarged lymph nodes, favoring ipsilateral mediastinal lymphadenopathy, in the aortopulmonary (AP) windows and a solitary pulmonary nodule at the left lower lobe were also noted. In addition, a tracheal bronchus was suspected. We thus reconstructed the chest CT images, which demonstrated a blind-ended bronchus arising from the right side of the lower trachea with an aberrant right upper lobe (RUL) lobe (Figure 3).

Under the impression of lung cancer, bron-

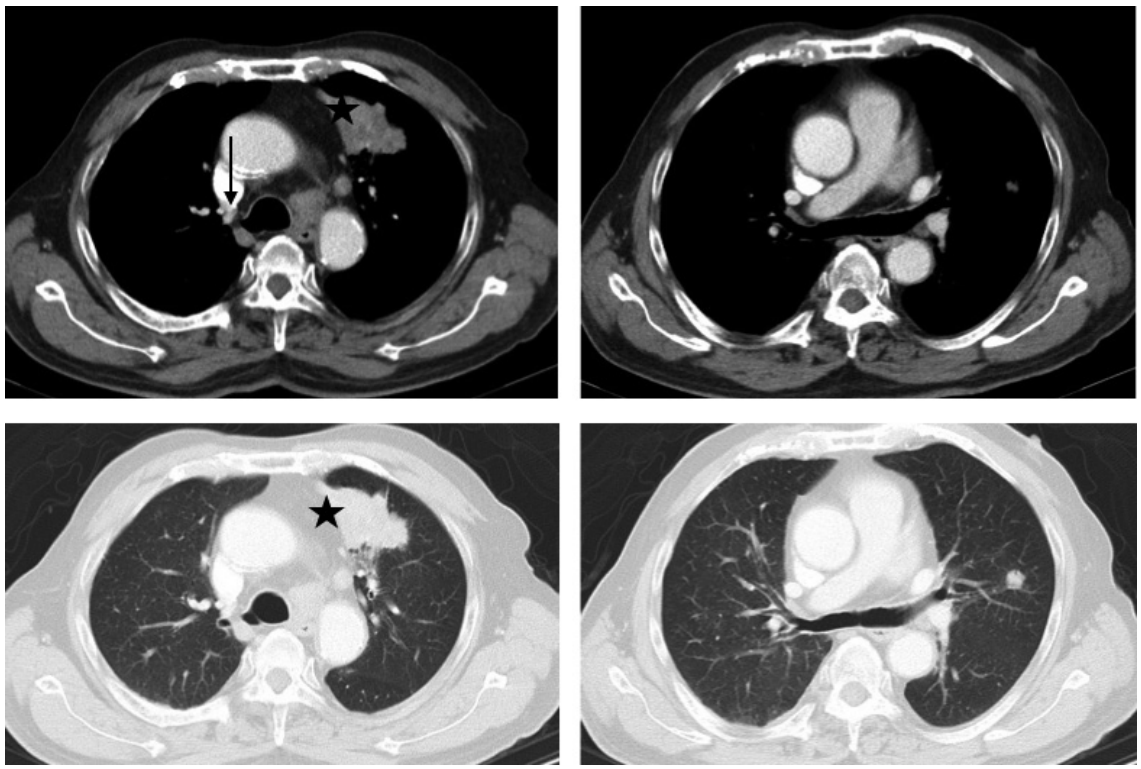

Fig. 2. Chest CT revealed a mass lesion at the left upper lobe (star) and a pulmonary nodule at the left lower lobe. A tracheal bronchus originating from the right-side tracheal wall (arrow).

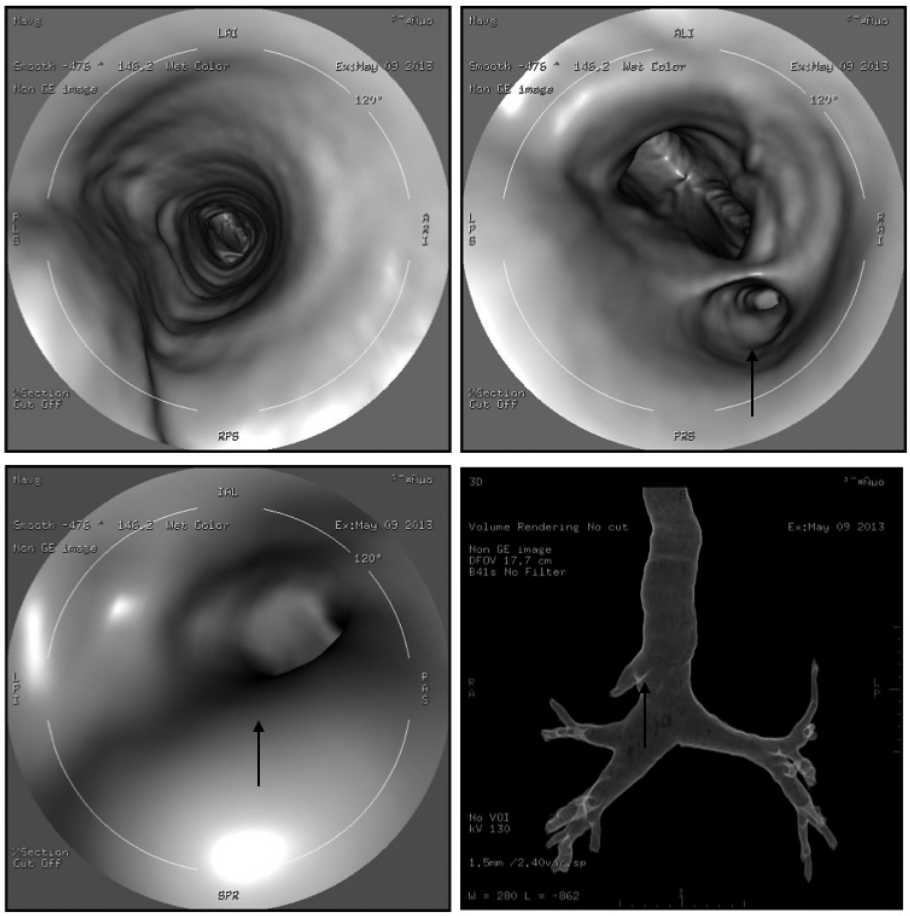

Fig. 3. Reconstruction of chest CT images revealed a blind-ended (arrow) tracheal bronchus arising from the right side with an aberrant RUL.

choscopy with biopsy was arranged (Figure 4), and showed a right-side tracheal bronchus. Forceps were unable to advance into the orifice of the tracheal bronchus. Otherwise, there was grossly no lesion within visible range, except mild submucosal infiltration at the LB3 orifice. Under fluoro-guidance, biopsy of the LUL lesion was performed via the LB3a orifice. The pathology of the biopsied specimens showed non-small cell carcinoma. The immunohistochemical profile of the specimens revealed they were immunoreactive for CK5/6 and p40, but non-reactive for CK7, TTF-1 and napsin stains, which was compatible with poorly differentiated squamous cell carcinoma of lung origin. The high sensitivity EGFR mutation test showed no variation. Subsequent staging showed negative on the whole body bone scan and brain magnetic resonance imaging. The clinical stage was T4N2M0, stage IIIB. Chemotherapy with concurrent radiotherapy was arranged, and oral navelbine plus cisplatin was given for 4 cycles. Radiotherapy with 6600cGy in 33 fractions was performed at the primary tumor and mediastinal lymphadenopathy. Partial response to the treatment was observed, and he was then placed under regular follow-up in our clinic.

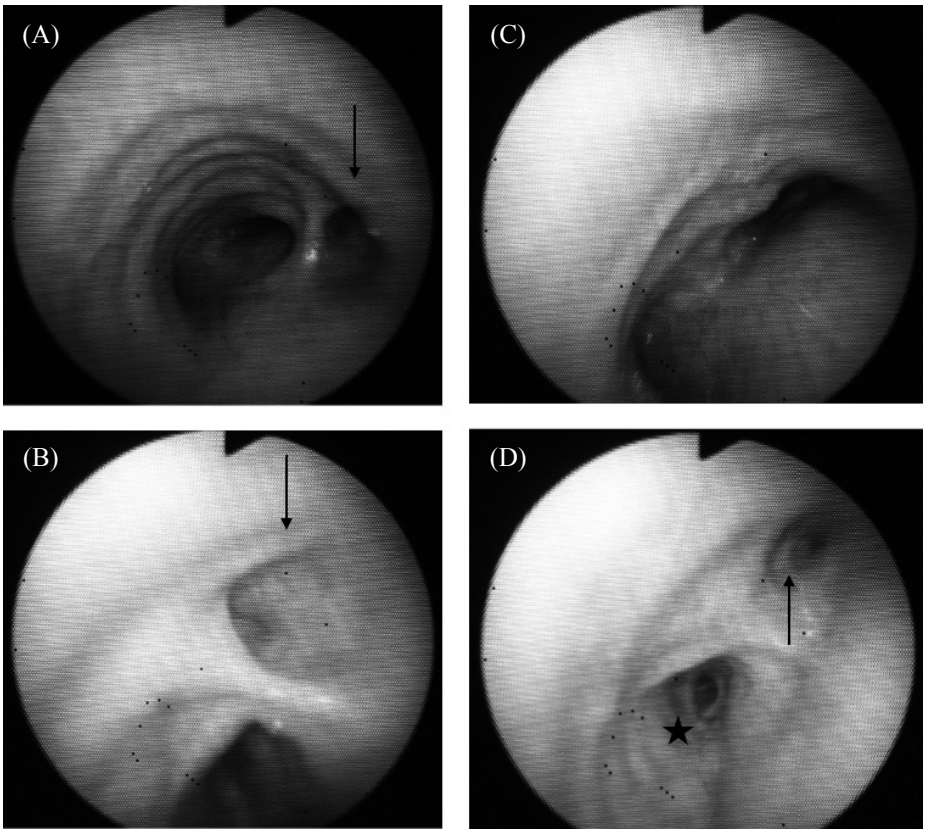

Fig. 4. (A) Lower trachea. Tracheal bronchus originating from the right-side wall of the trachea (arrow). (B) The orifice of the tracheal bronchus (arrow). (C) Carina. (D) The bifurcation of the right main bronchus consisted of a right middle lobe orifice (arrow) and a right lower lobe orifice (star).

Discussion

Tracheal bronchus was first described by Sandifort in 1785 [1]. In recent literature, the term "tracheal bronchus" has included a variety of bronchial anomalies originating from the trachea or main bronchus and directed to the upper lobe territory. The incidence of the presence of tracheal bronchus is 0.1-2% [2] and it is mainly an incidental finding in bronchoscopy or bronchography.

Contrary to the variations of lobar or segmental bronchial divisions, abnormal bronchi arising from the trachea or main bronchi are rare. Major bronchial abnormalities include accessory cardiac bronchus (ACB) and "tracheal" bronchus. Most tracheal bronchi arise from the right wall of the trachea within 2 cm of the carina, but they could originate at any location between the cricoid cartilage and the carina [3-4]. They can be classified into 2 types — ''displaced'' or ''supernumerary.'' [4-5] A displaced bronchus is an anomalous anteriorly and apically located RUL bronchus or any of its segments, most commonly an apical one. If the entire RUL takes off from the trachea, the right main bronchus is the bronchus intermedius, feeding the right middle and lower lobes. The supernumerary bronchus is less common than a displaced bronchus, and may coexist with nor-

mal RUL branching. The tracheal bronchus is occasionally called a ‘‘tracheal diverticulum’’ when it ends in a blind pouch. The case we presented was that of a tracheal bronchus of the displaced type. The RUL originated from the tracheal bronchus had a blind end.

Two theories were proposed for the development of tracheal bronchi [6]. The first hypothesis was that tracheal buds are present in utero and fail to regress during development. The second theory presumes that some unknown disturbance occurred during embryogenesis, leading to the formation of tracheal bronchus.

Tracheal bronchus can be associated with other congenital malformations, such as ribs, pectus excavatum, esophageal atresia, tracheoesophageal fistula, and congenital heart disease [6-8]. Patients with Down syndrome also have an increased incidence of tracheal bronchus [6-7,9]. Lung cancer in cases of true tracheal bronchus is rarely reported [10-11].

Although tracheal bronchi are generally asymptomatic, stridor is sometimes reported in children. It is also reported that infection and irritation can easily occur in patients with tracheal bronchus because of its structure. Some patients may have recurrent pneumonia [12], bronchiectasis or chronic bronchitis. The recognition of these anatomical variants is important in symptomatic patients, and surgical resection may be necessary in severe cases. However, asymptomatic cases may be incidentally found during bronchoscopy or on chest CT images.

The frequency of the diagnosis of the anomalies of lung and bronchial trees has increased as a result of refinements in modern imaging and classification. Spiral CT is able to demonstrate the anatomy down to the subsegmental level using various reformation techniques [13-14], including multiplanar reconstruction [15], shaded-surface display, minimum-intensity projection, maximum-intensity projection, sliding thin slab imaging [16], volume rendering, and virtual bronchoscopy [17]. The advances in these techniques have provided better understanding of the structure of congenital malformations [18]. Visualizing these malformations using these noninvasive methods can assist in the further management of patients with congenital malformation.

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以電腦斷層重組影像及虛擬支氣管鏡呈現一名肺癌合併氣管性支氣管之個案報告－病例報告

吳文碩 * 陳育民 *,*** 吳禮安 ** 張西川 *,***,**** 李毓芹 *,*** 周昆達 *,***

氣管性支氣管唯一罕見之先天性結構異常。其定義為一異常的支氣管分支自氣管的側壁，延伸到上肺野。大部份的病人都不會有症狀，所以通常是在支氣管鏡檢或是胸部電腦斷層影像檢查時的意外發現。有極少數的病人會以反覆的上呼吸道感染或是肺炎來表現，並且需要外科手術治療。本文將簡述一名八十一歲的病人，因懷疑肺癌於做支氣管鏡病理切片檢查時意外發現有氣管性支氣管的異常結構，並藉由電腦斷層重組的影像來呈現。*(胸腔醫學 **2015; 30: 48-54**)*

關鍵詞：氣管性支氣管，先天性結構異常，電腦斷層影像重組

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Metastasis to the Appendix from Lung Adenocarcinoma Manifesting as Acute Appendicitis: A Case Report

Yi-Fong Su*, Chi-Lu Chiang*, Fang-Chi Lin*, Chun-Ming Tsai*,**

Appendix metastasis from lung adenocarcinoma is very rare. Metastasis-induced acute appendicitis is extremely rare. We present the case of a 77-year-old woman with stage IV lung adenocarcinoma who presented with acute appendicitis. She was admitted to the emergency department with complaints of right lower quadrant pain, nausea and vomiting for 12 hours. Contrast-enhanced abdominal computed tomography showed a dilated appendix with a thickened wall suggestive of acute appendicitis. She underwent appendectomy, and the pathological examination of the appendiceal specimen demonstrated metastatic poorly differentiated adenocarcinoma from the lung. After treatment for acute appendicitis, she was discharged and recovered uneventfully, and was then referred to our thoracic oncology department to resume treatment for her lung cancer. ***(Thorac Med 2015; 30: 55-60)***

Key words: lung cancer, adenocarcinoma, acute appendicitis

Introduction

Lung cancer is the most common malignancy worldwide in terms of incidence and mortality in both men and women, and is also the leading cause of cancer death in Taiwan. Lung cancer metastasis is common, and the most commonly involved sites are the brain, bones, liver, adrenal glands and other regions of the body [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases, presents as metastatic disease in over half of all cases, and is associated with a poor prognosis [1-2]. In the past 2 decades, the incidence of adenocarcinoma has increased in both males and females [2-3]. In Taiwan, adenocarcinoma is the most common histological type of NSCLC [2,4]. Appendix metastasis from lung cancer is very rare, and may occur in the late stages of the disease. We present a 77-year-old woman with stage IV lung adenocarcinoma who presented with acute appendicitis. She underwent appendectomy, and pathology of the appendiceal specimen demonstrated metastatic poorly differentiated adenocarcinoma from the lung.

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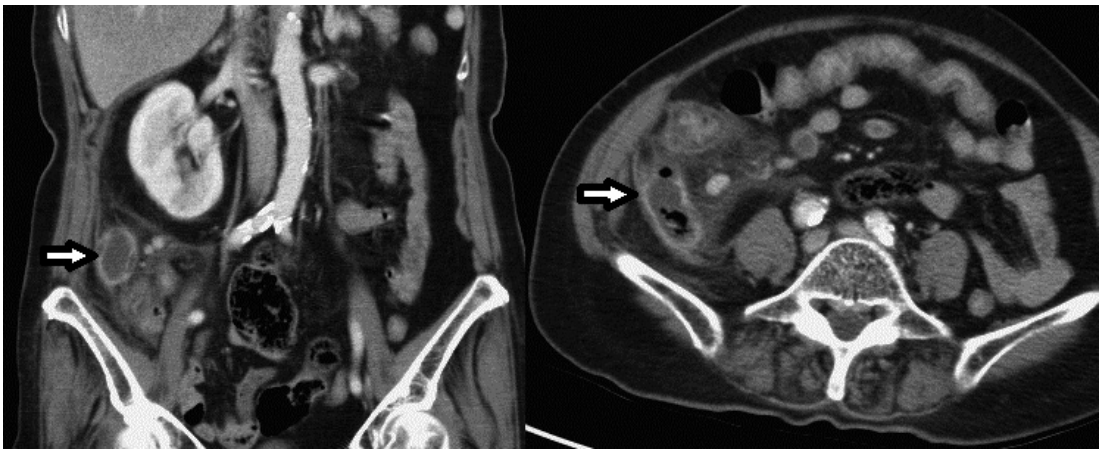

Fig. 1. Computed tomography scan showing a thickened wall and distended appendiceal tip, with infiltration of soft-tissue in the ileocecal region suggestive of acute appendicitis.

Case Report

A 77-year-old female patient was admitted to the emergency department with complaints of right lower quadrant pain, nausea and vomiting for 12 hours. A physical examination revealed notable tenderness to palpation in all quadrants, with rebound and guarding. Her vital signs were within normal limits, and laboratory results revealed a white blood cell count of 13400/mm^3 with 93% neutrophils, and a C-reactive protein level of 17.25 mg/dL. Her medical history indicated that she had been diagnosed with stage IV adenocarcinoma of the lung with brain metastasis (EGFR mutation: wild type) and was subsequently followed at our thoracic oncology department for 1 year. She had been given chemotherapy treatment with 4 cycles of pemetrexed plus carboplatin and had a partial response of the lung lesion. Gamma knife radiosurgery was used to treat her brain metastasis and achieved a partial response. Contrast-enhanced abdominal computed tomography (CT) was performed in the emergency room, and showed a dilated appendix with a thickened wall suggestive of

Fig. 2. Adenocarcinoma involving the serosa of the appendix (H&E, 40×).

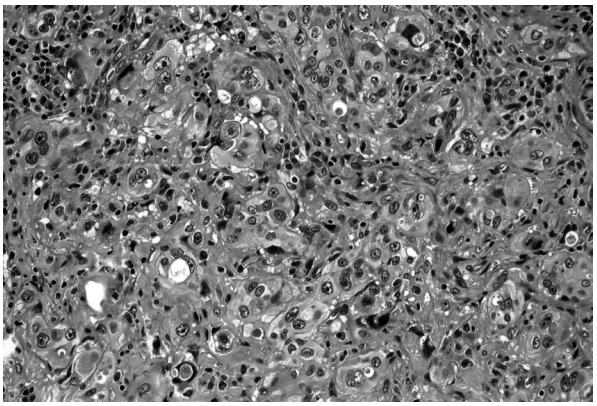

Fig. 3. Adenocarcinoma involving the serosa of the appendix (H&E, 200×).

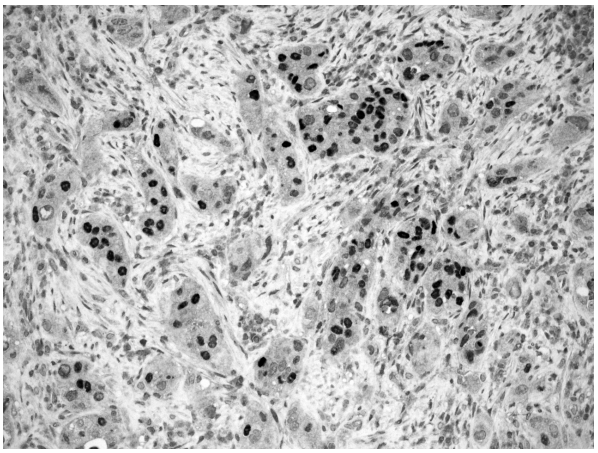

Fig. 4. Strong TTF-1 immunopositivity of the tumor and lymphovascular invasion (TTF-1 immunostain, 200×).

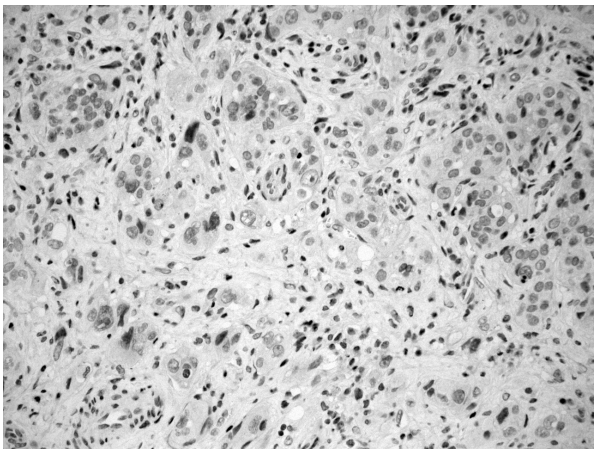

Fig. 6. Negative CK-20 immunopositivity of the tumor and lymphovascular invasion (CK-20 immunostain, 200×).

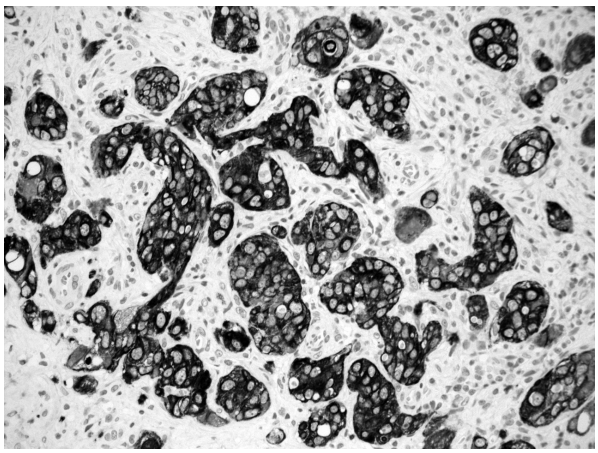

Fig. 5. Strong CK-7 immunopositivity of the tumor and lymphovascular invasion (CK-7 immunostain, 200×).

acute appendicitis (Figure 1). There was no evidence of intraperitoneal metastasis in the CT scan. Surgical exploration revealed a firm swelling appendix with perforation, and appendectomy was performed. There was no peritoneal metastasis or evidence of metastasis on the appendix. A histopathological examination showed multiple foci of adenocarcinoma metastasis in the appendix mucosa and serosa (Figures 2, 3). Immunohistochemical (IHC) staining revealed that the tumor cells strongly expressed thyroid transcription factor-1 (TTF-1) (Figure 4) and cytokeratin-7 (CK-7) (Figure 5), but showed negative reactivity for CK-20 (Figure 6). These findings confirmed adenocarcinoma of the lung. The patient was discharged with an uneventful recovery.

Discussion

Metastasis-induced acute appendicitis is an uncommon complication [5]. Previous studies have reported metastasis to the appendix from carcinomas of the breast, lung, pancreas, stomach, ovary, liver and kidney [5-11]. It has also been reported that metastatic cancers of the appendix do not present with any specific symptoms or signs [8-9]. Obstruction of the appendiceal lumen due to metastasis as seen in our case has been described in the majority of reported cases, and this may play a key role in the mechanism of acute appendicitis [8-10]. Malignancies are a rare but known cause of appendiceal obstruction and inflammation, most commonly involving primary tumors such as carcinoids or

adenocarcinomas. Cases of appendicitis from metastatic lung adenocarcinoma are exceedingly rare [12-13]. The rate of perforation has been reported to be 70% in cases of metastasis-induced acute appendicitis, compared to only 40% for simple acute appendicitis [7]. This high rate of perforation may be explained by the local effect of metastasis on the ability of the appendix to limit inflammation, obstruction of the lumen, or the general immunocompromised condition of cancer patients. Appendix cancer is extremely rare, affecting only an estimated 600 to 1,000 Americans each year. It accounts for only 0.4% of gastrointestinal tumors and is usually diagnosed incidentally in approximately 1% of all appendectomies [10-11]. The most common benign tumors of the appendix are carcinoids, and adenocarcinomas are the most common appendiceal malignancies. However, primary adenocarcinoma originating in the appendix is rare, and usually resembles metastatic adenocarcinoma. Carcinoids account for 2/3 of the cases of appendix cancer, with cystadenocarcinomas accounting for 20% and adenocarcinomas, 10% [10-11].

Carcinoids and adenocarcinomas with typical pathological features and specific tumor markers can be easily detected in the appendix. In patients who present with metastatic cancer, determining the primary site of origin may have a major impact on the choice of treatment and outcome. However, in spite of clinical, radiographic, and routine histologic studies, the primary site of origin remains uncertain in nearly 15% of cases [14]. A large proportion of these cases are adenocarcinomas, and they are challenging to treat. In our case, strong immunoreactivity for CK-7 and TTF-1 suggested the diagnosis of metastatic lung adenocarcinoma. Negativity for CK-20 excluded other possible adenocarcinomas and carcinoid tumors. Primary lung cancers themselves most commonly metastasize to the brain, bones, liver, and adrenal glands. IHC staining of a biopsy is often helpful in determining the original source. TTF-1, CK-7 and CK-20 have recently been reported to be useful in distinguishing between primary and metastatic lung adenocarcinoma. Previous studies have confirmed that the expressions of CK-7, CK-20, and TTF-1 are useful markers for the diagnosis of lung cancers and for the differential diagnosis of primary pulmonary adenocarcinomas from metastatic adenocarcinomas. TTF-1 is a sensitive IHC marker for pulmonary and thyroid adenocarcinomas and is expressed consistently in the terminal respiratory unit, which is composed of peripheral airway cells. Furthermore, the expression of TTF-1 has been reported to be maintained in 72% of adenocarcinomas of the lung [15].

Cytokeratins are intermediate filament proteins present in epithelial cells. They are expressed in normal organs and in the tumors that arise from them. IHC staining is used to evaluate the pattern of cytokeratin expression in cells of epithelial origin. Positive CK-7 staining is seen in lung, breast, endometrium, ovary, cervix, salivary gland, and thyroid cancers, cholangiocarcinoma, and adenocarcinoma of the pancreas. In contrast, CK-20 expression is observed in all colorectal adenocarcinomas and in the majority of gastric and pancreatic tumors. Prostate, kidney, and adrenocortical carcinomas, sarcomas, carcinoids, hepatocellular carcinomas and thymomas are negative for both CK-7 and CK-20 staining, while a large proportion of pancreatic, biliary, bladder and gastric tumors express both CK-7 and CK-20 [16].

In previous reports, the interval between the presentation of cancer and the presenta-

tion of appendicitis ranged from 1 month to 5 years [10-11], compared to nearly 1 year for our patient. With the improved survival of lung cancer patients, metastasis to the appendix may become more common in the future. While metastasis is an uncommon cause of appendiceal obstruction and appendicitis, it should be considered as part of the differential diagnosis when a patient with known cancer presents with symptoms consistent with appendicitis. Stage IV lung cancer has already spread beyond the lungs and is considered inoperable, as surgery would be unable to remove the tumor and offer a chance for a cure. Although these patients usually have a poor prognosis, acute appendicitis due to metastatic spread should be treated in the same manner as acute appendicitis of any other etiology.

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肺腺癌轉移至闌尾後以急性闌尾炎表現：個案報告

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肺腺癌轉移至闌尾在臨床上非常少見，轉移導致的闌尾炎更是少見。我們提出一位 77 歲女性病患，本身是第四期肺腺癌以急性闌尾炎表現，到急診抱怨右下腹痛並發噁心嘔吐十二小時，注射顯影劑的腹部電腦斷層發現闌尾腫脹且腸壁增厚懷疑急性闌尾炎，闌尾切除後病理確診為發現轉移肺腺癌。在經治療急性闌尾炎之後，病患狀況改善出院，於我們的胸腔腫瘤門診繼續接受肺癌的治療。*(胸腔醫學 **2015; 30: 55-60**)*

關鍵詞：肺癌，腺癌，急性闌尾炎

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