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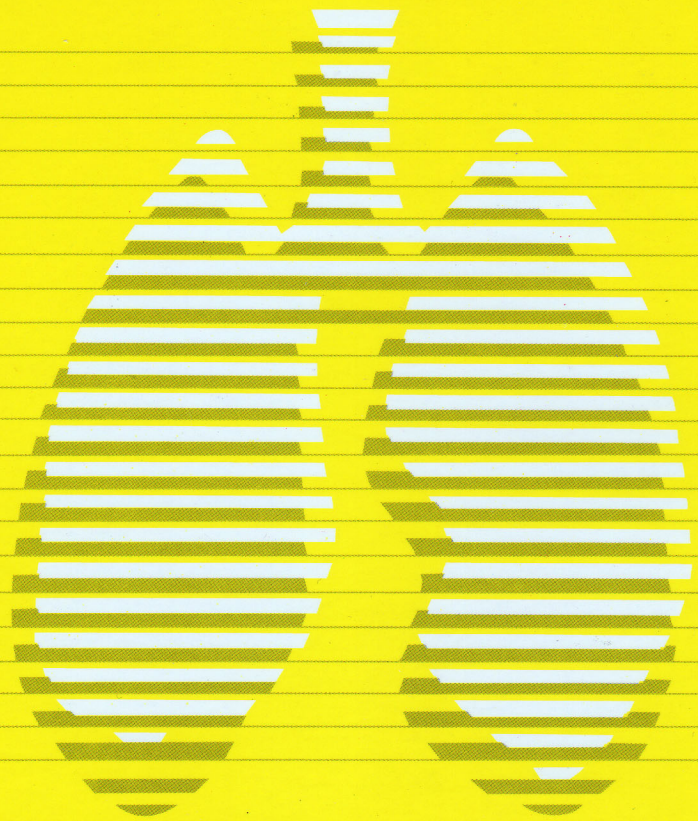

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Differences in Morning and Evening Blood Pressure in Patients with Obstructive Sleep Apnea

Shan-Chieh Huang, Chien-Ming Chu, Yu-Chih Liu, Chung-Chieh Yu

Introduction: Obstructive sleep apnea (OSA) is an independent risk factor for hypertension and is associated with increased cardiovascular mortality. Although a diurnal blood pressure (BP) variation is observed in OSA, it is not well documented. This study investigated the morning and evening BP variations in patients with OSA and estimated the effect of continuous positive airway pressure (CPAP) on BP.

Methods: This retrospective study enrolled 70 patients with newly-diagnosed OSA who underwent a 1-night CPAP titration. The evening BP before sleeping and the morning BP after waking were measured at 1 time point during polysomnography and CPAP titration. The average heart rate was also recorded during these 2 periods. BP in the evening and morning and the average heart rate were compared pre- and post-CPAP therapy.

Results: Systolic and diastolic BP in the morning (systolic, 140.44±18.09 mmHg; diastolic, 83.49±12.55 mmHg) were both significantly higher than in the evening (systolic, 135.17±16.51 mmHg; p=0.003; diastolic, 79.31±11.84 mmHg; p<0.001) during polysomnography. After 1 night of CPAP, both the apnea-hypopnea index and mean saturation showed marked improvement. Morning and evening BP was similar (systolic: 131.66±15.33 vs. 130.96±15.13 mmHg; p=0.618; diastolic: 78.03±11.68 vs. 78.84±11.88 mmHg; p=0.467). The average heart rate was reduced significantly after CPAP (pre-CPAP, 67.09±8.31 beats per min; post-CPAP 63.32±9.56 beats per min; p=0.001).

Conclusion: Patients with OSA have higher waking BP and greater diurnal BP variation. A 1-night CPAP therapy can significantly reduce morning BP, reverse any diurnal BP difference, and significantly reduce the average heart rate. ***(Thorac Med 2015; 30: 61-68)***

Key words: obstructive sleep apnea, blood pressure, continuous positive airway pressure

Introduction

Obstructive sleep apnea (OSA) is a common chronic disorder. The estimated prevalence is approximately 4-7% of the adult general population [1]. OSA, defined as an apnea-hypopnea index (AHI) of more than 5 events per hour as measured by polysomnography with

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clinical symptoms, is characterized by recurrent collapse of the pharyngeal airway during sleep, resulting in substantially reduced or complete cessation of airflow despite breathing efforts. The oropharynx is the most common site of upper airway obstruction [2], which leads to intermittent hypoxemia, hypercapnia, and frequent arousal, subsequently increasing sympathetic activity [3] and altering hormone regulation [4].

Patients with OSA, particularly if severe and untreated, are at increased risk of a broad range of cardiovascular morbidities, including systemic hypertension [5], coronary artery disease [6], heart failure [7], cardiac arrhythmias [8], and stroke [9]. Furthermore, OSA is an independent risk factor for systemic hypertension [10]. Staessen *et al*. [11] reported that night time blood pressure (BP) predicted cardiovascular morbidity and mortality more accurately than daytime BP. Another study showed that refractory hypertension in patients with OSA is more pronounced at night, and the associated nocturnal increases in systolic BP may have adverse effects on patients with hypertension [12].

Nasal continuous positive airway pressure (CPAP) is the mainstay of treatment, with well-documented effectiveness. Several studies have reported that CPAP can improve cardiovascular conditions and reduce BP [13-14]. Clinical observation has found that the BP of OSA patients after waking up is significantly higher than that before sleeping. Although 24-hour continuous BP monitoring is the most accurate method of measuring cyclic BP variations, it is expensive and cannot be used with most patients.

This study was conducted to investigate diurnal variation using a 1-time point BP measurement in the morning after waking and in the evening before sleeping. The immediate effects of CPAP on the diurnal BP variation were also evaluated.

Methods

Subjects and Study Design

This retrospective study investigated patients with OSA, defined by an AHI >5/h, who underwent CPAP titration from March to November 2013. Patients who were younger than 18 years or pregnant, or those with an adjustment of anti-hypertensive medication between the time of polysomnography and the CPAP titration study, with incomplete BP data, or who did not complete the CPAP titration were excluded.

The institutional review board of Chang Gung Memorial Hospital approved the study. BP was measured twice during both the polysomnography and CPAP titration periods. The first BP measurement was taken before sleeping in the evening and the second was after the patients had awakened in the morning. The mean heart rate data was obtained from the whole-night polysomnography records, including the periods when the patients were awake and asleep. The primary endpoint was a comparison of the evening and morning BP. The secondary endpoint was an evaluation of BP change and heart rate after eliminating sleep breathing events with CPAP.

Polysomnography and CPAP Titration

Standard overnight polysomnography included electroencephalography (EEG), bilateral electro-oculograms, submental electromyogram, electrocardiography, nasal and oro-nasal airflow (nasal pressure and thermistor), oximetry, chest and abdominal movements (inductance plethysmography), body position, sound intensity, and bilateral tibial electromyogram.

All signals were collected and digitized on a computerized polysomnography system (N7000 Embla, Broomfield, USA). Sleep stages were scored in 30-second epochs. Apnea was defined as the absence of airflow for 10 sec. Obstructive apnea was defined as the absence of airflow in the presence of rib cage and/or abdominal excursions, while central apnea was defined as the absence of airflow and rib cage and abdominal excursions.

Events with a visible reduction in airflow >50% lasting at least 10 sec and associated with either a 3% decrease in arterial oxyhemoglobin saturation or an appearance of EEG arousal were considered hypopnea. The AHI was defined as the average number of apneas and hypopneas per hour of sleep. All scoring methods met the American Academy of Sleep Medicine 2007 scoring criteria [15].

All of the patients underwent a nasal CPAP titration study, in which manual CPAP titration was conducted to determine the optimal CPAP level in the sleep laboratory on a separate night. For the study, a CPAP interface was individually fitted from a wide range of interfaces to maximize comfort and minimize leaks. All of the participants used an AutoSet Spirit S8 (ResMed, Sydney, Australia) throughout the study. The patients were prepared by a technician who supervised the study and corrected the initial mask position and fitting. The lowest CPAP pressure (4 cm H_2O) was used initially, but was increased incrementally when the patients fell asleep. The optimal CPAP pressure was determined as the pressure that eliminated apnea, hypopnea, desaturation, and snoring in the supine position and provided sleep quality as good as in rapid-eye movement sleep.

Statistical Analysis

Statistical evaluations were performed using SPSS Software (SPSS Inc., Chicago, Ill). Data were represented as mean±standard deviation (SD). Evening blood pressure (systolic and diastolic) was compared with morning BP (systolic and diastolic) by paired *t*-test. The average heart rate during polysomnography and CPAP titration was also compared by paired *t*-test. Statistical significance was set at $p<0.05$.

Results

Seventy-four patients were enrolled, but 4 were excluded because of incomplete BP recording and basic data. There were 55 males and 15 females; 38 patients had hypertension, including 6 who did not take anti-hypertension medication, 8 who used 1 kind of anti-hypertensive drug, 11 who were taking 2 kinds of anti-hypertensive agents, and 11 who were using 3 or more kinds of anti-hypertensive drugs. After CPAP therapy, the desaturation index, total arousal index, mean SpO_2, minimal SpO_2, and AHI were all significantly improved. Although sleep efficiency was mildly increased, there was no statistical difference (Table 1).

Before CPAP treatment, morning systolic BP was significantly higher than evening systolic BP (140.44±18.09 vs. 135.17±16.51 mmHg; $p=0.003$) (Figure 1), as was morning diastolic BP (83.49±12.55 vs. 79.31±11.84 mmHg; $p<0.001$) (Figure 2). However, the diurnal BP difference disappeared for both systolic (morning 131.66±15.33 mmHg vs. evening 130.96±15.13 mmHg; $p=0.618$) and diastolic BP (morning 78.03±11.68 mmHg vs. evening 78.84±11.88 mmHg; $p=0.467$) after CPAP was given (Figures 3 and 4). Moreover, the average heart rate markedly decreased after CPAP use

Table 1. Basic Characteristics of the Study Participants

Sex (Male/Female)	55/15
Age	52.51±11.62
BMI (kg/m^2)	28.77±4.82
NC (cm)	39.78±3.92
ESS	10.77±5.29
Without CPAP:	
AHI (events/hr)	52.66±20.70
DI (events/hr)	45.09±20.74
Mean SpO_2 (%)	92.15±2.89
Minimal SpO_2 (%)	71.8±11.11
Sleep Efficiency (%)	78.83±12.10
Total Arousal Index (events/hr)	39.55±18.08
Under CPAP:	
AHI (events/hr)	5.97±7.24
DI (events/hr)	3.38±5.47
Mean SpO_2 (%)	94.30±1.64
Minimal SpO_2 (%)	86.45±6.49
Sleep Efficiency (%)	82.28±16.45
Total Arousal Index (events/hr)	12.53±7.32

Data presented as mean±SD

Abbreviations: BMI, body mass index; NC, neck circumstance; ESS, Epworth Sleepiness Scale; DI, desaturation index; AHI, apnea-hypopnea index

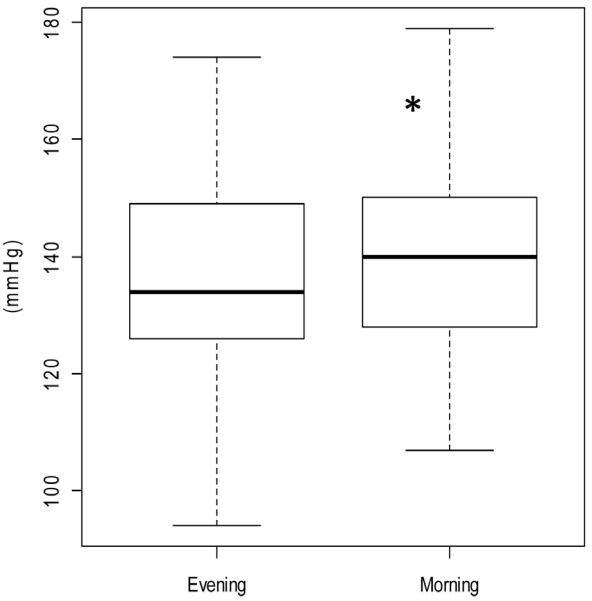

Fig. 1. Systolic blood pressure without continuous positive airway pressure (CPAP). *p<0.05

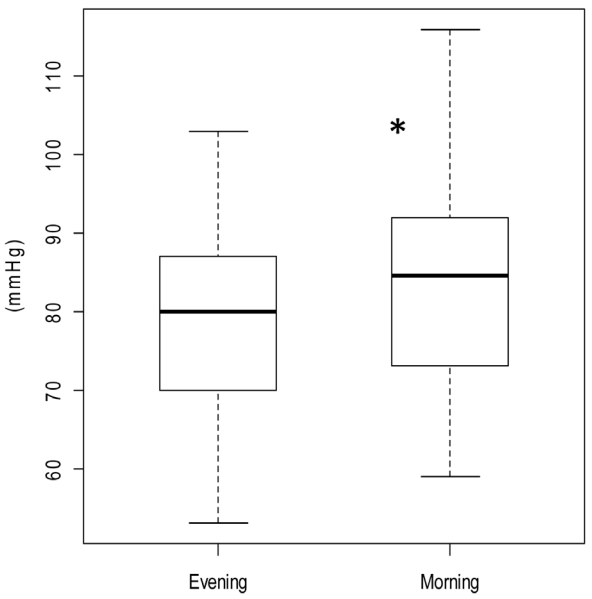

Fig. 2. Diastolic blood pressure without continuous positive airway pressure (CPAP). *p<0.05

(pre-CPAP 67.09±8.31 beats per min vs. post-CPAP 63.32±9.56 bpm; p=0.001) (Figure 5).

Discussion

This study found that both systolic and diastolic BP was higher in the morning than in the evening among patients with OSA, and that the difference was immediately reduced by CPAP treatment. The average heart rate also rapidly decreased after CPAP. The mechanism of elevated morning BP is not fully understood, but several possibilities have been proposed. One major possibility is elevated sympathetic activity at night time, with a higher norepinephrine release rate in response to intermittent hypoxia

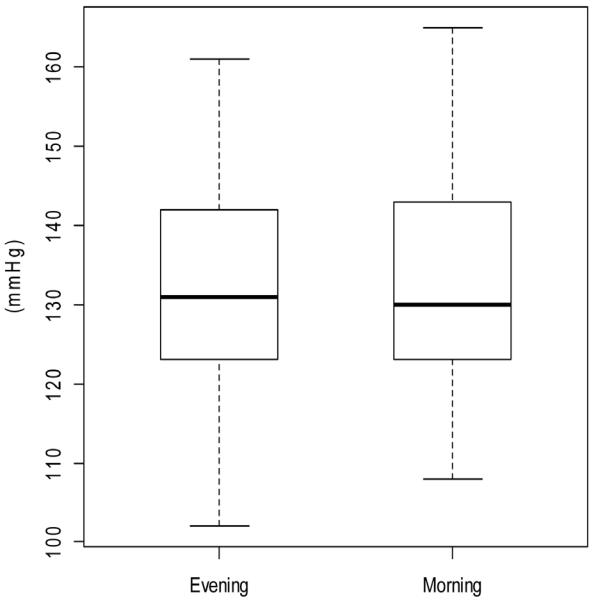

Fig. 3. Systolic blood pressure under continuous positive airway pressure (CPAP).

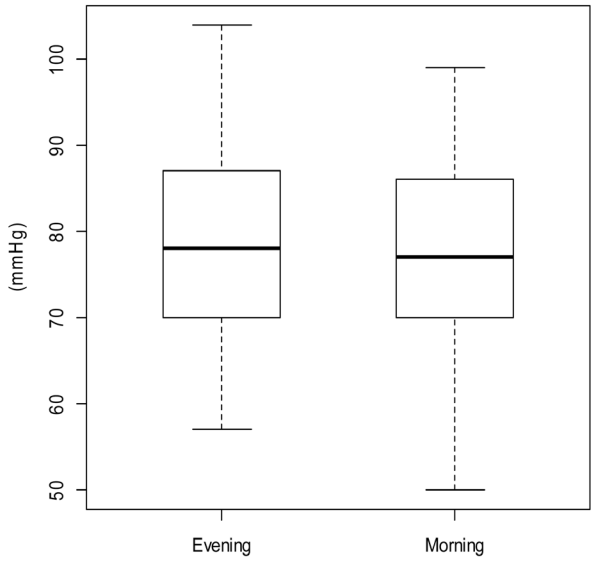

Fig. 4. Diastolic blood pressure under continuous positive airway pressure (CPAP).

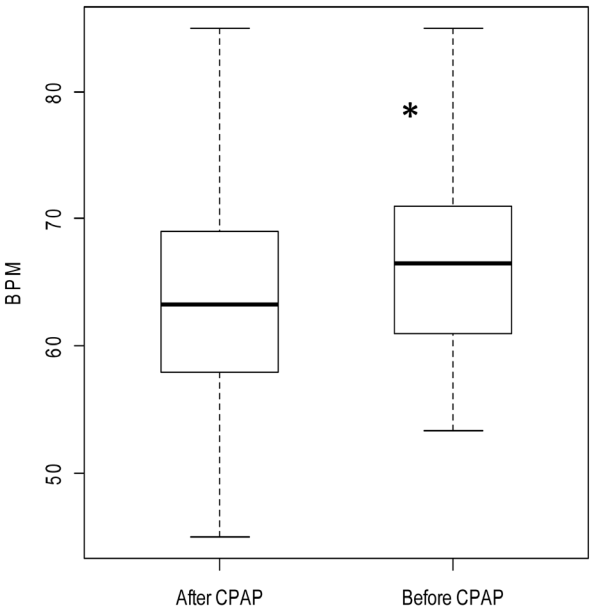

Fig. 5. Average heart rate change after continuous positive airway pressure (CPAP). bpm, beats per minutes

and arousal [16]. Other possible mechanisms include activation of the renin-angiotensin system, decreased baro-reflex sensitivity, and altered metabolism of salt and water due to respiratory events at night [17-18].

The cardiovascular-related mortality rate can be improved by CPAP. Despite some controversy, a large number of studies have demonstrated that CPAP can reduce BP [13-14]. Most studies revealed a decline in BP after CPAP use for durations extending from weeks to months, but there has been no study evaluating the CPAP effect on diurnal BP variation. The present study found that CPAP can reduce morning BP and improve diurnal variation. The effect is rapid and is seen after just 1 night of CPAP therapy. The mechanism involved is speculated to be the elimination of upper airway obstruction, which corrected the intermittent hypoxia and nocturnal arousal, and that those effects reduced the sympathetic activity surge at night time. Thus, the average heart rate was also markedly decreased after CPAP use.

BP normally varies during different physi-

ologic states and declines by 10-20% at night during sleep, compared to BP during daytime wakefulness. A nocturnal BP decrease <10% of daytime BP is defined as non-dipping [19] and is associated with a worse cardiovascular prognosis and increased target organ damage, including left ventricular hypertrophy, microalbuminuria, myocardial infarction, angina, ischemic stroke, and cardiovascular death [20]. One study reported that OSA patients had a higher rate of non-dipping BP related to the severity of AHI [21]. Although there is no direct evidence linking a 1-time measurement of diurnal BP variation with non-dipping BP measured via 24-hour BP monitoring, a high probability of correlation can be speculated.

This study has 2 limitations. First, it is retrospective and recorded evening and morning BP at 1 time point only. The correlation of non-dipping BP with diurnal BP variation with 1 time point measurement cannot be directly made. Nonetheless, 24-hour ambulatory BP monitoring is impractical and cannot be used widely in the current clinical setting, whereas 1-time BP measurement is more easily performed and useful in daily clinical practice. These interesting and important issues warrant further study. Another limitation of our study is that the mean heart rate included both the sleep and awake period. An awake time during sleep study may influence the heart rate. Our polysomnography device could not calculate heart rate after eliminating the awake period, and this possibly affected our heart rate result. However, the awake and sleep duration before and after CPAP therapy were similar and without statistical difference. Otherwise, the sample size and statistical power are enough. Therefore, the awake time influence on the heart rate was limited.

In conclusion, patients with OSA have greater daytime BP and diurnal BP variation. This can be rapidly reversed by CPAP.

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阻塞性睡眠呼吸中止症病患早上與傍晚血壓的差異

黃善結　朱建民　劉育志　于鍾傑

背景：阻塞性睡眠呼吸中止症是引發高血壓的獨立危險因子並且會增加心血管疾病的死亡率。雖然有研究顯示睡眠呼吸中止症的病人有日夜血壓變異的情況，但此現象尚未獲得確切的證實。這篇研究探討阻塞性睡眠呼吸中止症病人的日夜血壓變化以及正壓呼吸器治療對血壓的影響。

方法：這是一篇回溯性的研究，對象是 70 位初診斷為阻塞性睡眠呼吸中止症並且接受過一夜正壓呼吸器壓力滴定的病人，我們收集了病人接受多項睡眠生理檢查以及正壓呼吸器壓力滴定時晚上睡前和白天醒來時的血壓，以及這兩次檢查時的平均心跳速率。我們再將正壓呼吸器治療前後的血壓和心跳速率做比較。

結果：在正壓呼吸器治療前，白天醒來的收縮壓及舒張壓（收縮壓 140.44±18.09 mmHg；舒張壓 83.49±12.55 mmHg）皆明顯高於晚上睡前的血壓（收縮壓 135.17±16.51 mmHg；p=0.003；舒張壓 79.31±11.84 mmHg；p<0.001）。經過一個晚上正壓呼吸器治療後，睡眠呼吸暫停低通氣指數以及平均血氧飽和濃度都有顯著的改善。白天醒來和晚上睡前的血壓變得很接近（收縮壓 131.66±15.33 vs. 130.96±15.13 mmHg；p=0.618；舒張壓 78.03±11.68 vs. 78.84±11.88 mmHg；p=0.467）。平均心跳速率也明顯下降（正壓呼吸器治療前 67.09±8.31 beats per min；正壓呼吸器治療後 63.32±9.56 beats per min；p=0.001）。

結論：阻塞性睡眠呼吸中止症的病人白天醒來的血壓顯著上升，日夜血壓的差距也較大。一個晚上的正壓呼吸器治療可以明顯降低白天醒來的血壓和平均心跳速率。*(胸腔醫學* ***2015; 30: 61-68)***

關鍵詞：阻塞性睡眠呼吸中止症，血壓，正壓呼吸器

基隆長庚紀念醫院　胸腔暨重症加護及睡眠醫學科，長庚醫學大學，基隆長庚紀念醫院　呼吸治療部
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Management and Outcome of Tracheal Malignancy: Experience in a University-Affiliated Hospital

Shih-Hao Huang, Ping-Chih Hsu, Shih-Hong Li, Chih-Hung Chen, Ning-Hung Chen, Cheng-Ta Yang, Chien-Ying Liu

Background: Tracheal tumors are rare. The majority of the tumors in adults are malignant, with about 1/2 to 2/3 being squamous cell carcinomas (SCC). Adenoid cystic carcinomas (ACC) were the second most common of all and the most common for primary tracheal malignancy. Because of the rarity of tracheal tumors and the lack of clarity about their clinical outcome, we retrieved patient information from our cancer registration center and database for analysis.

Objective: To investigate the clinical manifestations, management and outcome of tracheal tumors.

Patients and Methods: Using tumor location in the trachea as the search term, data on 45 patients with tracheal malignant tumors from July 2002 to December 2013 were retrieved from the database of our cancer center. Histology, primary or metastatic, initial clinical manifestations, therapy and outcome were analyzed.

Results: Twenty-three patients (51%) had a primary tumor and 22 (49%) had a metastatic tumor. Among the primary tumors, 12 (52%) were ACC, 6 (26%) were SCC, and 3 (13%) were mucoepidermoid carcinoma. Of those patients with metastatic tumors, 13 (59%) had SCC, and 3 (13%) had adenocarcinoma. The most common manifestation was cough and the second most common was dyspnea. Nineteen patients (42%) underwent surgery, 23 (51%) radiation therapy, and 16 (35%) chemotherapy. Sixteen patients received a single modality of therapy, 17 patients, 2 modalities, and 14 patients, 3 modalities. The median survival of patients with primary tracheal tumor was 2674 days, and for those with metastatic cancer, 125 days. Among the primary tumors, the median survival of those with ACC was 3773 days.

Conclusions: Primary ACC patients had a better outcome than those with the other tracheal malignancies, and patients with metastatic tracheal malignancy had a poor survival outcome. ***(Thorac Med 2015; 30: 69-78)***

Key words: tracheal tumor, adenoid cystic carcinoma, primary tracheal tumor, secondary tracheal tumor

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Introduction

Tracheal malignant tumors are uncommon. The incidence of primary tracheal tumors was estimated to be about 2 cases per 1 million people per year [1]. Secondary tracheal tumors are defined as metastasis or local invasion from an adjacent malignancy. In adults, 90% of primary tracheal tumors were malignant, but in children, 80% were benign [1]. The reported outcome of tracheal tumors has varied, depending on the difference in histology [2]. The 5-year all-cause mortality rate of primary malignant tracheal tumors was 79% [3]. The diagnosis of tracheal tumors is often delayed due to their extreme rarity, so diagnosis requires a high degree of suspicion [4]. There have been few prospective clinical trials on the efficacy of current modalities of therapy, such as surgery, radiation therapy or chemotherapy [3,5]. Also, there have been only a few retrospective clinical studies on the therapeutic outcome of the tumor [3,5-6]. Because of the rarity of the disease, we undertook the present study to investigate the clinical features, management and survival of patients diagnosed with tracheal tumors at Chang Gung Memorial Hospital (CGMH) during the past 10 years.

Patients and Methods

Ethics statements

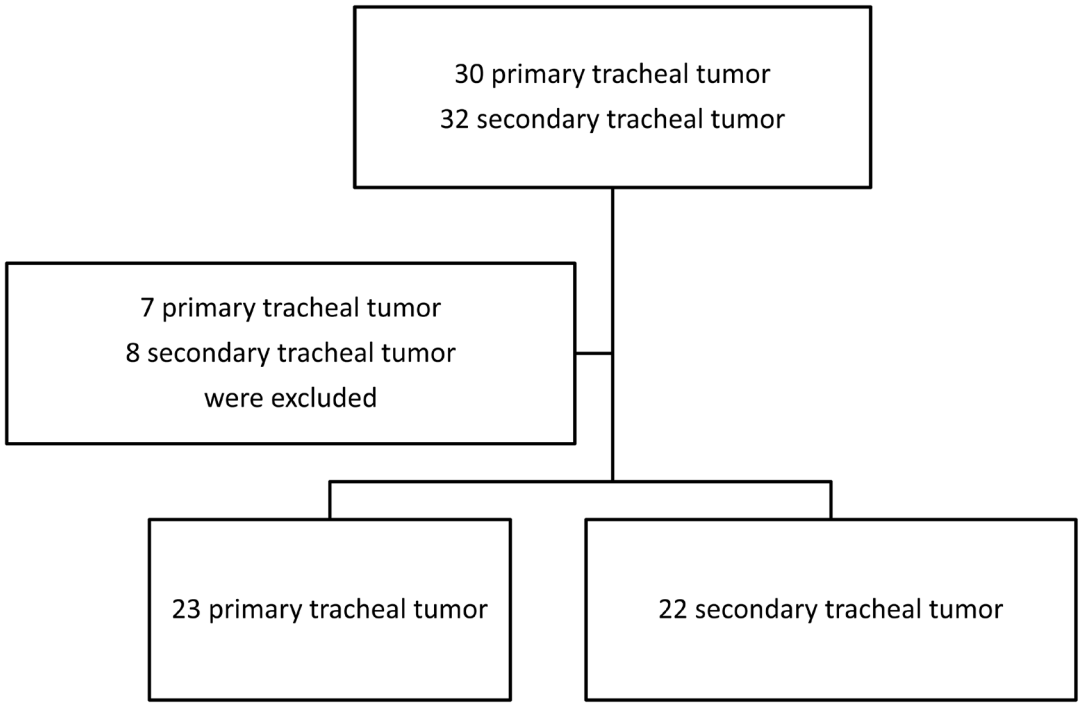
The study was conducted in accordance with the Guide for the Use of Clinical Information and the Regulations for Retrieving Clinical Information from the Patient Registry Center and Patient Database of CGMH as promulgated by the Medical Research Council of the hospital. All lung cancer patients enrolled in the present study were covered by the National Health Insurance (NHI) of Taiwan. According to the policies of the NHI set by the Bureau of National Health Insurance (BNHI), all key clinical information related to the diagnosis, management and outcome of cancer patients has to be registered and stored in the hospital database, and further submitted to the BNHI. The retrieval and analysis of the information from the patient database was approved by the hospital's Institutional Review Board (IRB, 102-5161A), and use of the personal informed consent form was waived by the IRB.

Histology and nomenclature of tracheal tumors

Types of tracheal tumors are determined by histological assessment and pathological reports. Malignant neoplasms are classified as ACC, SCC, adenocarcinoma, adenosquamous carcinoma, small cell carcinoma, carcinoid tumor, atypical carcinoid, mucoepidermoid carcinoma, chondrosarcoma, spindle cell sarcoma, rhabdomyosarcoma, pseudosarcoma, malignant fibrous histiocytoma, plexiform neurofibroma, squamous papillomata, pleomorphic adenoma, granular cell tumor, fibrous histiocytoma, leiomyoma, chondroma, chondroblastoma, melanoma, schwannoma, paraganglioma, hemangioendothelioma, and vascular malformation, according to WTO classification [4].

Subject recruitment and outcome analysis

Using the search term "histocytologically proven malignant neoplasms of the trachea", data on 45 patients with tracheal malignancy from July 2002 to December 2013 were retrieved from the patient database of the CGMH Cancer Center, Taiwan (Figure 1). In addition to primary tracheal tumors, we also collected data on secondary tracheal tumors, which are



The exclusion criteria included: 1) Insufficient clinical data (2) Poor medication compliance

Fig. 1. Flow Diagram of Patients Collected for Study

defined as malignancy arising from outside the trachea with either direct extension from adjacent organs or distant metastases to the trachea, and primary bronchogenic carcinoma with tracheal involvement by direct extension. All patients had received fiber-optic bronchoscopic examinations, and chest radiography or computed tomography (CT) scans for image confirmation of the tracheal tumor.

Histology, primary or metastatic characteristics, initial clinical manifestations, modality of therapy and outcome were analyzed. Stages of tracheal tumor were categorized based on the International Union Against Cancer (UICC) International System for Staging Lung Cancer version 6.0 and version 7.0 [Mountain 1997, 2010] and evaluated by chest CT scan, radiographic imaging, magnetic resonance imaging (MRI) or scintigraphy. Response to therapy was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [Padhani 2001]. Performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) score. Patients with insufficient clinical data were excluded.

Clinical characteristics and manifestations were collected from medical documents and records, and included: initial manifestations (dyspnea, hemoptysis, hoarseness, cough, chest pain, stridor/wheeze, body weight loss, dysphagia, pleural effusion, superior vena cava (SVC) syndrome), comorbidity (cerebral vascular disease, coronary artery disease, COPD or asthma, malignancy, diabetes mellitus, hypertension), therapy (surgery, chemotherapy, radiotherapy), and outcome. Overall survival (OS) time was

calculated from the initial diagnosis of the primary disease to patient death or last follow-up.

All regimens and protocols of chemotherapy were standardized by the Cancer Center of CGMH, and all therapies were audited and monitored by a Lung Cancer Group Meeting in the hospital. Toxicity profile was evaluated based on the criteria set in the US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTC) Version 3.0 [CTEP 2007].

Statistical analysis

Data are presented as mean±standard deviation except where otherwise mentioned. Since the data did not approximate a Gaussian distribution, non-parametric statistical analysis, the Mann-Whitney U test, was used for unpaired data to assess the significance of difference between 2 groups. Frequency distributions between the 2 groups were tested using the chi-square or Fisher's exact probability test. Survival rates were calculated using the Kaplan-Meier method, and comparison of survival curves was based on the log rank test. All p values were 2-sided and $p<0.05$ was considered statistically significant. GraphPad Prism (version 5.0; GraphPad Software, San Diego, CA) was used for all statistical analyses.

Results

Clinical characteristics and manifestations of patients

A total of 45 patients were enrolled in our study; 23 had primary tracheal tumor and 22, secondary tracheal tumor. The mean age was 59 years (range, 22 to 88 years), and 77% (n=35) of the tracheal cancer patients were male. The primary tracheal tumor group had better ECOG performance at diagnosis (3 compared to 12 in the secondary tumor group, p=0.0045). The ratio of smoking was lower among the patients with primary tracheal tumor (13% compared to 54% in the secondary tumor group, p=0.0027). SCC was the most frequent histological type of malignant tracheal tumor and accounted for 42.2% of cases, followed by ACC (26.6%), and mucoepidermoid carcinoma (8.8%). Among patients with primary tracheal malignancy (n=23), 52.2% (n=12) had ACC. As for those with secondary tracheal malignancy (n-22), 59.1% (n=13) had SCC (Table 1).

The most frequent presenting symptoms/signs were dyspnea and cough (86.6%), followed by body weight loss (51.1%), hemoptysis (48.8%), stridor (38.8%), hoarseness (31.3%) and others. Most of the symptoms were non-specific. Specific symptoms/signs indicating structural lesions of the trachea or nearby structures included stridor (38.8%), SVC syndrome (13.4%) and dysphagia (10.4%).

Treatment modalities

Nineteen of our patients underwent surgery (42.2%), 23, radiotherapy (51.1%) and 16, chemotherapy (35.5%). Sixteen patients received a single modality of therapy, 17 received 2 modalities (9 with surgery and radiotherapy, 1 with surgery and chemotherapy, 7 with radiotherapy and chemotherapy), and 14 received all 3 modalities. A higher proportion of those with primary tracheal tumor underwent surgery and radiotherapy. In contrast, a higher portion of patients with secondary tracheal tumor were managed with chemotherapy and additional therapy (tracheal stent, laser and cryotherapy). Late adverse effects after additional therapy, such as granulation or lumen stricture, were not significantly different between the primary

Table 1. Demographics and Clinical Characteristics of the Patients

	Total (No.)	Primary	Secondary	*p* value
Patients, No.	45	23 (51%)	22 (49%)	
Age, yr, mean±SD	59	59.91±19.91	59.86±15.28	0.9862
Gender (male/female)	45 (35/9)	16/7	19/2	0.1368
ECOG PS				0.0445
0-1	15	3	12	
2-4	30	20	10	
Smoking status				0.0027
Never	21	16	5	
Former/current	24	7	17	
Histology				0.0029
Adenocarcinoma	4	1	3	0.3463
Squamous cell carcinoma	19	6	13	0.0361
Small cell carcinoma	2	0	2	0.2333
Large cell carcinoma	1	0	1	0.4889
Adenoid cystic carcinoma	12	12	0	<0.0001
Mucoepidermoid carcinoma	4	3	1	0.6078
Other malignancy	4	1	2	0.6078
Initial symptoms				0.2296
Dyspnea	39	19	20	1.0000
Hemoptysis	22	10	12	0.7683
Hoarseness	12	5	7	0.7381
Cough	39	19	20	1.0000
Chest pain	5	0	5	0.0491
Stridor/Wheeze	27	12	15	0.5499
Body weight loss	23	7	16	0.0174
Dysphagia	11	7	4	0.3141
Pleural effusion	12	2	10	0.0165
SVC	3	0	3	0.1085
Comorbidity				0.6486
Cerebral vascular disease	4	1	3	0.6078
Coronary artery disease	2	1	1	1.0000
Malignancy	5	3	2	1.0000
Diabetes mellitus	1	1	0	1.0000
Hypertension	3	1	2	0.6078

Abbreviations: No., number; SD, standard deviation; PS, performance status

and secondary tumor groups. Chemotherapy in combination with radiotherapy was used mainly for patients with small cell carcinoma (n=2) or non-differentiated carcinoma (n=5). The major side effects after radiotherapy were granulation tissue formation (n=20) and tracheal stricture (n=8) (Table 2).

Outcome

The median OS varied widely with different histological types of tracheal tumors. Patients who were diagnosed with ACC or mucoepidermoid carcinoma had significantly better survival (OS=3773 days) than those with other histological types (Table 3, Figure 2). Those who were diagnosed with epidermoid carcinoma, adenocarcinoma or carcinosarcoma had statistically worse survival (OS=125 days) than those with other types of cancer. Those with primary tracheal tumor also had better OS (2674 days, compared with 125 days for secondary tracheal malignancy, p=0.0003) (Figure 3).

Discussion

Our patients with primary tracheal tumor had a better performance at diagnosis than the secondary tracheal tumor patients. Besides,

Table 2. Management of Patients and Adverse Effects of Therapy

Characteristics	Total	Primary	Secondary	*p* value
Patient no.	45	23	22	
Therapy				
Surgery	19 (42.2%)	16 (69.5%)	3 (13.6%)	0.0002
Radiotherapy	23 (51.1%)	13 (56.5%)	10 (45.4%)	0.5559
Chemotherapy	16 (35.5%)	5 (21.7%)	11 (50%)	0.0654
Additional therapy	20	5	15	0.0011
Stent	13	0	13	<0.0001
Laser	2	2	0	0.4889
Cryotherapy	5	3	2	1.0000
Late adverse effects post-treatment				
Granulation	20	10	10	1.000
Stricture	8	5	3	0.6995

Table 3. Survival of Primary Tracheal Tumor Patients with Different Histologies

Histology	Patient No.	Median (month)	Overall Survival (Day)	95% C.I.	HR
Adenocarcinoma	1	7			
Squamous cell carcinoma	6	11.8	125	-0.2508 to 0.3136	0.03141
Adenoid cystic carcinoma	12	58.93	3773	2.419 to 57.20	11.76

C.I.: Confidence interval, HR: Hazard ratio

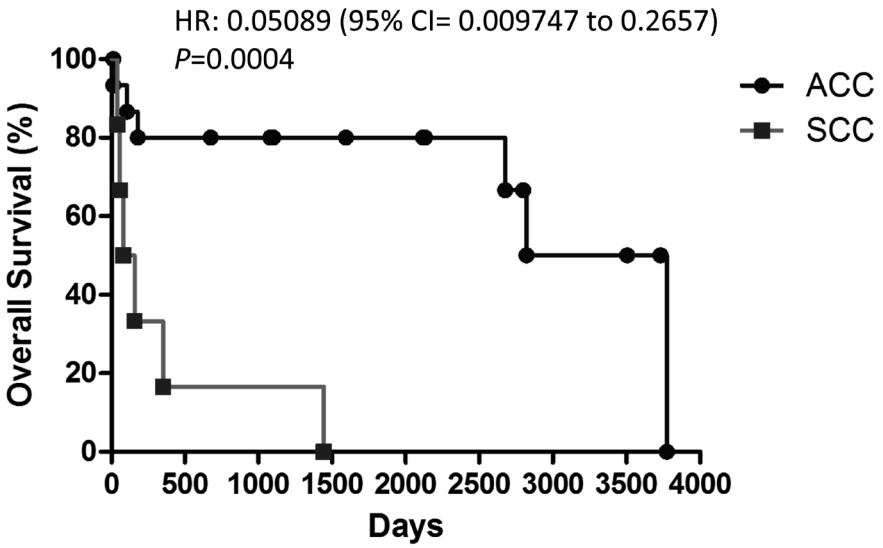


Fig. 2. Survival after Diagnosis of Different Histologies of Primary Tracheal Tumor

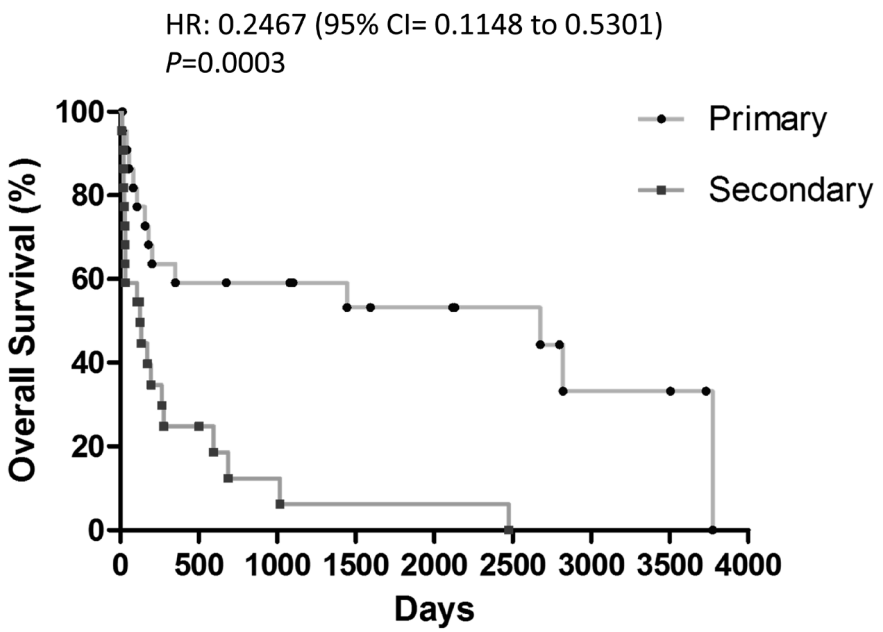


Fig. 3. Survival after Diagnosis of Tracheal Tumor

there was a higher ratio of smoking in the secondary tracheal tumor group. SCC was the most frequent histological type of malignant tracheal tumor. ACC, SCC and epidermoid carcinoma were the predominant types of primary malignant tracheal tumor. Patients with primary tracheal tumors, particularly ACC, had a better survival outcome than patients with secondary

tumors

Tracheal tumors are rare in incidence and the diagnosis is often delayed until months or years after symptoms occur. Tracheal tumors grow silently without symptoms until the airway lumen has a greater narrowing [7]. The initial symptoms are often like those of other common diseases, such as asthma, chronic bronchitis or airway infectious disease. The most frequent presenting symptoms and signs were exertional dyspnea and cough (86.6%). Most of the symptoms were non-specific. Specific symptoms/signs indicating structural lesions of the trachea or nearby structures included stridor (38.8%), superior vena cava (SVC) syndrome (13.4%) and dysphagia (10.4%). Hoarseness can be the result of reduced air flow across the airway, and it also can be due to recurrent laryngeal nerve problems. In our patient groups, some accompanying symptoms, such as chest pain, pleural effusion and body weight loss, indicated a higher ratio of secondary tracheal tumors with worse ECOG performance. Both SVC syndrome and hoarseness indicated that the patient's disease was at an advanced stage. Systemic symptoms including weight loss and dysphagia may be seen with metastatic tumors and may be poor prognostic signs.

Appropriate radiographic studies are required for diagnosis. Most of our patients received chest X-ray, chest CT, or MRI studies. Some tumors could be identified on posteroanterior and lateral chest radiographs [7]. Pulmonary function tests with an obstructive upper airway volume-flow curve or reduction in peak expiratory flow rate may suggest tracheal tumor. However, our patients with tracheal tumor often lacked pulmonary function studies due to dyspnea or inappropriate clinical situations. Bronchoscopic biopsy and tissue histology represent the mainstay of diagnosis for tracheal tumors. Unresectable tracheal tumors can be palliated with several different types of bronchoscopic treatment modalities, including stent insertion, tumor removal by laser or cryotherapy [7].

In our patient group, 16 patients received a single modality of therapy. 17 received 2 modalities and 14, all 3 modalities. Primary tracheal tumors are often treated with multimodalities of therapy, including surgical resection, radiation and chemotherapy [9]. Surgical resection was the first choice of treatment for locally confined disease; radiotherapy was the primary treatment modality if the patient could not undergo surgical treatment.

In our study, a higher proportion of patients with primary tracheal tumor received surgery and radiotherapy. In contrast, a higher proportion of patients with secondary tracheal tumor was managed with chemotherapy and additional therapy (tracheal stent, laser and cryotherapy). The majority of secondary tracheal tumors were managed with palliative treatment. Adjuvant radiotherapy was beneficial after resection of SCC and ACC. If the patient could not undergo an operation for unresectable tumor, radiotherapy was reserved as primary management. Late adverse effects after extra-therapy, such as granulation or lumen stricture, were not significantly different between the primary and secondary tumor groups. Overall, optimal management for tracheal tumors still depended on histology, tumor location, and comorbidities.

The median OS varied widely with different histological types of tracheal tumors. The OS rate of patients with ACC and mucoepidermoid carcinoma was much higher than that of patients with SCC. Patients with primary tracheal tumor also had better OS (2674 days, compared with 125 days for secondary tracheal malignan-

cy, p=0.0003).

There are some intrinsic limitations in this study. First, this was a retrospective study, and the subsequent treatments were determined based on the clinical decisions of the physicians caring for the patients, under the principle of intent to treat. Selection bias might exist, which could influence the OS. Second, all of the patients in the present study were evaluated for lesions by chest radiograph, CT, MRI, bone scintigraphy or PET, according to predetermined management protocols set by our cancer center; however, the intervals between evaluations were not as accurate as those in a prospective trial. Finally, our study population was relatively small. A study with a prospective design and a larger patient population is needed to validate and apply our findings to clinical practice.

Conclusions and Summary

In conclusion, patients diagnosed with ACC and mucoepidermoid carcinoma had a better prognosis and those with epidermoid carcinoma and adenocarcinoma had a worse prognosis. Clinical symptoms and signs other than general malaise and acute respiratory failure were not related to prognosis.

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氣管腫瘤的處置與預後－長庚醫院的經驗分享

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前言：氣管腫瘤發生的機會罕見，大多數氣管腫瘤都是惡性的，其中超過二分之一為鱗狀上皮癌，原發性的氣管腫瘤則大多數為腺樣囊狀癌（adenoid cystic carcinoma），氣管腫瘤相對其他肺部腫瘤發生的機率低，因而這個回溯性研究我們研究長庚醫院氣管腫瘤患者的診斷，治療處置，併發症和預後的分析。

方法：這個研究收集了資料庫自西元 2002 年 6 月至西元 2013 年 12 月，45 位氣管腫瘤病人，分析病人基本資料，病理切片結果，原發性和續發性的氣管腫瘤，臨床的症狀，治療，併發症和預後的資料，做變數分析。

結果：收集到的氣管腫瘤資料，23 位為原發性（51%），22 位為續發性（49%），原發性的腫瘤中以腺樣囊狀癌為大宗（52%），第二位為鱗狀上皮癌。續發性氣管腫瘤患者占多數為鱗狀上皮癌 13 位（59%），其次為腺癌。臨床上最常表現出來的症狀為咳嗽和喘。共計有 19 位病患（42%）接受手術治療，23 位（51%）接受放射線治療，16 位（35%）接受化學治療。總計有 16 位病患接受單一方式的治療，17 位病患接受兩種以上的方式治療，4 位病患接受 3 種以上的治療。平均存活日在原發性氣管腫瘤是 2674 天，續發性氣管腫瘤是 125 天，在原發性氣管腫瘤中，腺樣囊狀癌的平均存活日是 3773 日。

結論：原發性氣管腫瘤中，腺樣囊狀癌不論經由何種治療方式，有比較好的預後，而轉移到氣管的續發性腫瘤平均而言有比較差的預後。這篇研究顯示經由病患的症狀和影像學，若能早期診斷出氣管腫瘤，進而做出適當的處置，氣管腫瘤患者可以有較好的預後和生活品質。*(胸腔醫學* ***2015; 30: 69-78)***

關鍵詞：氣管腫瘤，腺樣囊狀癌，原發性氣管腫瘤，續發性氣管腫瘤

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Disseminated *Mycobacterium avium complex* Disease in an Immunocompetent Patient: A Case Report

Yen-Hsiang Tang, Rong-Luh Lin, Chien-Liang Wu

Disseminated *Mycobacterium avium complex* (MAC) infection rarely occurs in immunocompetent individuals. Besides pulmonary infection, the most common extrapulmonary sites of MAC infection are the bones and joints.

We presented an 80-year-old woman who complained of left flank pain and bilateral lower legs weakness for 2 weeks. Her previous history included the finding of frequent MAC colonization in sputum culture for years. CXR revealed multifocal consolidation in bilateral lung fields. The spinal MRI showed signal change involving the vertebral bodies from T7 to T9 presenting as hypointense on T1-FLAIR, and hyperintense on STIR sequence with strong enhancement. We initially considered the lesion as malignancy and a T8 spinal tumor was resected. The pathology disclosed granulomatous inflammation, and the tissue culture grew MAC. The patient's ileus, ascites, diarrhea and stool culture also grew MAC. Clarithromycin, rifampicin, and ethambutol were prescribed. Follow-up CXR 4 months later showed much resolution of the consolidation. Follow-up spinal X-ray revealed decreased T8 height with metallic device fixation. The patient could walk around with a walker after rehabilitation. Her diarrhea also resolved. ***(Thorac Med 2015; 30: 79-85)***

Key words: Disseminated *mycobacterium avium complex*, immunocompetent

Introduction

Disseminated *Mycobacterium avium complex* (MAC) infection rarely occurs in immunocompetent individuals. Besides pulmonary infection, the most common extrapulmonary sites of MAC infection are the bones and joints. In cases of disseminated MAC disease, in which clinical presentations could often mimic those of malignancies, the confirmed diagnosis must be made with a careful history-taking and thorough examinations.

Case Report

An 80-year-old woman presented with left flank pain and bilateral lower legs weakness for 2 weeks. She had had frequent MAC isolation in sputum cultures for 2 years. The chest X-ray (CXR) and chest computed tomography (CT) showed multiple ill-defined opacities and infiltrates in both lungs (Figure 1 & 2).

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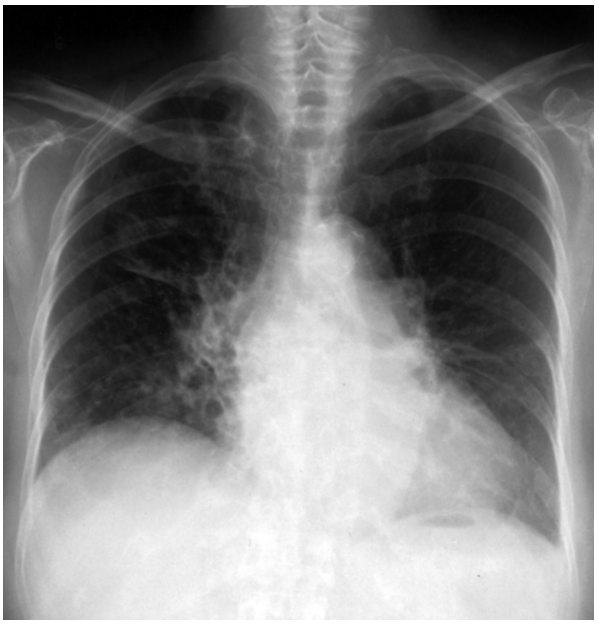

Fig. 1. CXR showed bronchiectasis in the right middle lung (RML) and infiltrates in both lungs.

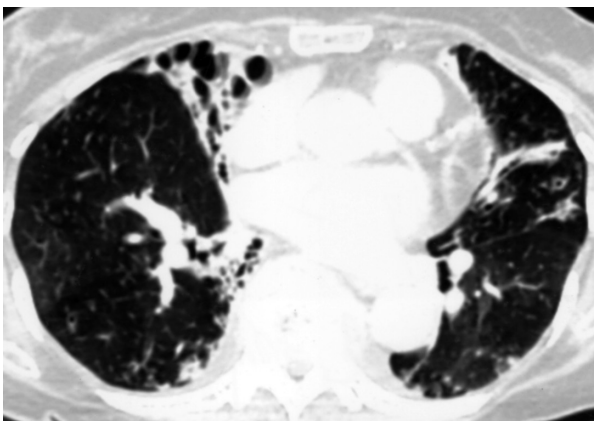

Fig. 2. Chest CT showed bronchiectasis of both lower lobes, with cicatrization atelectasis, and multiple ill-defined opacities and infiltrates.

She did not have fever, night sweats, abdominal pain, or weight loss. Upon physical examination at admission, the patient had clear consciousness, but an ill appearance. Her temperature was 37.2°C, blood pressure was 156/90 mmHg, respiratory rate was 24 per minute, and pulse rate was 100 per minute. Chest auscultation revealed rhonchi at both lower lungs. No decreased muscle power was documented.

The white blood cell count was 9,100/mm^3, with neutrophils accounting for 58% of these cells. The level of C-reactive protein was 4.90 mg/dl. A sputum acid-fast stain set revealed positive and grew MAC.

Due to progressive back pain, magnetic resonance imaging (MRI) of the thoracic and lumbar spine was performed and showed diffuse heterogeneous low signal change involving the vertebral bodies from T7 to T9, and collapse of the vertebral body of T8 (Figure 3). The bone scan also showed increased medronic acid (MDP) uptake in the T7-T9 vertebrae and left medial hip joint (Figure 4). Based on these image findings, a malignant disease was considered. The patient underwent a surgery that a T8 spinal tumor was then found and resected, followed by posterior fusion with bone graft and internal fixation. The pathologic findings revealed granulomatous inflammation, and the tissue culture grew MAC. However, the patient's respiratory symptoms deteriorated and acute respiratory failure ensued requiring mechanical ventilation. In the meanwhile, she suffered from intractable diarrhea and the stool culture was also positive for MAC.

Anti-MAC treatment was initiated with clarithromycin (1 g per day), rifampicin (450 mg per day), and ethambutol (800 mg per day). On the 48th hospital day, she was successfully weaned. Her diarrhea also resolved. Follow-up CXR 4 months later showed remarkable resolution of the consolidation, and serial sputum cultures did not show MAC. The spine X-ray disclosed decreased T8 height with metallic device fixation, without further pathologic change. After rehabilitation, she was able to walk with a

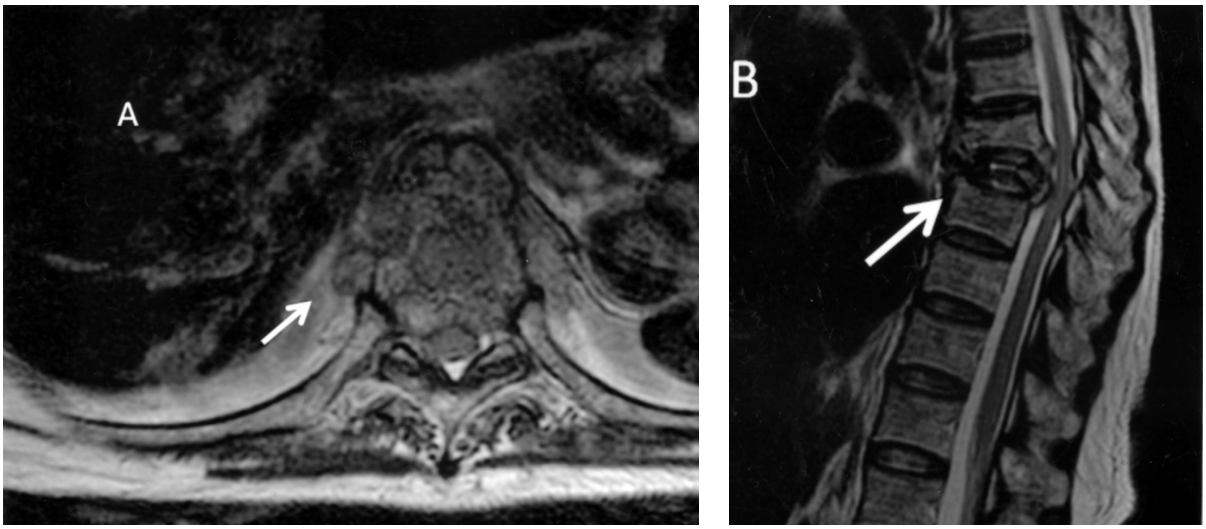

Fig. 3. Axial view (A) and sagittal view (B) of the lumbar spine MRI showed a destructive osteolytic lesion of the T8 spine with vertebral body collapse and epidural extension (arrow).

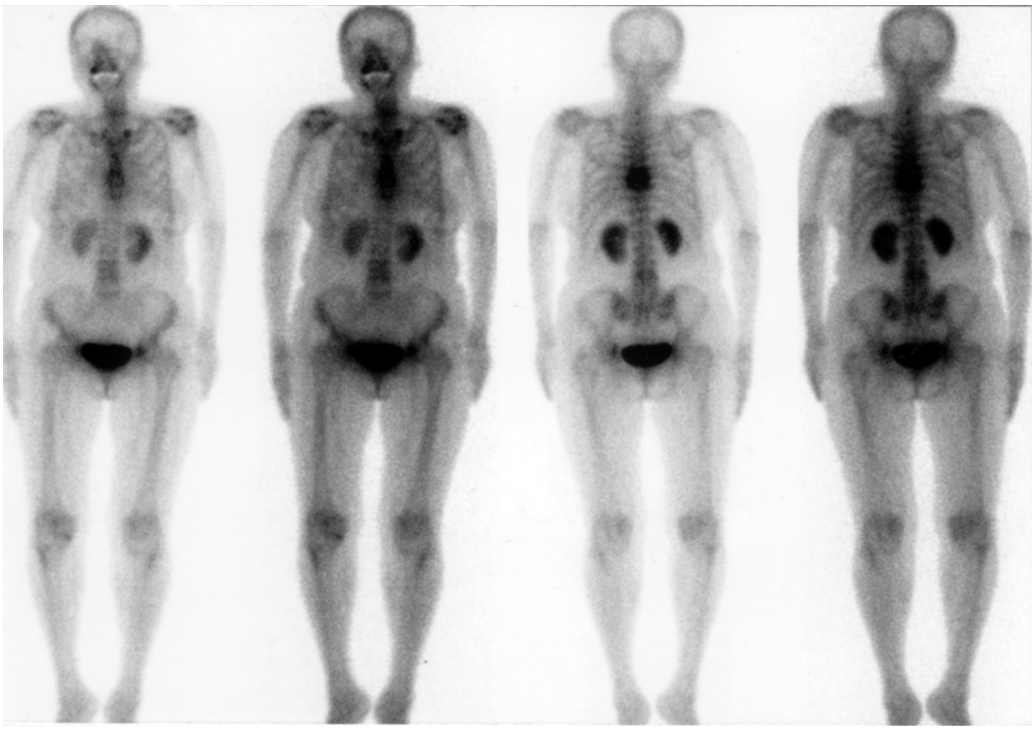

Fig. 4. Whole body bone scan showed increased MDP uptake in the T7-9 vertebrae and left medial hip joint.

walker.

Discussion

Nontuberculous mycobacterial (NTM) species are mycobacterial species other than MAC and *M. leprae*. NTM are widely distributed in the environment, and are inhabitants of natural waters, engineered water systems, soils, wild animals, milk and food products [1-2].

Decades ago, NTM were not considered as human pathogens. It was not until half a century later, however, that these mycobacteria were recognized to cause disease in humans, and by the 1980s they were recognized as causing a broad spectrum of diseases [3]. Current improvements in methodology in the mycobacteriology laboratory have resulted in more rapid and accurate identification of NTM, and thus, enhanced isolation of different species. This has increased awareness of the importance of NTM as human pathogens [4]. MAC is the most common of the NTM species causing disease in most series [4], and includes at least 2 mycobacterial species, *M. avium* and *M. intracellulare*.

These organisms are genetically similar and generally not differentiated in the clinical microbiology laboratory; they are differentiated only with specific DNA probes [4]. *M. avium* is the more important pathogen in disseminated diseases, and *M. intracellulare* is the more common respiratory pathogen [4].

Disseminated MAC disease is a severe infection, and occurs largely in patients with AIDS [5-6]. Disseminated MAC disease is very rare in any form of immunosuppression other than advanced HIV disease. However, it has been reported to occur in other immunosuppressed patients who have had a renal or cardiac transplant, chronic corticosteroid use, or leukemia [3,7-8]. The diagnosis of disseminated MAC infection is therefore easily missed in immunocompetent hosts because the most common symptoms of disseminated MAC are non-specific, and include fever, night sweats, abdominal pain, diarrhea, and weight loss. A local surveillance in Taiwan discovered a high percentage of patients who had a delayed diagnosis of disseminated disease [9]. The mean time from initial presentation to initiation of anti-MAC therapy was 5.14 months (ranging from 1 month to 17 months) [9]. In our case, the patient did not present with fever, night sweats, abdominal pain, or weight loss, but only left flank pain and lower legs weakness. The accurate diagnosis was made after receiving the pathology report; we started an anti-MAC regimen 3 months after the onset of symptoms.

The portals of entry for the organism appear to be the respiratory and gastrointestinal tract, with bacteremia following dissemination via the lymphatics. The bacteremia is thought to arise from infection of a mucosal surface (lung or intestines), followed by local multiplication and entry into the bloodstream with seeding of other organs and tissues. Therefore, patients who have MAC colonization of the respiratory and gastrointestinal tracts are at higher risk of developing disseminated disease [10].

The risk of MAC bacteremia was increased 2.3-fold for patients with respiratory MAC and 6.0-fold for patients with fecal MAC, compared to those without respiratory or fecal MAC, respectively [11]. In our case, the patient was an elderly person and had MAC colonization in both sputum and stool. Thus, disseminated MAC infection should be considered in immunocompetent patients with repeated MAC colonization of respiratory or gastrointestinal tracts.

There have been various MRI presentations of disseminated MAC disease with spinal involvement. Wong *et al*, reviewed published studies that reported that the radiographic imaging revealed destructive lesions, paraspinal abscess, and osteolytic lesions [12]. Wang *et al*, presented a case with an expansile lesion with multilevel heterogeneous signal change of the spine [13]. In our case, the MRI showed enhancing T7 and T9 spinal lesions with paraspinal and epidural extension, and collapse of the T8 spine with epidural extension that caused spinal stenosis. Also, the bone scan showed increased MDP uptake in the T7-9 vertebrae and left medial hip joint. The above findings mimicked metastatic bone lesions. Only after an operation and pathology report could we exclude the diagnosis of malignancy. We then confirmed the diagnosis of disseminated MAC and started treatment.

The timing of treatment of MAC infection is controversial, but untreated disseminated MAC is a life-threatening illness. In the pre-antiretroviral era, only 13% of 191 patients with AIDS diagnosed with disseminated MAC survived 1 year without treatment [14]. In the ATS criteria, NTM lung disease (including MAC) should be treated in symptomatic patients with radiographic changes, positive AFB smears with positive culture and exclusion of other diseases.

Initial treatment for disseminated MAC is clarithromycin, 1,000 mg/day or 500 mg twice daily. Ethambutol should be given at a dose of 15 mg/kg daily. Rifabutin, if added, should be used at a dose of 300 mg daily [4]. In our case, the patient was treated with clarithromycin 500 mg twice daily, ethambutol 800 mg (15-20 mg/kg) daily, and rifampicin 450 mg daily. The disseminated MAC infection in the lungs and spine improved gradually after medical treatment and rehabilitation.

Conclusion

Disseminated MAC infection should be included in the differential diagnosis of immunocompetent patients with repeated respiratory or gastrointestinal MAC colonization and concurrent bone lesions, which may lead to a suspicion of malignancy. One should carefully approach such patients, take a thorough history, and collect as much sputum, and as many stool cultures and tissue pathologic examinations as possible. Likewise, pay attention to patients with repeated respiratory or gastrointestinal MAC colonizations who do not receive anti-MAC treatment. These patients are at high risk of developing disseminated MAC disease. In this way, one could make a more accurate diagnosis and not miss the potentially life-threatening disseminated MAC disease, even among immunocompetent patients.

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免疫功能正常的病人感染彌漫性鳥型分枝桿菌疾病：一病例報告

湯硯翔　林榮祿　吳健樑

彌漫性鳥型分枝桿菌感染罕見於免疫功能正常的病人。除了肺臟之外，最常見的 肺外感染病灶是骨頭及關節。

我們報導一位 80 歲女性，在兩星期前開始有左側腰痛以及雙側小腿無力的症狀。此病人多年前即頻繁的在痰液培養出鳥型分枝桿菌。胸部 X 光片顯示在雙肺野多發性的實質化病灶。脊椎核磁共振照影顯示第七節胸椎至第九節胸椎的椎體，在 T1-FLAIR 影像上是低顯影，而在 STIR 影像上則是高顯影。起初我們判斷這些病灶是惡性腫瘤造成的，因此施行第八節胸椎腫塊切除手術。病理報告顯示肉芽腫性發炎反應，組織則培養出鳥型分枝桿菌。病人同時併有腸阻塞，腹水，腹瀉且糞便也培養出鳥型分枝桿菌。我們給予 clarithromycin，rifampin，以及 ethambutol 治療。四個月後追蹤的胸部 X 光顯示之前的實質化病灶消散許多。追蹤的脊椎 X 光片則顯示高度縮減的第八節胸椎與金屬板固定。在接受復健後，此病人可以靠著輔具自行行走。而且她的腹瀉亦停止了。*(胸腔醫學 **2015; 30: 79-85**)*

關鍵詞：彌漫性鳥型分枝桿菌，免疫功能正常

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Syncope Caused by Pulmonary Embolism after Lung Resection – A Case Report

Chien-Kuang Chen, Chih-Yi Chen, Pin-Ru Chen

Pulmonary embolism (PE) after lung resection is a rare occurrence in Taiwan. It is associated with a high mortality rate, but the diagnosis is difficult because the symptoms and signs can be confused with those commonly seen after lung resection. We report a patient who developed PE after lung resection. Syncope was the first presenting symptom. Coagulation screening showed elevated levels of D-dimer. Diagnosis of PE was confirmed by ventilation/perfusion (V/Q) scan and high-resolution computed tomography (HRCT). The patient recovered well with anticoagulant treatment and oxygen support, and was discharged after 19 days. HRCT scan at the 6-month follow-up revealed no filling defect in the pulmonary artery. We reviewed the literature on the risk factors, prophylaxis, treatment and diagnosis of PE. Reports showed that D-dimer seems to be useful in screening. Although the incidence of PE after surgery is lower in ethnic Chinese populations, we should keep this uncommon disease in mind and manage the patients carefully. ***(Thorac Med 2015; 30: 86-91)***

Key words: pulmonary embolism, lung resection, D-dimer

Introduction

Pulmonary embolism (PE) is a severe complication following lung resection and is associated with a high mortality rate [1]. Some reports have suggested a low prevalence of PE and deep venous thrombosis in Asian patients [2]. Although the incidence of PE is low in Taiwan [3], we should not ignore it.

Case Report

An obese 49-year-old female with a BMI (body mass index) of 26.7 and a history of hypothyroidism underwent a right lower lobectomy for an adenocarcinoma (pT1N0M0, stage Ia) using an open-method operation. The operative time was about 210 minutes. The patient did not adhere to ambulation guidelines after the operation. On the second postoperative day, she experienced an episode of syncope while she was walking to the toilet. After this episode, the patient complained of dyspnea and chest tightness, and required continuous oxygen support via a nasal cannula. Oxygen saturation from the pulse oximeter fell to 88% as she was leaving oxygen support. No focal neurological signs were noted. EKG revealed a normal

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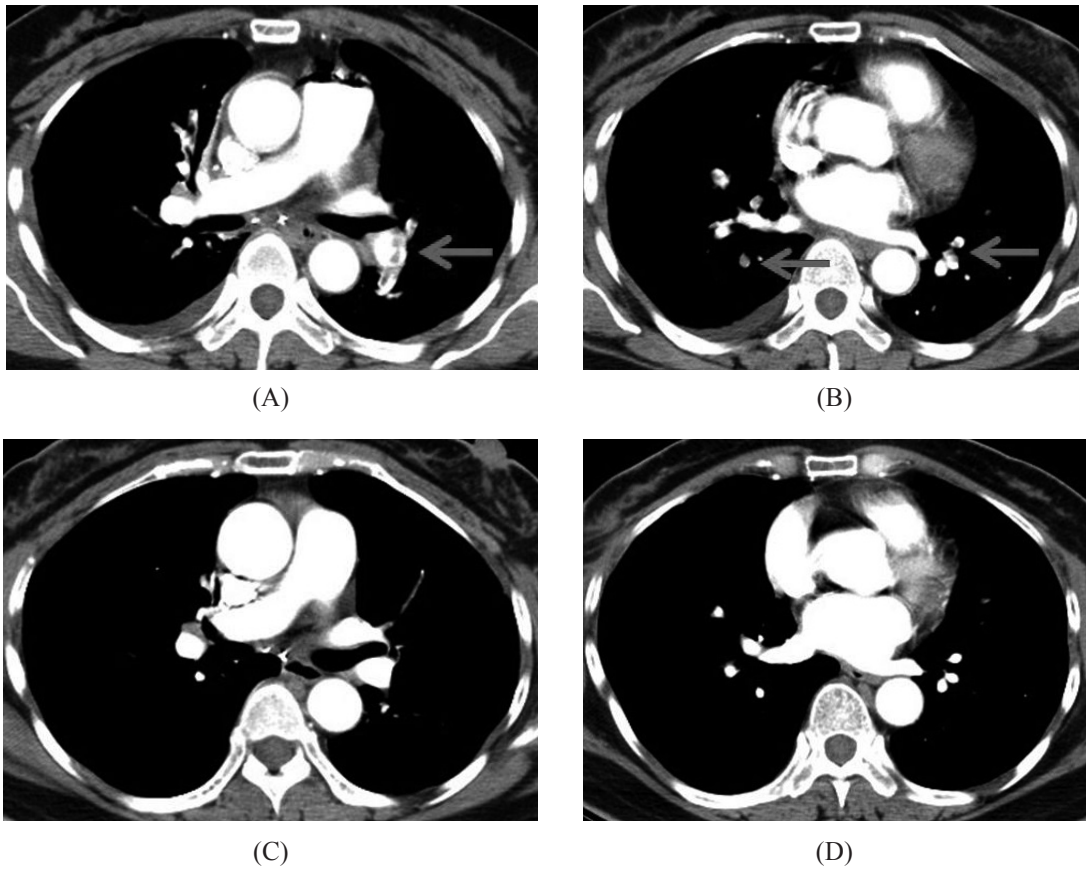

Fig. 1. HRCT of the patient with pulmonary embolism after lung resection. A and B: Chest CT, contrast, at the time of pulmonary embolism. Filling defect noted in the distal left main pulmonary arteries and bilateral peripheral pulmonary arteries (arrow site); C and D: Chest CT, contrast, at follow-up 6 months later. Filling defect could no longer be seen in the pulmonary arteries.

sinus rhythm. Brain CT showed no metastasis or focal lesion. Cardiac enzymes were within normal ranges. No aspiration pneumonia, pulmonary edema or specific findings were seen in the chest X-ray examination. D-dimer levels increased from 1541 to 3049 ng/ml within 2 days after the episode. PE was suspected and confirmed by high-resolution computed tomography (HRCT) and ventilation/perfusion (V/Q) scan. HRCT revealed a filling defect in the distal left main pulmonary artery and bilateral peripheral pulmonary arteries (Figure 1). V/Q scan showed a mismatch between the perfusion and ventilation scans, indicating a high probability of PE (Figure 2). Heparin was administered immediately. Activated partial thromboplastin time (APTT) was maintained in the range of 50-70 seconds with heparin for 5 days. Warfarin was administered concomitantly with heparin for the first 5 days, after which, heparin was discontinued. The international normalized ratio (INR) was maintained in the range of 2-3. The patient was discharged 19 days after the lobectomy. Warfarin was continued in the OPD follow-up for 6 months. No emboli could be found in the HRCT scan 6 months later (Figure

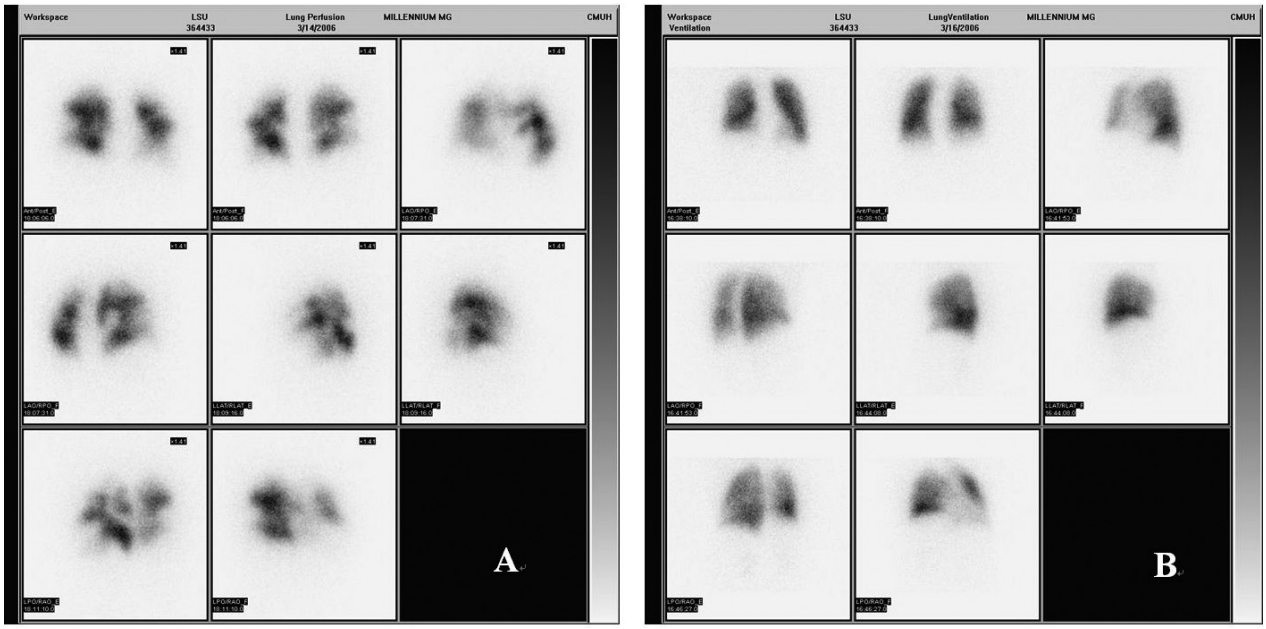

Fig. 2. Perfusion/ventilation scan of the patient. A: perfusion scan; B: ventilation scan. The lung perfusion/ventilation scan shows multiple moderate to large segmental V/Q mismatched defects involving both lungs. The V/Q scan findings suggest a high probability of pulmonary embolism in both lungs.

1).

Discussion

Pulmonary embolism is a cause of acute fatality after lung resection [1]. According to an epidemiology study from Hong Kong [2], the incidence of PE was 3.9 per 100,000 people, and the in-hospital mortality rate of PE was about 23.8%. The incidence of venous thromboembolism in ethnic Chinese is lower than that in Caucasians. The incidence of postoperative PE varies depending on the type of operation. Cardiovascular surgery has the highest incidence, at 0.27%. In thoracic surgery, the incidence is about 0.15%. In a study from Taiwan [3], PE after surgery had an incidence of 0.02%.

Risk factors for thromboembolism in thoracic surgery patients can be acquired or inherited. The risk has been shown to rise with age, beginning at age 40, and with malignancy [4]. The prophylaxis of thromboembolism includes mechanical and pharmacologic methods. Mechanical methods include early ambulation, graduated compression stockings, intermittent pneumatic compression devices and inferior vena cava filters. Pharmacologic methods comprise anticoagulation and antiplatelet agents, such as heparin and warfarin, respectively. Because of the increased risk of bleeding associated with pharmacologic methods, patients with deep vein thrombosis and a bleeding tendency should be managed with an inferior vena cava filter rather than an anticoagulant [4].

Aspirin is an effective thromboprophylaxis agent. It has been shown to reduce the risk of PE and DVT in patients by at least 1/3, largely irrespective of the use of any other thromboprophylaxis. The bleeding risk is low, and there is no increase in fatal, cerebral, or disabling bleed-

ing episodes [5]. Since the incidence of PE is low in ethnic Chinese populations, routine use of prophylaxis is not suggested [2].

Syncope was the initial presentation of our patient. The sudden onset of the episode could be considered to result from an acute neurologic problem and cardiovascular events. Series examinations revealed normal brain structure and heart function. The only possible causes were seizure, vagal reflux problems or arrhythmia, but they could not have resulted in persistent dyspnea or desaturation. After the syncope episode, there was persistent dyspnea without an airway problem or active lung lesion on the chest X-ray exam. Therefore, PE could be considered. In central PE, the blood clot blocks the pulmonary artery and increases the pressure of the pulmonary artery and right ventricle. Dilatation of the right ventricle will occur, resulting in myocardial infarction and arrhythmia, presenting as syncope [6]. PE could result in a series of events in the patient.

The available tools used to reveal a suspected PE include angiography, V/Q scan, CT, echocardiography, and the D-dimer test. The gold standard is angiography, but it is a very invasive procedure. High-probability reports in V/Q scans have a sensitivity of 41% and a specificity of 97%. A normal V/Q scan could exclude PE [7]. CT is a powerful tool for diagnosis of PE. It is a fast procedure and can clearly show evidence of thrombus and other features that are not evident on chest radiography. Dual-section helical CT was reported to have a sensitivity of 90% and a specificity of 94% [8].

A prospective cohort study of 3306 consecutive patients with clinically suspected acute PE reported that D-dimer testing and CT were effective in the evaluation and management of patients with clinically suspected PE [12]. If a patient has difficulty moving for the CT scan, echocardiography at bedside is another available image study.

D-dimer is a fibrinolytic product of cross-linked fibrin. The existence of D-dimer indicates the existence of a blood clot. It can be used to predict the existence of PE. However, since the D-dimer level is increased in traumatic patients, its usefulness is lessened. Some investigators have observed that the level of D-dimer in traumatic patients decreases rapidly within the first 48 hours. But during that time, the difference is not clear and is without statistical meaning [9-10].

The sensitivity of D-dimer assay is 98%, but the specificity is only 39%. The negative predictive value is high, about 98% [11]. Therefore, the assay is a good tool only for screening and excluding the possibility of PE. Our patient's D-dimer level continued to elevate, even 2 days after operation. The possibility of PE could not be eliminated; the diagnosis was confirmed finally by the following CT and V/Q scans.

The key to appropriate therapy is risk stratification [6]. Low-risk patients have an excellent prognosis with anticoagulants alone. High-risk patients might benefit from thrombolysis or embolectomy in addition to other invasive methods. Heparin provides immediate anticoagulation and serves as a bridge until oral anticoagulation is fully effective. The APTT should be kept within 60-80 seconds initially, and oral anticoagulants and heparin should be given concomitantly. After the oral anticoagulants have proven to be fully effective, the heparin can be stopped and the treatment shifted to oral drugs. INR should be kept within 2-3. For most patients with an initial PE after trauma, surgery, or immobilization, 6 months of anticoagulant

treatment suffices. Since no mortality benefit has yet been demonstrated, thrombolysis should be limited to patients with massive PE.

In severe PE cases, extracorporeal membrane oxygenation (ECMO) could be considered. Animal experiments showed that ECMO provided excellent support in dogs with PE [13]. Tayama et al reported using ECMO to manage patients with severe PE. They concluded that ECMO stabilizes hemodynamics and improves gas exchange. Application of ECMO is recommended only for severe PE cases [14].

PE is rare in Taiwan. The incidence is much lower than that reported from Hong Kong. Missed diagnoses could reasonably be suspected. D-dimer seems to be useful in screening, and CT could be used for rapid diagnosis. Routine prophylaxis of PE is not suggested because of the low incidence in ethnic Chinese populations. If a patient develops dyspnea without an explainable chest X-ray exam or airway problem, PE should be considered. We should keep the possiblity of this uncommon disease in mind and deal with our patients carefully.

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肺切除手術術後併發肺栓塞導致暈厥－病例報告

陳建光　陳志毅　陳品儒

肺切除後發生肺栓塞的案例在台灣非常少見。它死亡率很高。因為手術後的常見的症狀與肺栓塞的症狀相似，造成診斷上的困難。在此我們將介紹一名肺切除手術術後併發肺栓塞的病人，暈厥是她的第一個表現症狀。其 D-dimer 的血漿濃度上升。診斷上經由核醫灌流 / 通氣檢查與電腦斷層確認。在接受抗凝血治療與氧氣支持後，她逐漸康復，共住院治療 19 天。六個月後電腦斷層檢查追蹤，無任何肺栓塞情形。在此我們回顧文獻關於肺栓塞的相關資料，包括：危險因子、預防方法、診斷工具與治療方式。D-dimer 似乎適合用來做為篩選的工具。雖然在華人中，肺切除手術術後併發肺栓塞的機會不大，但還是要將此診斷放在心中，並且小心的處理病人。*(胸腔醫學* ***2015; 30: 86-91)***

關鍵詞：肺栓塞，肺切除，D-dimer

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Desmoplastic Malignant Mediastinal Mesothelioma Presenting as Superior Vena Cava Syndrome: A Case Report and Literature Review

Kah-Mee Law, Yu-Feng Wei, Jiun-Ting Wu

Mediastinal mesothelioma is rare, accounting for less than 5% of all cases of mesothelioma. Primary pericardiac mesothelioma is also a rare type of mesothelioma, with a reported incidence of less than 0.0022% among 500,000 cases in a large necropsy study. Herein, we report the case of a 48-year-old man who presented to our outpatient department due to progressive cough with prominent body weight loss within 2 months. Chest computed tomography showed a right mediastinal mass encasing the superior vena cava with obliterated vessels. The pathology of the mass revealed desmoplastic mesothelioma, which was most likely pericardial in origin, based on the imaging findings. Echocardiography showed tumor thrombus in the superior vena cava, extending to the right atrium. The patient died of sepsis after chemotherapy 5 days later. ***(Thorac Med 2015; 30: 92-98)***

Key words: desmoplastic, malignant mediastinal mesothelioma, superior vena cava syndrome

Introduction

Malignant mesotheliomas are derived from the mesothelial or submesothelial connective cells covering the tunica serosa. Mediastinal mesotheliomas account for less than 5% of all mesotheliomas [1]. Most malignant mediastinal mesotheliomas are considered to originate from the pericardium [2]. This type of mesothelioma is associated with exposure to asbestos, but only 14% of cases of malignant mesothelioma have a history of asbestos exposure. The mechanism of asbestoses in pericardial mesothelioma is still under investigation.

Desmoplastic mesothelioma is another rare mesothelioma subtype. More than 50% of the specimen consists of dense, hypocellular collagenous tissue in epithelial, sarcomatous and mixed or biphasic subtypes. Desmoplastic malignant mesothelioma was first described by Kannerstein and Churg in 1981, and accounts for 5% to 10% of all malignant mesotheliomas [3]. Although more than 350 cases of primary pericardial mesothelioma have been reported, no cases of primary pericardial mesothelioma with superior vena cava syndrome have been

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reported to date. Herein, we present a case of desmoplastic malignant pericardial mesothelioma with invasion to the adjacent superior vena cava and right atrium, causing superior vena cava syndrome and distant metastasis.

Case Report

A 48-year-old man with no history of exposure to asbestos first came to our chest medicine outpatient department due to progressive cough with whitish sputum production accompanied with prominent body weight loss of 4 to 5 kg and progressive exertional dyspnea for the last 2 months. He had a smoking history of more than 30 pack/years. He presented in April 2013 with swelling of his upper extremities and a swollen face. A physical examination revealed superficial vein engorgement in the right anterior chest wall with a crackling sound in both lungs when breathing. No other symptoms such as fever, chest pain, dyspnea, or palpitation were noted. His vital signs showed only mild tachycardia. The significant laboratory findings included leukocytosis with a left shift and hyperuricemia, and tumor markers such as carcinoembryonic antigen and alpha-fetoprotein within a normal range, which suggested inflammation or an infection. Chest radiography (CXR) revealed increased soft tissue opacity at the right lower paratracheal region, with a left blunt C-P angle (Figure 1). Chest computed tomography (CT) (Figures 2a, 2b) showed a prominent right mediastinal mass 5×5 cm in size encasing the superior vena cava with obliterated vessels and suspected tracheal wall invasion.

Bronchoscopy was arranged and showed a bulging mass with mucosa swelling in the right main bronchus. We arranged video-assisted thoracic surgery (VATS) to obtain a tissue sample.

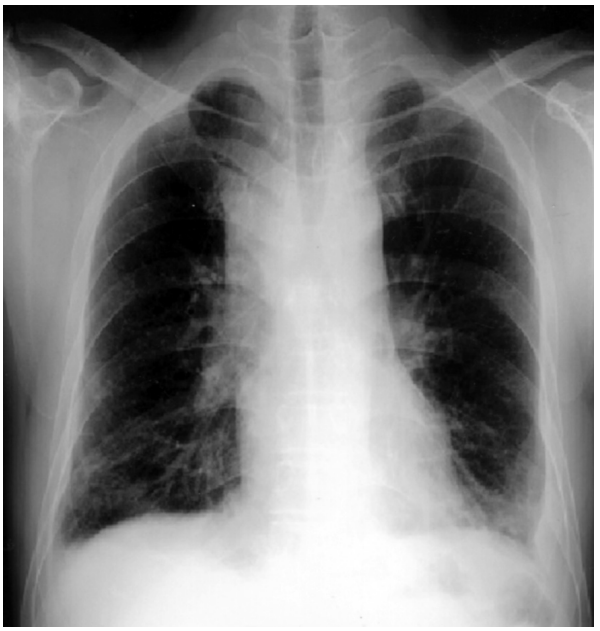

Fig. 1. CXR showed increased soft tissue opacity at the right lower paratracheal region, with bilateral costophrenic angle blunting.

During the operation, the mediastinal mass was found to be adherent to the right upper lobe of the right lung with active oozing. The pathology report of the mediastinal mass showed mesothelioma, and immunohistological staining was positive for calretinin (Figure 3a) and cytokeratin (CK) (Figure 3b), and negative for various tumor cell markers, including CD5 (T-cell neoplasma), CD34 (Ewing's sarcoma/primitive neuro-ectodermal tumor (PNET)), CD56 (small cell lung carcinoma), CD68 (histiocytic lymphoma), CD117 (gastrointestinal stromal tumors (GISTs)), CK5/6 (pulmonary squamous carcinoma), S-100 (melanomas, schwannomas, neurofibromas), WT-1 (Wilms' tumor), and TTF-1 (pulmonary adenocarcinomas). Histoimmunology confirmed desmoplastic mesothelioma (Figure 3c, 3d). For staging purposes, brain magnetic resonance imaging showed an 8-mm enhanced nodule with perifocal edema at the right parasagittal occipital region, favor-

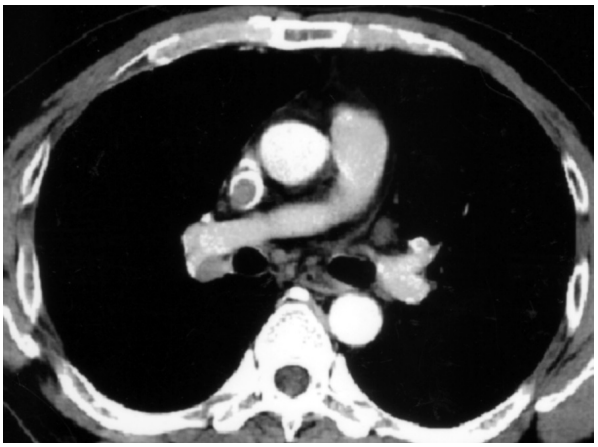

Fig. 2 (a). Thrombus within the superior vena cava with left aortopulmonary lymphadenopathy in the chest CT.

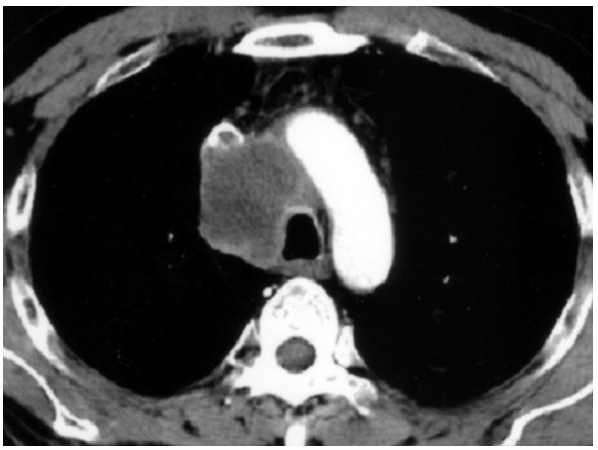

Fig. 2 (b). Middle mediastinal mass causing nearly total occlusion of the superior vena cava with suspected tracheal wall invasion in the chest CT.

ing a metastatic lesion. A bone scan was also performed which showed a reaction in the right 5-6th ribs, also suggesting metastasis.

After VATS, empyema developed and antibiotics were prescribed for the infection. Radiotherapy was performed for progressive orthopnea related to superior vena cava syndrome. Chest CT with contrast was done 2 months later, and showed progressive superior vena cava thrombus with occlusion and tumor invasion to

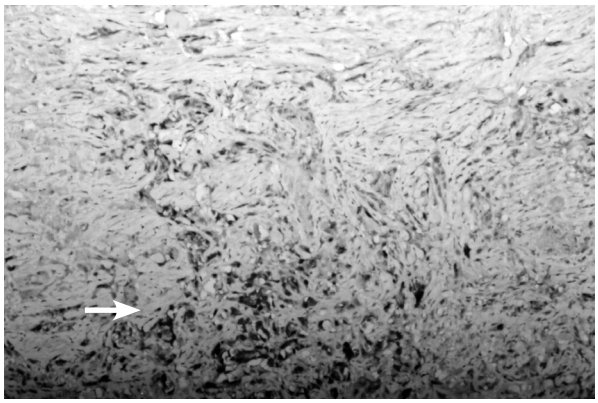

Fig. 3 (a). Positive staining for calretinin. (brown color stain) (as arrow)

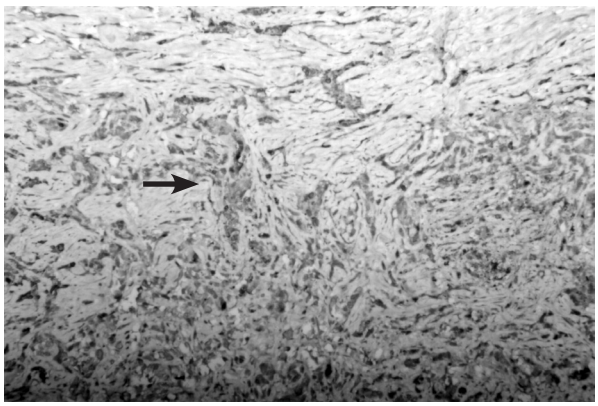

Fig. 3 (b). Positive staining for CK (brown color stain) (as arrow)

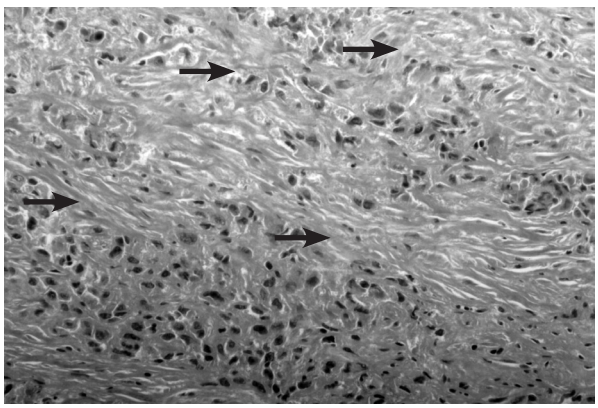

Fig. 3 (c). HE under 200 magnification power showed a collagen fiber bundle (as arrow)

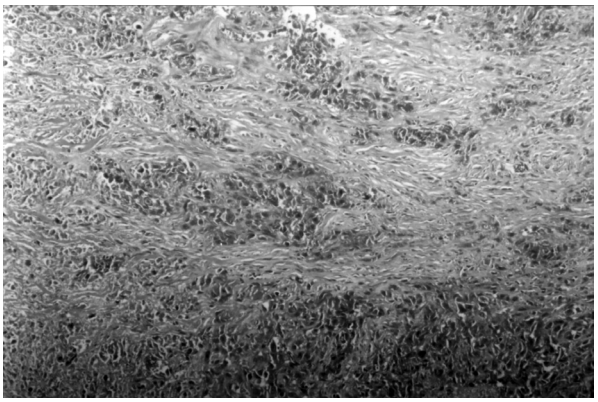

Fig. 3 (d). HE under 100 magnification power showed positive staining for Masson's Trichrome (blue color stain indicates collagen fiber, red color stain indicates muscle fibrin)

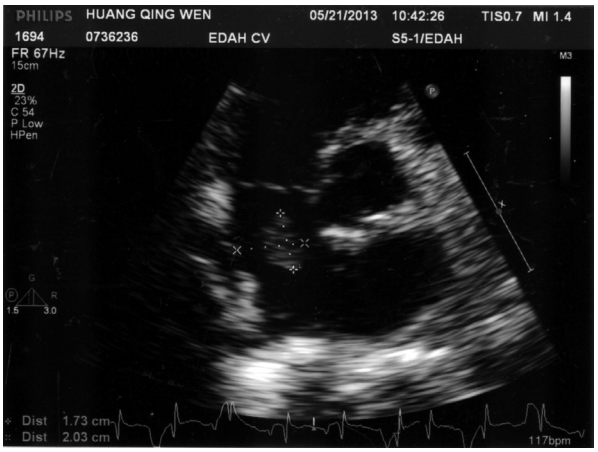

Fig. 4. Tumor thrombus within the right atrium in echocardiography.

the right atrium. Cardiac sonography (Figure 4) was also performed later and showed diastolic dysfunction with a small amount of pericardial effusion. A 2.0×1.7 cm mass at the tricuspid valve atrial site, suspected to be vegetation or thrombus, was also found.

We started pemetrexed and cisplatin treatment for the mesothelioma in combination with antibiotics after discussing the situation (the high risk of infection deterioration after chemotherapy) with the patient. Five days after initiation of chemotherapy, he developed an irritable mood with dyspnea. He expired the same day due to suspected sepsis progression. The patient had a "do not resuscitate" will.

Discussion

Malignant mesothelioma is not rare, with a reported average of more than 3000 cases annually in the United States [4-5]. Up to 80% of malignant mesotheliomas are associated with exposure to asbestos [6]. Mesotheliomas have a long latency period of 30 to 40 years from first exposure to asbestos to developing the disease [7]. Besides the pleural cavity (80%), mesotheliomas also occur in the peritoneum, tunica vaginalis testis and pericardium (10%, <5%, and <5%, respectively) [8]. The mean age of patients with malignant mesothelioma is 60 years, and the mean average survival time is 6 months [9].

Pericardial mesothelioma is extremely rare, although it is the most common primary malignant pericardial tumor. The reported incidence was less than 0.0022% among 500,000 cases in a large necropsy study [10-11]. Many case reports of malignant pericardial mesothelioma have been published, in which some presented with diffuse pericardial nodules, diffuse pericardial thickening, or a solitary nodule in the parietal and visceral pericardium, causing obliteration of the pericardial space or cardiac chamber encasement [12]. In our case, the tumor initially appeared as a solitary mediastinal tumor without direct invasion to the pericardium, and only encasing of the superior vena cava caused partial obliteration. The tumor was found to have invaded the right atrium chamber 2 months later.

Most primary pericardial malignant me-

sotheliomas present clinically as constrictive pericarditis, cardiac tamponade and congestive heart failure either by serous effusion or by direct tumor invasion causing heart constriction [13]. In our case, the patient presented as superior vena cava syndrome due to invasion of the mediastinal mass into the superior vena cava, with symptoms of progressive orthopnea and exertional dyspnea and swelling of the bilateral upper extremities.

Localized pericardial mesothelioma is considered to be a distinct, rare variant of malignant mesothelioma [2]. Although localized, this type of mesothelioma can still cause direct invasion to adjacent organs [14-15]. Most localized primary pericardial mesotheliomas can be resected by surgery, with good overall survival. Allen *et al* suggested differentiating localized mesothelioma from the diffuse type due to the superior prognosis of the former compared to diffuse malignant mesothelioma [16].

The current standard treatment for malignant mesothelioma is combination therapy with a folic acid antagonist such as pemetrexed plus a platinum-based anticancer drug such as cisplatin [17]. Treatment for primary pericardial mesothelioma is mainly palliative due to its poor response to radiotherapy and chemotherapy, as well as being surgically unresectable. However, studies on new regimens for pericardial mesothelioma have been published [18-19].

Three types of pathology are found in mesotheliomas: epithelial, sarcomatous, and mixed or biphasic. These patterns are found in roughly 55%, 15%, and 30% of cases, respectively [3]. Desmoplastic malignant mesothelioma has since been described in a number of reports with documented exposure to asbestos [3]. Our case did not have a history of exposure to asbestos. Mangano *et al* proposed the following histological criteria for desmoplastic malignant mesothelioma: a paucicellular fibrotic pleural lesion with a storiform or patternless pattern, plus 1 or more of the following; invasion of the chest wall or lung, bland necrosis, a frank sarcomatoid area, and distant metastasis [19]. In our case, the pathology was desmoplastic epithelial mesothelioma, and histo-immunological staining was positive for calretinin and CK, and negative for CD5, CD34, CD56, CD68, CD117, CK5/6, S-100, WT-1, and TTF-1. The report by Nicolini *et al* showed findings similar to our case, including a huge white tumor mass surrounding and encasing the heart and large vessels (aortic arch, pulmonary artery, and veins and vena cava) with strong pleuropulmonary adherence and macroscopically invaded myocardial tissue, and the pathology showed desmoplastic mesothelioma in primary pericardial mesothelioma [10]. We also found the same characteristics of encased great vessels with invasion into the right atrium, as well as distant metastasis. The prognosis of desmoplastic variant mesothelioma depends on whether it is derived from the epithelial, sarcomatous, or biphasic type, with a reported survival of 5-8 months for the sarcomatous variant and 6-8 months for the biphasic variant [3]. The recommended treatment is the same as for primary pericardial mesothelioma, which is mainly palliative care.

There are many differential diagnoses for an invasive mediastinal mass, including metastatic lesions from other primary sites such as primary non-small cell lung cancer, lymphoma, leukemia, angioimmunoblastic lymphadenopathy and solitary fibrous tumors of the pleura. We considered the possibility of metastatic lesions of other primary origins or lymphoma; however, after consultation with a pathologist,

mesothelioma was determined to be the most likely diagnosis for this case. Pathological proof and the histo-immunological diagnosis are very important to establish a final diagnosis.

In conclusion, desmoplastic malignant mediastinal mesothelioma is a rare type of mesothelioma. It presents with rapidly invasive metastasis and has much less of a superior vena cava syndrome. We reported this rare case to remind clinicians to be aware of this important differential diagnosis of mediastinal tumor.

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纖維惡性縱膈腔間皮癌以上腔靜脈症候群爲臨床表現：病例報告及文獻回顧

劉嘉美　魏裕峰　吳俊廷

惡性縱膈腔間皮瘤是一種很稀少的間皮瘤，大約佔了所有間皮瘤的 5% 以下，而心包膜間皮瘤是屬於更稀少的間皮瘤。根據一項驗屍解剖個案統計，在 500,000 個案裡面，其發生率小於 0.0022%。我們報告的病例是一位 48 歲男性病患，第一次出現在門診的主訴是咳嗽合併白色痰液及體重減輕已有 2 個月的時間。胸腔電腦斷層之下表現為右側獨立性縱隔腔腫瘤，且侵犯到上腔靜脈以及氣管。病理報告顯示為纖維性間皮瘤 ,並從影像學上判斷應是從心包膜長出來的間皮瘤。這病人在進行化學治療後 5 天因敗血症病逝。
(胸腔醫學 ***2015; 30: 92-98)***

關鍵詞：纖維性，惡性縱膈腔間皮瘤，上腔靜脈症候群

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Solitary Peripheral Pulmonary Artery Aneurysm Presenting as an Endobronchial Tumor: A Case Report

Shao-Hao Wu*, Heng-Sheng Chao*, Jin-Hwang Liu**, Shi-Chuan Chang*,***

Pulmonary artery aneurysms (PAAs) are rare. Hemoptysis is a common symptom of PAAs, but there are only a few case reports in the literature describing the bronchoscopic findings of PAAs. We report the case of an 18-year-old male with a solitary peripheral PAA, who presented with hemoptysis and an endobronchial tumor at the proximal left posterior basal segmental bronchus. Subsequent pulmonary artery angiography confirmed the diagnosis, and the patient was successfully treated with endovascular coil embolization. This case highlights the importance of including PAAs in the list of differential diagnoses of endobronchial tumors. Endobronchial ultrasound can provide more clues before invasive procedures are initiated. A biopsy should be avoided to prevent fatal hemorrhage. ***(Thorac Med 2015; 30: 99-104)***

Key words: pulmonary artery aneurysm, endobronchial tumor, hemoptysis, endobronchial ultrasound, coil embolization

Introduction

Pulmonary artery aneurysms (PAA) are rare, and can be classified into proximal and peripheral types. While the proximal type involves the main pulmonary trunk or main pulmonary arteries, the peripheral type involves smaller intrapulmonary arteries. PAAs are associated with several congenital and acquired conditions, among which, infection is the most important. We describe a cancer patient with a newly developed solitary, peripheral PAA that presented as an endobronchial tumor.

Case Report

An 18-year-old male was admitted to the ward due to intermittent hemoptysis for 10 days. Six weeks earlier, he was diagnosed as having acute monoblastic leukemia presenting as fever, non-healing oral ulcer and pancytopenia. He was hospitalized and received induction chemotherapy with cytarabine plus idarubicin. After this, febrile neutropenia developed. He complained of productive cough without hemoptysis. A chest radiograph showed pneumonia in the left lower lung field. Blood cultures

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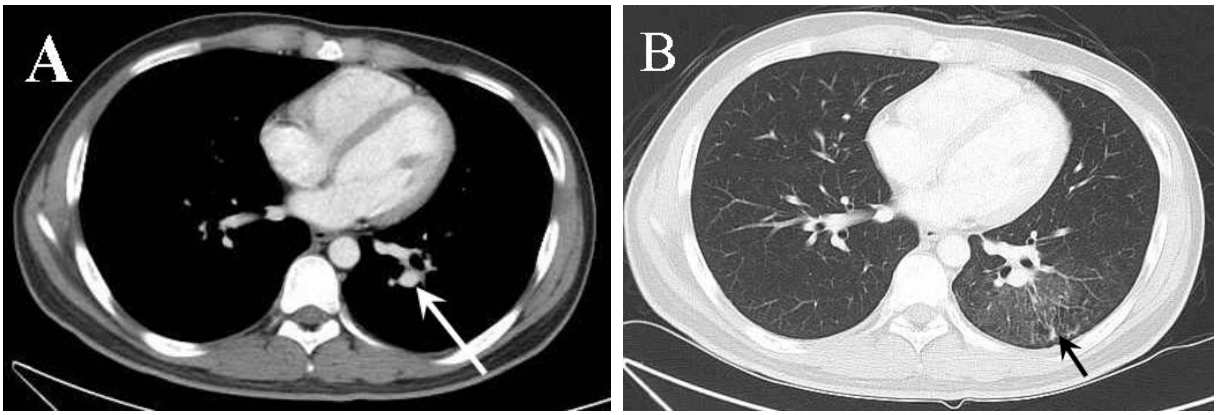

Fig. 1. A. Contrast-enhanced CT of the chest shows a strong enhancing nodule (white arrow) in the left lower lung. B. CT of the chest at the same level as A showed mild ground-glass opacity (black arrow), consistent with retained hemorrhage.

and sputum cultures yielded no growth. Broad-spectrum antibiotics were prescribed for the febrile neutropenia. Two weeks after completion of induction chemotherapy, his hemogram gradually appeared to be normal and his fever subsided. Follow-up chest radiograph showed resolution of pneumonia in the left lower lung. The patient was discharged smoothly.

Four days after discharge, the patient began to have intermittent hemoptysis. The total amount of blood was around 30 mL per day. The symptom could not be controlled by oral medications. He denied fever, chest pain, dyspnea, low extremity swelling or calf pain. Physical examination at admission was unremarkable except for mild coarse crackles in the left lower chest. The results of laboratory tests, including platelet count, prothrombin time, and activated partial thromboplastin time, were within normal limits. Microbiological examinations, including smears and cultures as well as serological tests for *Mycobacterium tuberculosis* and fungus, showed no yields. A contrast-enhanced computed tomography (CT) scan of the chest showed a strong enhancing nodule about 1.1 cm in the left lower lobe (LLL) and mild ground-glass opacities and subsegmental atelectasis of the LLL (Figures 1A and 1B). A vascular lesion with focal pulmonary hemorrhage could not be excluded. There was no evidence of pulmonary embolism.

The patient underwent flexible bronchoscopy, which demonstrated a protruding, pulsatile, white-colored tumor at the proximal left posterior basal segmental bronchus (LB10) with a suspicious bleeding nevus (Figures 2A and 2B). An endobronchial ultrasonography system (EU-ME1, Olympus Optical Co. Ltd., Tokyo, Japan) equipped with a 20 MHz radial-mechanical type ultrasound probe (UM-BS20-26R, Olympus Optical Co. Ltd., Tokyo, Japan) showed a deformable, hypoechoic lesion (Figure 3) with pulsation. Since all the findings were highly suggestive of a vascular lesion, bronchoscopic biopsy was not performed. A selective pulmonary artery angiography was then done and established the diagnosis of PAA, measuring 0.90×0.99 cm, arising from the proximal left posterior basal segmental artery (Figure 4). Some contrast extravasation to the LB10 bronchial tree was noted. The aneurysm was then successfully embolized with 4 helical coils and

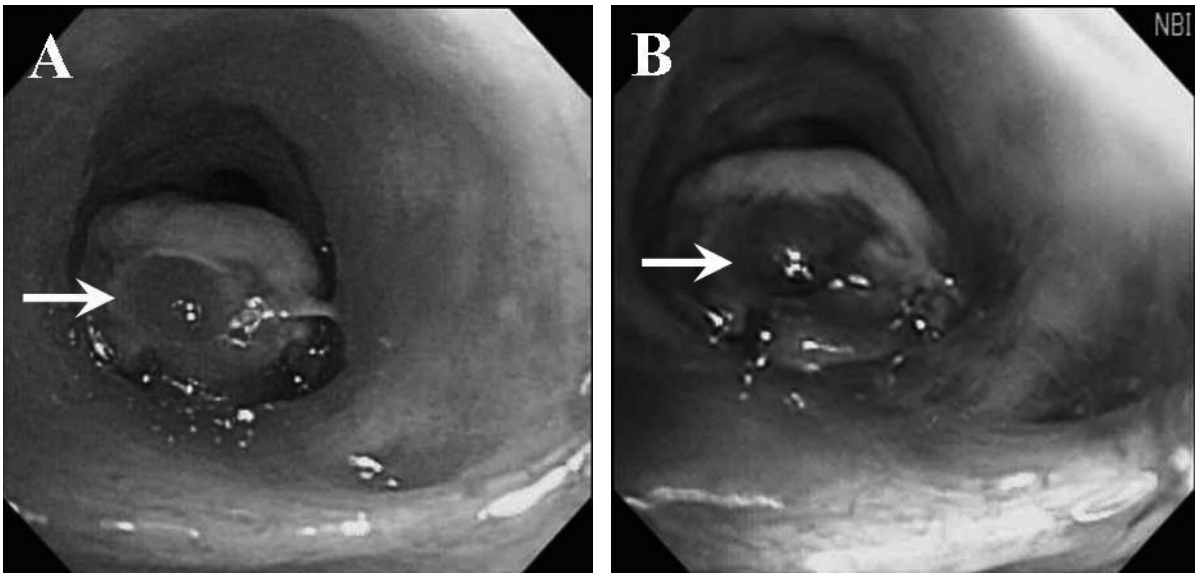

Fig. 2. Flexible bronchoscopy revealed a protruding, pulsatile, white-colored tumor at the proximal left posterior basal segmental bronchus with a suspicious bleeding nevus (white arrow). A. White light. B. Narrow band imaging.

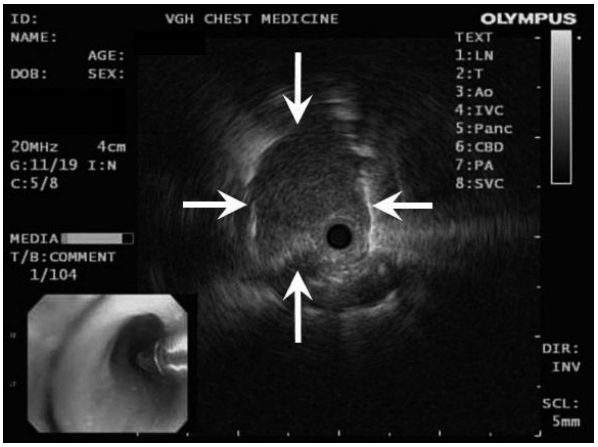

Fig. 3. Endobronchial ultrasonography shows a deformable, hypoechoic lesion with pulsation.

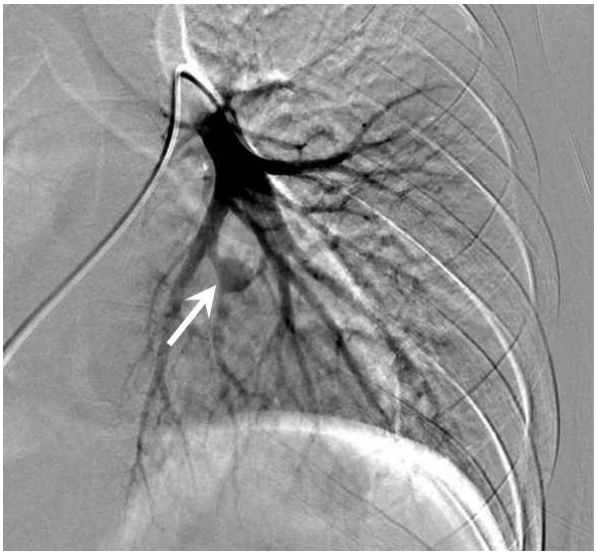

Fig. 4. Selective pulmonary artery angiography shows an aneurysm arising from the proximal left posterior basal segmental artery.

2 tornado coils. The procedure was uneventful and the patient's hemoptysis ceased. A follow-up chest radiograph 3 months later showed the presence of embolization coils in the left lower lung field (Figure 5).

Discussion

Determining the accurate incidence of PAA is difficult, but it appears to be quite rare. In 1947, Deterling and Clagett reported 8 cases

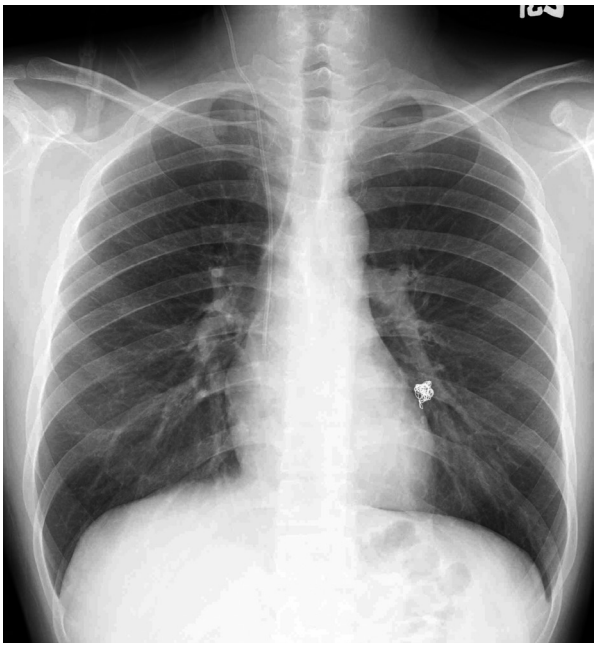

Fig. 5. A chest radiograph taken at 3 months after coil embolization shows the presence of embolization coils at the left lower lung field.

(0.0073%) of PAA in 109,571 autopsies [1]. Peripheral PAA alone has a much smaller share of all types of PAA. In a literature review by Bod LJ *et al*, only 22 cases of peripheral PAAs (19.8%) were found in a total of 111 cases with PAA [2].

Several congenital and acquired conditions can manifest with PAA. Bartter *et al* subdivided PAA cases into those with and without abnormal arteriovenous communication [3]. In the latter group, the underlying conditions included infection, congenital heart disease, vascular abnormalities (connective tissue disorders, vasculitis), pulmonary hypertension, trauma (both extravascular and endovascular), and idiopathic conditions. Proximal PAA is usually associated with congenital heart disease, while peripheral PAA may tend to develop in patients with infection, pulmonary hypertension, and/or a vascular defect [4]. Infection is the most important cause of acquired PAA [3]. In the pre-antibiotic era, tuberculosis (TB) and syphilis were the 2 major etiologies of PAA; however, the pathogeneses are different. Tuberculous PAAs, also called "Rasmussen aneurysms", result from invasion and erosion of the vessel wall by an adjacent infectious focus. Therefore, Rasmussen aneurysms tend to occur in peripheral pulmonary arteries. In contrast, syphilis usually causes proximal PAAs due to infection of the vasa vasorum. In addition to TB and syphilis, several bacteria and fungi, such as *Staphylococcus aureus*, streptococcal species, Aspergillus species, and Candida species, have been implicated as causes of mycotic PAA [3]. A third pathogenic process is bacteremia and endovascular seeding. The mechanism is supported by the fact that PAAs have developed in patients with endocarditis, osteomyelitis, skin abscess, and pneumonias. In our case, the patient had no history of syphilis and TB. Although blood cultures and serologic tests failed to detect causative organisms, the PAA was still thought to be mycotic because pneumonia had occurred previously in the same location and there was high probability of bacteremia in patients with febrile neutropenia.

PAA often presents with hemoptysis [3]. A study revealed that peripheral pulmonary artery pseudoaneurysms occurred in up to 11% of patients undergoing bronchial angiography for hemoptysis [5]. Massive hemoptysis caused by ruptured aneurysm is the most serious complication. Monchik J *et al* reported that of 35 patients with a solitary peripheral PAA, 21 died from PAA rupture [6]. On the chest radiograph, peripheral PAAs may present as single or multiple nodules. An endobronchial tumor, however, is an extremely rare presentation. A search of the English literature in PubMed

using the search terms “pulmonary artery aneurysm” and “endobronchial” revealed only 3 published cases [7-9]. In 2 of the 3 cases, the patients died from massive bleeding after bronchoscopic procedures. In addition, Park GY *et al* described 3 types of bronchoscopic findings of endobronchial vascular lesions in 5 patients with hemoptysis: tubular bulging type, mass-like type, and endobronchial hemangioma type [10]. One of the 2 patients with mass-like endobronchial vascular lesions experienced massive bleeding upon biopsy. In our reported case, the endobronchial tumor appeared to have a soft, deformable and pulsatile appearance. We remained alert to the possibility of vascular lesion. Endobronchial ultrasound confirmed the hypoechoic nature of the lesion. It was unclear why there was no Doppler function to demonstrate the blood flow on such a mini ultrasound probe. Given the bronchoscopic observations and chest CT findings, we spared the patient from a dangerous, even fatal, bronchoscopic biopsy.

The treatment options for peripheral PAAs include surgical resection and embolotherapy. Nowadays, percutaneous embolization is a safe and effective alternative to surgery and has become an optional choice of treatment [11].

In summary, peripheral PAAs are rare and are usually associated with infection. Although unusual, PAAs should be considered among the differential diagnoses of endobronchial tumors. Biopsy should be avoided to prevent fatal hemorrhage. Contrast-enhanced CT may demonstrate the vascular nature of the lesion. Pulmonary artery angiography with embolization is both diagnostic and therapeutic for solitary peripheral PAAs.

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以支氣管內腫瘤表現的孤立性週邊肺動脈瘤：病例報告

吳紹豪 * 趙恆勝 * 劉俊煌 ** 張西川 *,***

肺動脈瘤很少見，咳血為一常見的臨床表現。目前的文獻中，僅有少數的病例報告描述肺動脈瘤在支氣管鏡下的所見。我們報告一位 18 歲患肺動脈瘤的男性，臨床表現為咳血以及位於左下肺支氣管內腫瘤。病人接受肺動脈血管攝影確診後，成功地接受血管內線圈栓塞術治療。此病例凸顯須將肺動脈瘤列入支氣管內腫瘤的鑑別診斷之重要性。另外，在進行侵入性檢查前，支氣管內超音波能提供更多相關的資訊。當懷疑肺動脈瘤時，臨床醫師應該避免施行切片檢查以避免致命性的出血。*(胸腔醫學 **2015; 30: 99-104**)*

關鍵詞：肺動脈瘤，支氣管內腫瘤，咳血，支氣管內超音波，線圈栓塞術

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Delayed Pericardial Effusion after the Nuss Procedure for Pectus Excavatum – A Case Report and Literature Review

Chin-Chieh Hsu*, Yi-Chang Lin***, Jian-Bo Cheng**

A 31-year-old male presented to our emergency department with symptoms of chest pain and progressive dyspnea that had persisted for 2 days. A series of examinations revealed massive pericardial effusion that required drainage and appeared to be caused by a flipping bar for a pectus excavatum repair 4 weeks before. An urgent subxiphoid pericardiostomy was done and anti-inflammatory drugs were administered subsequently. We report the present case to illustrate a rare but potentially life-threatening complication after the Nuss procedure and to suggest a treatment strategy. ***(Thorac Med 2015; 30: 105-110)***

Key words: pectus excavatum, pericardial effusion, Nuss procedure, subxiphoid pericardiostomy

Introduction

In 1998, Nuss et al introduced a minimally invasive technique for the correction of pectus excavatum without cartilage resection [1]. Since then, the Nuss procedure has become a standard procedure in many institutions worldwide because of its simplicity and good results. However, a variety of complications can occur, and life-threatening problems have occasionally been reported. Here, we report a case of symptomatic pericardial effusion that occurred in a patient 4 weeks after the Nuss procedure. We treated the patient successfully with surgical drainage and anti-inflammatory drugs without revision surgery or removal of the displaced bar.

Case Report

Our patient was a 31-year-old male who worked in the service industry. He was a smoker with 15 pack-years, and had a history of bipolar affective disorder for 8 years and hepatitis B for 3 years with stable disease control. The patient had pectus excavatum since his childhood. He was admitted to our hospital in June 2013 for the treatment of chest tightness and frequent palpitations during the previous 6 months. Physical examination revealed a caved-

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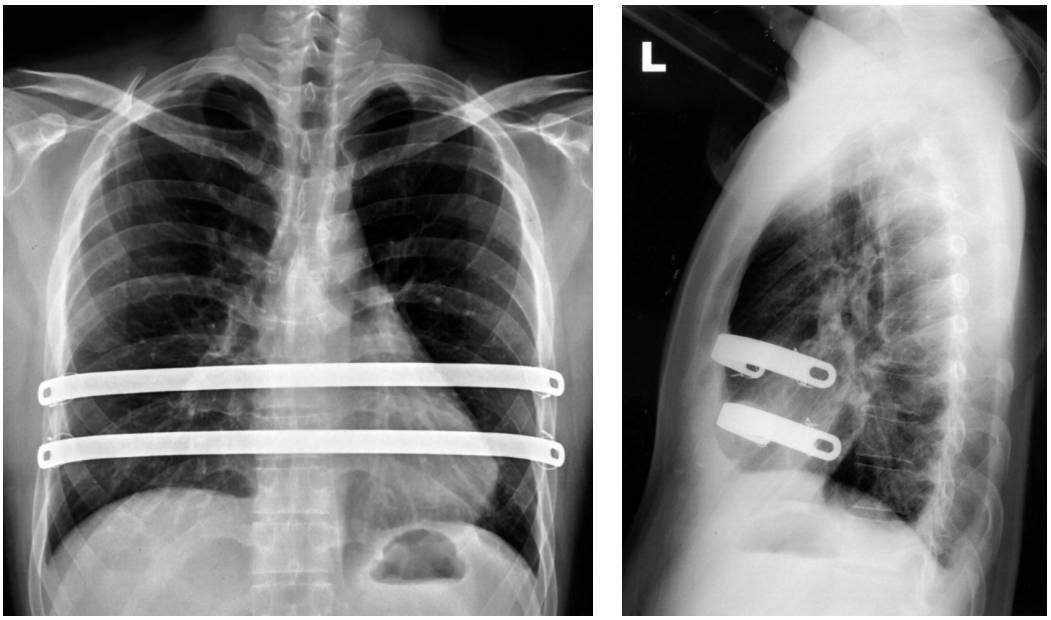
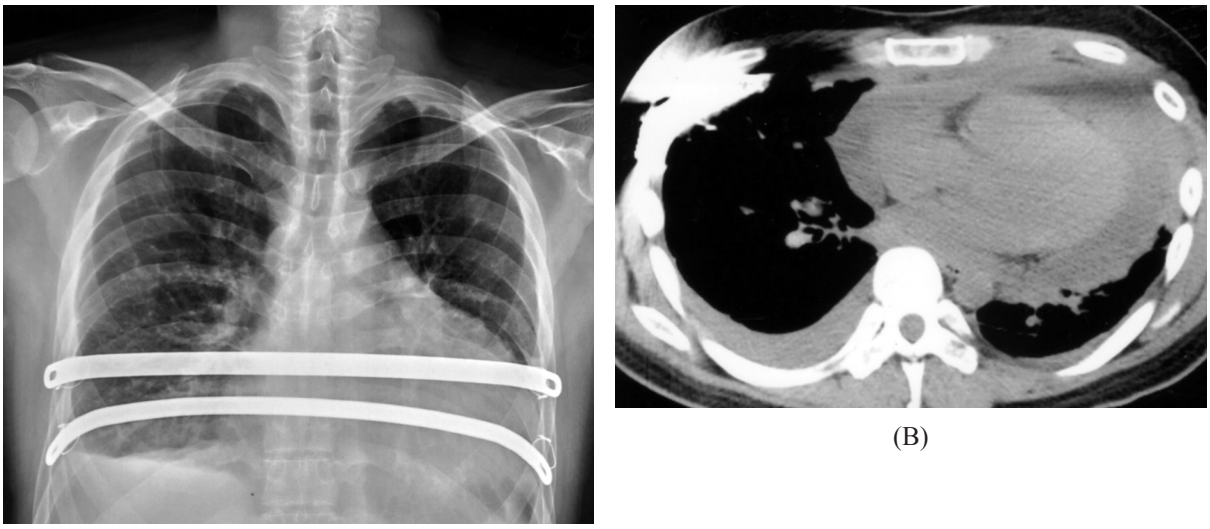


(A) (B)

Fig. 1. Posteroanterior view (A) and lateral view (B) chest radiographs on the 2nd day after the Nuss procedure, showing normal cardiac size and the accurate placement of pectus bars.

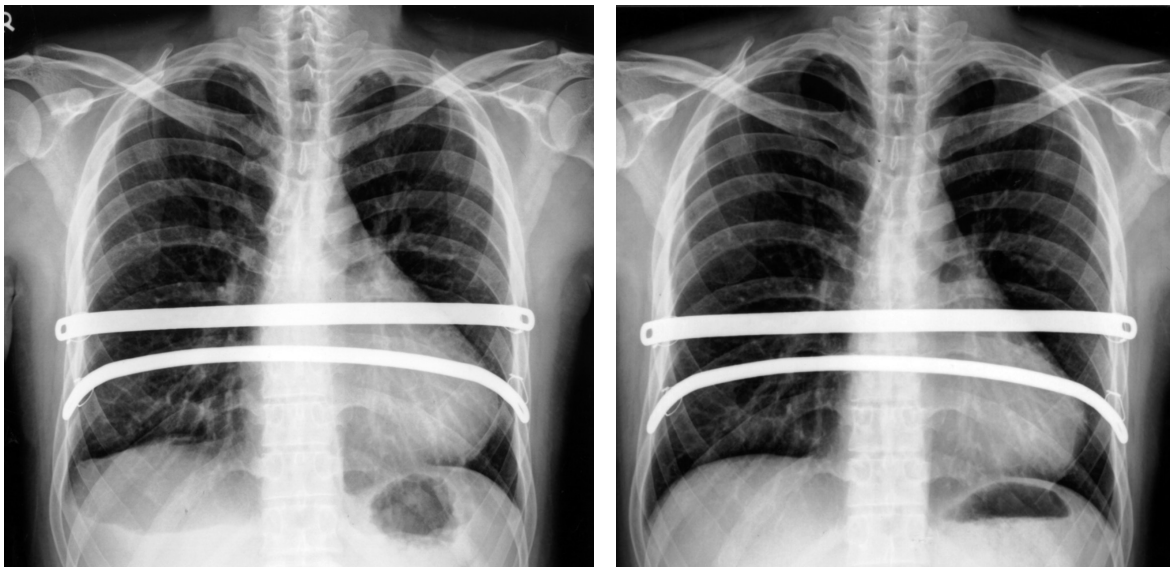
in appearance from the anterior middle to the lower chest wall. Echocardiography revealed no abnormality and a pulmonary function test showed mild restrictive impairment. The Haller index was 4.8 on chest computed tomography (CT). We performed the Nuss procedure under thoracoscopic guidance by inserting 2 12-inch pectus bars with a bridge shape under the sternum through the 4th and 5th intercostal spaces. He was discharged 10 days after the operation without adverse events, and chest x-ray showed a normal appearance without displacement of either pectus bar (Figure 1).

However, 4 weeks after the operation, the patient presented to our emergency department reporting progressive dyspnea and chest pain during the previous 2 days. Physical examination revealed mild tachycardia with a pulse rate of 96 beats/min, tachypnea with a respiratory rate of 24/min, and distant heart sounds. Laboratory results were as follows: hemoglobin, 10.2 g/dL; white blood cells, 17,430/mm^3; platelets, 480,000/mm^3; international normalized ratio of prothrombin time, 1.2; and activated partial prothrombin time, 34.2 s. Chest x-ray showed a displacement of the lower pectus bar, and chest CT revealed a moderate amount of pericardial effusion (Figure 2). We performed subxiphoid pericardiotomy for drainage, and >700 mL of light brown pericardial fluid was removed from the pericardial space. The drain was removed on the 5th postoperative day. The results of fluid analysis were negative for bacterial culture, acid-fast bacilli, and malignant cells. The patient was discharged on the 7th postoperative day. At follow-up in the outpatient department 4 weeks later, he was in good health and did not show pericardial effusion (Figure 3).



(A) (B)

Fig. 2. (A) Chest radiograph 4 weeks after the Nuss procedure showing increased cardiac size and displacement of the lower pectus bar. (B) Chest CT revealing fluid accumulation in the pericardial cavity.



(A) (B)

Fig. 3. (A) Chest radiograph on the 7th day after subxiphoid pericardiotomy revealing normal cardiac size. (B) Chest radiograph obtained in the outpatient department 4 weeks after subxiphoid pericardiotomy, showing improvement.

Discussion

In 1998, Nuss *et al* reported their 10-year experience with a minimally invasive procedure for the repair of pectus excavatum, which was performed by the insertion of convex steel bars

under the sternum and required neither cartilage incision nor excision [1]. The Nuss procedure has excellent long-term results with few complications and has become the procedure of choice in many institutions worldwide. Park *et al* reported complications of the Nuss procedure and noted a total postoperative complication rate of 16.1%. Complications can occur early (within a month) or late (after a month) and include pneumothorax, bar displacement, wound seroma, and pericardial effusions [2]. The complication rate for pericardial effusion after the Nuss procedure is relatively low, and is reported to be between 0% and 2.5% [3]. In the authors' hospital, a total of 582 patients underwent the Nuss procedure for pectus excavatum from 2005 to 2014, and only 2 (0.34%) suffered from postoperative pericardial effusion.

The clinical presentation of pericardial effusion includes dyspnea, chest tightness, tachycardia, jugular venous distention, arterial hypotension, and even shock in severe tamponade cases. The etiology of the pericardial effusion in the present case appears to be related to post-pericardiotomy syndrome, which is a relatively common complication following cardiac surgery [4]. A displacement of the pectus bar or minor trauma to the pericardium during the creation of the substernal tunnel during the Nuss procedure could have caused the pericarditis and pericardial fluid accumulation in our patient. The mechanism of direct pericardial injury is less likely the cause in this case because of the late onset. The underlying pathophysiology in the present case is hypothesized to be an immune-mediated reaction following damage to the pericardium that induced the production of immune complexes that caused a local inflammatory reaction with exudation [4]. Empirical anti-inflammatory therapy with adjunctive colchicine has been shown to be effective as treatment. Pericardiocentesis is indicated for pericardial effusion with hemodynamic compromise, and many procedures can be performed for drainage, including the placing of an indwelling pericardial catheter, subxiphoid pericardiotomy, or more invasive pericardiectomy [5]. To treat this patient, we chose subxiphoid pericardiotomy combined with oral anti-inflammatory therapy including acemetacin 90 mg po bid and prednisolone 5 mg po bid for 2 weeks. The patient's recovery was unremarkable, and we saw no need to remove or revise the displaced steel bar at this stage. The patient was still in good condition 11 months after pericardiotomy, without evidence of recurrence.

Although the Nuss procedure for pectus excavatum is considered safe and effective, some postoperative complications, such as pericardial effusion or tamponade, can lead to life-threatening situations. Intraoperative video-assisted thoracoscopic surgery (VATS) with the Nuss procedure may be useful for the prevention of most pericardial injuries, and postoperative education of the patient is equally important. Our policy for a patient's postoperative care following the Nuss procedure is bed rest for at least 1 week to help prevent bar displacement. However, this patient tended to lie in the prone position to rest and sleep because of postoperative irritation and pain -- we believe this was the cause of the bar displacement. We suggest patient-controlled epidural analgesia combined with intravenous non-steroid anti-inflammatory drug treatment for the patient's postoperative pain management during the first 3 days. The careful placement and fixation of the pectus bars are useful for the prevention of such complications, and regular postoperative follow-up in the outpatient department is also necessary for the early detec-

tion of minor complications.

In conclusion, postoperative pericardial effusion after the Nuss procedure is relatively rare, but is potentially life threatening. Application of intraoperative VATS and careful placement and fixation of the pectus bars may decrease the risk of such complications. If complications do occur, adequate drainage and anti-inflammatory medical therapy can lead to satisfactory recovery without sequelae.

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漏斗胸病患接受納氏矯正手術後併發延遲性心包膜積液：病例報告及文獻回顧

許晉杰 * 林宜璋 *** 程建博 **

一位三十一歲的男性，因為胸痛及漸發性呼吸喘，症狀持續兩天，而至本院就診。一連串檢查發現，病患罹患大量心包膜積液需要引流。我們認為，造成原因與病患四周前接受漏斗胸矯正手術之矯正板移位有關。作者採用經劍突下切口執行心包造口術引流（subxiphoid pericardiostomy），合併使用口服抗發炎藥物而成功治療。此病例為納氏漏斗胸矯正手術後之罕見、卻潛在威脅生命之併發症，我們提供病例報告及與治療策略相關之文獻回顧。*(胸腔醫學 **2015; 30: 105-110**)*

關鍵詞：漏斗胸，心包膜積液，納氏矯正術，劍突下心包造口術

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Pulmonary Alveolar Proteinosis Treated with Multiple Selective Lobar Lavage by Fiberoptic Bronchoscopy with Non-Invasive Ventilation under Procedural Sedation: A Case Report

Chang-Wei Lin, Ting-Yu Lin, Yu-Lun Lo

Pulmonary alveolar proteinosis (PAP) is a rare disease. The current standard treatment for PAP is whole-lung lavage (WLL). An alternative treatment is selective lobar lavage via fiberoptic bronchoscopy (FOB). However, some patients still require intubation with sedation for this procedure. Herein, we report a case of multiple selective lobar lavage via FOB with non-invasive positive pressure ventilation (NIPPV) support under procedural sedation for the treatment of a patient with PAP diagnosed by wedged resection via video-assisted thoracoscopic surgery. As the patient refused to undergo WLL and could not tolerate FOB, we performed lobar lavage by FOB for the affected segment, according to chest CT images, with designed NIPPV and procedural sedation. This new technique is safe and effective, improves patients' quality of life, and can possibly be performed at outpatient clinics to decrease treatment cost. ***(Thorac Med 2015; 30: 111-117)***

Key words: pulmonary alveolar proteinosis, bronchofiberscopic lobar lavage, non-invasive positive pressure ventilation, procedural sedation

Introduction

Pulmonary alveolar proteinosis (PAP), also known as pulmonary alveolar phospholipoproteinosis, is a diffuse lung disease characterized by the accumulation of amorphous, periodic acid-Schiff (PAS)-positive lipoproteinaceous material in the distal air spaces [1-3]. Because of the unknown pathogenesis, the most effective treatment for PAP is the mechanical removal of the accumulated protein via whole lung lavage (WLL) [4-7]. However, WLL may cause severe hypoxemia during the procedure, even under general anesthesia and with double lumen endotracheal tube (ETT) placement. Because of disadvantages such as severe hypoxemia in PAP patients and the difficulty of the technique, the use of WLL in medical centers and for more advanced cases has been limited [8-10].

An alternative choice for the treatment of PAP is selective lobar lavage by fiberoptic bronchoscopy (FOB) under general or local anes-

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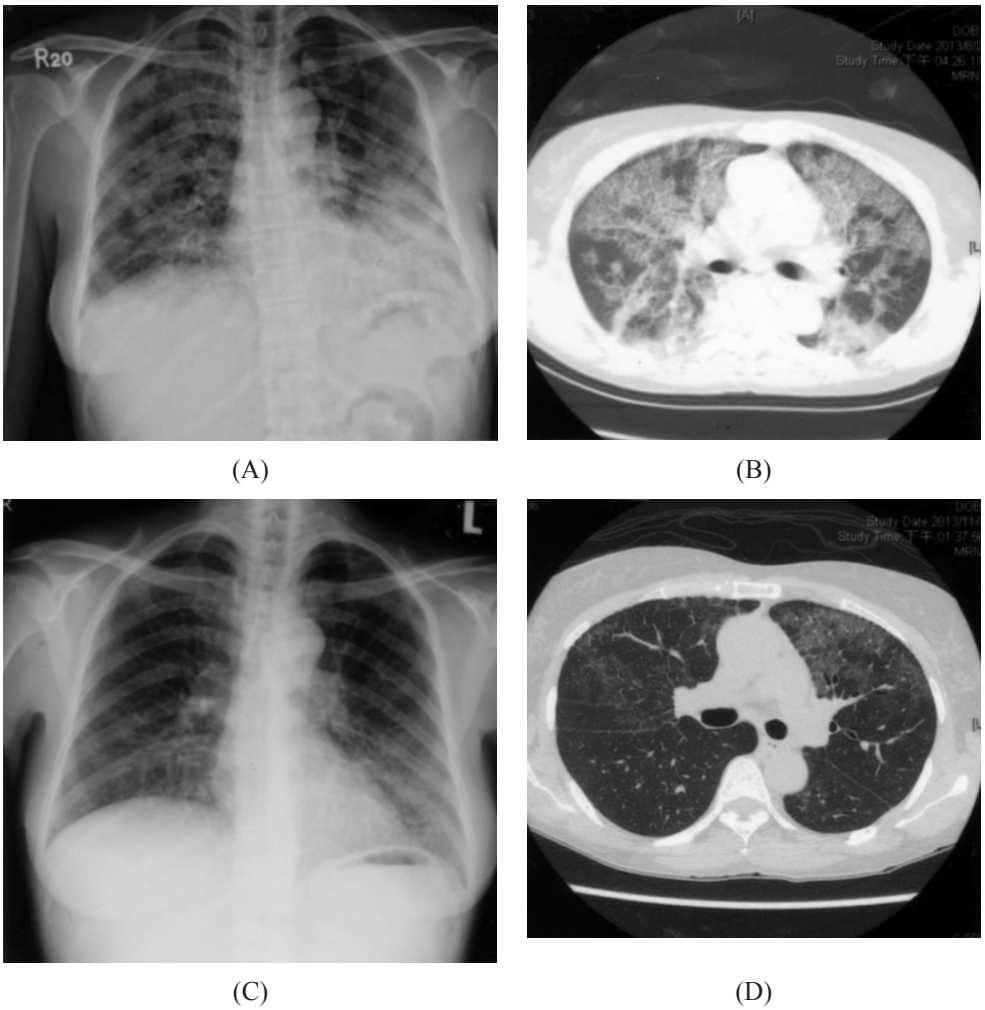

Fig. 1. Chest radiography showing diffuse alveolar opacities before lavage (A); High-resolution CT scan of the chest showing the classic finding of widespread airspace consolidation with thickened interlobular septa (B); Decreased bilateral lung parenchyma infiltration on post-lavage day 13 (C); Improvement in widespread airspace consolidation with thickened interlobular septa on post-lavage day 53 (D).

thesia [11-13]. In this study, we report the successful treatment of a PAP patient who refused intubation under general analgesia and could not tolerate FOB.

Case Presentation

A 45-year-old woman with hypertension and a gout history had suffered from cough and dyspnea on exertion since June 2013. On August 2, 2013, the patient went to a regional hospital for treatment of a dog bite, and diffuse interstitial lesions were noted on chest X-ray at that time (Figure 1A). Further chest computed tomography (CT) revealed diffuse, bilateral, ground-glass attenuation with superimposed interlobular septal thickening and intralobular lines in both lung fields, including all lobes, similar to a crazy-paving pattern (Figure 1B). FOB was subsequently performed. However,

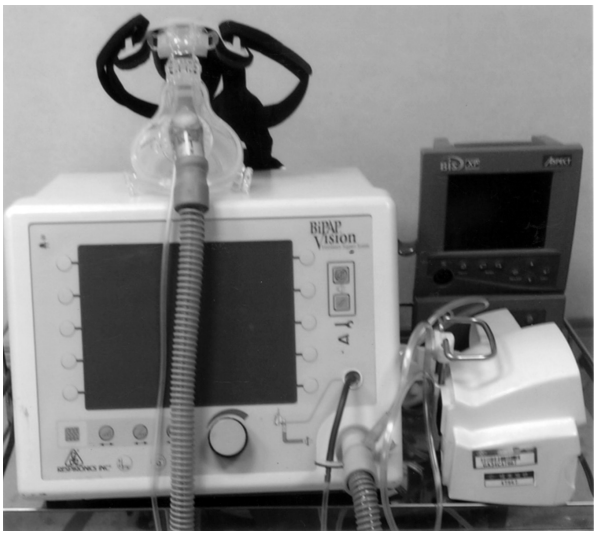

Fig. 2. Designed CPAP and procedural sedation equipment

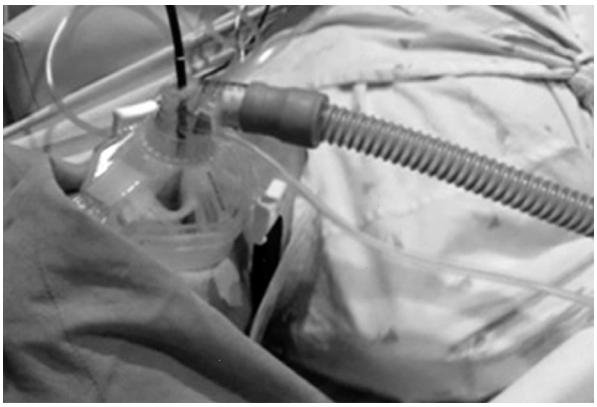

Fig. 3. Designed CPAP and procedural sedation equipment

owing to inconclusive results and the milk-like fluid obtained from the bronchoalveolar lavage (BAL), surgical biopsy was necessary. A right lower lobe wedge resection was performed through video-assisted thoracoscopic surgery. Pathology revealed the accumulation of amorphous eosinophilic PAS-positive materials in the section and confirmed the diagnosis of PAP. The patient was referred to our hospital for further treatment in September 2013. Physical examinations were generally normal, except for coarse crackles in the area of the lower lung fields. Chest radiography (Figure 1A) revealed diffuse alveolar infiltrates, especially in the lower lobes. Arterial blood gas analysis of the patient on arrival showed a pH of 7.426, $PaCO_2$ of 34.7 mmHg, and PaO_2 of 59.2 mmHg, with oxygen saturation of 91.5% while breathing room air. A pulmonary function test administered 4 days after admission showed the following results: FEV_1, 1.61 L (62% of the predicted value); FVC, 1.84 L (59% of the predicted value); and FEV1/FVC, 88%. Previous chest CT scans indicated the classic finding of widespread airspace consolidation with thickened interlobular septa (Figure 1B). WLL was indicated for PAP treatment. However, the patient refused intubation under general analgesia, and could not tolerate FOB because of dyspnea and severe cough during her previous experience. After discussion with the patient, multiple selective lobar lavage by FOB with non-invasive positive pressure ventilation (NIPPV) was performed twice under procedural sedation at the interventional bronchoscope suite.

Before performing the procedure, the blood pressure of the patient was monitored with an automated pressure cuff, and heart rate and rhythm were monitored by 3-lead electrocardiography. A peripheral pulse oximeter was used to monitor oxyhemoglobin saturation (SpO_2), and the patient was under continuous positive airway pressure (CPAP) with oxygen supplementation. The CPAP mask was designed to allow the bronchoscope to pass through it (Figures 2-3). The initial CPAP setting was 8 cm H_2O and 60% FiO_2. An intravenous catheter was placed in the forearm for drug administration. A disposable BIS Quatro Sensor (Aspect Medical System Inc, Newton, MA, USA) was attached to the forehead of the patient. The sensor was

connected to the A-2000 XP BIS monitor (version 3.11, Aspect Medical Systems, Inc.). A BIS value was displayed once all impedances were acceptable. The smoothening time was set at 15 s. All parameters were monitored continuously, except blood pressure, which was recorded every 3 min.

Induction was performed using alfentanil (1:10 dilution, 5 μg/kg bolus), following an initial administration of 0.5 mg/kg intravenous propofol bolus. The dose of propofol was then carefully titrated by administering 10-20 mg of boluses until the BIS index reached 70. The duration between the boluses was 20 s. The propofol infusion (3-12 mg/kg/h) was then administered using a syringe pump (Injectomat Agilia, Fresenius Kabi, France) to maintain the BIS index between 65 and 75 [14].

The left lower lobe (LLL) was selected for the first therapeutic BAL, based on the chest CT findings. Each segmental bronchus of the LLL was lavaged sequentially with 200 ml of saline solution (at room temperature). During the first cycle of therapeutic lavage, 750 ml of sterile normal saline were used and 210 ml of white fluid were retrieved. The entire procedure lasted approximately 60 min. After the first therapy, the patient felt much better, and arterial blood gas analysis on the subsequent day showed a pH of 7.418, $PaCO_2$ of 37.8 mmHg, and PaO_2 of 59.7 mmHg, with oxygen saturation of 91.4% while breathing room air.

The second BAL was performed on the following day. A total of 1400 ml of sterile normal saline were used and 850 ml of fluid were retrieved successively from the right middle and lower lobes. The patient was sent to the intensive care unit for recovery and post-procedure observation. After 3 h, the CPAP mask was removed from the patient and the Venturi mask was used instead (15 L/min and 50% FiO_2); on the following day, a nasal cannula (3 L/min) was employed. The patient was transferred to the general ward on the same day. Subjective improvement of dyspnea was noted after the therapeutic lung lavage. One week after the procedure, the arterial blood gas data obtained in room air were as follows: pH, 7.36; $PaCO_2$, 37.7 mmHg; PaO_2, 77.9 mmHg; and SaO_2 95.2%. The pulmonary function test results were as follows: FEV_1, 1.71 L (69% of the predicted value); FVC, 2.11 L (72% of the predicted value); and FEV_1/FVC, 81%. The patient was discharged, and the chest X-ray taken 1 month later revealed a regressive change in the infiltration of both lungs (Figure 1C). In addition, high-resolution CT on post-lavage day 53 revealed improvement in widespread airspace consolidation with thickened interlobular septa (Figure 1D).

Discussion

WLL remains the standard treatment for PAP [4]. The procedure is performed under general anesthesia with a rigid bronchoscope after selective intubation. The patients also need post-procedure observation in the intensive care unit. The major adverse effect of WLL is hypoxemia. Because of severe hypoxemia and de-saturation, some patients cannot tolerate the WLL procedure; therefore, selective lobar lavage by bronchoscopy has been reported as a possible alternative. Multiple selective lobar lavage by FOB has always been performed in patients with PAP under general anesthesia and mechanical ventilation [11-12]. The advantage of using bronchofiberscopic lobar lavage is that we can instill the fluid into the orifice of the affected segment that is selected and continue to

observe fluid aspiration [11]. This selective lobar lavage by bronchoscopy using chest CT images can preserve the normal segment to maintain adequate oxygenation. However, selective intubation and mechanical ventilation may be the cause of severe complications such as barotrauma, pneumothorax, and infections [15].

Successful treatment of PAP with multiple segmental or lobar lavage by FOB without sedation or general anesthesia has also been reported in adult patients. However, the major complications have been severe cough and hypoxemia during lavage [12]. Multiple lavages make the procedure less tolerable than WLL [16]. To the best of our knowledge, there have been no reports on sequentially selective lobar lavage by FOB with NIPPV under procedural sedation.

In conclusion, in this case report, we propose a new technique to improve oxygen exchange and reduce discomfort in patients with less advanced disease. This method may be an alternative treatment choice for those patients who cannot tolerate bronchoscopy or intubation with general anesthesia. We used a CPAP mask through which the bronchoscope could be passed to improve oxygen exchange and employed procedural sedation to reduce the patient's discomfort during selective lobar lavage. We found that multiple selective lobar lavage by FOB with NIPPV under procedural sedation is safe and effective, reduces the patient's discomfort during bronchoscopy, and can possibly be performed at outpatient clinics without intubation, thereby decreasing the treatment cost.

Acknowledgments

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在非侵入性正壓通氣及鎮靜下多次支氣管內視鏡選擇性肺葉沖洗術治療肺泡蛋白質沉著症－病例報告

林倡葦　林定佑　羅友倫

肺泡蛋白質沉著症（pulmonary alveolar proteinosis, PAP）是少見的疾病。全肺沖洗術（whole lung lavage, WLL）仍是現今標準的治療方式。支氣管內視鏡選擇性肺葉沖洗術是另一個選擇的方式。但仍有些病人需插管及麻醉下進行此方式。我們報告一個蛋白質沉著症患者在非侵入性正壓通氣及鎮靜下，使用支氣管內視鏡作多次肺葉沖洗術的經驗。因為病人拒絕插管及無法忍受支氣管內視鏡所造成的不舒服，病患無法執行全肺沖洗術。我們根據電腦斷層選擇受影響嚴重的肺葉，並在設計過的非侵入性正壓通氣面罩及鎮靜使用下，分別進行左下肺葉及右中下肺葉的支氣管內視鏡肺葉沖洗術。每次以生理食鹽水從支氣管鏡內注入及洗出。病患對執行過程忍受度良好。我們的經驗顯示，支氣管內視鏡肺葉沖洗術在非侵入性正壓通氣及鎮靜使用下，對無法容忍全肺沖洗術的蛋白質沉著症患者或無法忍受支氣管內視鏡所造成的不舒服，是有效，安全的治療方式且可以改善病人生活品質，甚至可在門診執行以減少醫療花費。*(胸腔醫學* ***2015; 30: 111-117)***

關鍵詞：肺泡蛋白質沉著症，支氣管內視鏡肺葉沖洗術，非侵入性正壓通氣，處置過程鎮靜

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Recurrent Post-Obstructive Pulmonary Edema Secondary to Compression by a Large Nodular Thyroid Goiter – A Case Report

Sheng-Chieh Huang*, Kuo-An Wu*, Chung-Yueh Hsieh**

Post-obstructive pulmonary edema (POPE), also known as negative pressure pulmonary edema, is a potentially life-threatening complication in which pulmonary edema occurs shortly after relieving the patient of an upper airway obstruction. The most common causes are laryngospasm during intubation or extubation and upper airway tumors in adult populations. The incidence of POPE has been reported to be as high as 1 in 1000 general anesthetic cases. We report a patient with recurrent POPE induced by intubation of the airway for external compression by a large nodular thyroid goiter. The patient was weaned successfully after lobular thyroidectomy, without respiratory distress. ***(Thorac Med 2015; 30: 118-124)***

Key words: post-obstructive pulmonary edema (POPE), negative pressure pulmonary edema (NPPE), airway obstruction, nodular thyroid goiter

Introduction

Post-obstructive pulmonary edema (POPE), also known as negative pressure pulmonary edema (NPPE), is a potentially life-threatening complication of different associated etiologies, most commonly post-extubation laryngospasm and upper airway tumors in adult populations [1]. A markedly negative intra-thoracic pressure that develops with an increased inspiratory effort can cause pulmonary edema [2]. We encountered a case of pulmonary edema that developed immediately after intubation of the airway for chronic external compression by a large nodular thyroid goiter. After lobular thyroidectomy, the patient was weaned successfully without recurrent pulmonary edema or direct compression by goiter-induced upper airway obstruction.

Case Report

A 64-year-old woman had experienced at least 6 months of mild shortness of breath and noise while breathing. She was mildly obese with a body mass index of 26.2. She was a non-smoker, and had a history of coronary artery disease (CAD) with regular cardiology outpa-

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tient department visits for 5 years. She denied any history of travelling or exposure to potential occupational or environmental agents. Six months later, she had her first episode of sudden onset dyspnea with cyanosis, followed by decreased consciousness.

On arrival at the emergency department, the patient's body temperature was 36.2 degrees centigrade, respiratory rate was 26 breaths/min, pulse rate was 115 beats/min, blood pressure was 222/115 mmHg and peripheral oxygen saturation was 88%; her Glasgow Coma Scale score had deteriorated to 11. Blood gas analysis revealed pH 7.19, PCO_2 79.1 mmHg, PO_2 71.9 mmHg and HCO_3 30.5 mmol/L, which was consistent with chronic respiratory acidosis and superimposed acute respiratory acidosis. Initial physical examination showed diffuse rales and some wheezing on auscultation; neck inspection and palpation revealed thyroid enlargement of grade II (goiter visible with neck in normal position), and there was no jugular venous engorgement. There were no S3 gallops on auscultation, and no pedal edema on inspection and palpation. Pupils equally reactive to light were also noted. The patient was immediately intubated, before the initial chest radiograph was taken, due to severe respiratory distress. After emergency endotracheal intubation, the patient regained consciousness. The endotracheal tube contained copious amounts of a pink frothy secretion. Chest radiography done after intubation showed ground-glass opacities bilaterally, suggestive of pulmonary edema (Figure 1). Diuretics with furo-semide were administered for pulmonary edema, and she was admitted to our intensive care unit for further management.

Laboratory testing revealed the following: white blood count: 20.46×10^6/L; hemoglobin: 14.5 g/dL; platelet count: 336×10^3/L; neutrophils: 27%; lymphocytes: 65%; monocytes: 4%; eosinophils: 3%. C-reactive protein (CRP) was within normal range. Biochemistry results, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, sodium, and potassium, were within normal range. Electrocardiography showed sinus tachycardia. Further laboratory results were as follows: creatine phosphokinase (CPK) 74 (normal 13-167) U/L, creatine phosphokinase-myocardial bands (CK-MB) 28.7 (normal <25) U/L and troponin I <0.01 (normal <0.50) μg/L.

Subsequent chest X-ray, 19 hours after intubation, showed dramatic resolution of the interstitial, patchy infiltration. Coronary angiography was done on the 2nd day of admission due to a suspicion of acute coronary syndrome and further elevation of cardiac enzyme. The angiography revealed 50% stenosis in the distal region of the left anterior descending artery, and 30% stenosis in the ostium and proximal region of the left main coronary artery.

Blood WBC returned to a normal range on the 3rd day of admission. Bacterial culture, acid-fast smear, and fungus culture of sputum were negative. Blood culture, antigen of chlamydia, and mycoplasma were negative. Results of thyroid function and virus serologic tests were negative. Due to the stable hemodynamic status after 8 days of admission and the clear chest plain film, the endotracheal tube was removed after weaning criteria were met and after a successful spontaneous breathing trial with a T-piece circuit. Three hours after extubation, the patient had an episode of respiratory distress accompanied with stridor with hypoxemia and agitation. Laryngeal edema was considered at first. Her condition was unresponsive to intravenous hydrocortisone and inhaled

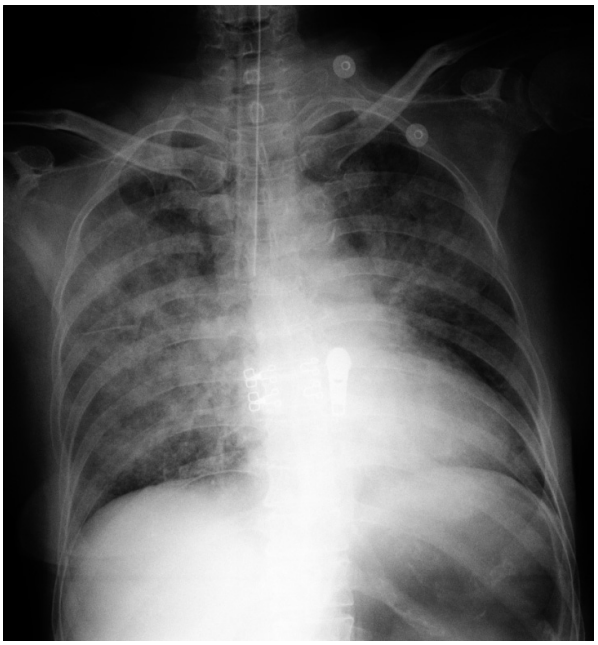

Fig. 1. Chest radiograph (anteroposterior view) revealing bilateral perihilar alveolar infiltrates and cardiomegaly, suggestive of pulmonary edema (Note: the intubation was too deep, and was drawn into an adequate position after this chest X-ray.

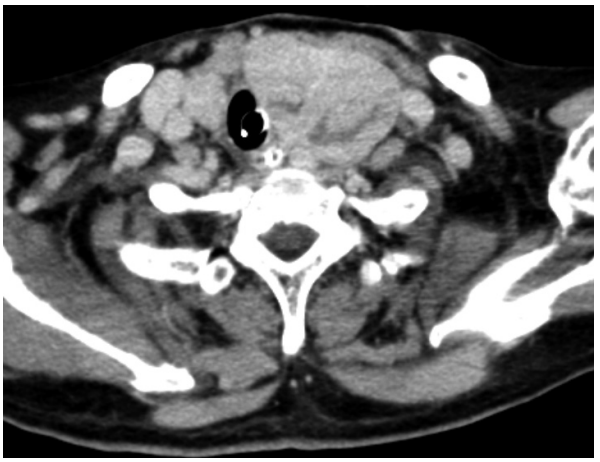

Fig. 2. Computed tomography scan of the chest at the thoracic inlet showing an enlarged left thyroid lobe compressing the trachea, which is splinted by the endotracheal tube.

beta-agonist. After re-intubation, she recovered immediately. Chest X-ray post-endotracheal intubation revealed perihilar alveolar infiltrates bilaterally, suggestive of pulmonary edema. Bihilar infiltrates regressed within 1 day after diuretics therapy. Echocardiogram revealed normal cardiac dimensions, normal left ventricular ejection fraction (LVEF), wall motion and normal pulmonary artery systolic pressure, but minimal tricuspid and mitral regurgitation. The thyroid function was normal. Computed tomography of the chest with contrast indicated no filling defect in the pulmonary arteries, which excluded pulmonary embolism, but a left thyroid lobe mass that measured 5.9×5×3 cm in size was visualized, and was suggestive of goiter (Figure 2). Thyroid sonogram demonstrated enlargement of bilateral thyroids with multiple variable-sized heterogeneous nodules with external compression on the trachea, and the results of ultrasound-guided fine-needle aspiration cytology of the thyroid nodules were non-diagnostic. Pulmonary edema occurred again post-re-intubation, 2 weeks after the previous extubation failure, and cleared dramatically after diuretics therapy and fluid restriction.

We suspected she had external compression-related tracheal stenosis caused by the large goiter, then, diagnostic bronchoscopy showed spontaneous closure of the upper trachea while slowly pulling out the endotracheal tube (Figure 3); external compression by the thyroid mass was highly considered.

Under the suspicion of upper airway obstruction caused by compression by a thyroid goiter, surgical intervention was advised in discussion with the patient and her family. The patient's family asked to transfer her to a medical center for the operation. Lobular thyroidectomy was performed and the pathology findings determined the existence of a thyroid goiter (Figure 4). The patient was weaned successfully without respiratory distress or recurrent pulmonary

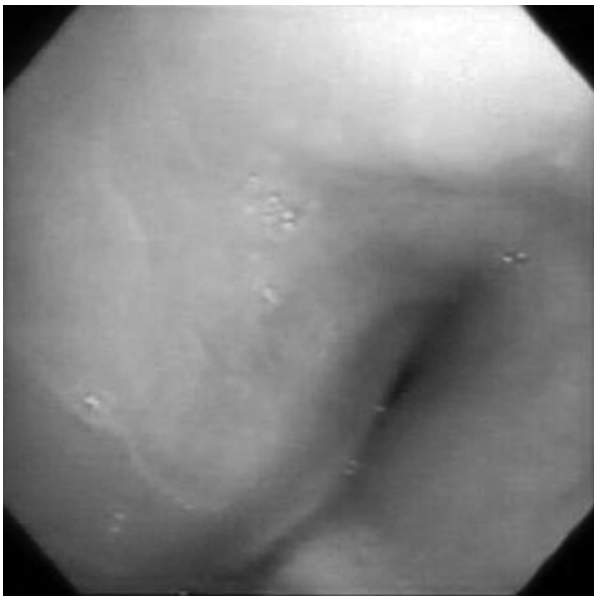

Fig. 3. Bronchoscopy demonstrated closure of the upper trachea while slowly pulling out the endotracheal tube.

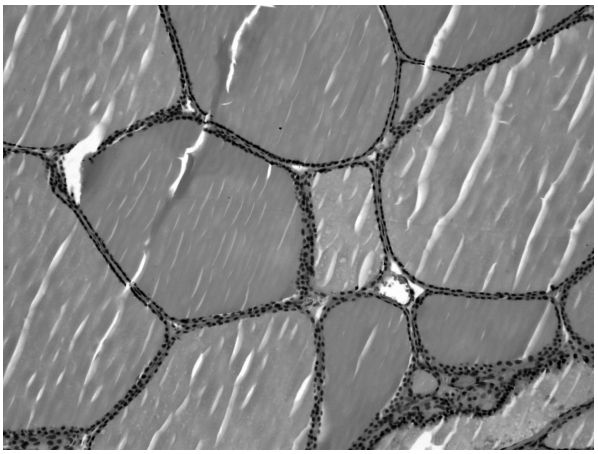

Fig. 4. The pathology of the thyroid goiter revealed variable follicles lined by flat follicular epithelial cells with abundant colloid material from the thyroid gland tissue. (Hematoxylin & Eosin stain, 200X)

edema thereafter.

Discussion

Pulmonary edema associated with upper airway obstruction was first described in an experimental dog model in 1927 as prolonged inspiration against a fixed resistance, resulting in pulmonary edema [3]. POPE is a potentially life-threatening complication in which pulmonary edema occurs shortly after relieving the patient of an upper airway obstruction [1]. POPE is most commonly caused by laryngospasm and upper airway tumors in the adult population; epiglottitis, croup, and laryngotracheobronchitis are more common etiologies in the pediatric age group [1].

There are 2 types of POPE. Type I is associated with intensive inspiratory effort due to acute airway obstruction, such as that caused by laryngospasm after extubation, epiglottitis, croup, choking or foreign-body aspiration. Type II occurs after relieving a chronic partial airway obstruction by surgical intervention, such as resection of a laryngeal tumor, adenoids/tonsils or intra-thoracic goiters [4]. The pathophysiology of POPE is multifactorial, involving components of NPPE, hypoxia, and a hyperadrenergic state. Intra-thoracic pressures, which vary from -2 cm to -12 cm H_2O during normal inspiration, can fall to as low as -50 cm H_2O with airway obstruction [5,6]. The major component of type I POPE is triggered by forced inspiration against the occluded airway; this event leads to negative intra-thoracic pressure, then the occurrence of an increased venous return to the right heart and a decreased left heart outflow, which results in increased pulmonary blood volume and elevated pulmonary venous pressures, then an increase in hydrostatic pressures and edema formation and transudation from the pulmonary capillary space to the interstitium, which leads to pulmonary edema [7,8]. In addition, hypoxia and acidosis also depress myocardial contractility and deteriorate pulmonary edema. Type II POPE is triggered with

expiration against an upper airway obstruction (Valsalva maneuver), resulting in an increase in intra-thoracic pressure. The sudden relief of obstruction leads an abrupt fall in intra-thoracic pressure followed by an increase in venous return, pulmonary blood volume and hydrostatic pressure, which then leads to pulmonary edema [9]. As seen in our case, the patient had diffuse rales and wheezing sounds on auscultation before endotracheal intubation, which implicated that pulmonary edema might have developed before intubation, so we thought that the etiology of a first attack of pulmonary edema could have been type I POPE; the second and third episodes of pulmonary edema could have resulted from type I POPE, as well, because the pulmonary edema developed immediately after extubation, when the upper airway occlusion by goiter recurred.

Although POPE is an important etiologic factor for acute respiratory distress, the other differential diagnoses, including pneumonia with septic shock, aspiration pneumonia, pulmonary thromboembolism, anaphylaxis, iatrogenic volume overload, and cardiogenic or neurogenic pulmonary edema, must also be taken into account [10]. Rapid onset and resolution of radiologic changes, and concomitant clinical changes excluded the possibility of aspiration pneumonia or pneumonia with septic shock. The lack of a filling defect in the pulmonary artery also excluded the possibility of pulmonary thromboembolism. The history of progressive dyspnea, stridor and pupils equally reactive to light did not support the diagnosis of an intracerebral catastrophe with neurogenic pulmonary edema. Although the patient had a history of pre-existing coronary atherosclerosis, but no jugular venous engorgement, the S3 gallop and pedal edema, and the unremarkable elevation of cardiac enzyme and normal LVEF did not support the diagnosis of recurrent pulmonary edema due to myocardial infarction or decompensated congestive heart failure (CHF). However, a previous report has shown that cardiac diseases, such as cardiomyopathy and valvular heart diseases, as in our patient, may also predispose to POPE [11].

Tracheal compression was reported to occur in as many as a 1/3 of patients referred to thyroid clinics, but little correlation exists between symptoms predictive of upper airway obstruction and the presence of an abnormal flow-volume loop, and while airway obstruction is detected, as many as 42% of patients are asymptomatic and 72% are not breathless [12]. A flow volume loop is essential in assessing airway obstruction in these individuals, although there is poor correlation between symptoms and clinical examination results. Our patient had been breathless for a prolonged period and her symptoms were erroneously ascribed to CHF because of a CAD history. In this context, the cardiovascular changes were mistakenly thought to reflect an acute coronary syndrome in a patient with CAD. Although a pulmonary function test was not administered to our patient due to refractory weaning failure, we still suggest pulmonary function testing, including flow-volume loop and diffusing capacity or transfer factor of the lung for carbon monoxide (DLCO), is essential in assessing individuals who experience an acute or long duration of dyspnea to detect the possible underlying airway obstruction earlier.

Treatment depends on the severity of the symptoms but is similar for type I and II POPE. A systematic review suggested that management commonly include supportive measures, positive pressure ventilation, diuretics and

steroids [13]. However, diuretics may worsen hypovolemia and hypoperfusion, so their role in POPE remains controversial [14]. Although steroids are thought to improve the physical damage to the alveoli and capillaries from the high negative pressures of POPE, their role is also uncertain [15]. The role of inhaled beta-agonists is limited in upper airway obstruction. However, in POPE, beta-agonists may accelerate alveolar fluid clearance and facilitate elimination of pulmonary edema via increased active cation transport [16].

In conclusion, recurrent pulmonary edema in a patient with preexisting CAD should be carefully evaluated. A flow-volume loop is essential in assessing airway obstruction in these individuals who experience chronic dyspnea so as to recognize earlier those patients with possible upper airway obstruction. We recommend that POPE should be put into the list of differential diagnoses of any patient presenting with bihilar alveolar infiltrates in the radiographic picture.

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大型結節性甲狀腺腫壓迫氣管造成反覆性阻塞後肺水腫：病例報告

黃聖傑 * 吳國安 * 謝忠岳 **

阻塞後肺水腫（post-obstructive pulmonary edema），又稱為負壓性肺水腫（negative pressure pulmonary edema），發生在短暫性移除上呼吸道阻塞後造成的潛在性危害生命的併發症。其最常見原因為氣管插管或拔管後所造成的喉部水腫（laryngoedema）及上呼吸道腫瘤。已有文獻報告約在接受全身麻醉的案例約有千分之一的發生率。

我們提出一個因大型結節性甲狀腺腫（nodular thyroid goiter）壓迫氣管造成的反覆性阻塞後肺水腫，個案於確診後接受甲狀腺切除手術後，成功拔管。*(胸腔醫學 **2015; 30: 118-124**)*

關鍵詞：阻塞後肺水腫，負壓性肺水腫，呼吸道阻塞，結節性甲狀腺腫

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