The Outcome of Terminal Cancer Patients Requiring Prolonged Mechanical Ventilation

Chun-Yao Huang*, Yao-Kuang Wu*, Chung-Chi Huang*,**,***,
Ying-Huang Tsai*,***

Background: Approximately 76% of patients with malignancies die because of respiratory failure, excluding pneumonia and pulmonary embolisms, in intensive care centers (ICU). Currently, no published paper has described the outcome of adult cancer patients who require prolonged mechanical ventilation (PMV) (more than 21 days) for respiratory failure. The objective of this study was to describe the outcome of terminal cancer patients requiring PMV.

Methods: A retrospective study of 1124 patients who were admitted to our respiratory care center (RCC) from November 1999 to August 2004 was carried out. All terminal cancer patients with respiratory failure requiring prolonged mechanical ventilation were included in the study group. Demographic and clinical variables, such as age, gender, APACHE score at RCC admission, biochemistries, Glascow coma scale, ICU admission day, cancer types, and blood gas result, were obtained from consecutive respiratory failure patients. Information regarding vital status after hospital discharge was also acquired.

Results: Our analysis was based on data from 92 adult terminal cancer patients who met the criteria. Twenty-three patients were transferred out of the RCC, including 15 successfully weaned patients and 8 ventilator-dependent patients. In the successfully weaned group, 8 patients expired within 3 months, and the other 7 were discharged from the hospital, but all of them died within 4 months. In the ventilator- dependent group, 1 patient died in the hospital, and 7 were transferred to a local respiratory care ward (RCW). After being admitted to the RCW, 5 of 7 patients expired within 2 months, and only 2 survived more than 2 months. The overall observed in-hospital mortality was 84%, and mean survival time after discharge from the RCC was 70 days. The APACHE II score (p=0.001) and serum BUN (p= 0.0049) were significantly lower in the successfully weaned group, and the Glascow coma scale was higher in this group (p= 0.004). In our analysis, age, gender, cancer type, and ICU admission days were not significant factors influencing the outcome.

Conclusion: The overall in-hospital mortality of terminal cancer patients requiring PMV was as high as 84%, and mean survival times after discharge from the RCC were only 70 days. The patients with a lower BUN level and severity of disease had a higher ventilator weaning rate. This result may be of help to physicians and families when discussing whether aggressive or hospice care is more suitable for terminal cancer patients with respiratory failure. ***(Thorac Med 2006; 21: 305-312)***

Key words: terminal cancer patients, respiratory failure, prolonged mechanical ventilation

*The Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital, Taoyuan; **The Department of Respiratory Therapy, Chang Gung Memorial Hospital, Taoyuan; ***The Department of Respiratory Care, Chang Gung University, Taoyuan
Address reprint requests to: Dr. Ying-Huang Tsai, Division of Pulmonary and Critical Care Medicine, Chang Gung Memorial Hospital, 5 Fu-Hsing St. Kweishan, Taoyuan, Taiwan

Introduction

For many years, it has been assumed that the outlook for patients with cancer who require mechanical ventilation for respiratory failure is grim [1-10]. Approximately 76% of patients with cancer die of respiratory failure (excluding pneumonia and pulmonary embolism) in intensive care units (ICU) [10]. Patients were conventionally defined as prolonged mechanical ventilation (PMV) if they had been intubated and received mechanical ventilator support for more than 21 days [11]. Respiratory failure developing in cancer patients is usually considered a consequence of an advanced pulmonary disease that does not respond to conventional palliative chemotherapy, radio-therapy or other supportive care [10]. It is reasonable to assume that the prognosis may vary according to the severity and cause of respiratory failure, associated organ failure, comorbidities, and characteristics related to the underlying malignancy.

The decision to mechanically ventilate a cancer patient with respiratory failure is often contentious. The emotional suffering, failed expectations, and financial costs are extraordinarily high. Currently, no published paper has described the outcome of adult cancer patients who require PMV for respiratory failure. The objective of this study was to seek the outcomes of terminal cancer patients requiring PMV, and the status after discharge from the respiratory care center (RCC).

Materials and Methods

The data for 1124 patients in the Chang Gung Memorial Hospital RCC, from November 1999 to August 2004, were retrospectively collected to develop a multivariate logistic regression model for estimating the probability of hospital mortality among cancer patients requiring PMV. All cancer patients requiring mechanical ventilation were included. Demographic and clinical variables were obtained on RCC admission within 1 day of initiation of mechanical ventilation; in addition, the patient's vital status at hospital discharge was acquired.

Variables were recorded in duplicate on standardized study forms, and then entered into a computerized database. The response variable used in the analyses was hospital discharge vital status (successfully weaned or failed weaning) based on ventilator use during discharge. Univariate analyses were performed using t tests to examine the association between vital status and 18 potential prognostic factors. Factors including age, gender, biochemistries, consciousness level (Glascow coma scale), ICU admission days, cancer types, blood gas result, comorbid disease, severity of disease status (APACHE score at RCC admission), total ventilation days, RCC stay days, nutrition status, and RCC and hospital discharge status, were recorded.

For most variables, values recorded just after RCC admission was used in the analysis. A new continuous variable representing the time from hospitalization was created from the information collected for each patient on the date of hospitalization, date of admission to the RCC, and the categorical variable time from RCC admission to PMV. Kaplan-Meier (KM) survival analysis to estimate the overall survival of the 2 groups of patients was also performed. Long-term outcomes after discharge from the RCC were ascertained using a review of hospital medical records, and direct inquiry of the family members through telephone interviews.

Results

Our analysis was based on 92 adult terminal cancer patients who met all of the inclusion criteria. Patients were classified as being in 1 of 8 tumor groups: lung cancer, head and neck cancer, gastrointestinal cancer, hepatobillary tract cancer, breast cancer, genitourinary tract cancer, gynecological cancer, and others (Table 1). The overall observed in-hospital mortality was 84%, and mean survival time after discharge from the RCC was 70 days. All patients were cared for in an RCC setting. Twenty-three patients were transferred out of the RCC, including 15 successfully weaned patients and 8 ventilator-dependent patients. In the successfully weaned group, 8 patients expired within 3 months, and the other 7 patients were discharged, but all of them died within 4 months. In the ventilator-dependent group, 1 patient died in the hospital, and 7 were transferred to a local respiratory care ward (RCW). After admission to the RCW, 5 of 7 patients expired within 2 months and only 2 patients survived more than 2 months (Figure 1).

The characteristics of the terminal cancer patients and the RCC outcomes are presented in Table 2. The results of univariate analyses of categorical variables using the chi-square test are presented in Table 3. The incidence and relation to weaning of common clinical factors such as: gender; comorbidity with heart disease (heart failure, arrhythmia), lung disease (COPD, pulmonary fibrosis, asthma), liver disease (liver cirrhosis, alcoholism, hepatitis), or DM; whether or not created with tracheostomy; with or without pleural effusion; and lung cancer or extra-pulmonary malignancy, were analyzed, and these factors were not significant in influencing the outcome. The KM survival rate estimates for 23 terminal cancer patients discharged from our RCC, 15 successfully weaned patients, and 8 difficult-to-wean patients, are shown in Figures 2 and 3.

Table 1. Patients According to Type of Malignancy

	Patient No.	Patient %
Lung	49	55
Head and Neck	7	8
Gastrointestinal	14	15
Hepatobillary	3	3
Breast	6	7
Genitourinary	5	2
Gynecological	3	3
Others	5	5
Total	92	100

Discussion

We presented the clinical risk factors that can be used to estimate the probability of hospital mortality in adult cancer patients receiving mechanical ventilation for respiratory failure. The model is based on data collected from 92 cancer patients in our hospital. The variables in the model segregate into 2 groups: disease status or extent of underlying malignancy as represented by the diagnostic tumor group, and treatment status. The negative impact of organ system failure on hospital survival in mechanically ventilated cancer patients has been described by Snow *et al.* [1]. That there were no 6-month survivors among mechanically ventilated cancer patients with an increasing number of failing organ systems in the Snow is well accepted to be the case among medical patients with adult respiratory distress syndrome complicated by multi-organ system failure. Six studies reported 100% mortality in cancer patients who were mechanically ventilated for more than 10 days, but 6 other studies found that duration of mechanical ventilation was not an absolute predictor of death. It is unrealistic to

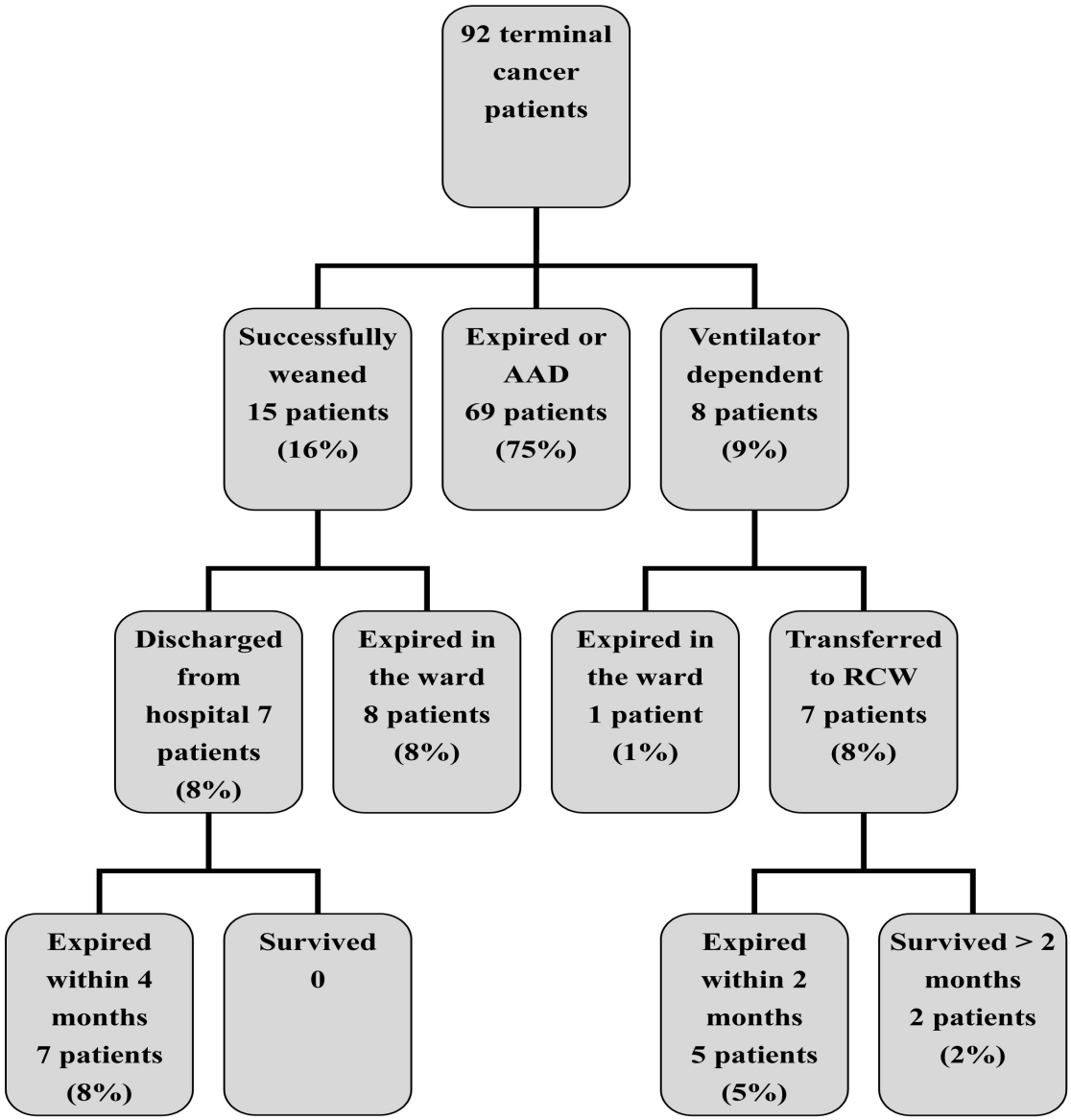

Fig.1. The outcome of 92 terminal cancer patients after RCC discharge

expect that the number of days of mechanical ventilation will predict death with 100% sensitivity. However, it is important to acknowledge that cancer patients require PMV, like those who develop respiratory failure more than 24 hours after hospitalization, have an ominous prognosis.

As noted above, the prognosis of cancer patients with respiratory failure requiring mechanical ventilation is uniformly grim. The mortality in our study was higher than the hospital mortality values reported for medical patients requiring mechanical ventilation for acute respiratory failure (31%) [12], adult respiratory distress syndrome (36%) [13], community acquired pneumonia (36%) [14], and nosocomial or ventilator associated pneumonia (33%) [15]. However, it

Table 2. Characteristics of Terminal Cancer Patients and RCC Outcomes (n=92)

	Successfully weaned (n=15)	Failed weaning* (n=77)	*p*
Age (y/o)	69.8 ± 13.42	66.99 ± 16.19	0.53
RCC days	17.87 ± 7.29	20.69 ± 18.07	0.316
ICU days	29.27 ± 14.7	26.82 ± 10.81	0.453
ICU MV days	28.67 ± 13.76	27.03 ± 10.79	0.608
Total MV days	43.33 ± 16.18	47.57 ± 21.22	0.478
GCS	9.4 ± 0.99	8.17 ± 2.77	0.004
APACHE II	15.5 ± 1.95	18.33 ± 5.09	0.001
Albumin (g/dL)	2.5 ± 0.5	2.5 ± 0.5	0.984
BUN (mg/dL)	27.9 ± 17.3	48.4 ± 47.4	0.005
Cr (mg/dL)	0.8 ± 0.5	1.2 ± 0.88	0.33

*Failed weaning group includes ventilator dependent and expired patients

Table 3. Univariate Analysis of Categorical Variable for Ventilated RCC patients (n=92)

	Successfully Weaned (n=15)	Failed Weaning* (n=77)	*p*
Sex			
Male	11 (73.3%)	46 (59.7%)	0.483
Female	4 (26.7%)	31 (40.3%)	
Heart disease			
Yes	14 (93.3%)	75 (97.4%)	0.986
No	1 (6.7%)	2 (2.6%)	
Airway			
Tracheostomy	14 (93.3%)	53 (68.8%)	0.102
Endotracheal tube	1 (6.7%)	24 (31.2%)	
Cancer			
Lung	5 (33.3%)	44 (57.1%)	0.159
Other	10 (66.7%)	33 (42.9%)	
Pleural effusion			
Yes	2 (13.3%)	21 (27.3%)	0.415
No	13 (86.7%)	49 (72.7%)	
Liver disease			
Yes	15 (100%)	76 (98.7%)	1.0
No	0 (0%)	1 (1.3%)	
Lung disease			
Yes	13 (86.7%)	67 (87.0%)	1.0
No	2 (13.3%)	10 (13.0%)	
DM			
Yes	1 (6.7%)	14 (18.2%)	0.47
No	14 (93.3%)	63 (81.8%)	

*Failed weaning group includes ventilator dependent and expired patients

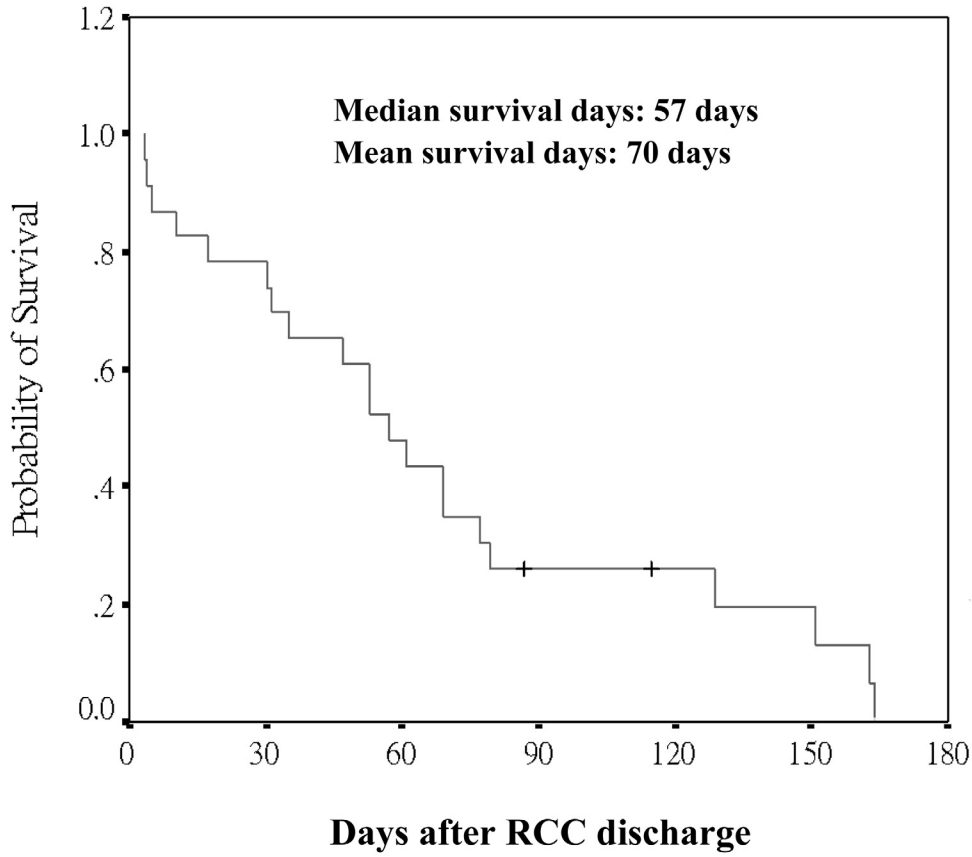

Fig. 2. Survival curve of terminal cancer patients discharged from RCC

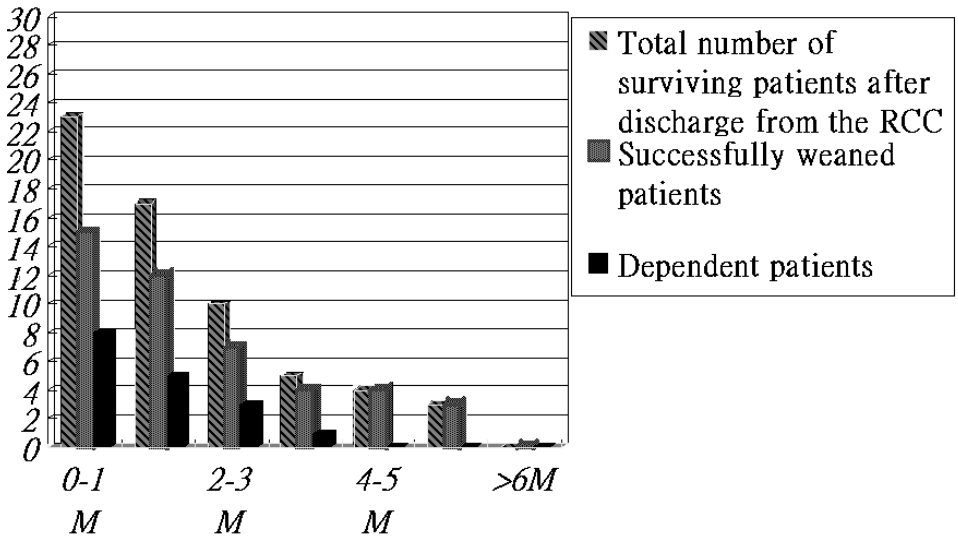

Fig. 3. Number of surviving terminal cancer patients discharged from RCC

was similar to the mortality of older patients (> 80 years old) requiring mechanical ventilation more than 15 days (91%) [16], and critically ill patients with 3 or more failed organs for at least 3 days (98%) [17]. Clearly, a reappraisal of predictors of mortality in terminal critically ill cancer patients is important, and may help in deciding for critical care for those with a chance of survival. Cancer patients and their families should be told the chances of long-term survival using mechanical ventilation before the recognition of incipient respiratory failure. Further work is needed with respect to predicting outcomes for mechanically ventilated cancer patients, but this study represents an important step. It is appropriate for physicians to provide aggressive supportive care for critically ill patients with respiratory failure, although routinely providing mechanical ventilation to cancer patients may be inappropriately aggressive. The decision should be made on an individual basis. The findings of our study can be of assistance to physicians caring for cancer patients in their discussions with colleagues and with patients and their families.

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癌症末期病患需要長期呼吸器之預後

黃俊耀 * 吳燿光 * 黃崇旂 *,**,*** 蔡熒煌 *,***

背景：有將近 76% 比率的癌症病患在加護病房因呼吸衰竭死亡。而其呼吸衰竭的原因並非肺炎或是肺栓塞。目前並無論文刊載有關成人癌症病患因呼吸衰竭需要長期使用（超過二十一天）呼吸器之預後。本研究之目的主要在探討及描述末期癌症病患因呼吸衰竭需要長期使用呼吸器之預後。

方法：回溯性的數據收集，從西元 1999 年 11 月到 2004 年 8 月將近五年，針對 1124 位住進成人呼吸照護中心的病患加以分析。所有末期癌症之病患，因呼吸衰竭需要長期呼吸器使用者全部進入本研究。連續性的統計數據及變數收集: 包括年齡、性別、住進成人呼吸照護中心當時的疾病嚴重度（APACHE score）、生化指數、病患意識昏迷指數（Glascow coma scale）、加護病房留置天數、腫瘤種類、及動脈血氣體分析數據等。轉出成人呼吸照護中心及出院後之生命指數狀況以醫院之病歷記錄和直接電話訪問病患家屬追蹤獲得。

結果：總計 92 位末期成人癌症之病患符合本研究之條件。有 23 位病患後來轉出成人呼吸照護中心。其中有 15 位病患成功脫離呼吸器，有 8 位病患長期依賴呼吸器。在成功脫離呼吸器這一組之病患，有 8 位病患在 3 個月內在院內死亡，其他 7 位病患順利出院。但是全部都在出院後 4 個月內死亡。在長期依賴呼吸器這一組之 8 位病患，有 1 位病患在院內死亡，其他 7 位病患順利出院轉至地區呼吸照護病房。在下轉地區呼吸照護病房之 7 位病患，其中 5 位病患在 2 個月內死亡，只有 2 位病患存活超過 2 個月。所有 92 位末期成人癌症病患平均住院死亡率為 84% ，轉出呼吸照護中心之平均存活天數為 70 天。在成功脫離呼吸器這一組之病患，其疾病嚴重度（APACHE II score, p=0.001）和血清尿素氮（BUN, p=0.0049）值明顯低於長期依賴呼吸器這一組。病患意識昏迷指數（Glascow coma scale, p=0.004）值明顯高於長期依賴呼吸器這一組。在本研究之分析: 年齡、性別、生化指數、加護病房留置天數、腫瘤種類、及動脈血氣體分析數據等並非明顯影響預後之變數因子。

結論：所有末期癌症病患需要長期呼吸器使用者之平均住院死亡率高達 84% ，轉出呼吸照護中心之平均存活天數只有 70 天。病患有較低疾病嚴重度、血清尿素氮，和較高意識昏迷指數者，明顯有較高之呼吸器脫離率。本研究之結果，可以提供臨床醫師和病患家屬討論，當末期癌症病患呼吸衰竭時，積極插管治療或者安寧照護是比較合適的。*(胸腔醫學* ***2006; 21: 305-312)***

關鍵詞：末期癌症病患，呼吸衰竭，長期依賴呼吸器

* 林口長庚醫院 胸腔內科，** 林口長庚醫院 呼吸治療科，*** 長庚大學 呼吸治療學系
索取抽印本請聯絡：蔡熒煌醫師，林口長庚醫院 胸腔內科，桃園縣龜山鄉復興街 5 號

Comparison of Somnologica 3 Computerized Polysomnographic Systems Analysis and Manual Assessment of Sleep Apnea

Po-Jui Chang, Meng-Heng Hsieh, Yu-Lun Lo, Chun-Yu Lo, Fu-Tsai Chung, Chih-Hsia Kuo, Horng-Chyuan Lin

Sleep disorders are increasingly being recognized by physicians, raising demand at sleep laboratories, and prompting a search for user-friendly methods of data analysis. Computerized polysomnographic systems have become a commonly used tool in sleep laboratories in Taiwan and throughout the world.

This study was designed to compare the accuracy of data analysis using computerized Somnologica 3 systems and manual interpretation. Twenty-three patients with suspected respiratory sleep disorders were referred to our department from outpatient clinics. Each individual underwent a full-night sleep study in our sleep laboratory. Recorded data were simultaneously analyzed using the computerized Somnologica 3 system (Version II software) and interpreted by a pulmonologist thoroughly experienced in polysomnography, using the standard Rechtschaffen and Kales criteria.

When comparing autoscoring and manual analysis, our results revealed that the computerized system produced more substantial errors with respect to the duration of each sleep stage (S1 sleep time: 34.9 ± 5.7 vs. 74.2 ± 10.4 min; S2: 94.5 ± 15.1 vs. 208.9 ± 15.8 min; S4: 36.4 ± 5.4 vs. 14.5 ± 4.1 min; REM: 26.1 ± 5.4 vs. 55.4 ± 6.2 min, respectively; all $p<0.05$), thus leading to a reduction not only in estimated total sleep time (226.2 ± 19.9 vs. 376.4 ± 16.4 min; $p<0.05$), but also a decrease in the number of hypopnea/apnea events (AHI 13.0 ± 19.5 vs. 18.9 ± 3.6, $p<0.05$).

Based on the evidence from this study, therefore, we suggest that polysomnographic records autoscored by Somnologica 3 systems are inaccurate and will underestimate the severity of sleep-related disorders. A thoroughly experienced polysomnographer is needed for all data interpretation in clinical practice. ***(Thorac Med 2006; 21: 313-320)***

Key words: obstructive sleep apnea syndrome, computerized polysomnographic systems

Introduction

Sleep disorders are being recognized by physicians with increasing frequency. This fact places demands on sleep laboratories to search for user-friendly methods for data analysis.

Department of Thoracic Medicine, Chang Gung Memorial Hospital, Chang Gung University, Taipei, Taiwan
Po-Jui Chang and Meng-Heng Hsieh contributed equally to the work for this study as first authors.
Address reprint requests to: Dr. Horng-Chyuan Lin, Department of Thoracic Medicine, Chang Gung Memorial Hospital, Chang Gung University, #5 Fushing Street, Gueishan Shiang, Taoyuan, Taiwan

Computerized polysomnographic systems are now more commonly used in sleep laboratories in Taiwan to meet this demand.

Obstructive sleep apnea (OSA) is associated with conditions that account for the leading causes of mortality in adults: hypertension and cardiovascular and cerebrovascular diseases [1-2]. In addition, several neurobehavioral morbidities, potentially impacting on public health and the economy (including motor-vehicle and occupation-related accidents), are linked with OSA [3-5]. Despite several studies reporting a higher OSA prevalence in Western populations [6-9], precise epidemiological data is still lacking for Taiwan. Two community studies from Hong Kong have revealed that the prevalence of OSA, defined as an apnea/hypopnea index (AHI) of 15 or more, is around 5% and 2% in middle-aged Chinese males and females, respectively [10-11]. The high prevalence increases demand on sleep laboratories for quality studies that define an analytical method that is both user-friendly and cost-effective. To cater to this demand, computerized polysomnographic systems have become a commonly used tool in sleep laboratories in Taiwan and around the world. Despite the prevalence of literature demonstrating the potential advantages of computerized over standard manual polysomnography [12-13], few commercial, computer-based systems have been scrupulously evaluated for accuracy, analysis time, or cost-effectiveness relative to the paper-based variant [14-15]. Computerized Somnologica 3 systems are widely used to autoscore sleep apnea severity in Taiwan. Since manual analysis of sleep, breathing, and oxygenation records remains the "gold standard" for diagnosing sleep abnormalities, this comparative study was designed to evaluate discrepancies in data analysis between the computerized, autoscoring Somnologica 3 system and manual analysis.

Materials and Methods

Patient selection and study design

Between March 2003 and September 2003, 23 adult patients (14 males and 9 females, aged from 34 to 76) were referred from the pulmonary outpatient clinic at Chang Gung Memorial Hospital. Sleep breathing disorders were suspected in all cases. For each individual, the body mass index (BMI) was recorded and the Epworth Sleepiness Scale questionnaire was completed (Table 1). All patients underwent a full-night sleep study in our sleep laboratory.

Data recording and polysomnography analysis

The following signals were simultaneously recorded on separate channels using Somnologica 3 computerized systems (Somnologica Studio, Medcare Flaga, Reykjavik, Iceland): 4 EEG (2 central and 2 occipital), 2 EOG, sub-mental EMG, nasal-oral airflow (thermistor), chest and abdominal wall motion (piezo electrodes), arterial oxygen saturation, EKG, body position, and snoring (tracheal microphone). The Somnologica 3 software was loaded onto an ACER TravelMate 270 computer and data was stored in raw form on the hard disk without compression.

Each patient's nocturnal polysomnographic data was analyzed in 2 ways: autoscoring using Somnologica 3 Version II software, and, inter-

Table 1. Subject Demographics

Gender	
male	14
female	9
Age, yr (mean ± SD)	53.1 ± 11.9
BMI (mean ± SD)	26.4 ± 3.0
ESS (mean ± SD)	10.5 ± 4.0

Definition of abbreviations. AHI=apnea-hypopnea index; BMI=body mass index; ESS=Epworth sleepiness scale

pretation by a pulmonologist with at least 2 years' polysomnography experience, epoch by epoch, based on the standard Rechtschaffen and Kales criteria [16].

For the manual interpretation, sleep latency was defined as the interval from lights off to the first epoch of stage 1 or 2, whichever came first; total sleep time was the sleep-period time minus waking time; and sleep efficiency was the time asleep as a percentage of the sleep-period time. Arousals were defined as at least 3 seconds of alpha or increased EEG frequency. Episodes of apnea were defined as complete cessation of airflow for 10 seconds or more, and hypopnea as a decrease of more than 50% in oronasal airflow lasting for at least 10 seconds, closely followed by either an arousal or an associated 4% decrease in arterial oxyhemoglobin saturation. Pulse oximetry data were also collected for the polysomnography. Oxygen desaturation was recorded if the saturation level fell by 4% or more. Respiratory events were scored only in sleeping epochs.

Stored raw uncompressed and unprocessed data were also autoscored using the *S*omnologica 3 Version II software. No attempt was made to adjust the default parameter settings for individual patients.

Statistical analysis

The simple paired Student's t test was used to compare the computerized and manual analyses. If a significant difference was demonstrated, a multiple comparison procedure (Dunn's method) was used to determine the source of the difference (Sigmastat; SPSS, San Rafael, CA). All values are expressed as mean ± standard deviation (SD), unless otherwise specified. A p value of $p<0.05$ was considered statistically significant.

Results

The results of the study are summarized in Tables 2 and 3, with the automatic computer scoring and manual analysis differing in a number of important respects (Table 2). Substantial differences were demonstrated in terms of the distribution of sleep stages (except S3). In addition, the mean sleep efficiencies and total sleep times were different (both $p<0.001$). Comparing the respective means for autoscoring and manual analysis revealed less time in stage 1 (34.9 vs. 74.2 min), stage 2 (94.5 vs. 208.9 min), and REM (26.1 vs. 55.4 min), but longer waking time (218.9 vs. 77.3 min) and stage 4 sleep (36.4 vs. 14.5 min). Sleep latency, as determined by automatic computer scoring, was approximately 25 minutes longer (52.1 vs. 28.5 min).

The number of respiratory events and the oxygen saturation values are presented in Table 3. The computer-derived scores for respiratory events tended to be lower in comparison to the manual analogs (total apneas: 6.1 ± 3.0 vs. 22.4 ± 10.4, respectively [$p=0.09$]; total hypopneas, 33.0 ± 7.9 vs. 102.3 ± 20.7, respectively [$p<0.001$]; and, total apneas/hypopneas, 39.1 ± 9.4 vs. 124.8 ± 28.6, respectively [$p<0.01$]), which, in turn, contributed to fewer AHIs (13.0 ± 19.5 vs. 18.9 ± 3.6, $p<0.05$). Therefore, significant errors were demonstrated when comparing assessments using the computer-based system and the manual polysomnography equivalent.

No significant difference was demonstrated for mean oxygen saturation, however, a higher minimum oxygen saturation (82.1±1.5% vs. 78.4 ± 1.6%, $p=0.05$) and a lower oxygen desaturation index (16.1 ± 3.3 vs. 20.2 ± 3.8, $p<0.05$) were determined by the computerized analysis.

Table 2. Manual Score Versue Somnologica 3 Autoscore in Sleep Parameters

Variable	Manual Score		Somnologica 3		*p* value
	Mean	SD	Mean	SD	
Total sleep time (min)	376.4	16.4	226.2	19.9	<0.001
Sleep efficiency (%)	83	2.3	50.8	4.1	<0.001
Sleep latency (min)	28.5	6.2	52.1	9.5	<0.001
Wake (min)	77.3	10.2	218.9	23.3	<0.001
S1 (min)	74.2	10.4	34.9	5.7	0.003
S2 (min)	208.9	15.8	94.5	15.1	<0.001
S3 (min)	23.3	3.1	29.1	6.8	0.434
S4 (min)	14.5	4.1	36.4	5.4	<0.001
REM (min)	55.4	6.2	26.1	5.4	0.01

Definition of abbreviations. REM=rapid eye movemen

Table 3. Manual Score Versus Somnologica 3 Autoscore in Respiratory Events and AHI/ODI

Variable	Manual Score		Somnologica 3		*p* value
	Mean	SD	Mean	SD	
Total apnea events	22.4	10.4	6.1	3	0.099
Total hypopneas events	102.3	20.7	33	7.9	0.001
Apneas + hypopneas	124.8	28.6	39.1	9.4	0.003
AHI (events/hr)	18.9	3.6	13	19.5	0.01
REM AHI (events/hr)	26.5	5.3	9.3	3.2	0.004
NREM AHI (events/hr)	17.3	3.8	13.6	20.4	0.173
ODI	20.2	3.8	16.1	3.3	0.019
Minimal SaO2	78.4	1.6	82.1	1.5	0.05
Mean SaO2 (%)	94.5	0.5	94.5	0.5	0.909

Definition of abbreviations. AHI=apnea-hypopnea index; NREM=non rapid eye movement; REM=rapid eye movement; ODI=oxygen desaturation index; Mean SaO2=mean oxygen saturation; Minimal SaO2=minimal oxygen saturation

Discussion

Our results showed that there is a significant discrepancy between polysomnogrphic analysis conducted automatically by computerized scoring systems and manual analysis. Epoch-by-epoch analysis by the computer-based system revealed a trend toward wakefulness or lighter sleep, in contrast to manual analysis, suggesting that when allowed to autoscore, a reliance on Somnologica 3 systems can lead to significant interpretative errors.

Despite the fact that computerized polysomnography systems are now commonplace around the world [14], there has been only limited evaluation of their accuracy, analysis time, and cost-effectiveness relative to the analogous manual analysis performed by thoroughly experienced pulmonologists. Further, although there is substantial literature on the computerized analysis of sleep [15], few of the commercially available systems have been subjected to careful scientific

scrutiny, and none of the systems currently in use in Taiwan have been evaluated in a rigorous fashion. To our knowledge, this is the first study to thoroughly assess the clinical application of such a system in Taiwan.

Several technical and mathematical approaches have been used for automatic sleep-stage analysis [17]. Although reasonable discrimination has been demonstrated for sleep stage 2 and slow-wave sleep with most of these methods, all appear to have a problem discriminating REM from the waking stage and sleep stage 1. Another problem that remains unsolved is that while the automated systems work reasonably well with normal volunteers, they are not adequately robust for sleep-disturbed patients, where accuracy can be critical [18-19].

In their comparison of computer-based systems, Ehlert *et al*., (1998) demonstrated a 0.2% underestimation of sleep stage 2 in a mixed sample of 38 patients with sleep-related disorders [20]. Problems such as restless leg syndrome, periodic limb movement syndrome, insomnia, obstructive sleep apnea, snoring, and hypnotics-dependent sleep disorder were recorded with the QUISI device, and sleep stage 2 was underestimated by 5.2% with the Oxford Medilog 9000 recorder. White and colleagues (1998) have suggested that when allowed to autoscore, the Healthdyne ALICE 3 computerized systems produced substantial errors in sleep staging [13]. Our study also showed a similar trend for the Somnologica 3 computerized system, which often assessed the sleep stage incorrectly, thus failing to discriminate many apnea and hypopnea events (Table 2).

These misinterpretations are due to the original design of the software, which discriminates between sleep stages. All of the setup parameters in these systems provide an interpretation of the current sleep stage, with the final result derived from a composite decision. This result reflects the estimated probability for measurements accurately indicating a given sleep stage. For the waking stage, computer systems cannot accurately differentiate between artifacts relating to EEG and EOG signals. Furthermore, Somnologica 3 computer analysis relies only on a single EOG channel, resulting in increased detection of false eye movements and longer waking time scores. Therefore, total sleep time and sleep efficiency are lower when assessed with this system. In addition, assessment of time in the S1 stage is also decreased because it is scored as waking. For S2, the default parameter that defines the stage only takes into consideration the sleep spindle and not the K complex. Further, the 3-minute criterion results in the computer system scoring less S2 stage sleep. By contrast, the definition for delta wave is relatively flexible, with computerized systems only taking into account the frequency and not the wave amplitude. These are the reasons for the reduction in S1 and S2 stage time in Somnologica 3 analysis relative to the manual analog.

For the REM stage, the errors were derived from the system settings, which specify that REM duration must exceed 240 sec, and intervals between REM events must exceed 60 sec. These settings contradict the standard Rechtschaffen and Kales criteria, and, as the computer cannot determine the beginning of the REM stage regressively, this contributes to the shorter REM sleep time in the autoscoring of our sample (Table 2).

The frequency of apnea/hypopnea events in our syudy, as assessed by Somnologica 3 computerized analysis systems, was lower. Many apnea/hypopnea events were ignored because the REM stage was misinterpreted as the waking stage. Furthermore, mistakes in the determination

of respiratory events were more severe in the sleep stage than in the waking stage. Therefore, the apnea/hypopnea index from autoscoring was also lower than the manual equivalent, despite the fact that total sleep time was shorter.

A significant difference was demonstrated when comparing the computer analysis and manual assessment of the number of AHIs in the REM stage (p=0.004), but not in the NREM stage (p=0.173). Given the greater inaccuracy in autoscoring with respect to the REM stage relative to the NREM stage, it seems reasonable to suggest that there would be a greater misinterpretation of the frequency of apnea/hypopnea events in the REM stage relative to the NREM stage.

Minimal oxygen saturation and the oxygen desaturation index (ODI) were lower in manual analysis compared to autoscoring. In sleep breathing disorders, desaturation always occurs during respiration events in the REM stage. The higher the frequency of the apnea/hypopnea events in the REM stage, the lower the oxygen saturation. Analysis of our polysomnography data suggests that the higher minimal oxygen saturation from autoscoring may be a consequence of AHI misinterpretation in the REM stage.

In this study, the intra-rater agreement of the polysomnographers for sleep staging may lead to dispute; however, we believe that the accuracy of sleep stage data analysis, as scored by a thoroughly experienced polysomnographer, is adequate. The reliability of human scoring has been proven in a previous study [21], and our score-rescore results are similar to those of White [13].

It appears reasonable to suggest that the autoscoring results might have been more accurate if the parameter settings had been improved. This is not possible with the Somnologica 3 software, however, as parameter settings, such as the definition in the delta wave, are relatively fixed, and current systems are unable to integrate all the tracing information, thus making it difficult to improve analytical accuracy.

Although the previously described findings of personal analysis are encouraging, adverse consequences, including the increased cost and time required to score manually, have also been observed. Depending on the illness, it may take 2-4 hours for an experienced scorer to evaluate a polysomnographic sleep recording [16, 22]. By contrast, autoscoring is more temporally efficient, with less than 10 minutes required. What we sought to emphasize in this study, however, was that supplementary manual analysis of the sleep data is always necessary with Somnologica 3 systems because of interpretational inaccuracies. Importantly, these misinterpretations may lead to an incorrect diagnosis and inadequate treatment for all patients with sleep disorders.

Conclusion

This is the first study to compare Somnologica 3 and manual-visual analyses of sleep parameters using a sample of patients with primary snoring and obstructive sleep apnea. Based on our results, it appears reasonable to suggest that autoscoring polysomnography records with Somnologica 3 computerized systems may be inaccurate and underestimate the severity of sleep-related disorders. Total sleep time, sleep efficiency, and number of respiratory events were lower with the autoscoring assessment in comparison to manual analysis, and sleep architecture was also far from a reasonable sleep pattern. We conclude that a thoroughly experienced polysomnographer is needed for all data interpretation of every patient in clinical practice.

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使用 Somnologica 3 電腦分析睡眠呼吸中止和人工評估的比較

張博瑞　謝孟亨　羅友倫　羅君禹　鍾福財　郭志熙　林鴻銓

睡眠疾患愈來愈為臨床醫師所重視，睡眠實驗室應運而生，且尋找對使用者方便的資料分析方式。電腦化的多重睡眠檢查系統已成為台灣和全世界睡眠實驗室的一個常用工具。

本實驗設計比較使用電腦化的 Somnologica 3 和人工判讀的準確性。23 位懷疑呼吸睡眠疾患的病人經由門診轉介至本部門，每位都在我們睡眠實驗室接受整晚的睡眠檢查。記錄下來的資料同時以電腦化的 Somnologica 3 系統（版本 II 軟體）及專精於多重睡眠檢查的胸腔科醫師以標準 Rechtschaffen 和 Fales 準則解讀。

我們的結果顯示，比較自動和人工分析，電腦系統判讀在每一期睡眠的時間產生較多的錯誤（S1：34.9 ± 5.7 vs. 74.2 ± 10.4 分鐘；S2：94.5 ± 15.1 vs. 208.9 ± 15.8 分鐘；S4：36.4 ± 5.4 vs. 14.5 ± 4.1 分鐘；REM：26.1 ± 5.4 vs. 55.4 ± 6.2 分鐘；每一項 p 值皆小於 0.05），不只造成全部睡眠時間的低估（226.2 ± 19.9 vs. 376.4 ± 16.4 分鐘；$p<0.05$），也導致淺呼吸／呼吸暫停事件的次數減少（AHI 13.0 ± 19.5 vs. 18.9 ± 3.6, $p<0.05$）。

因此，基於此實驗的證據，我們提出以 Somnologic 3 系統自動分析多重睡眠檢查記錄是不夠準確的，且會低估睡眠相關疾患的嚴重度。在臨床工作上，所有的資料應由有經驗的多發睡眠檢查專家來分析。*(胸腔醫學* ***2006; 21: 313-320)***

關鍵詞：阻塞性睡眠呼吸中止症候群，電腦化多重睡眠檢查系統

林口長庚紀念醫院　胸腔內科
索取抽印本請聯絡：林鴻銓醫師，林口長庚紀念醫院　胸腔內科，桃園縣龜山鄉復興街 5 號

Role of Cough Officer Screening in Early Detection of Pulmonary Tuberculosis in Inpatients

Cheng-Hung Tsai, Ching-Hsiung Lin, Chul-Feng Lin**, Chun-Eng Liu*,
Mei-Li Huang**, Jen-Ho Wen, Woei-Horng Chai

Background: In order to avoid the transmission of tuberculosis within the hospital, the early detection and treatment of active cases are fundamental tuberculosis control strategies. The aim of this study was to evaluate a computerized protocol, the so-called cough officer screening, for the early detection of pulmonary tuberculosis in inpatients.

Materials and Methods: A computerized cough officer screening protocol was used in Changhua Christian Hospital from Oct 2004 to Sep 2005. All inpatients were enrolled and their cough history recorded. The computerized physician order entry system reminded the doctors to survey those patients who had a cough of more than 5 days in duration. Chest radiography, sputum smears, and cultures were prescribed to determine if patients had active pulmonary tuberculosis.

Results: A total of 57,745 inpatients were recruited into this study. The cough officer screening system identified 6,971 (12%) patients with cough duration longer than 5 days. Among them, 2,088 (30%) patients had chest radiography and/or sputum acid-fast smear and culture examinations. Eighteen were diagnosed with active pulmonary tuberculosis, and all were admitted to the medical ward. Based on the TB reporting information system, 151 inpatients were diagnosed with pulmonary tuberculosis during this study period, and the case detection rate using cough officer screening was 12% (18/151). The average cost per case finding was NT$49,865.

Conclusions: Cough officer screening is effective in the early detection of active pulmonary tuberculosis in inpatients. Strategies to improve doctors' compliance with this screening system will increase the case finding rate. In terms of cost-effectiveness, the internal medicine department is the most important target for screening. Determining the most appropriate cutoff point for cough duration requires further study. ***(Thorac Med 2006; 21: 321-327)***

Key words: cough officer screening, pulmonary tuberculosis (PTB)

Introduction

Although the mortality rate has been decreasing year after year, the incidence of tuberculosis has begun to increase again recently, with many outbreaks of pulmonary tuberculosis (PTB)

Division of Chest Medicine, Department of Internal Medicine, Changhua Christian Hospital; *Division of Infectious Disease, Department of Internal Medicine, Changhua Christian Hospital; **Infection Control Committee, Changhua Christian Hospital
Address reprint requests to: Dr. Ching-Hsiung Lin, Changhua Christian Hospital, 135 Nanshiao Road, Changhua, 500, Taiwan

reported; tuberculosis has reemerged as a major public health problem in the world [1]. Transmission of *M. tuberculosis* is a risk in health-care settings, although the risk of transmission varies by setting, occupational group, prevalence of TB in the community, patient population, and effectiveness of TB infection control measures. Factors contributing to TB outbreaks include delayed diagnosis of TB disease, delayed initiation and inadequate airborne precautions, lapses in precautions for cough-inducing and aerosol-generating procedures, and lack of adequate respiratory protection [2]. In order to avoid PTB nosocomial transmission, establishing a useful protocol for the early detection of PTB is imperative.

Cough is the most frequent symptom of active PTB, and increases the risk for infectiousness; the other symptoms have varied in their prevalence [3]. We developed a computerized protocol, the so-called cough officer screening, for the early detection of PTB in inpatients. The aim of this study was to evaluate the case finding rate of the cough officer screening protocol and analyze its cost-effectiveness.

Materials and Methods

Patient population

Patients who were admitted to our hospital between Oct 1, 2004 and Sep 30, 2005, including the intensive care units (ICU) and general wards, with various diagnoses, were all enrolled in our study.

The cough officer screening protocols

Cough officer screening is a screening protocol that was devised for the early detection of pulmonary tuberculosis, and to prevent its spread. When nurses used their computers to check orders every morning during patient admission, they recorded if the patient had complained of cough or not, including during the pre-admission period. Or, if the patient complained of cough at any other time of day, the nurses could record this in the computer at any time. The computerized physician order entry system would remind the doctors to survey those patients who had a cough of more than 5 days in duration, using chest radiography, sputum smears, and cultures to determine if he or she had PTB. The cough duration was the interval from the first day of cough to the day that the doctor prescribed examinations for suspected PTB. If the patient had had a cough for more than 5 consecutive days, the alarm window in the computers would remind the doctor to arrange chest radiography and/or sputum smear/culture for suspected PTB every day until the doctor had dealt with the suspicion by ordering the examinations. The doctor could ignore the alarm window and give other orders once he had ruled out the possibility of PTB, or if the patient was already on treatment for tuberculosis, or he was a consultant. Once the sputum smear or culture had a positive result for pulmonary tuberculosis, the patient would be isolated and receive anti-tuberculosis treatment.

Results

A total of 57,745 patients were admitted to our hospital for various kinds of diseases, and all of them were monitored by cough officer screening to see if the patient had had a cough lasting more than 5 days. Our computerized database revealed that 6,971 patients had met the criteria of cough officer screening. Chest radiography and/or sputum smears and cultures were performed for 2,088 inpatients that had had a cough of ≥5 days' duration, as detected by cough officer screening, between October 1, 2004 and Sep-

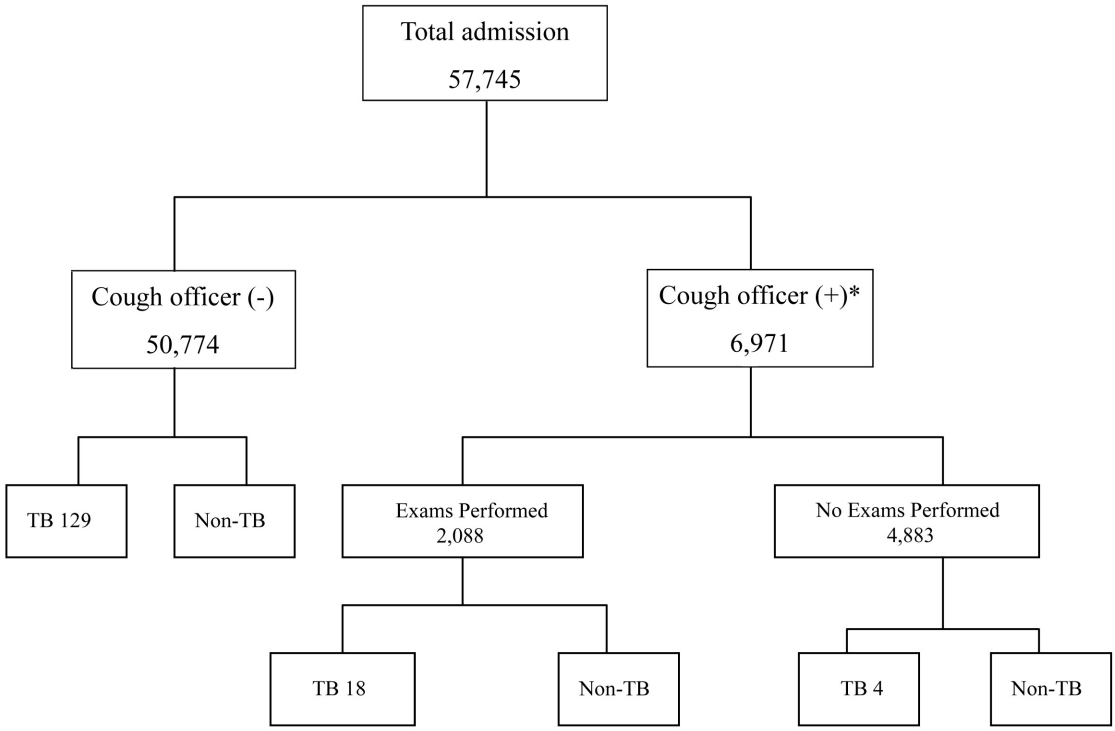

Fig. 1. Flow Chart of the Cough Officer Screening Process
*: Cough officer (+) indicates those with cough duration longer than 5 days consecutively

tember 30, 2005. The others (4,883 patients) had no data available. Eighteen of the 2,088 patients were diagnosed with pulmonary tuberculosis (Figure 1). The departmental distribution of the patients who were detected by cough officer screening is shown in Table 1. The pediatrics and internal medicine departments were the 2 departments with the largest patient groups in this study.

Based on the TB reporting information system, 151 hospitalized patients were diagnosed with pulmonary tuberculosis during this study period. The case finding rate of cough officer screening was 12% (18/151). All of these patients were admitted to the medical wards (Table 1). Among the 18 patients documented with PTB, 94.4% (17/18) of the coughers had a cough of more than 6 days' duration. The average age was 71 years, males were predominant (14:4), and the mean cough duration was 6.2 days (Table 2). Most of

Table 1. Cough Officer Screening and TB Reported Patient Distribution

	Medicine	Surgery	GYN	Pediatrics	Total
Cough officer (+)	3,180	372	3	3,416	6,971
TB reported	18	0	0	0	18

GYN: Gynecology

Table 2. Characteristics of Patients with Pulmonary Tuberculosis Detected by Cough Officer Screening

Patient	Age	Gender	Ward	Smear	Culture	CXR severity	Cough duration
1	68	M	Chest	(-)	(+)	minimal	6
2	66	F	CV	(-)	(+)	minimal	5
3	77	M	Infection	(+)	(-)	minimal	6
4	52	M	Chest	(+)	(+)	mod*	6
5	76	M	Chest	(+)	(+)	mod*	6
6	63	M	GI	(+)	(+)	mod*	6
7	71	M	Chest	(+)	(+)	mod*	6
8	71	M	Chest	(-)	(-)	mod*	6
9	87	F	Chest	(-)	(+)	minimal	6
10	42	F	Chest	(+)	(+)	mod*	6
11	66	M	PGY	(+)	(+)	mod*	6
12	55	M	Chest	(+)	(-)	minimal	6
13	86	M	Chest	(-)	(+)	mod*	6
14	87	M	Chest	(+)	(+)	mod*	6
15	83	M	PGY	(+)	(+)	mod*	7
16	78	M	ER	(+)	(+)	mod*	7
17	75	F	Chest	(+)	(+)	minimal	7
18	73	M	Chest	(+)	(+)	mod*	8

F: Female; M: Male; CV: Cardiovascular; GI: Gastrointestinal; PGY: Post-graduate year; ER: Emergency Room

*: moderately advanced

these patients (61%) were diagnosed based on both a positive sputum TB smear and culture. Only 1 patient was diagnosed based on clinical symptoms and CXR infiltration without a positive sputum study; the patient did not receive complete treatment due to mortality during hospitalization. All of the patients had various degrees of severity of lung infiltration. The aver-age cost of each case finding was NT$49,865 (Table 3).

Table 3. Costs of Cough Officer Screening for PTB Suspects

	Number	Cost*
Sputum	1,210	511,785
CXR	1,929	385,800
Total cost	--	897,585
No of cases diagnosed	18	--
Cost per diagnosed case	--	49,865

*: NT dollars

Discussion

The incidence of tuberculosis has increased again recently, and many outbreaks of PTB have been reported [1]. The incidence of pulmonary tuberculosis in Taiwan increased from 396 per million in 2002 to 435 per million in 2004. It is necessary to improve the detection and control of PTB in order to prevent nosocomial transmission at medical centers where the prevalence rate of TB is high. According to the 2002 database of the Center for Disease Control (CDC) in Taiwan, the top 5 case-reporting hospitals were all medical centers, and our hospital, Changhua Christian Hospital, placed third. In our hospital, cough officer screening has been used to facilitate the early detection of PTB and prevent its

nosocomial spread since September, 2004. In this investigation, only 2,088 (30%) of 6,971 patents who had had a cough for more than 5 consecutive days underwent CXR, sputum smear, and culture for suspected PTB. The compliance rate of the TB survey after a cough officer warning was only moderate, although education and a computerized reminding system were used. However, in our hospital, patients in some special units and groups, such as those who are admitted for suspected TB or pneumonia, and those admitted to the ICU with pulmonary infiltration, routinely undergo a sputum smear and culture for tuberculosis. We found 3,416 episodes of positive cough officer screening in the pediatric department, but no active case was identified. This might be related to the low incidence (12 per million in 2002) of pulmonary tuberculosis in children (0~14 years old) in Taiwan.

Santha *et al*. found that the detection rate of smear-positive TB cases can be substantially improved by actively eliciting the history of cough from all outpatients, and by changing the screening criteria for performing sputum microscopy among outpatients with cough ≥3 weeks to ≥2 weeks [4]. There is no data suggesting when we should perform examinations for suspected pulmonary tuberculosis for inpatients. The choice of a 5-day duration cough threshold as a guide for requesting sputum smear/culture and chest radiography was based on the need for the early detection of active pulmonary tuberculosis and the prevention of its spread in a medical center. Although a chronic cough of more than 3 weeks' duration was suggested as the timeline for TB screening with chest radiography and sputum investigation [5-6], 2 considerations led us to shorten the cough duration for tuberculosis screening in inpatients in a hospital setting such as a tertiary medical center. First, seriously ill patients who need admission and have a short history of cough should be investigated for PTB by sputum smear/culture examination in order to obtain an early diagnosis and begin treatment which might be life-saving. Second, in a high-risk environment, such as an overcrowding of hospitalized patients in a medical center, it might be necessary to screen patients with short cough duration in order to prevent the rapid and widespread transmission of *M. tuberculosis*. There have been variable mean totals of delay (including patient delay and doctor delay) in every country [7-9]. Doctor delay refers to the interval between the first visit and the diagnosis, which was mainly attributable to a delay in performing the examination and an insufficient medical checkup [10]. These delays may result in an increased risk for transmission of infection [11]. In order to shorten the doctor delay, it is important to recommend to all doctors to pay attention to those patients with cough with sputum, and to perform sputum examinations.

This study leaves some important questions unanswered. First, the cough duration threshold that would be appropriate and more cost-effective in raising a suspicion of PTB and arranging examinations was not investigated in this study. Second, there are high-risk groups for developing PTB: those in close contact with active cases, persons with human immunodeficiency virus (HIV) infection and other medical risk factors that increase the risk of tuberculosis if infected, intravenous drug abusers, residents and employees of high-risk congregation settings, health care workers who serve high-risk clients, foreign-born persons recently arrived from high-prevalence countries, some medically underserved, low-income populations, some high-risk racial or ethnic minority populations, and infants, children, and adolescents exposed to adults in high-risk categories [12-14]. If we limit the cough officer

screening strategy to selective high-risk patients, including those with HIV infection, end-stage renal disease, diabetes mellitus, weight loss ≥10% below ideal body weight, silicosis, prolonged corticosteroid therapy, leukemia, or lymphoma, and intravenous drug abusers, the sensitivity of the detection rate might be elevated. However, further research is required to confirm these findings.

In conclusion, cough officer screening is effective in the early detection of active pulmonary tuberculosis in inpatients. Strategies to improve doctors' compliance with this screening system will increase the case finding rate. In terms of cost-effectiveness, the internal medicine department would be the most important target for screening. Determining the most appropriate cutoff point for cough duration requires further study.

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咳嗽偵測機制在住院病人早期發現肺結核的角色

蔡政宏　林慶雄　林瑞鳳 **　劉尊榮 *　黃美麗 **　溫仁和　蔡偉宏

背景：為避免院內結核病的傳播，早期診斷與治療是必要的結核病防治策略。本篇研究的目的是評估一套電腦化的咳嗽偵測機制用於早期偵測住院病人是否患有肺結核之可行性。

方法：本院實施一套電腦化的咳嗽偵測機制，從 2004 年 10 月到 2005 年 9 月，所有住院病人皆納入偵測機制並紀錄咳嗽天數。一旦病人咳嗽 5 天以上，醫師的電腦醫囑系統會提醒醫師評估這些病人是否需要作肺結核檢查，包括胸部 X 光、肺結核痰液抹片以及培養。

結果：本篇研究期間共有 57,745 位住院病人，由咳嗽偵測機制提醒醫師病人已連續咳嗽 5 天以上的病人數為 6,971 位（12%），其中有 2,088 位（30%）有進行胸部 X 光及痰液檢查。這當中有 18 位確診為肺結核，且都是內科住院病人。由疾病管制局肺結核通報資訊系統得知，在此研究期間本院共通報 151 位住院病人確診肺結核個案。本咳嗽偵測機制的 TB 發現率為 12%（18/151），而藉由本機制診斷一位肺結核病患平均需花費為新台幣 49,865 元。

結論：咳嗽偵測機制用於早期肺結核之偵測是有其效益的，致力增加醫師對此機制的實行將會提升TB發現率。就經濟效益而言，內科住院病人是本機制實施之最重要族群。到底住院病人最適當的咳嗽天數以開始啟動本機制是最有效益的仍需更進一步的研究。*(胸腔醫學* ***2006; 21: 321-327)***

關鍵詞：咳嗽偵測機制，肺結核

彰化基督教醫院　內科部胸腔內科，* 內科部感染科，** 感染管制委員會
索取抽印本請聯絡：林慶雄醫師，財團法人彰化基督教醫院　內科部胸腔內科，彰化市 500 南校街 135 號

Treatment and Outcome of Traumatic Tracheobronchial Injuries

Ching-Yang Wu, Yun-Hen Liu, Yi-Cheng Wu, Ming-Ju Hsieh, Po-Jen Ko, Yen Chu, Hui-Ping Liu

Background: Traumatic tracheobronchial injuries are rare, but have been increasing in incidence in recent years. We summarize and analyze the presentations, management, and outcome of tracheobronchial injuries through a presentation of our experience and a review of the literature.

Patients and methods: From October 2001 to June 2005, we managed 11 patients with tracheobronchial injuries due to both blunting and penetrating etiologies. Clinical presentations, diagnostic modalities, management, and complications were reviewed retrospectively.

Results: Eleven patients with traumatic tracheobronchial injuries were identified: 6 were male and 5 were female, with a median age of 43.9 years (range, 9~85 years). Physical findings were closely related to the lesion site, and subcutaneous emphysema (6/11) was the most common clinical finding. All of our patients underwent a further survey of associated injuries after vital signs had been stabilized. High incidences of associated injuries were noted in both groups; however, there were no esophageal or great vessel injuries in our study. All patients received surgical treatment and recovered well, except 2 patients with anastomotic granulations in the serial follow-up.

Conclusion: Early diagnosis and early management is crucial for traumatic tracheobronchial injury. The morbidity and mortality of tracheobronchial injury is influenced by associated injuries. Bronchoscopy can provide detailed information on airway injury and lead surgeons to choose the proper method. We performed debridement and mobilization of the airway prior to primary repair with absorbable suture. Intensive chest care and adequate inhalation therapy is important for airway toilet. Extubation should be performed as soon as possible to avoid positive-pressure ventilation injury. ***(Thorac Med 2006; 21: 328-336)***

Key words: traumatic tracheobronchial injuries, airway trauma

Introduction

Traumatic tracheobronchial injuries are rare, but potentially life-threatening [1-2]. Early diagnosis and individualized planning according to the type of injury can lead to successful treatment. However, there is a high incidence of associated injuries in tracheobronchial injuries [1,3]. If the

Division of Thoracic & Cardiovascular Surgery, Chang Gung Memorial Hospital, Chang Gung University
Address reprint requests to: Dr. Yun-Hen Liu, Division of Thoracic & Cardiovascular Surgery, Chang Gung Memorial Hospital, 5 Fushing Street, Kweishan, Taoyuan, Taiwan 333, R.O.C.

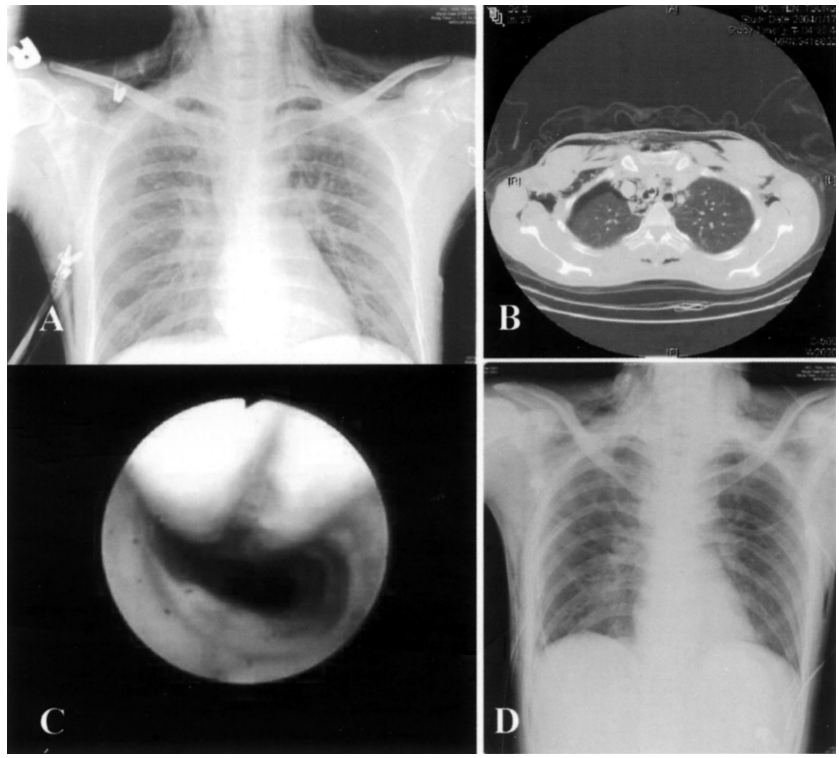

Fig. 1. Image studies of patient 2
A: Pre-operative chest plain film showed extensive subcutaneous and mediastinal emphysema
B: Pre-operative CT demonstrated extensive subcutaneous and mediastinal emphysema
C: Pre-operative bronchoscopy identified laceration at the posterior membrane portion of the trachea
D: Post-operative chest roentgenogram: ameliorated subcutaneous and mediastinal emphysema in comparison with previous images

symptoms of tracheobronchial injuries are minor, the injuries may be masked by other associated injuries [1]. Surgical debridement and interrupted absorbable suture are utilized for the repair of tracheobronchial injuries [1]. Maintenance of effective ventilation and oxygenation are important in post-operative care [1]. Herein, we present our experience with the management of tracheobronchial injuries.

Materials and Methods

From October 2001 to June 2005, we managed 11 patients with complex tracheobronchial injuries due to various etiologies. A retrospective study was undertaken to analyze the pattern of clinical presentations, the techniques of airway management and surgical repair, and the morbidity and mortality. Clinical data from medical records were reviewed retrospectively (Table 1).

Results

Eleven patients with tracheobronchial injuries were identified; 6 were male and 5 were female, with a median age of 43.9 years (range, 9 ~ 85 years). There were 8 blunt injuries (72.7%), 6 motor vehicle accidents, 1 fall, and 1 iatrogenic

Table 1. Patients Characteristics

No	Age	Gender	Mechanism	Pre-operative symptoms	Procedure	Operative finding	Complication
1	60	Female	Fall	Subcutaneous emphysema	Primary repair	Membrane portion laceration (6 cm)	Nil
2	27	Male	MVA	Subcutaneous emphysema	Primary repair	Posterior wall laceration (4.5 cm, above carina 4 cm)	Nil
3	54	Male	MVA	Subcutaneous emphysema Dysphonia, Pneumothorax	Primary repair	Complete tracheal disruption (cricoid-1st tracheal ring)	Hoarseness (Laryngeal cyst, right)
4	70	Female	CPCR with ET + MV	Subcutaneous emphysema Pneumo-mediastinum Air-leak from ET tube	No 8 Shiley insertion	Posterior wall laceration (6 cm, 3 cm above carina) Unable to repair	Ventilator-depend
5	85	Male	Suicide	Neck penetrating wound Left pneumothorax	Primary repair	Anterior and posterior wall of trachea laceration (4th ~ 7th tracheal ring)	Nil
6	54	Male	MVA	Stridor (EDH with skull fracture)	Endotracheal tube stenting	70% stenosis (arytenoids and supraglottic region)	Nil Hoarseness
7	23	Male	MVA	Neck hematoma Bilateral vocal palsy	No 13 T-stent Revision of stent	Cricotracheal junction total disruption Severe destruction of cricoid cartilage	Residual granulation
8	55	Female	Penetrating injury	Bilateral hemo-pneumothorax Neck stabbing wound	Primary repair	Complex fracture of the trachea, Partial amputation of the thyroid cartilage	Anastomosis stricture
9	9	Male	MVA	Bilateral pneumothorax subcutaneous emphysema Right lung collapse	primary repair	Right upper lobe bronchus and trunchus intermedialis complete disruption	Nil
10	21	Female	MVA	Subcutaneous emphysema Vocal cord paralysis	Primary repair No. 13 T-stent	2nd ~3rd tracheal ring total disruption Complete disruption of 3rd tracheal ring	Granulation Sputum impaction
11	25	Female	Penetrating injury	Neck cutting wound 10 cm	Primary repair	Left SCM and strapes muscle total disruption Tracheal partial disruption	Nil

MVA: motor-vehicle accident; CPCR: cardiopulmonary resuscitation; ET: endotracheal tube; MV: mechanical ventilator

Table 2. Clinical Symptoms of Traumatic Tracheobronchial Injuries

	Blunt injury	Penetrating injury
Subcutaneous emphysema	6	0
Tracheal deviation	3	0
Neck stab wound	0	3
Loss of thyroid prominence	1	0
Neck ecchymoses	1	0
Neck hematoma	1	0
Stridor	1	0
Air leak from wound/endo	1	3
Dysphonia	1	0

Table 3. Characteristics of Chest Roentgenogram of Traumatic Tracheobronchial Injuries

	Blunt injury	Penetrating injury
Subcutaneous emphysema	6	0
Pneumothorax	2	2
Pneumomediastinum	2	0
Hemothorax	0	1
Rib fracture	1	0
Deep neck emphysema	1	0

injury. The other 3 were penetrating injuries (27.3%), all stab wounds. Ten patients had cervical tracheal lesions, and 1 had intra-thoracic tracheal and bronchial lesions.

Physical findings were closely related to the lesion sites. Among patients with cervical tracheal lesions, subcutaneous emphysema (6/11) was the most common clinical finding. Also, tracheal deviation (3/11), neck stab wound (3/11), loss of thyroid prominence (1/11), neck ecchymoses, (1/11), neck hematoma (1/11), stridor (1/11), dysphonia (1/11), and air leakage from an endotracheal tube or wound (4/11) were found initially (Table 2).

All our patients received a chest roentgenogram, and 8 of 11 (72.7%) had abnormal findings. The most common findings were subcutaneous emphysema (6/8), pneumothorax (4/8), pneumo-mediastinum (2/8), hemothorax (1/8), rib fracture (1/8), and deep neck emphysema (1/8) (Table 3).

A further survey of associated injuries was undertaken after vital signs had been stabilized. Seventy-five percent of the patients (6/8) with blunt injuries had associated injuries. These injuries included lung contusion (3/8), long bone fracture (1/8), PCL injury (1/8), recurrent nerve injury (3/8), and epidural hemorrhage (1/8). In the penetrating injuries group, only 2 patients had lung lacerations (2/3). No esophageal or great vessel injuries were found in our study. Table 4 shows the injuries associated with the traumatic tracheobronchial injuries of our patients.

Bronchoscopic evaluation was performed

Table 4. Associated Injuries of Traumatic Tracheobronchial Injuries

	Blunt injury	Penetrating injury
No associated injury	2	1
Lung (contusion/laceration)	3	2
CNS	1	0
Extremity	2	0
Recurrent laryngeal nerve	3	0

Table 5. Lesion Sites of Traumatic Tracheobronchial Injuries

	Blunt injury	Penetrating injury
Membranous portion	3	0
Supraglotic region	1	0
Trachea	3	3
Bronchus	1	0

Table 6. Complications

	Blunt injury	Penetrating injury
Granulation	2	1
Sputum impaction	2	1

after the airway had been established. The locations of the tracheobronchial injuries were recognized, as well as the extent of the lesions. Of the blunt injuries, 75% (6/8) were located in the trachea. The anatomic locations of the penetrating injuries were similar to those of the blunt injures; all injuries were located on the trachea. Table 5 shows the details of the lesion sites.

All patients in our series received surgical treatment. The 8 patients with blunt injuries underwent a collar incision approach; another patient, a 9-year-old boy, was found to have a total disruption of the right upper lobe bronchus and right intermediate bronchus at the orifice level, and received a right posterolateral thoracotomy for primary repair. In the penetration group, only 1 patient was explored via a neck collar incision and bilateral exploratory thoracotomy, due to a complex fracture of the trachea with partial amputation of the thyroid cartilage, and bilateral lung laceration.

The most common complications in our series were anastomotic granulations. These may have led to airway stenoses and the following sputum impaction, which may be related to the patients' extensive airway injuries. All patients with anastomotic stenosis had problems with airway toilet. Sputum impaction was found in all of these patients, below the anastomotic site. Table 6 presents the details of the complications related to the procedures.

Discussion

Tracheobronchial injuries are rare, but potentially life-threatening [1-2], possibly due to a

missed diagnosis that was masked by associated injuries or mild clinical presentations [1]. Additionally, most patients die before they reach the hospital. Therefore, the true incidence of tracheobronchial injuries has been difficult to establish [1,4-5]. With the improvement in pre-hospital care and specialized regional trauma units, the incidence of tracheobronchial injuries has increased. A best guess was an increase of 1 ~ 2% [1, 4].

The first repair of tracheobronchial injury was performed by Ambroise Paré in the 16th century, but no patient survived [4-6]. In the studies of Krinitski, patients were able to survive despite lung atelectasis caused by bronchial rupture, which was revealed in the autopsy [4,7]. Successful repair of bronchial injuries was achieved in the 1940s [4,7].

Tracheobronchial injuries can be caused by either a penetrating or blunting mechanism [1]. Penetrating injuries are caused by a knife or gun shot. Blunt injuries to the airway could be caused by the mechanism Kirsh and Orringer proposed, including a sudden increase in intra-tracheal pressure with a closed glottis and deceleration – and acceleration shearing force [1-2,4-5,7-13]. We can explain the injuries in our series with the proposed mechanism.

A variety of signs and symptoms results from isolated tracheobronchial injury, depending on whether there is free communication between the site of injury and the pleura [14]. In our series, subcutaneous emphysema was the most common (6/11) symptom. However, none were pathognomonic signs [1]. There were leading symptoms and signs for tracheal and main bronchus rupture. For tracheal rupture, we found hemoptysis, stridor, dysphonia, pneumomediastinum, and massive cervical emphysema [14]. If pneumomediastinum and complete collapse of the ipsilateral lung were found, main bronchus rupture was highly suspected [14]. The most urgent and life-threatening problem during the initial evaluation is airway control [4-5,7-8]. In-line stabilization of the cervical spine is crucial prior to intubation [4]. Also, further trauma to the trachea should be avoided when an airway is established [4]. Cricothyroidotomy and tracheostomy were needed if intubation failed [4]. Three patients (patients 6-7, 10) in our series were suspected of having extensive airway injuries, and received bronchoscopically-guided nasotracheal tube intubation for airway establishment; other patients underwent an oro-tracheal tube insertion. Of crucial importance is selecting the proper size of endotracheal tube, retracting the stylet when the balloon cuff passes through the vocal cord, inflating the cuff slowly with proper volume and pressure, and deflating the cuff first when redepositing the tube [15].

After the airway was established in our patients, a chest roentgenogram was taken, and an esophagogram and computed tomography were performed to rule out other associated injuries. However, esophagography was performed selectively, depending on the patient's general condition. Associated injuries are common and related to the mechanism and location of the tracheobronchial injury [3,7]. There are many vital organs in the neck and thorax; therefore, we should identify the possible associated injuries after establishing the airway [5]. These diagnostic modalities could give us detailed information and help in deciding the proper approach.

We performed debridement and mobilized the airway within 24 hours prior to primary repair. The first operative goal, before proceeding with tracheal repair, must be vascular control, if major blood vessels have been injured [4-5]. The recurrent laryngeal nerve runs in the tracheo-esopha-

geal groove, so in order to avoid injury the nerve, we should dissect as close to the trachea as possible [5]. We used absorbable suture, and tied knots outside to avoid granulation. Early surgical repair is preferable and associated with a better outcome and reduced incidence of complications, such as perichondritis and eventual stenosis [1]. If a large tracheal defect was noted, we kept the patient in neck flexion posture with a chin suture for at least 7 days. Non-operative management should be considered only in patients with a small perforation and a delayed diagnosis [8]. One of our patients (patient 4) continued using the tracheotomy tube to bypass the lesion, due to an inability to repair and co-morbidity. Post-operative care is crucial in the management of tracheobronchial injury. The most important factor is the maintenance of effective ventilation and oxygenation [1]. Prolonged positive pressure ventilation or pressure exerted by an endotracheal tube might adversely affect healing. Therefore, we prescribed adequate pain control and intensive chest care, and attempted extubation as soon as possible. In addition, we employed therapeutic modalities to reduce airway edema and secretion. We found that the most common (3/11) complication was anastomotic stenosis, which may be related to the greater destruction of the trachea and greater tension after primary repair. We employed a rigid bronchoscope and laser ablation, and deployed an airway stent to keep the airway patent. One patient remained ventilator-dependent, and 2 patients have maintained the use of the Montgomery T-tube.

The outcome of tracheobronchial injury does not appear to be related to the mechanism of the injury, but is influenced by associated injuries [1]. Since fewer associated injuries coexisted in our patients, a better outcome was achieved. All patients survived after management. Two patients were found to have anastomotic stenoses, and continued using the Montgomery T tube. This may be related to the greater destruction of the airway. Eight patients (8/11) recovered well and resumed their daily activities, as before.

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外傷性氣道損傷的治療與預後

吳青陽　劉永恆　吳怡成　謝明儒　柯博仁　朱彥　劉會平

背景：外傷性氣道損傷在臨床上雖是少見但近年來發生率有上升的趨勢。為了進一步瞭解氣道損傷的相關臨床處理，我們針對歷史文獻及本院實例作回溯性的分析並嘗試對氣道損傷的臨床處理流程作系統性的歸納。

方法：自 2001 十月到 2005 六月我們共處理十一位外傷性氣道損傷的病患。我們針對外傷性氣道損傷的臨床症狀表現、診斷方式、治療方式以及可能的併發症作回溯性的研究。

結果：在十一位外傷性氣道損傷的病患中，有六位是男性,有五位是女性；其平均年齡為 43.9 歲（9～85 歲）。其臨床症狀表現與氣道受損的為置有密切關係。

最常見的重狀就是皮下氣腫。在病人生命徵象穩定之後,我們才針對可能相關的損傷作更一步的檢查。我們發現不論是鈍傷或是穿刺傷所引起的氣道損傷都有相當高的比率會伴隨其他損傷。所有病人都接受外科手術治療而且術後恢復良好，但有兩個病人在術後追蹤在吻合端出現肉芽組織增生。

結論：早期診斷以及早期處理對外傷性氣道損傷是很重要的。氣道損傷的致病變（morbidity）以及致死率（mortality）會因不同相關損傷而有所影響。若高度懷疑氣道損傷，在作更進一步檢查之前必須維持氣道通暢。在維持氣道通暢後才可以針對相關損傷所進一步的檢查。支氣管鏡可以提供更多更詳細的氣道損傷狀況提供外科醫師作適當的術前規劃。我們針對氣道損傷作適度的清創以及用可吸收線修補缺損。胸腔姿勢引流（intensive chest care）以及適當的呼吸治療（inhalation therapy）在氣道清潔（airway toilet）上是很重要的。術後應儘早拔管以及盡量避免正壓機械呼吸（positive-pressure ventilation）以免影響修補處的癒合。*(胸腔醫學* ***2006; 21: 328-336)***

關鍵詞：外傷性氣道損傷、氣道外傷

長庚紀念醫院　胸腔及心臟血管外科系，長庚大學　胸腔及心臟血管外科系
索取抽印本請聯絡：劉永恆醫師，長庚紀念醫院　胸腔及心臟血管外科系，333 台灣省桃園縣龜山鄉復興街 5 號

Pulmonary *Mycobacterium Avium* Complex Infection in a Middle-age Woman with Bronchiectasis

Li-Chiao Kuo, Wei-Juin Su*, Reury-Perng Perng*

Mycobacterium avium complex (MAC) is the most frequent pathogen causing nontuberculous mycobacterial pulmonary infection. Herein, we report a 55-year-old non-smoking female who had been diagnosed with bronchiectasis previously. She had also had small discrete nodules running a very slow, progressive course for at least 3 years, and was eventually diagnosed with MAC lung disease. In a patient with bronchiectatic imaging findings, especially with associated nodular lesions, pulmonary MAC infection may be considered as a possible etiology. ***(Thorac Med 2006; 21: 337-342)***

Key words: *Mycobacterium avium* complex, nontuberculous mycobacteria, bronchiectasis

Introduction

Mycobacterium avium complex (MAC) lung disease is becoming increasingly prevalent [1-2]. It usually occurs in patients with chronic lung disease or deficient cellular immunity [3]. In the non-HIV population, MAC can complicate pre-existing lung diseases like chronic obstructive pulmonary disease, bronchiectasis, and cystic fibrosis, and can also cause lung disease in previously healthy people, usually thin, middle-aged-to-elderly women [4-7]. The clinical presentation of MAC infection depends on the population studied [7]. We report a case of very slowly progressive MAC lung disease in a non-smoking middle-aged-to-older female with bronchiectasis, review the literature, and discuss the relationship of MAC to bronchiectasis.

Case Report

This 55-year-old, thin female was a lifelong nonsmoker. She had suffered from chronic productive cough off and on for about 4 years, and was under intermittent treatment at our outpatient department (OPD) for bronchiectasis. In December 2003, she visited our OPD for mild hemoptysis and exacerbation of cough. There was no fever or leucocytosis. Chest X-ray (CXR) revealed bronchiectatic changes and diffuse small nodules. Her sputum acid-fast bacilli (AFB) smear in 3 specimens were all negative, but the cultures turned out to be 2 to 4 + of mycobacterium. Further identification disclosed *Mycobacterium*

Division of Chest Medicine, Department of Internal Medicine, I-LAN Hospital, Department of Health, Affiliated with Taipei Veterans General Hospital
*Chest Department, Taipei Veterans General Hospital
Address reprint requests to: Dr. Wei-Juin Su, Chest Department, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei 11217, Taiwan

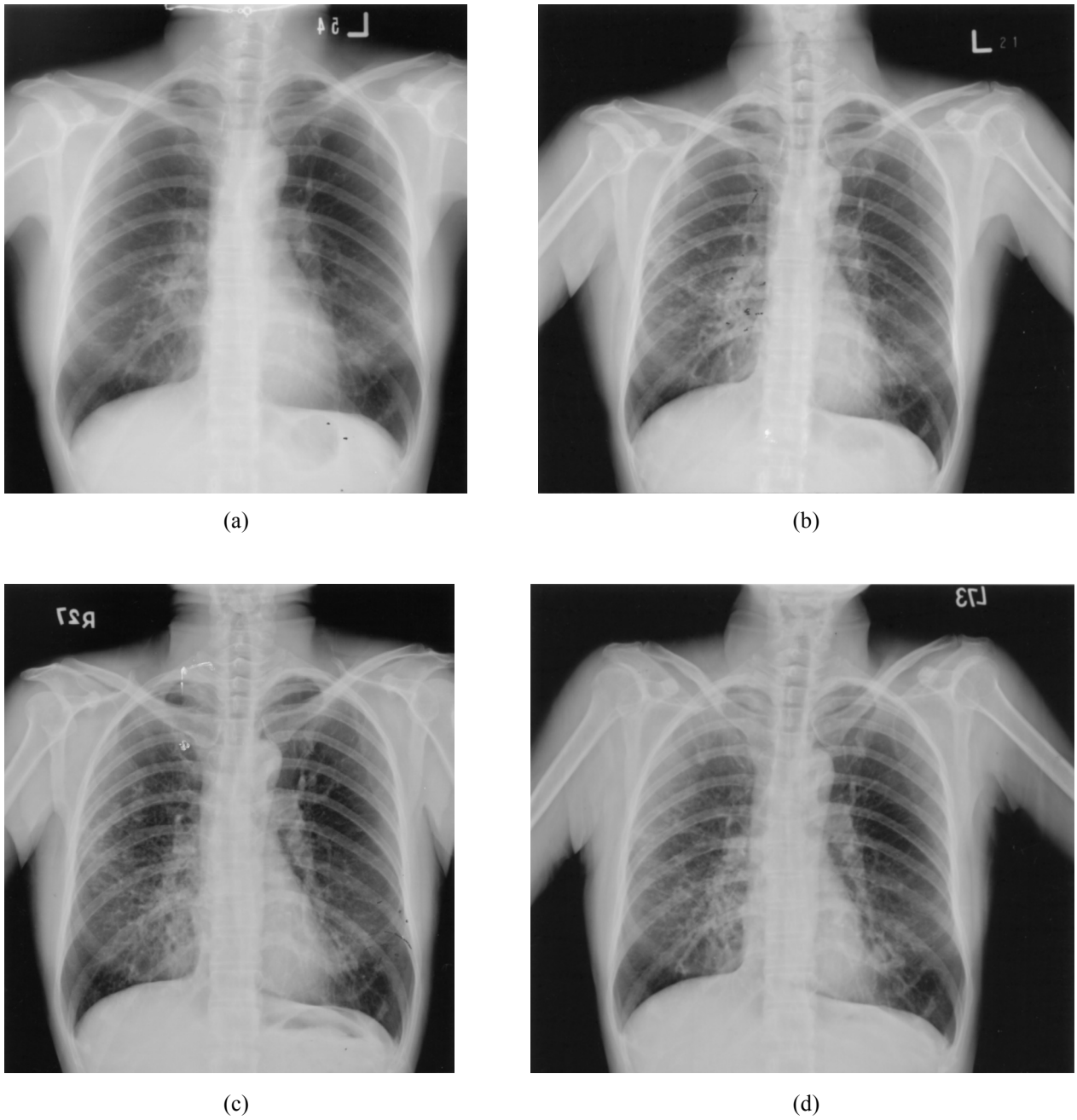


Fig. 1. Serial chest radiographs for (a) April 2001, (b) May 2003, and (c) March 2004 show a very slow progression of multiple small nodular lesions in both lungs, with right lung predominance. The radiograph for (d) November 2004, shows minimal improvement after 9 months of medication.

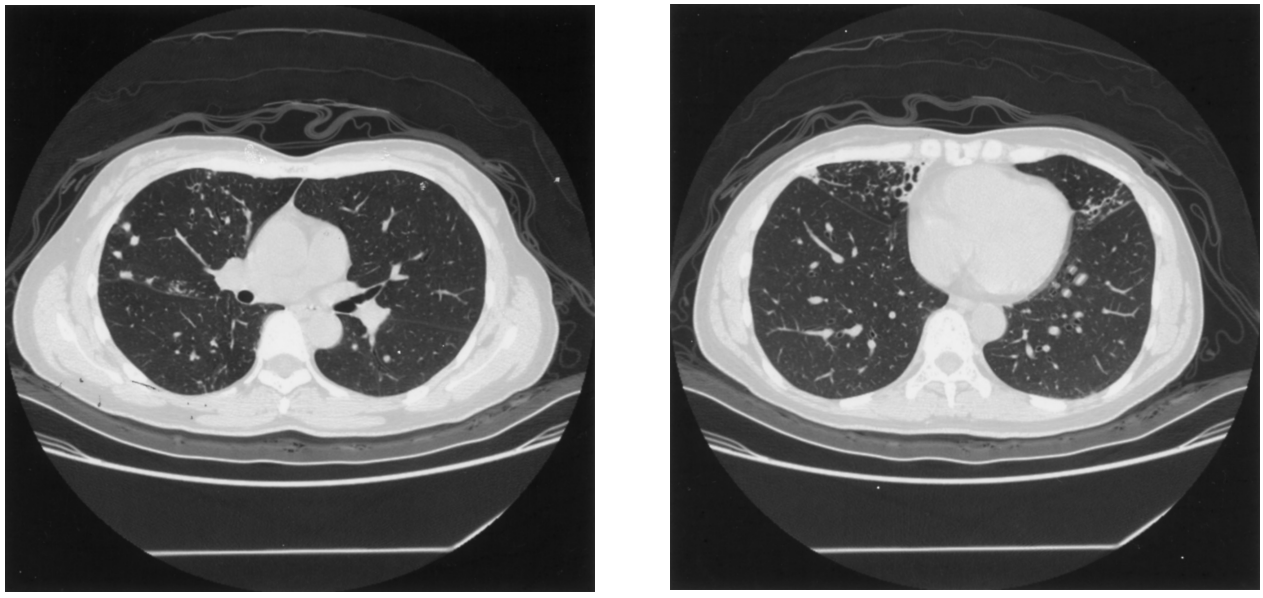
avium complex which was resistant to all first-line antituberculosis drugs. On tracing back her past serial chest radiographs, lesions had been noted 3 years previously, with slow, progressive changes (Figure 1a, b, c). The initial high resolution computerized tomography in March 2002 also showed some small nodular lesions in the right upper lobe, apart from the bronchiectatic

changes in the right upper lobe, right middle lobe and lingular lobe (Figure 2). Anti-microbial therapy with levofloxacin 500 milligram (mg), rifampicin 450 mg, ethambutol 800 mg, and clarithromycin 500 mg were given daily, beginning in March 2004. But serial CXRs showed minimal improvement (Figure 1d), with persistently positive sputum cultures (1+ to 4+) for MAC throughout 9 months of treatment. The patient was lost to follow-up thereafter.

Discussion

Chronic pulmonary disease is the most common localized clinical manifestation of nontuberculous mycobacterium (NTM) [8]. *Mycobacterium avium* complex is the most frequent pathogen causing NTM lung disease [1, 6]. In the non-HIV population, an increased risk of MAC lung infection exists in patients with predisposing lung conditions, such as cystic fibrosis [4-5], COPD, inactive or active tuberculosis, bronchiectasis, silicosis, esophageal disease, chronic aspiration pneumonia, alcoholism, and bronchogenic carcinoma, or in those who have undergone gastrectomy [9-10]. But MAC lung disease is increasingly noted in persons without predisposing conditions, particularly middle-aged and elderly women [2-3].

The American Thoracic Society (ATS) review of NTM in 1997 [6] stated that MAC lung infection has an unpredictable course in HIV-negative patients. It appears to be related in part to the presence of two types of clinical presentation. The traditional presentation of apical fibrocavitary lesions occurs mostly in males with a heavy smoking habit and alcohol abuse. This form of disease generally progresses within 1 to 2 years, if left untreated. MAC may also present as a bilateral nodular, interstitial pattern or isolated right



(a) (b)

Fig. 2. High-resolution CT of the chest in March 2002 showing (a) small nodular lesions in the right upper lobe and (b) bronchiectatic changes in the right middle lobe and left lingular lobe.

middle lobe or lingual lobe bronchiectasis in middle-aged-to-elderly non-smoking females [3, 6, 11-13] This form has a much slower progression, and long-term follow-up for 5-10 years was often needed to show clinical or radiographic changes [6]. In our case, imaging findings and the slow progressive course lasting at least 3 years was compatible with the latter pattern.

The patient was recognized to have bronchiectasis at first, but high resolution CT at that time also showed small peripheral nodules in the right upper lobe. Bronchiectasis predominantly in the right middle lobe and/or lingular lobe, together with small peripheral nodules, are increasingly the major image findings in MAC lung disease [11-14]. Whether bronchiectasis is a risk factor for MAC or a consequence of bronchial involvement by the disease is still under debate [15]. Moore has shown that airway disease in these patients is frequently progressive, and has suggested that bronchiectasis may not be a predisposing condition, but rather a consequence of atypical mycobacterial infection [16]. Fujita J *et al*. also demonstrated that destruction of fundamental bronchial structures due to extensive granuloma formation throughout the airways was likely the main cause of bronchiectases in MAC infection. MAC was demonstrated in the granulomas of the bronchiectasis lesion using a fluorescence microscope [17].

Why MAC is prevalent in middle-aged-to-older females is still unknown. A Japanese study suggested that being thin was a risk factor for progression of disease in patients with fibronodular bronchiectasis [18].

Treatment for MAC lung disease with fibronodular bronchiectasis was recommended in the 1997 ATS statement on NTM [6]. This recommendation was based on studies using high-resolution CT (HRCT) scans [11, 16], which demonstrated specific radiographic features of parenchymal disease in addition to multifocal bronchiectasis and the slow progression of the lung disease. The ATS statement also made clear that if the clinical decision is made to withhold therapy, careful monitoring for disease progression is mandatory [6]. Unfortunately, there are no prospective, controlled trials that have yielded data on estimating the risk of these patients acquiring progressive lung disease. In the absence of controlled trials, it is unknown how frequently sputum will spontaneously convert to negative, what proportion of patients with *M. avium* in their sputum will acquire progressive lung disease, and whether treatment will alter the course of the disease [7]. In our case, mild chest symptoms and persistent sputum cultures positive for MAC were still noted after 9 months of antimicrobial therapy, and serial CXR findings showed minimal improvement. But the patient failed to continue in follow-up thereafter.

In conclusion, in patients with bronchiectatic imaging findings, especially with associated nodular lesions, MAC infection should be considered as a possible etiology. The slow progression of MAC lung disease, sometimes over decades, in patients with fibronodular bronchiectasis, has demonstrated the importance of recognizing and treating these patients.

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鳥型分枝桿菌肺部感染在一位中年女性支氣管擴張症病例

郭麗巧　蘇維鈞 *　彭瑞鵬 *

本篇報告一例鳥型分枝桿菌之肺部感染。病人為一位五十五歲女性，因咳血到門診求診，胸部影像學檢查發現病患有支氣管擴張症合併肺部小結節。痰液細菌培養初步發現為分枝桿菌，後來經鑑定為鳥型分枝桿菌感染。我們比較病患以前的胸部 X 光片發現肺部浸潤有更惡化的現象，於是開始使用藥物治療。鳥型分枝桿菌是非典型分枝桿菌在肺部感染中最常見的菌株。影像學上若表現為支氣管擴張症合併肺部小結節者，則應考慮病患是否感染非典型分枝桿菌，特別是鳥型分枝桿菌的感染。*(胸腔醫學* ***2006; 21: 337-342)***

關鍵詞：鳥型分枝桿菌，非典型結核分枝桿菌，支氣管擴張症

行政院衛生署立宜蘭醫院胸腔內科（委託台北榮民總醫院經營），* 台北榮民總醫院　胸腔部
索取抽印本請聯絡：蘇維鈞醫師，台北榮民總醫院　胸腔部，台北市石牌路二段 201 號

Irinotecan-related Pulmonary Toxicity — A Case Report

Geeng-Bin Chen*, Ching-Yi Lee*,**, Kuo-Shuen Chen***, Tzu-Chin Wu*, Ming-Fang Wu*,****

Irinotecan is a widely used chemotherapeutic agent for colorectal, gastric, lung, and esophageal cancer. We present the case a 55-year-old man with advanced esophageal cancer who developed progressive interstitial lung infiltrates and who suffered respiratory failure following 3 courses of irinotecan. Progressive pulmonary insufficiency and death were also reported in the initial Japanese studies, despite the institution of empiric steroid therapy for a syndrome similar to that which our patient experienced. As the clinical indications for the use of irinotecan are expanding, we would like to emphasize that irinotecan-associated pulmonary toxicity is a potentially serious adverse effect. Patients with pre-existing pulmonary disease may be at higher risk for this complication, and clinicians should be alert to this possibility. ***(Thorac Med 2006; 21: 343-348)***

Key words: irinotecan, esophageal cancer, pulmonary toxicity, pneumonitis, acute respiratory distress syndrome

Introduction

Pulmonary toxicity due to irinotecan is rare, and has been reported in approximately 1.8% of patients given irinotecan [1-2]. We present a 55-year-old man with advanced esophageal cancer who underwent irinotecan therapy and developed bilateral interstitial infiltrates and progressive respiratory insufficiency, which was initially responsive to systemic corticosteroid. The patient was later complicated with infection and died of acute respiratory distress syndrome.

Case Report

A 55-year-old man with a history of heavy smoking presented with progressive dysphagia and body weight loss of about 3-4 kg over a half-year period. Upper panendoscopy on October 13th 2003 revealed multiple masses with ulcerative surfaces on the middle and lower esophagus, and invasion to the gastric cardia. A tumor biopsy was performed. The pathology revealed squamous cell carcinoma. A chest computed tomography (CT) scan showed esophageal wall thickening at the middle and lower third, extending to the

Divisions of *Chest Medicine, ***Cardiovascular Medicine, and ****Medical Oncology, Department of Internal Medicine, Chung Shan Medical University Hospital; **Department of Internal Medicine, Cheng-Ching Hospital
Address reprint requests to: Dr. Ming-Fang Wu, Department of Internal Medicine, Chung Shan Medical University Hospital, No. 110, Section 1, Chien-Kuo N. Road, Taichung 402, Taiwan

esophago-cardiac junction. Multiple lymphadenopathy in the mediastinum and epigastric region around the celiac trunk was found. The clinical staging was $T_4N_1M_{1a}$, stage IVa.

Because of local advanced-stage esophageal cancer, the paitent received radiotherapy (total 6840 cGy in 38 fractions) concurrent with 3 courses of chemotherapy. The first course of chemotherapy included a cisplatin (80 mg/m^2) intravenous injection on day 1, and 5-fluorouracil (5-FU) (480 mg/m^2/day) 24 hours continuous infusion (CI) for 4 successive days. In an attempt to increase the local control rate, the regimen of chemotherapy was shifted to weekly cisplatin (30 mg/m^2) plus paclitaxel (53 mg/m^2) intravenously on day 1 and day 8 every 3 weeks in the second and third courses. After completion of concurrent chemoradiotherapy, a chest CT scan examination on December 17th 2003 revealed a slight regression of the esophageal tumor. The patient received another 2 courses of chemotherapy with weekly cisplatin (30 mg/m^2), palitaxel (53 mg/m^2), 5-FU (2000 mg/m^2) and leucovorin (150 mg/m^2) 24 hours continuous infusion on day 1 and day 8 of every 3 weeks.

The follow-up chest CT on March 19th 2004 revealed more advanced esophageal cancer with lymphadenopathy in the right paraesophageal region and aorto-pulmonary window. Bilateral pleural tumor involvement was also noted. Because of disease progression, the chemotherapy regimen was shifted to irinotecan (57 mg/m^2) intravenous injection plus 5-FU (2000 mg/m^2) and leucovorin (150 mg/m^2) 24 hours continuous infusion on days 1, 8, and 15 of every 4 weeks, from April 2nd to June 22nd 2004, for a total of 3 courses. The chest radiography on June 4th 2004 revealed no pulmonary infiltration, but left pleural thickening and elevation of the left hemidiaphragm. The picture was the same as the chest radiograph on April 16th 2004. The chest CT scan on June 4th 2004 showed no change of tumor size, less left-side pleural effusion, and a clear lung parenchyma in the lung window (Figure 1).

Two weeks after completion of 3 courses of irinotecan, the patient was admitted to the emergency department due to productive cough and progressive shortness of breath for 2 days.

On admission, the patient had fever (38.2°C). Tachypnea (22 breaths per min) was present with inspiratory crackles audible at the right lung base. Severe arterial hypoxemia (PaO_2 42.9 mmHg, $PaCO_2$ 26.7 mmHg) was found in ambient air. Chest radiography showed ground-glass density in the right lower lung field and interstitial infiltrates in the left lung and right lower lung field (Figure 2). The white blood cell count was 4570 cells/μL, with 74.8% segmented neutrophils, 11.2% lymphocytes, 11.4% monocytes, and 1.5% eosinophils. C-reactive protein was 12.93 mg/L. Other blood chemistry and urinalysis tests were within normal limits. Blood cultures were sterile.

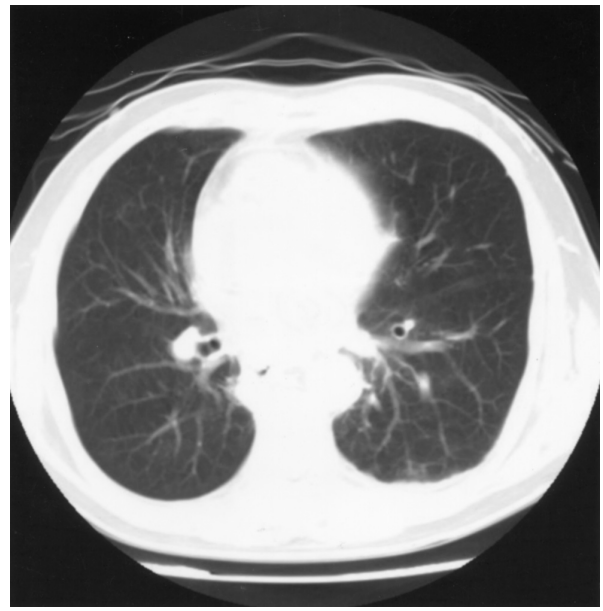

Fig. 1. Chest tomography scan showing clear lung parenchyma in the lung window.

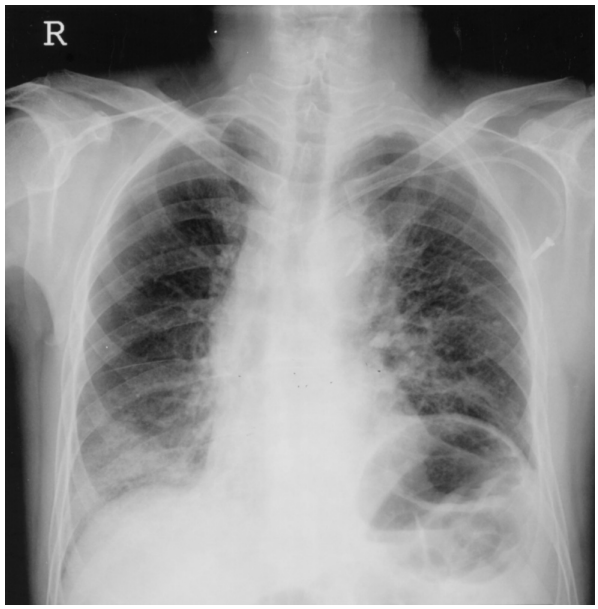

Fig. 2. Chest radiography on day 1 of admission (after 3 courses of irinotecan) revealing ground-glass density in the right lower lung region, and interstitial infiltrates in the left lung and right lower lung region.

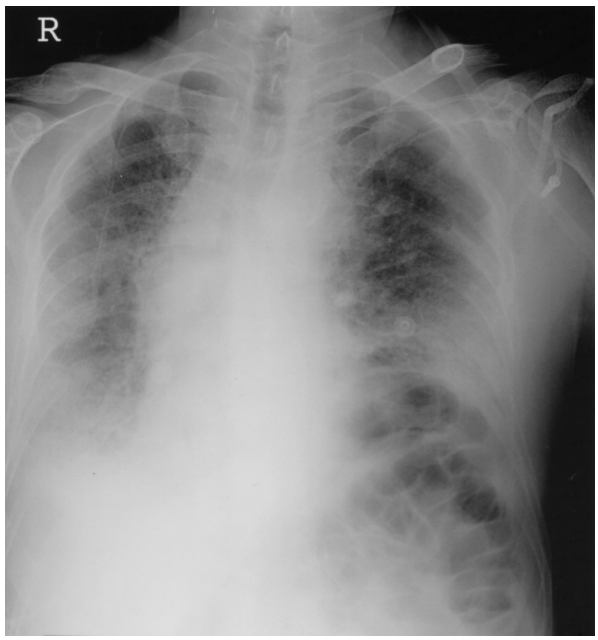

Fig. 3. Chest radiography on day 5 of admission showing progression of bilateral interstitial infiltrates.

Urinary antigen of pneumococcus was absent. Direct examination of the sputum was negative for bacteria or acid-fast bacilli.

Empiric antibiotic therapy with amoxicillin and clavulanic acid was initiated. Due to persistent fever and hypoxemia, piperacillin and tazobactam plus amikacin were substituted on day 3. A non-rebreathing mask was used due to poor oxygenation. The sputum smear still yielded moderate polymorphonuclear leukocytes, but no microorganism in the subsequent sets. Because there was no clinical improvement and no evidence of bacterial pneumonia, trimethoprim-sulfamethoxazole was used from day 4 as a therapeutic trial, in consideration of the possibility of *Pneumocystis carinii* pneumonia. For coverage of atypical pathogens, moxifloxacin was added on day 5 (Figure 3). He was transferred to the intensive care unit (ICU) on day 9 after admission (Figure 4), and endotracheal intubation with mechanical ventilator support was performed due to progressive hypoxemia. The alveolar-arterial oxygen gradient was 598 mmHg.

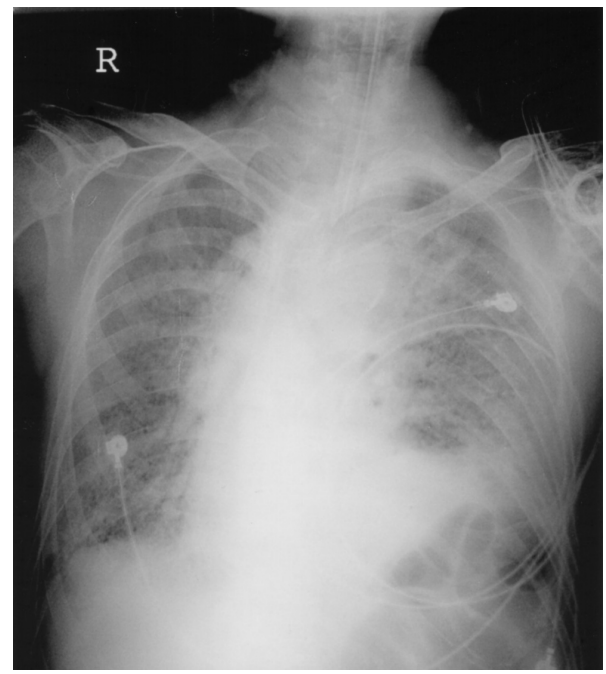

Fig. 4. Chest radiography on day 9 of admission revealing more diffuse interstitial infiltrates. The endotracheal tube is also noted.

His PaO_2/FiO_2 was far less than 200 mmHg. The central venous pressure was 5 mmHg. An initially high oxygen demand was noted with FiO_2 100% under full pressure controlled ventilation. Chemotherapy-related pneumonitis was considered, and systemic corticosteroid was used because of the lack of evidence of microbial infection after a week-long series of examinations. After administration of methylprednisolone 120 mg/day, oxygen demand gradually decreased and FiO_2 could be tapered to 55-60%.

The ventilator was set at a pressure control mode with 16-20 cm H_2O and positive end-expiratory pressure of 12 cm H_2O during the ICU stay. On day 16, right-sided pneumothorax due to barotraumas developed. A chest tube was inserted and the right lung expanded. On day 23, left-sided pneumothorax was found and another chest tube was inserted. Fever developed on day 26 and sputum culture later yielded multidrug-resistant *Acinetobacter baumanii* and oxacillin-resistant *Staphylococcus aureus*. Meropenem and vancomycin were prescribed. Progressive pneumonia and refractory hypoxemia developed. The patient died of refractory hypoxemia-related pulseless electrical activity on day 36 after admission.

Discussion

Irinotecan (CPT-11) is a semisynthetic camptothecin derivative and a new chemotherapeutic topoisomerase-I inhibitor. It is an active drug and is widely used for colorectal, gastric, lung, and esophageal cancer. The common adverse reactions of irinotecan are early diarrhea, late diarrhea, nausea/vomiting, alopecia and myelosuppression.

Pneumonitis following irinotecan administration has been reported in 1.8% of patients enrolled in early Japanese registration trials for lung cancer [1-2]. The clinical presentation was dyspnea and fever, with a reticulonodular pulmonary infiltrate. Although empiric steroid therapy was recommended, some patients died from progressive pulmonary insufficiency attributed to irinotecan-associated pulmonary toxicity. Patients with pre-existing pulmonary disease may be at higher risk for this complication.

Our case had a similar clinical presentation of dyspnea, fever, and interstitial pulmonary infiltrates initially responsive to steroid therapy. This presentation was compatible with irinotecan-induced pneumonitis, as the Japanese registration trials had reported. Radiation-induced pneumonitis is 1 of the differential diagnoses. Radiation-induced lung injury has classically been divided into acute and late. Acute pneumonitis typically presents 1 to 6 months after radiotherapy, with symptoms of shortness of breath, cough, and occasionally, mild fever [3]. Radiographic abnormalities include a diffuse hazy infiltrate or a more dense consolidation in a characteristic distribution around the radiation port. In our case, the presentation of pneumonitis was not confined to the radiation port, so radiation pneumonitis was not likely. *Pneumocystis carinii* pneumonia was considered, but unlikely because there was no significant response after treatment. Viral pneumonia, especially cytomegalovirus pneumonia, is usually concomitant with *Pneumocystis carinii* pneumonia, but the definite diagnosis required a lung biopsy tissue specimen. Because of his critical condition, the invasive procedure was not performed.

Pulmonary fibrosis has not been described during treatment with irinotecan in any patient enrolled in the US phase II studies [4-8]. Of the 481 patients enrolled in phase I and II clinical trials in the United States up to December 1995,

only 1 (0.4%) has died of pulmonary toxicity possibly related to irinotecan administration. This individual developed adult respiratory distress syndrome in the setting of polymicrobial sepsis, although the investigator felt that a potential relationship between the respiratory failure and irinotecan could not be excluded. Our case had an initial response to steroid therapy, later complicated with barotrauma and polymicrobial sepsis.

Conclusion

Irinotecan is a newer, promising agent that is widely used, and has an expanding clinical application. Although serious pulmonary toxicity due to irinotecan is rare, it should still be kept in mind. Early intervention may be life-saving.

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化學治療相關的肺毒性—病例報告

陳耿彬 * 李勁毅 *,** 陳國勳 *** 吳子卿 * 吳銘芳 *,****

Irinotecan 是一個廣泛應用於大腸直腸、胃、肺及食道惡性腫瘤的化學治療藥物。我們報告一位 55 歲晚期食道癌男性病人，在接受三個 irinotecan 療程後，產生進行性肺部浸潤和呼吸衰竭。在日本最初的研究，雖然經驗性使用類固醇，病人仍然因進行性肺部浸潤和呼吸衰竭而死亡。由於 irinotecan 臨床使用適應症增加，我們描述 irinotecan 相關肺毒性。有肺部疾病的病人可能會有較高的危險。醫師應對這種可能性保持警覺。*(胸腔醫學* ***2006; 21: 343-348)***

關鍵詞：irinotecan ，食道癌，肺毒性，肺炎，急性呼吸窘迫症候群

中山醫學大學附設醫院 * 胸腔科 *** 心臟內科 **** 腫瘤內科，** 澄清醫院 內科部
索取抽印本請聯絡：吳銘芳醫師，中山醫學大學附設醫院 內科部，台中市建國北路一段 110 號

Successful Weaning from Invasive Ventilation in Late-onset Pompe's Disease — A Case Report

Chiu-Ping Kuo, Chang-Yi Lin, Chien-Liang Wu

Pompe's disease is an autosomal recessive inheritable disorder involving a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA). The incidence is 1 in 40,000 births. It predominately affects the heart, skeletal, and respiratory muscles. The clinical spectrum ranges from a rapidly progressive infantile form leading to death within the first year of life to a slowly progressive late-onset form of the disease that affects mobility and respiratory function. Both types are generally characterized by progressive muscle weakness and breathing difficulty, but the severity of the disease can vary widely depending on the age of onset and the extent of organ involvement. Patients with the late-onset form who become symptomatic in childhood are more severely affected and typically die by the second or third decade of life. As the disease progresses, patients lose mobility, or become wheelchair bound or bedridden. Respiratory muscle involvement is common, may occur early in the course of the disease, and is the most frequent cause of mortality. We present the case of a 31-year-old woman who was diagnosed with late-onset Pompe's disease 5 years previously, and who developed pneumonia with acute respiratory failure. She was successfully weaned from the ventilator after intensive respiratory muscle training. ***(Thorac Med 2006; 21: 349-354)***

Key words: pompe's disease, ventilator weaning

Introduction

In 1932, Dutch pathologist J.C. Pompe described a 7-month-old infant who died suddenly from a disease associated with widespread tissue accumulation of glycogen. In 1963, H.G. Hers and colleagues linked the disease to an inherited absence or deficiency of enzymes within the lysosome, making Pompe's disease the first to be classified as a lysosomal storage disease. People with the disorder have a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA), which is involved in the breakdown of glycogen. Excess glycogen accumulates in the lysosome, eventually resulting in disruption of normal cellular function. Although glycogen is stored in a variety of cells, muscles are primarily affected, particularly the heart and skeletal muscles. The age of onset and the range of organ involvement usually correlate with the amount of residual GAA enzyme activity. It is estimated that approximately one-third of patients with Pompe's disease

Division of Chest Medicine, Department of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Chiu-Ping Kuo, Division of Chest Medicine, Department of Internal Medicine, Mackay Memorial Hospital, No. 92, Section 2, Chung-Shan N. Rd, Taipei, Taiwan

have the infantile-onset form, while the majority have the slowly progressive late-onset form [1].

Late-onset Pompe disease can present anytime from early childhood through adulthood, with a wide array of symptoms. In many cases, the first symptom may be difficulty walking or climbing stairs, as the progressive muscle weakness primarily affects the trunk and lower limbs. This form of Pompe's disease may mimic 1 of the varieties of muscular dystrophy. In other cases, weakening of the respiratory muscles may result in subtle symptoms such as sleep apnea, morning headaches, and daytime drowsiness, all prior to any sense of leg muscle weakness. Most patients become wheelchair-dependent and may eventually require artificial ventilation; the longer the duration of the disease, the higher the probability of ventilator dependency. Most patients, regardless of age at diagnosis, will have a shortened lifespan due to progressive respiratory failure.

Case Report

A 31-year-old woman developed progressive proximal weakness of all 4 limbs beginning at 15 years of age. She gradually became unable to climb stairs and could not stand from the squatting position. She had recurrent respiratory tract infections and was hospitalized twice with pneumonia in her twenties. She had a baby by spontaneous vaginal delivery at age 24, but subsequently felt too weak to work. She developed increasing dyspnea on exertion and had to sit upright to breathe better. A muscle biopsy 5 years before the present report revealed a glycogen storage disease, and blood tests demonstrated a GAA deficiency. Late-onset Pompe's disease was therefore diagnosed. In the 6 months prior to admission, she required a bilevel positive airway pressure (BiPAP) mask at night because of respiratory muscle weakness.

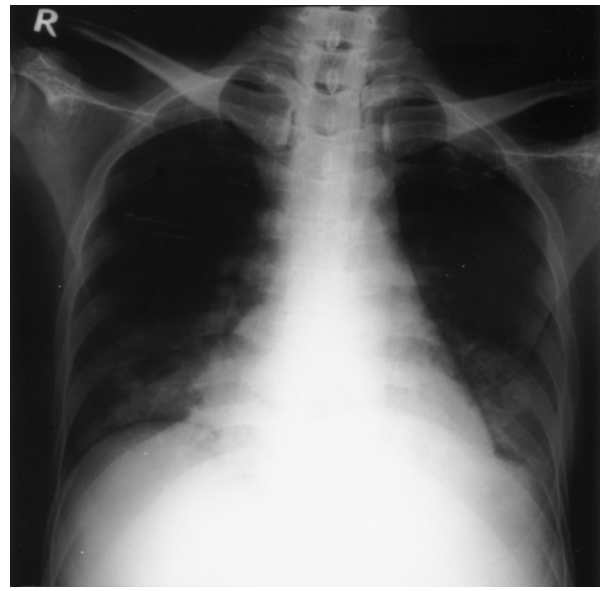

Fig. 1. Chest radiograph on admission shows pneumonic patches at the bilateral basal areas.

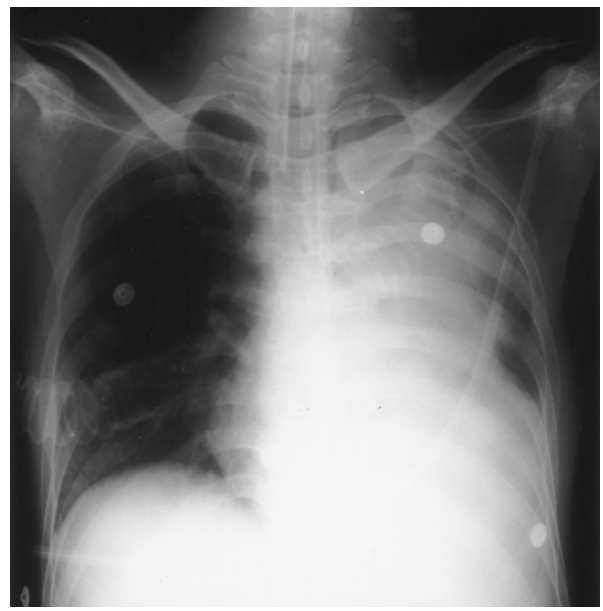

Fig. 2. Chest radiograph on the 3rd hospital day demonstrates left upper lobe collapse, which was later re-expanded, after immediate bronchial hygiene.

She was brought to the emergency department because of intermittent fever, productive

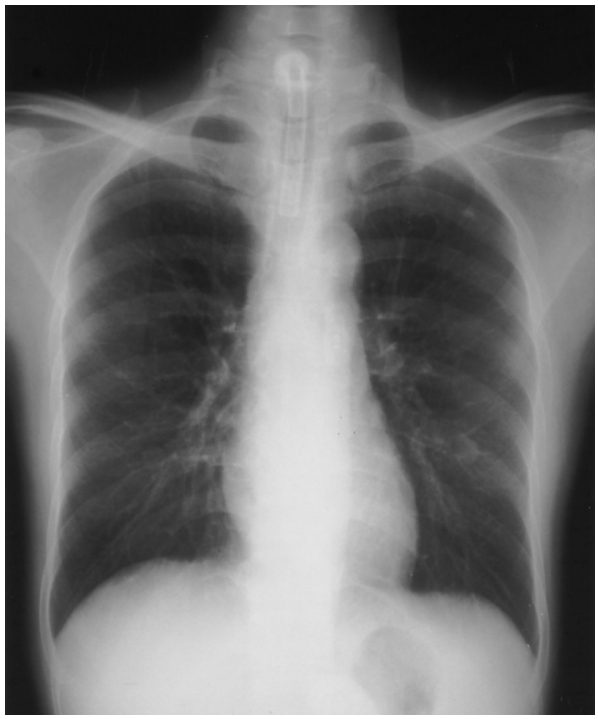

Fig. 3. Normal chest radiograph at the OPD follow-up 6 months after discharge.

cough, and progressive dyspnea with drowsiness for 1 week. Her blood pressure was 124/79 mmHg, temperature 38.2°C, and heart rate 142/min. Coarse crackles were present diffusely in both lung fields. The white cell count was 22,000/μl. Blood biochemistry values were within normal limits. A chest radiograph demonstrated bilateral pneumonia. Arterial blood gas analysis while she was receiving oxygen at 3L/min showed a pH of 7.145, $PaCO_2$ 108.9 mmHg, PaO_2 153.1 mmHg, HCO_3 36.7 mEq/L, and BE +7.7. She was deemed to have acute-on-chronic hypercapnic respiratory failure and was intubated and placed on a mechanical ventilator set on an assist/control mode with pressure control ventilation. Arterial blood gas results with 35% FiO_2 were then a pH of 7.444, $PaCO_2$ 50.1 mmHg, PaO_2 65.3 mmHg, HCO_3 33.5 mEq/L, and BE +9.4.

On the 3rd hospital day, the patient's left upper lobe collapsed, so fiberoptic bronchoscopy was performed for bronchial hygiene, resulting in re-expansion of the lobe. On the 5th hospital day, she was clinically improved, with resolution of the fever and leukocytosis, and improvement seen on chest X-ray. She had poor triggering of the ventilator and a mild air hunger respiratory pattern. Inspiratory and expiratory muscle training was performed, using the abdominal pad method with an expiratory resistor. She was also given upper extremity bicycle exercises and a high-protein diet. Chest physiotherapy included postural drainage, chest percussion, and vibration. A permanent tracheostomy was performed on the 24th hospital day. A T-piece trial with CPAP on the 30th day failed, with the patient complaining of headache and having shallow tachypnea.

Respiratory muscle training was continued, coupled with increasing lengths of time off the ventilator. Dyspnea and muscle strength gradually improved beginning about the 45th hospital day. The patient could tolerate short periods of ambulatory activity while still receiving pressure support ventilation. She was finally successfully weaned from mechanical ventilation on the 54th hospital day. Arterial blood gas testing at that time on 40% FiO_2 with a T-piece showed a pH of 7.377, $PaCO_2$ 61.9 mmHg, PaO_2 85.3 mmHg, HCO_3 35.5 mEq/L, and BE +7.9. She was discharged with a recommendation to continue using nocturnal BiPAP at home. As it turned out, she did not use the BiPAP after she returned home. At the time of this writing, she had had no further episodes of pneumonia or respiratory distress for more than 6 months.

Discussion

Currently, there is no effective treatment for

Pompe's disease. Previous attempts at bone marrow transplantation have not met with success. In 2000, Van den Hout and colleagues published the first evaluation of enzyme replacement therapy (ERT) [2]. Winkel *et al*. demonstrated substantial benefits from long-term intravenous administration of recombinant human GAA derived from rabbit milk in patients with late-onset Pompe's disease, similar to that found in patients with infantile disease [3]. Gene therapy is another approach in the early stages of investigation. In the absence of curative treatment for Pompe's disease, multidisciplinary, supportive therapy is used to manage symptoms and minimize complications whenever possible. While this approach cannot generally alter the disease course, it is designed to help patients maintain the best quality of life possible [4].

In a study of late-onset Pompe's disease, the time from recognition of the first symptoms of muscular weakness to the onset of dyspnea was 9.3 ± 6.1 years (range, 2 to 17 years), and from dyspnea to ventilator dependence 2.0 ± 0.5 years (range, 1 to 3 years) [5]. Disease with an onset later in life generally progresses at a slower pace. Some patients with less severe symptoms remain functional for years with only minimal disability, while others may eventually require mechanical ventilation. In a study of 255 children and adults with Pompe's disease, respiratory support was used by 45% of the participants, including 11% on invasive ventilation via a tracheotomy, and 29% on noninvasive ventilation with a face mask; the type of ventilation was not recorded for the remaining 5% [6]. The median number of hours of ventilation per day was 10.5. The use of respiratory support increased slightly with age. The percentage of patients requiring respiratory support and the number of hours of support needed daily all increased with disease duration [7].

Weakness of the diaphragm, in addition to weak abdominal and intercostal muscles, also makes it difficult for patients to cough, increasing susceptibility to infection and aspiration. Diaphragm dysfunction appears critical to the development of respiratory failure, and has an unfavorable impact on sleep-disordered breathing. A recent cross-sectional study of 27 patients with Pompe's disease revealed a close relationship between diaphragmatic strength, lung function, and gas exchange, with diaphragmatic weakness being the main factor contributing to symptomatic nocturnal hypoventilation [8].

The relatively short interval between the onset of dyspnea and the need for ventilatory support indicates that overt dyspnea is a late symptom of respiratory compromise. Inspiratory muscle training using an inspiratory resistance device may improve respiratory reserve. Though there is no strong evidence to support the effect of inspiratory muscle training on weaning, some studies suggest inspiratory muscle training in combination with progressive spontaneous breathing periods do aid in weaning patients from mechanical ventilation. [9-10]. Depending on the patient and the degree and type of respiratory difficulty, noninvasive methods such as BiPAP or CPAP may be useful, although many patients will eventually require invasive ventilation, most likely with a tracheostomy [11-12].

Our case demonstrates that successful weaning from the ventilator may be possible in a patient with late-onset Pompe's disease who has an episode leading to an acute decrease in an already compromised respiratory function. The factors contributing to success may include resolved pneumonia, respiratory muscle training, a high protein diet, and chest physiotherapy. In the long run, however, progressive respiratory muscle weakness is inevitable. Therefore, education in

the use of nocturnal BiPAP, self-evaluation of the respiratory function, inspiratory muscle training, and enhancing airway secretion clearance (by controlled cough or huff coughing) are all important to prevent or minimize secondary complications of the disease and delay the onset of ventilator dependency [13].

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晚發型龐貝氏患者成功脫離呼吸器—病例報告

郭秋萍　林長怡　吳健樑

龐貝氏症是一種罕見的遺傳疾病，主要影響的是心肌、骨骼肌及呼吸肌的功能，依發生的早晚，可分為早發型及晚發型。早發型通常進展快速，大多數患者在一歲前死亡；而晚發型進展較緩，逐漸影響到日常活動與呼吸功能。我們報告此病例是一位 31 歲女性，在 5 年前被診斷是晚發型龐貝氏症，此次因肺炎合併呼吸衰竭而被插管使用呼吸器。經過漸進式的吸氣阻力及增加肌肉的耐力訓練，再加上營養補給，終於成功脫離呼吸器。

雖然在疾病的自然進程中，大多數龐貝氏患者最終會面臨呼吸惡化而縮短壽命，但是在他們因肺部感染導致急性呼吸衰竭時，適度的呼吸肌訓練，加上物理治療及營養補充，來協助其脫離呼吸器，也許需要投入更長的時間與更多的人力，但仍是值得且必須一試的。*(胸腔醫學* ***2006; 21: 349-354)***

關鍵詞：龐貝氏症，脫離呼吸器

台北馬偕紀念醫院　胸腔內科
索取抽印本請聯絡：郭秋萍醫師，台北馬偕紀念醫院　胸腔內科，台北市中山北路二段 92 號

Tracheobronchial Mucoepidermoid Carcinoma in a 17-year-old Girl: A Case Report and Review of the Literature

Chien-Te Li, Ching-Hsiung Lin, Shang-Yun Ho*, Huei-Mei Chang**, Ching-Yuan Cheng***

Tracheobronchial mucoepidermoid carcinoma is rare. It is classified as a carcinoma of the salivary gland type in lung cancer, and comprises only 0.1-0.2% of primary lung cancers. The tumor is classified as either a low- or high-grade malignancy. The low-grade growth can slowly appear in any age group, and is readily cured by excision. The high-grade tumor behaves aggressively, infiltrates widely in the salivary gland, and produces lymph node and distant metastases. Mucoepidermoid carcinomas account for about 21% of the malignant tumors of the parotid gland and 10% of those of the sublingual gland. They are the most common malignant tumor of the parotid.

We report the case of a 17-year-old girl, a high school student previously in good health and without systemic disease, who suffered from non-productive cough off and on for 8 months. Initially, she was treated at a local clinic as having a common cold, until chest tightness and dyspnea on exertion developed, and then she visited our OPD. The chest radiograph revealed a total collapse of the left lung parenchyma. The chest computer tomography examination demonstrated a contrast medium-enhanced and hypervascular irregular tumor obstructing the left main bronchus. Fibroflexible bronchoscopy revealed a tumor near the carina, coated with whitish debris, and protruding from the left main bronchus with lumen total occlusion. Several transbronchial biopsies were performed, but yielded no definite diagnosis. We consulted the chest surgeon, and a rigid bronchoscopy was performed; the frozen tissue of the excised biopsy taken during the operation revealed only a suspected endocrine tumor, possibly a carcinoid tumor. Finally, a left pneumonectomy, including lymph node dissection was done, and the pathology reported mucoepidermoid carcinoma, low grade.

A literature review revealed that low-grade tracheobronchial carcinoma can be cured by surgical excision. No other metastasis was detected in this patient, and she recovered well with no symptoms after surgical treatment. At the end of a 1-year follow up and short-term pulmonary rehabilitation, she was well and without residual symptoms. ***(Thorac Med 2006; 21: 355-361)***

Key words: mucoepidermoid carcinoma, tracheobronchial tree

Division of Chest Medicine, Department of Internal Medicine, *Department of Radiology, **Department of Pathology, and ***Department of Chest Surgery, Changhua Christian Hospital, Changhua, Taiwan, ROC
Address reprint requests to: Dr. Chien-Te Li, Division of Chest Medicine, Department of Internal Medicine, Changhua Christian Hospital, 135 Nashiao Road, Changhua, 500, Taiwan

Introduction

Primary lung tumors in adolescent patients are rare [1]. Mucoepidermoid carcinoma of the tracheobronchial tree is an extremely rare variant of malignant neoplasm arising from the submucosal bronchial glands, and accounts for approximately 0.1 to 0.2% of all primary respiratory malignancies [2-3]. Patients with this kind of tumor may vary from being asymptomatic to commonly presenting with bronchial obstruction due to the endobronchial location. The symptoms are frequently related to irritation or obstruction of the tracheobronchial tree. Therefore, recurrent episodes of pneumonia, dyspnea, asthma, cough, and less commonly, hemoptysis, are the most frequent presenting complaints in 20% to 30% of patients. The age at presentation varies, but approximately 60% of patients are between 45 and 70 years of age [4]. A chest radiograph often reveals a solitary, centrally located mass with distal pneumonia or atelectasis. Mucoepidermoid carcinoma has a variable outcome, and the long-term prognosis depends on the histologic appearance. We report the case of a 17-year-old girl with left main bronchus mucoepidermoid carcinoma, which was successfully treated with wide local excision. During a 1-year follow up at the chest medicine outpatient department (OPD), she was well and had no evidence of local recurrence or distant metastasis.

Case Report

A 17-year-old previously healthy young girl suffered from non-productive cough off and on for 8 months, and was initially treated at a local clinic as having a common cold. Since her symptom showed little improvement with medication, she visited our OPD for help, where she complained of newly developed chest tightness and exertional dyspnea for 1 week. She denied any systemic disease, such as asthma or heart disease. On physical examination, the vital signs were stable, and there was no fever and systemic positive finding, except that the left lung field brea-

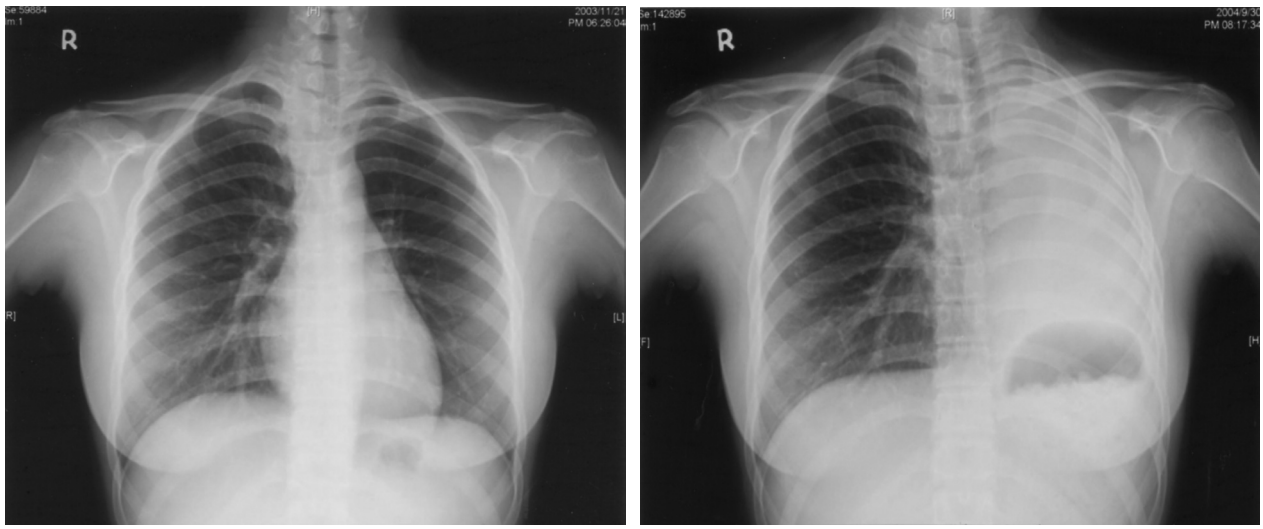

Fig. 1. Left side: Normal chest X-ray film 10 months previous. Right side: Total left lung parenchymal collapse with the mediastinum and heart shifted to the left side.

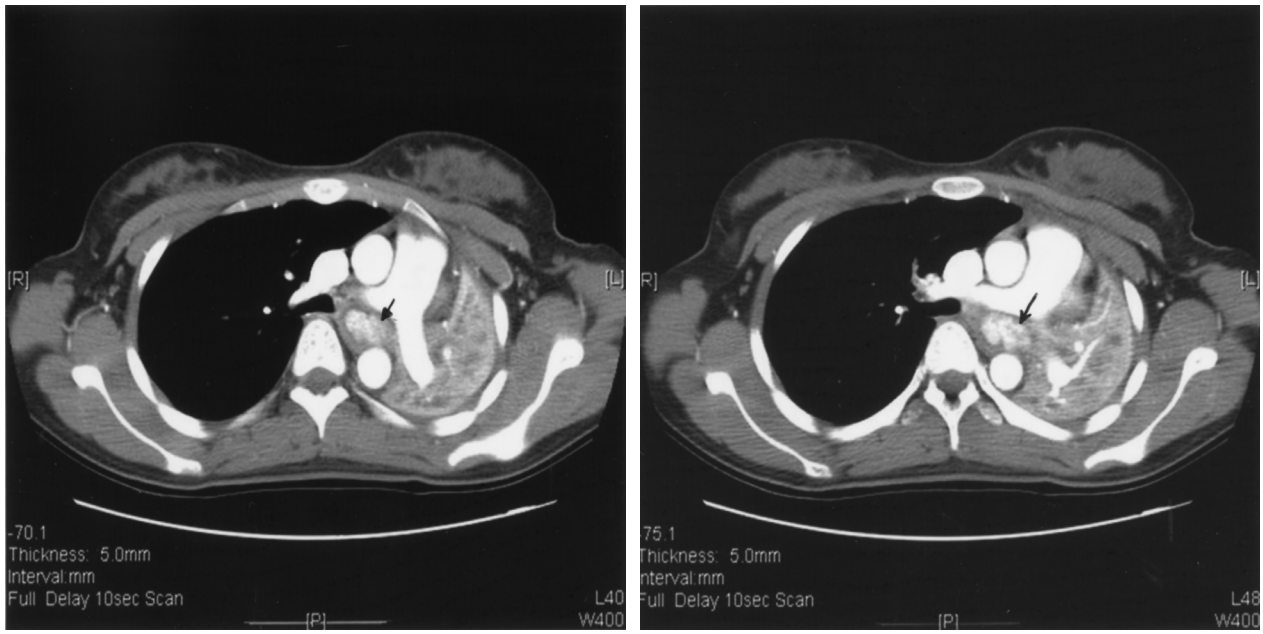

Fig. 2. Chest CT scan revealed an endobronchial hypervascular irregular tumor (arrow) in the left main bronchus causing left lung total collapse.

thing sounds had decreased. No wheezes and no stridor were audible. There was no palpable neck, axillary lymph node, or tracheal deviation. The chest radiograph (CXR) revealed total left lung parenchymal collapse (Figure 1). Further thoracic computed tomography (CT) demonstrated an irregular hypervascular tumor obstructing the left bronchus and causing post-obstructive pneumonia (Figure 2). She was admitted to our internal chest medicine department for further evaluation and management. During hospitalization, the abnormal laboratory examination result revealed leukocytosis (WBC 16.5 x 10^3/μL with a mild left shift), and the spirometry showed severe restrictive ventilatory impairment (FEV1=1.38L, predicted:44%; FEV1/FVC=1.38/1.38=100%; FVC=predicted: 39%). A fibroflexible bronchoscopy was performed and revealed a whitish-appearing tumor protruding from the left main bronchus, with lumen total occlusion. A repeat transbronchial biopsy was done, but the pathology reported no definite diagnosis (Figure 3).

We consulted a chest surgeon, and a rigid bronchoscopy was performed under general anesthesia. The frozen pathology of the tumor biopsy showed only a suspected endocrine tumor, possibly a carcinoid tumor. Since much secretion was noted in the post-obstructive bronchus, a left pneumonectomy was performed, including lymph node dissection. The pathology reported mucoepidermoid carcinoma, low grade, composed of irregular nests of so-called intermediate cells with focal squamoid differentiation intermixed with mucin-secreting cells; mitosis was minimal. Immunohistochemical study of the tumor cells revealed CEA (-), NSE (±), chromogranin (-), S-100 (-) and mucin (+) (Figure 4). No lymph node metastasis was found. The patient recovered well after operation, and was free of any symptoms after undergoing post-operative pulmonary rehabilitation. The spirometry after surgery showed only mild restrictive ventilatory impairment. She is now regularly followed up at our chest OPD.

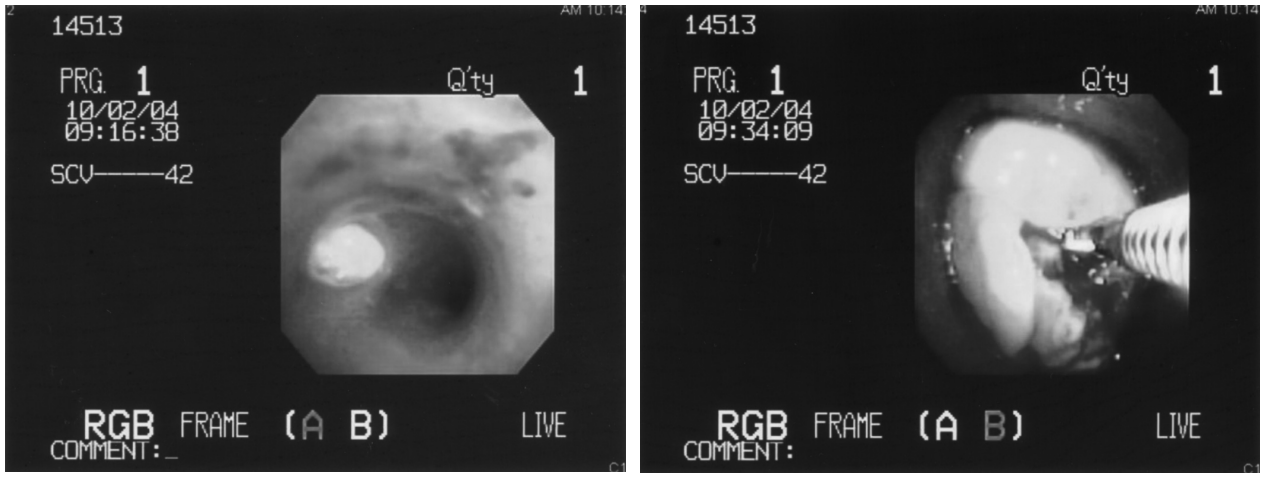

Fig. 3. Bronchoscopic finding showed a protruding whitish tumor in the left main bronchus with total lumen occlusion (left side), and the biopsy procedure (right side).

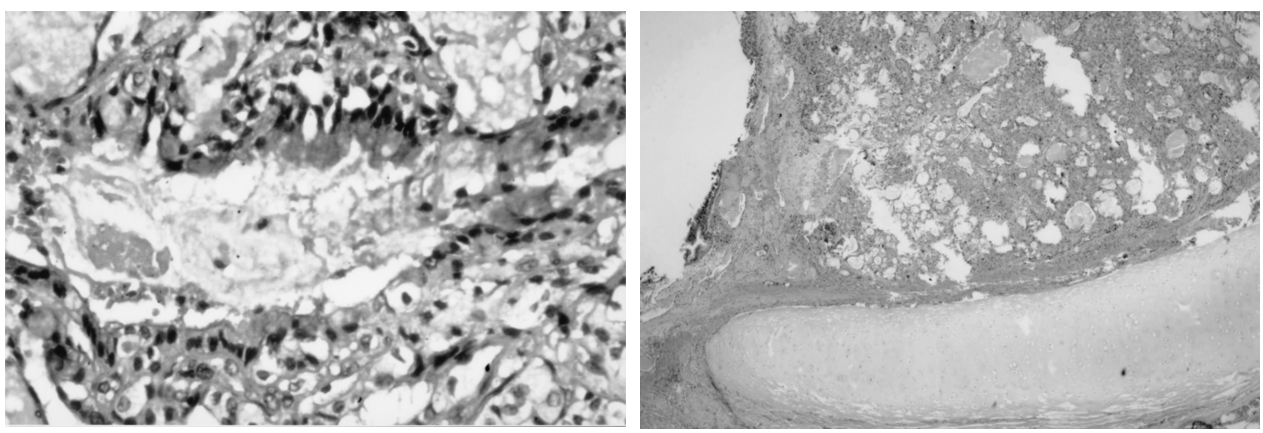

Fig. 4. Left side: The tumor shows a variably solid and cystic appearance with goblet cells forming glandular arrays surrounded by solid nests of polygonal cells exhibiting squamoid differentiation. (H&E, 100X). Right side: Mucicarmin stain reveals abundant cytoplasmic mucin in the goblet cells. (Mucicarmin stain, 100X)

Discussion

Mucoepidermoid carcinoma, adenoid cystic carcinoma, mixed tumors, and carcinoid tumors are distinct histologic types of slow-growing neoplasms that formerly were called bronchial adenomas [2, 5]. All these tumors are usually low-grade malignancies rather than benign neoplasms, so the term bronchial adenoma is a misnomer and should be corrected [2]. The mucoepidermoid carcinoma was believed to arise from the excretory ducts of the submucosal bronchial glands, with a common origin in the salivary glands. A recent cytogenetic study indicated that the identical t (11; 19) (q14-21; p12) may be associated with the mucoepidermoid phenotype [6].

Mucoepidermoid carcinomas are usually located in segmental bronchi and less commonly arise within the trachea, main bronchus, or lobar bronchus. They are usually easily visualized at bronchoscopy, and macroscopically polypoid. On

thoracic CT imaging, the tumors are central, smoothly oval or lobulated, and homogenous; they may contain calcification, and may show mild contrast enhancement [2]. Bronchoscopy is useful for diagnosis. Although CT is of value in assessing central airway disease, important limitations with regard to bronchoscopy have been noted. CT is of limited value, for example, in the detection of endobronchial lesions smaller than 2 to 3 mm. In our previously mentioned case, the CT finding of central airway obstruction with a hypervascular tumor could have been reported to represent either a benign or a malignant tumor.

The most common benign tumor that can be differentially diagnosed in cases like ours is the hamartoma, which accounts for more than 75% of benign lung tumors. Only 5 to 15% of hamartomas present as endobronchial tumors; they are usually diagnosed in patients older than 50, and are twice as common in men as in women. The CT finding always contains fat, soft tissue, and calcification. Nearly 65% of hamartomas can be diagnosed using high-resolution CT, because of visible fat, either focal or diffuse (CT numbers ranging from -40 to -120 HU), or a combination of fat and calcification. [7]

Other common endobronchial neoplasms presenting as hypervascular tumors include bronchogenic carcinoma, endobronchial metastases (kidney, breast, colon, melanoma, and thyroid) and bronchial carcinoid. There is very great difficulty in differentiating the 2 former types of lesions in cases like ours, using only chest CT scan imaging. Biopsy tissue may be needed for proof. Carcinoid tumors account for 1 to 2% of tracheobronchial neoplasms. Typical carcinoid tumors occur most commonly in patients 40 to 60 years of age, and approximately 80% of them occur centrally, in the main, lobar, or segmental bronchi; 1% is intratracheal. In CT imaging, calcification of central carcinoid tumors is seen in nearly 40% of cases. Patients who have central carcinoid tumors associated with bronchial obstruction tend to present at a younger age than patients with peripheral lesions. [7]

In patients with low-grade tumors, as our case, resection of the bronchus, a lobectomy with clear surgical margins, or pneumonectomy with lymph node dissection is usually curative. Advances in minimally invasive surgery have led to a less traumatic approach for the treatment of many chest abnormalities. Video-assisted surgery should be the preferred method to treat these lesions, because the proposed technique is simple, feasible, and as effective as open surgery, with good clinical outcomes and better cosmetic results [8]. This latter advantage is very important, above all, in young and adolescent patients.

Postoperative radiation therapy or chemotherapy is unnecessary in the low-grade variant of these tumors [9]. High-grade mucoepidermoid carcinoma carries a worse prognosis, and must be treated as a non-small cell lung cancer with more radical surgical resection, even if this lesion is known to have a better prognosis than bronchogenic carcinoma. There was no evidence of distant metastasis in our patient, including the bone scan results. The National Comprehensive Cancer Network (NCCN®) practice guidelines in oncology (2004 edition) for LUNG NEURENDO CRINE TUMORS suggests that close observation is indicated for such patients.

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發生在17歲女孩的氣管支氣管惡性黏液類上皮癌—病例報告

李建德　林慶雄　何上芸*　張惠媚**　鄭清源***

發生在氣管、支氣管惡性黏液類上皮癌相當罕見，被歸類為唾液腺型態腫瘤，佔原發性肺癌的0.1~0.2%，其中又分為低度及高度惡性程度。低惡性度生長緩慢，好發於任何年齡層，可以全切除治癒。高惡性度生長較快，可浸潤於唾液腺內並且淋巴或遠處轉移。惡性黏液上皮癌佔腮腺惡性腫瘤的21%，為最常見的腮腺惡性腫瘤，佔舌下腺惡性腫瘤的10%。

我們報告一位17歲健康的高中女生，因斷續乾咳8個月，在診所當感冒治療無法治癒，接著因有胸悶及活動性呼吸困難的症狀求診，胸部X光顯示不明原因左肺完全塌陷，進一步胸部電腦斷層掃瞄檢查顯示左支氣管內有一不規則腫瘤。經軟式支氣管鏡檢查病理切片仍無法診斷出病因，因而會診外科至手術室接受硬式支氣管鏡檢查，冷凍病理切片證實為低度惡性黏液類上皮癌，最後接受左肺完全切除及淋巴節擴清手術。

手術後病患身體恢復良好，並且持續追蹤至今一年，沒有復發或轉移的現象，我們在此回顧以前的病例報告，顯示低度惡性黏液類上皮癌可以因完全手術切除而治癒。*(胸腔醫學* ***2006; 21: 355-361)***

關鍵詞：惡性黏液類上皮癌，氣管支氣管

彰化基督教醫院　內科部胸腔內科　放射線科*　病理科**　胸腔外科***
索取抽印本請聯絡：李建德醫師，彰化基督教醫院　胸腔內科，彰化市南校街135號

Symptomatic Mediastinal Bronchogenic Cyst Mimicking Esophageal Lesion in a Patient with Chronic Cough — A Case Report and Literature Review

Gang-Yu Shen, Kuo-Hwa Chiang, Yao Fong*, Jiunn-Min Shieh

We present a rare case with a presentation of symptomatic bronchogenic cyst mimicking an esophageal lesion in a patient with chronic cough. The patient later suffered from hematemesis. The CXR revealed a middle mediastinal mass with an air-fluid level. The majority of adult patients with bronchogenic cyst are asymptomatic. In this case, the cyst was inflammatory and compressed surrounding organs such as the esophagus and bronchus.

At first, an attempt was made to use video-assisted thoracoscopy to remove the cystic lesion, but this failed. Finally, a right-side thoracotomy was used to excise the cystic lesion, due to its firm adhesion and inflammatory change. We review the related literature and discussed the clinical presentation and management. ***(Thorac Med 2006; 21: 362-368)***

Key words: middle mediastinal mass, bronchogenic cyst

Introduction

The majority of mediastinal bronchogenic cysts remain asymptomatic, especially in adulthood [1].A circular and homogenous mediastinal shadow in a chest radiograph should prompt one to include bronchogenic cyst in the differential diagnosis. The differential diagnosis of mass-like lesions with an air-fluid level on the chest radiographs should include esophageal carcinoma, achalasia, esophageal duplication cysts, bronchogenic cyst, etc. If an air-fluid level is present on the chest radiographs, we should list infected bronchogenic cyst or communication to the respiratory tree in our differential diagnosis. The adherence or communication of the bronchogenic cyst to the adjacent vital organs must be studied before surgical intervention [2].

Video-assisted thoracoscopy is preferred to open thoracotomy for resection. Interestingly, neither size nor mediastinal location were the determining factors for successful thoracoscopic resection. Rather the presence of adhesions and vascular complications determined the need for the more traditional thoracotomy approach [1].

Division of Chest Medicine, Department of Internal Medicine
*Division of Thoracic Surgery, Department of Surgery, Chi Mei Medical Center, Tainan, Taiwan
Address reprint requests to: Dr. Kuo-Hwa Chiang, Division of Chest Medicine, Department of Internal Medicine, Chi Mei Foundation Medical Center, 901, Chung Hua Road, Yung Kang City, 710 Tainan, Taiwan, R.O. C

Case Report

A 45-year-old male had been healthy until he began suffering from productive cough, chest tightness and weight loss of 10 kgs which lasted for more than 3 months. On admission, no fever, chillness, poor appetite, dysphagia or dizziness were found. At first, the patient went to visit our OPD for his cough. The chest examination showed symmetrical expansion and normal vesicular breathing sounds. The chest X-ray revealed a middle mediastinal lesion (Figure 1). Later, he suffered from hematemesis, accompanied with light yellowish sputum at night. So, he was brought to our ER for help. At our ER, the chest X-ray showed a well-defined cystic lesion with an air-fluid level just under the carina (Figure 2).

Chest examination revealed symmetrical expansion and normal vesicular breathing sounds. The chest CT scan revealed a round mass with soft tissue density and air-fluid level. Esophageal lesions were initially considered. Due to a suspicion of esophageal carcinoma, esophageal achalasia or duplication cyst, he was admitted to our ward for further management and evaluation. At that time, he underwent a serial examination. The UGI series (Figure 3) showed a cystic mass (9-10 cm at the widest point) with an air-fluid level in the mediastinum and displacement of the lower esophagus; no evidence of achalasia or a feeding defect was found. The bronchoscopy showed no communication with the adjacent organs and narrowing of the orifice of the RML bronchus due to external compression. A spiral chest CT

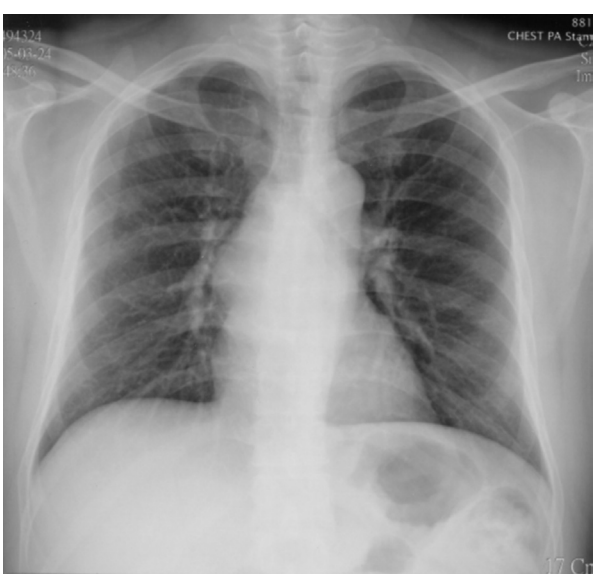

Fig. 1. Chest X-ray showing a middle mediastinal mass.

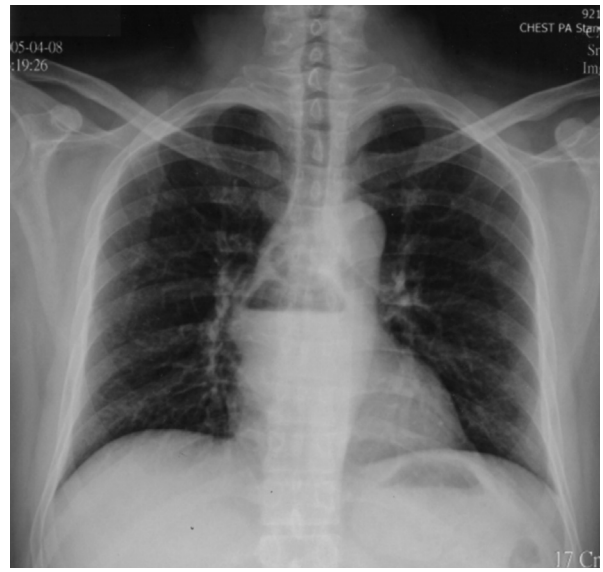

Fig. 2. Chest X-ray showing a middle mediastinal mass with an air-fluid level.

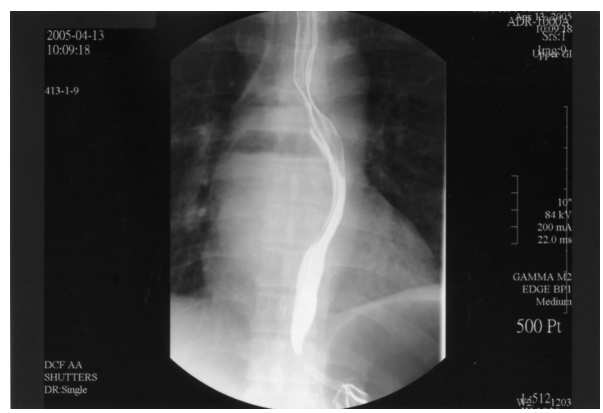

Fig. 3. UGI series shows no evidence of esophageal achalasia or any other defect, except external compression.

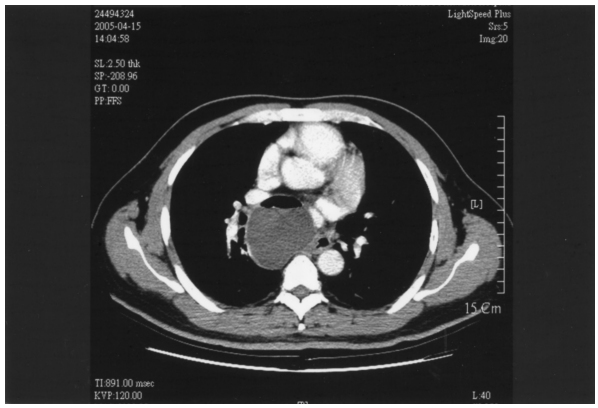

Fig. 4. Chest CT with enhancement revealing a cyst with an air-fluid level just below the carina.

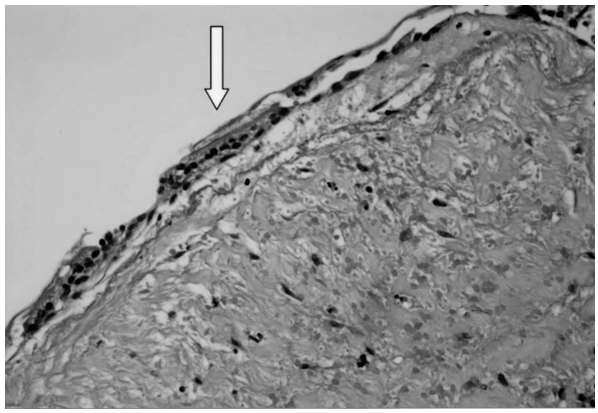

Fig. 5. Histopathology showing a cystic space with the sloughing cystic lining of the ciliated columnar epithelium. (arrow) (Hematoxylin & Eosin stain 400X)

(Figure 4) was performed for an analysis of the cystic characteristics of adhesion or communication to adjacent structures before surgical intervention. Pneumolysis with a mediastinal cyst excision was performed. The surgical findings included a 5x5 cm cystic lesion with brown jelly-like content noted below the carina firmly adhered to the carina, esophagus and pericardium, due to the previous inflammatory change, and easy oozing during pneumolysis. The mediastinal cyst-like lesion was diffuse and dense. Histologic findings (Figure 5) included acystic space with sloughed cystic lining and a ciliated columnar epithelium.

Bronchogenic cyst was later confirmed. The postoperative course was generally smooth except complaints of wound pain. He was discharged in a stable condition.

Discussion

The majority of adult patients with bronchogenic cyst are asymptomatic [1-3]. In symptomatic adults, chest pain and dysphagia are the most common [5]. In this case, the chest X-ray revealed a middle mediastinal lesion. The patient presented with hematemesis and body weight loss of 10 kgs for more than 3 months, so esophageal carcinoma ,esophageal achalasia, and duplication cyst should be ruled out.

Characteristically, the bronchogenic cyst is round or oval in shape. Occasionally, an air-fluid level or peripheral calcification can be found. There will be dense pericystic adhesions to the adjacent structures at the time of acute infection [7]. In our case, the chest X-ray later showed a well-defined cystic lesion with an air-fluid level just under the carina. The cyst became infected and compressed the surrounding organs such as the esophagus, bronchus and pericardium. So, a circular and homogeneous mediastinal shadow in a chest radiograph should prompt the physician to include bronchogenic cyst in the differential diagnosis [3].

Mediastinal bronchogenic cysts have been classified into 5 types: paratracheal, carinal, hilar, paraesophageal, or miscellaneous [1]. The paratracheal and carinal types may produce symptoms such as dyspnea and chest pain, due to compression of the trachea or bronchi. A giant bronchial cyst of the carinal type would be expected to produce left atrial compression [2]. Seventy-two percent of bronchogenic cysts produce some sym-

ptoms, but 90% of mediastinal-type bronchogenic cysts are reported to be asymptomatic [3]. In later childhood or adulthood, bronchogenic cysts are more commonly asymptomatic, but symptoms eventually develop with the increasing size of the cyst. Chest pain, cough and dyspnea are the most common complaints in adults. Some cysts may cause symptoms because of infection or compression of the surrounding organs, such as the esophagus, bronchi and heart. According to Ribet and colleagues, bronchogenic cysts in subcarinal or paratracheal locations were more apt to provoke compression symptoms. Children with narrow or soft airways are vulnerable to compression by expanding cysts [4]. St. Georges *et al*. reviewed 86 bronchogenic cysts and found major complications, such as fistulization with an airway, and ulcerations or hemorrhage in mediastinal cysts [5]. An important issue is that malignancy is associated with bronchogenic cysts [6].

Diagnostically, bronchogenic cysts can be identified on plain chest radiographs in up to two-thirds of cases in any age group. Characteristically, the bronchogenic cyst is round or oval in shape. A well marginated shadow of fluid attenuation in the middle mediastinum is quite suggestive. The radiographic appearance depends on whether the cyst is air-filled, fluid-filled, or air and fluid-filled. An air-filled cyst has the appearance of a pneumatocele. Completely fluid-filled cysts cannot be discriminated from solid masses on plain film. Bronchogenic cysts may not be visible on chest radiographs due to surrounding mediastinal structures and inflammation [7]. In one-half of all bronchogenic cysts, the CT density can vary from a low soft-tissue range to a higher-than-muscle density, likely due to intracystic hemorrhage, protein, or calcium. A contrast CT scan through the region of interest affords a detailed delineation of the relationship of the cyst to the surrounding structures. Computed tomography helps to better define the cyst in terms of fluid content, wall thickness, solitary or multiple nature, location, and other findings. Magnetic resonance imaging is also potentially useful for differentiating problematic soft-tissue-attenuation cysts from mediastinal neoplasia [8].

The fluid found within is mucoid and clear or white, unless hemorrhage has occurred, in which case the contents are thick and brown. Calcium crystals may also be seen. The fluid within bronchogenic cysts is usually a mixture of water and proteinaceous mucus. However, descriptions of the fluid have ranged from a thin, watery liquid to hemorrhagic fluid, and a very viscous, mucoid material. This variability in cystic content is likely responsible for the variability of attenuation seen on CT scans, and signal intensity characteristics seen on MR images [9-10].

Early recognition of these relatively rare lesions would lead to immediate and appropriate surgical intervention. Early surgical intervention is also important, because a definitive histologic diagnosis can only be established by means of surgical extirpation. Some argue that the treatment for bronchogenic cysts is still controversial. Conservative (watch-and-wait) treatment has been advocated in asymptomatic adults or other high-risk patients. Percutaneous catheter drainage or sterile alcohol ablation has been performed in selected cases. In poor surgical candidates, a cyst can be aspirated to confirm a benign diagnosis. Instillation of a sclerosing agent is another therapeutic option. A history of infection, a large cyst size, and adhesions to vital structures, are all factors associated with a higher chance of conversion to thoracotomy [11].

Some clinicians consider that surgery should be performed as soon as such a cyst has been diagnosed, because of the possible occurrence of

complications such as fistula formation, bronchial ulceration, bleeding, or infection. Asymptomatic simple cysts, if observed, have the potential to grow, and can result in higher rates of perioperative complications once they become symptomatic. There is also a rare association of bronchogenic cysts with rhabdomyosarcoma. Symptomatic cysts should be resected (either at thoracotomy or by means of video-assisted thoracoscopy) regardless of patient age, unless surgical risks are unacceptably high [12].

Martinod *et al*. were able to excise 65% of the bronchogenic cysts via thoracoscopy. Interestingly neither size nor mediastinal location were the determining factors for successful thoracoscopic resection. Rather, the presence of adhesions and vascular complications determined the need for the more traditional thoracotomy approach. Martinod and associates have reported a series of 20 patients with mediastinal bronchogenic cysts with whom thoracoscopic resection was attempted. Thirteen cysts (65%) were resected completely by thoracoscopy. Conversion to thoracotomy was effected in the remaining 7 cases due to bleeding (2 cases) and adhesion to vital structures (5 cases). There were no recurrences during a follow-up period [1]. Hazelrigg *et al* reported thoracoscopic removal of mediastinal cysts in 9 patients, of which 7 were bronchogenic cysts. Complete resection was possible in all but 1 patient in whom the cyst wall was adherent to the vital structures[13]. Ribet and colleagues followed up 2 patients with bronchogenic cysts who refused surgery for 15 years, and found that 1 patient remained free of symptoms and the other died of a malignancy of unknown origin. Ribet *et al*. analyzed the operative records and found that the VATS approach was hazardous in 11 % to 30% of patients with bronchogenic cysts because of pericystic adhesions or communication of the cysts with tracheobronchial or esophageal structures [4]. VATS may be an acceptable surgical procedure for patients with mediastinal cysts, which are rarely malignant [13-14].

In summary, a circular and homogenous mediastinal shadow in a chest radiograph should prompt the physician to include bronchogenic cyst in the differential diagnosis. The characteristics of adherence or communication with adjacent structures in cases of bronchogenic cyst must be detailed to rule out adherence to vital organs before surgical intervention.VATS is used preferentially over an open technique for resection.

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一慢性咳嗽成人症狀性縱膈腔支氣管源性囊腫模擬食道病變—一病例報告及文獻回顧

沈耿裕　江國華　馮瑤 *　謝俊民

我們報告一例，罕見慢性咳嗽成人症狀性縱膈腔支氣管源性囊腫模擬食道病變病例。後來伴有吐血發生，此時X光顯示中縱膈腔質塊伴含有氣液平面。大部分支氣管源性囊腫成人是無症狀。我們這例支氣管源性囊腫有發炎性且壓迫鄰近食道及支氣管。起初影像輔助式胸腔手術試圖取出囊腫卻失敗。最後用右側胸廓切開術，完全切除了，因穩固沾粘及發炎變化的囊腫。我們回顧了相關文獻，討論支氣囊腫臨床表現及治療方法。*(胸腔醫學* ***2006; 21: 362-368)***

關鍵詞：中縱膈腔質塊，支氣管源性囊腫

台南奇美醫院內科部　胸腔內科，外科部　胸腔外科 *
索取抽印本請聯絡：江國華醫師，台南奇美醫院內科部　胸腔內科，台南縣永康市中華路 901 號

Wegener's Granulomatosis Presenting as Breast Masses in a Patient with Sjogren's Syndrome

Chun-Yu Lo, Chih-Wei Wang, Yueh-Fu Fang, Meng-Heng Hsieh, Po-Jui Chang, Fu-Tsai Chung, Chih-Hsia Kuo, Horng-Chyuan Lin

Wegener's granulomatosis is a necrotizing vasculitis. The etiology is not known. Although it may involve any organ, Wegener's granulomatosis predominantly involves the upper and lower respiratory tracts together with glomerulonephritis. Herein, we report the case of a 55-year-old woman with Sjogren's syndrome and Wegener's granulomatosis which unusually presented as breast masses. Her breast and pulmonary lesions were successfully treated with high-dose corticosteroid and cyclophosphamide. ***(Thorac Med 2006; 21: 369-375)***

Key words: wegener's granulomatosis, breast, sjogren's syndrome, anti-neutrophil cytoplasmic antibody

Introduction

Wegener's granulomatosis (WG) is a chronic multisystem vasculitis affecting mainly the upper and lower respiratory tracts together with glomerulonephritis. The condition was first described by Peter McBride in 1897 [1]. The pathological-anatomical picture was described by Klinger in 1931 [2], and a detailed description was reported by Friedrich Wegener in 1936 [3]. Pulmonary manifestations of WG ranged from asymptomatic nodules, to fleeting infiltrates, and alveolar haemorrhage [4]. A breast mass was considered an unlikely feature of WG, and its presence was regarded as an alternative diagnosis. Our patient was unusual in that the breast was the site of WG involvement. To our knowledge, this is also the first reported case of a patient with Sjogren's syndrome and cytoplasmic-antineutrophil cytoplasmic antigen (c-ANCA).

Case Presentation

A 55-year-old woman with progressive exertional dyspnea and hemaptysis was referred to our hospital for a survey of nodular lesions in her lungs and breasts. The patient had suffered from intermittent fever and chills since December 25, 2004, as well as productive cough with whitish sputum and intermittent exertional dyspnea. A body weight loss of 10 kg developed in the month before admission. She had been admitted to another hospital on January 27, 2005 for leg swelling. There was neither gross hematuria nor a decrease in the amount of urine. After diuretic therapy, the swelling was improved. However,

Department of Thoracic Medicine, Chang Gung Memorial Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Horng-Chyuan Lin, Department of Thoracic Medicine, Chang Gung Memorial Hospital, #5 Fushing Street, Gueishan Shiang, Taoyuan, Taiwan

the chest radiographs revealed several nodules in bilateral lung fields. She was given intravenous systemic antibiotics. The chest radiographs did not show any improvement. Subsequently, the patient developed several painless, movable, nodular lesions within the bilateral breasts (1-3 cm, right * 2 and left * 1), without erythematous change or local heat on the overlying skin. Right neck swelling was also noted. After excising 1 of the nodular lesions in her right breast, she was transferred to our hospital on February 17, 2005 for further management.

The patient was married and had 1 daughter. She had undergone aortic valve replacement and mitral valve replacements due to valvular heart disease. She also had a history of atrial fibrillation and gastric ulcer.

On arrival, the patient's temperature was 36.5^{o}C, the pulse rate 89 beats per minute, and the respiratory rate 19 breaths per minute. The blood pressure was 140/65 in both arms, and the arterial oxygen saturation was 98% while the patient was breathing ambient air. Initial laboratory tests revealed the following findings: normocytic anemia without leukocytosis, mild elevation of AST and ALT, and an albumin-globulin ratio of 0.43, with polyclonal increase of gammaglobulin. The serum creatinine and urinary status were normal. The levels of anti-nuclear antibodies and complement factor C3 and C4 were normal. Several test findings for tumor markers, i.e. CA 19.9, CA 15.3, CEA, AFP, SCC and CA-125, were unremarkable. The chest radiograph obtained on the 1st hospital day showed metallic wires fixation in the sternum, mitral valve prosthesis, multiple nodes in the bilateral lung fields and a blunting of the costophrenic angle on the right (Figure 1). A 2-dimensional transthoracic echocardiography on the 3rd hospital day showed normal wall motion without vegetation. A computed

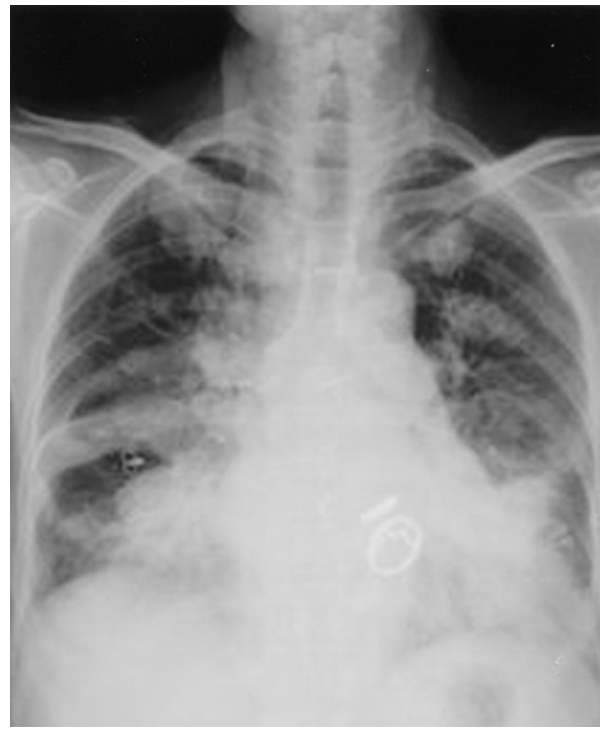

Fig. 1. Chest radiograph before treatment revealing metallic wires fixation in the sternum, mitral valve prosthesis and multiple nodular lesions in the bilateral lung fields.

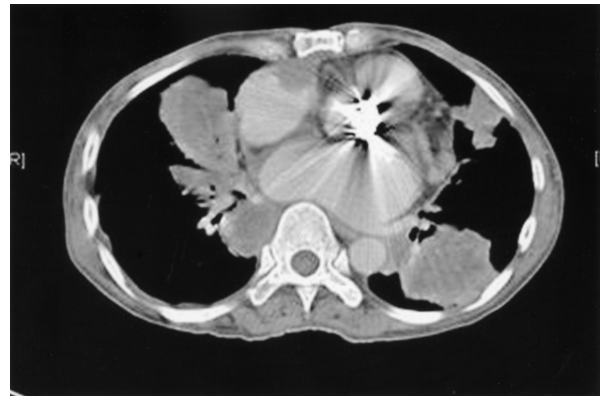

Fig. 2. Computed tomograph before treatment revealing multiple opacities in bilateral lungs.

tomography on the 5th hospital day showed opacities in the bilateral maxillary sinuses, and multiple consolidation in the bilateral lungs, with unremarkable findings in the bilateral kidneys (Figure 2). A bronchoscopic study performed on the 13th hospital day showed mucosa infiltration in the

right bronchus intermedius and right middle bronchus, which easily bled after touching. The endobronchial ultrasonography showed a lesion with a thickened peribronchial wall and hyperdensity in RB4 and RB5 (Figure 3). The transbronchial lung biopsy showed necrosis and granulomatous inflammation with negative acid fast stain findings (Figure 4). The nasopharynx biopsy on the 21st hospital day also showed granulomatous inflammation. Another transbronchial lung biopsy from RB9 done on the 23th hospital day yielded granulomatous inflammation and a CD4/CD8 ratio of 0.36. Therefore our pathologists reviewed the breast specimens from the previous hospital, which showed necrotizing granulomatous vasculitis with marked infiltration of neutrophils and other inflammatory cells in the breasts. None of the special stains showed a micro-organism (Figure 5). The serum anti-neutrophil cytoplasmic antibody, using the indirect immunofluorescence method, showed a positive finding for C-ANCA, but a negative finding for P-ANCA.

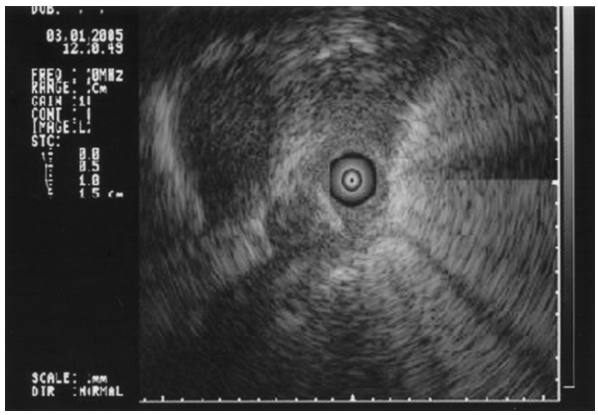

Fig. 3. Endobronchial ultrasound showing thickening of the peribronchial wall with an adhered vessel, a high density lesion in the lower field, and suspected granulomatous tissue.

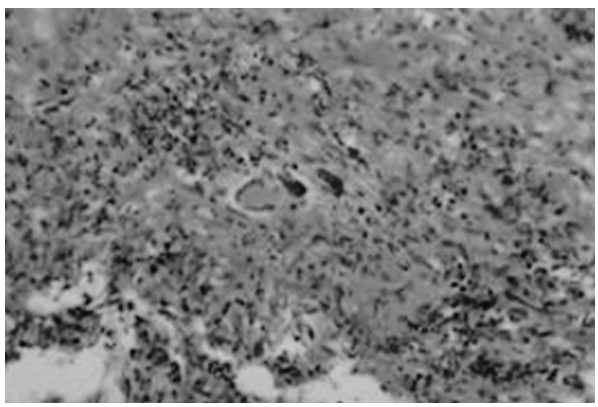

Fig. 4. Lung biopsy disclosing necrosis and granulomatous inflammation (H&E, 40X).

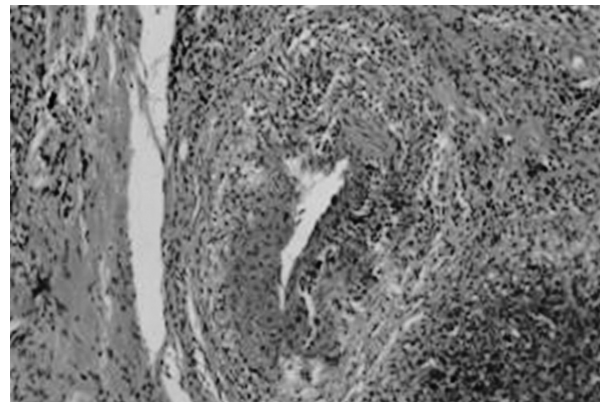

Fig. 5. Breast biopsy disclosing necrosis, granulomatous inflammation, and vasculitis (H&E, 100X).

The patient also mentioned dry mouth and dry eyes. She denied arthralgia, skin rash and photosensitivity. Saliva production was decreased (0.86 g/2 minutes, normal range: >3 g/2 minutes). The anti-SSA was positive (14.1 U/ml) and the anti-SSB was negative. The anti-cardiolipin immunoglobulin G was positive (25.2 gpl units/ml) but immunoglobulin M was negative.

On the basis of the features described, a diagnosis of WG involving the nasopharynx, lungs and breast tissue, combined with Sjogren's syndrome, was made. The masses in the breast and neck regressed before medical treatment was applied. Systemic prednisolone was started at a dose of 40 mg daily on the 26th hospital day. Cyclophosphamide was not given. The chest radiograph revealed regression of the pulmonary

nodules. The patient was discharged on the 37th hospital day in stable condition.

On the 60th day after discharged, the patient experienced an episode of falling accident followed by a right subdural hematoma and subarachnoid hemorrhage. She was sent to another hospital, and a tracheostomy was created because of a poor cough function after craniotomy. Although the patient was underwent warfarin treatment for the prosthetic valve, WG of the brain could not be excluded. Therefore, cyclophophamide (50 mg/day) was prescribed, with predniosolone thereafter. Seven months after diagnosis of WG and Sjogren's syndrome, the chest film disclosed only a few small nodular lesions in the bilateral lower lung fields. Her renal function was normal and there were no more breast lesions.

Discussion

WG is distinct for the diversity of locations, 12 in all (breast, kidney, mediastinum, lungs, central nervous system, orbit, pancreas, Eustachian tube, pleura, heart, gingiva, retroperitoneum), of the tumor-like lesion presentations [5]. Respiratory involvement is a common manifestation of WG; however, breast manifestations, both as presenting events or during the course of disease, are rare [4]. In a comprehensive review of previous reports, only few cases with breast WG were seen. The first case of WG of the breast was reported in 1965 by Kraus, who described a 62-year-old woman with painful induration in a scar on the right breast; the histopathology showed granulomatous inflammation with leucocytes in the center of the granulomas [6]. Twenty cases with WG in the breasts have been reported in the last 4 decades [7-11], predominantly presenting with a unilateral mass. The average age at diagnosis was 47.1 ± 10.7 years. Although WG influences males and females equally [12], there has been only 1 case of breast involvement in a male [11]. However, to the best of our knowledge, this unusual presentation of breast WG and positive c-ANCA in a patient with Sjogren's syndrome has not been reported before.

As far as we can determine, only WG, giant cell arteritis (GCA) and polyarteritis nodosa (PAN) have been described in vasculitis of the breast [5]. WG usually presents with both extravascular granulomatous inflammation and necrotizing vasculitis. The vessels in GCA exhibit nodular thickening with a reduction of the lumen, granulomatous inflammation, multinucleated giant cells, and fragmentation of the internal elastic lamina. PAN is characterized by transmural inflammation of the arterial wall, fibrinoid necrosis, and fibrous thickening of the vessel wall [13].

Merkel *et al.* [14] demonstrated that WG patients are at increased risk for venous thrombotic events (VTEs). de Leeuw *et al*. [15] also reported that ANCA can activate endothelial cells and increase serum levels of soluble intracellular adhesion molecule 1, vascular cell adhesion molecule 1 (VCAM-1), and E-selectin. Therefore, endothelial cell dysfunction and eventually atherosclerosis can be expected to occur in WG. Our case suffered an episode of CNS bleeding (subdural hematoma and subarachnoid hemorrhage) after discharge. Although the cause may have been the falling accident, CNS WG cannot be excluded. Therefore, our results may have several clinical implications and offer suggestions for the care of WG patients, as well as a future research agenda. At a minimum, clinicians caring for patients with WG should now maintain a heightened awareness of the possible risks for VTE, including deep venous thrombosis or pulmonary embolism, as well as CNS thrombosis and hemorrhage.

Sjogren's syndrome is characterized by ocular symptoms of inadequate tear production, oral symptoms of decreased saliva production, and occular signs of corneal damage due to inadequate tearing. The histopathology of the salivary gland demonstrates foci of lymphocytes. Examinations indicate an impaired salivary gland function and the presence of autoantibodies (anti-Ro/SSA, anti-La/SSB, or both) [16]. A relationship among antineutrophil cytoplasmic antigens (ANCA), WG, microscopic polyangiitis (MPA), and "renal-limited" vasculitis (pauci-immune glomerulonephritis without evidence of extrarenal disease) has been reported [17-18]. Patients with Sjogren's syndrome develop multiple autoantibodies. Some patient with Sjogren's syndrome (6.8% to 13.1%) showed positivity for p-ANCA, but not cytoplasmic-ANCA [19-21]. Antibodies against proteinase 3 (PR3) and myeloperoxidase (MPO) are also useful in clinical practice. However, positivity for anti-PR3 and anti-MPO in such patients is rare. Two Mexican patients were reported to have atypical ANCA: these 2 atypical ANCA presentations became c-ANCA when paraformaldehyde fixation was applied, but ELISA findings showed that the 2 patients had antibodies against MPO, and no patient had antibodies against PR3 [22]. This may be an epiphenomenon of polycolonal B-cell activation, or may be due to WG. Therefore, the positivity of c-ANCA in our patient may have been caused by WG and not Sjogren's syndrome.

In summary, WG is a granulomatous necrotizing vasculitis. Although lesions are limited to the respiratory tract, lung and kidney in most cases, it may develop in other organs, including the breast and central nervous system. In addition to breast cancer with multiple metastasis, systemic vasculitis should be included in the differential diagnosis when a breast mass coexists with multiple nodular lung lesions.

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韋格納氏肉芽腫及舍格蘭氏症候群併乳房腫塊：病例報告

羅君禹　王志偉　枋岳甫　謝孟亨　鍾福財　張博瑞　郭志熙　林鴻銓

韋格納氏肉芽腫是一種壞死性血管炎。其病名尚不明。雖然此病也可能影響到其他器官，但主要仍以上下呼吸道及腎絲珠腎炎為主。此處我們提出一個55歲罹患韋格納氏肉芽腫及舍格蘭氏症候群的女性，其特殊臨床表現為乳房腫塊。她的乳房及肺部病灶在使用高劑量類固醇及環磷酰胺後成功控制。*(胸腔醫學 **2006; 21: 369-375**)*

關鍵詞：韋格納氏肉芽腫，乳房，舍格蘭氏症候群，抗嗜中性球細胞質抗體

林口長庚紀念醫院　內科部胸腔科
索取抽印本請聯絡：林鴻銓醫師，林口長庚紀念醫院　內科部胸腔科，333 桃園縣龜山鄉復興街5號

Complicated Hemothorax after Administration of Aspirin, Dipyridamole and Nadroparine for Brain Infarction — A Case Report

Chien-Ming Chu, Huang-Pin Wu, Wen-Bin Shieh*, Chung-Ching Hua

A 75-year-old man arrived at the Keelung Chang-Gung Hospital emergency department due to a choking episode. CPR was successfully performed. A chest radiography done afterward revealed pneumonia located in the left lung, with no evidence of rib fracture. The patient remained unconscious for 7 days after our administration of CPR. The attending neurologist diagnosed a brain infarction, for which aspirin, dipyridamole and nadroparine were prescribed. Progressive ecchymosis on the left forearm and hemothorax in the left chest developed 6 days after administration of ASA and LMWH, resulting in a 21.6% decrease in hematocrit. The hemothorax required tube thoracostomy and a blood transfusion. Aspirin, dipyridamole and nadroparine were discontinued and the hemothorax did not recur. The possibility of complicated hemothorax must be considered in patients for whom low molecular weight heparin, aspirin, and dipyridamole are concurrently prescribed. ***(Thorac Med 2006; 21: 376-381)***

Key words: hemothorax, nadroparine

Introduction

Nadroparine is a form of low-molecular-weight-heparin (LMWH). LMWH is used in prophylaxis and in the treatment of thromboembolic events in high-risk patients, such as those in a perioperative period or suffering from pulmonary embolisms or brain infarctions [1]. Combined with aspirin, it is used to treat unstable angina and non-Q myocardial infarctions [2]. Currently, no laboratory test is able to measure anticoagulation levels with adequate precision, due to the fact that patients with LMWH typically register normal prothrombin and activated partial thromboplastin times (PT and aPTT, respectively) [3].

Bleeding is rare in the treatment of LMWH. A study of treatment experience with ischemic stroke found both systemic and central nervous system (CNS) hemorrhagic transformations to be rare, and the result of treatment with nadroparine to be similar to treatment with a placebo (10/203 [4.9%] vs. 9/105 [8.6%]) [4]. Another randomized study comparing unfractionated heparin

Division of Pulmonary Medicine, Department of Internal Medicine, Chang-Gung Memorial Hospital, Keelung, Taiwan, R.O.C.; *Department of Internal Medicine and Department of Respiratory Care, Medical College, Chang Gung University, Taoyuan, Taiwan
Address reprint requests to: Dr. Chung-Ching Hua, Division of Pulmonary Medicine, Department of Internal Medicine, Chang-Gung Memorial Hospital, 222, Mai-Chin Road, Keelung 204, Taiwan, R.O.C.

to nadroparine in the treatment of venous thrombosis showed that side effects accompanied by major bleeding occurred in 4 patients treated with standard heparin (2%) and 1 patient treated with nadroparine (0.5%) [5]. A similar rate of bleeding (1.5%) was found when LMWH was prescribed in treatment of unstable angina and silent ischemia [6]. Our research indicates that no case of hemothorax resulting from LMWH treatment has yet been reported [7].

Hemothorax is often associated with penetrating chest trauma, blunt chest trauma, frank bleeding into the pleural space, and hematologic disorders [8]. All delayed hemothoraces occurred in patients who evidenced bony thoracic injuries at the time of their hospital admission [9], and, as stated above, there has been no case of hemothorax developing after LMWH treatment. A search of the literature on MEDLINE returned 1 case that reported delayed traumatic hemothorax following treatment of a coronary stent with concurrent rib fractures using ticlopidine and aspirin [10], and no case of LMWH-induced hemothorax.

We report herein our experience with a patient who underwent CPR and did not have radiographically evident rib fracture, and who, 6 days later, developed hemothorax due to the administration of aspirin, dipyridamole and nadroparine. We suspect that the hemothorax may have resulted from LMWH use.

Case Report

A male, a 75-year-old retired coal miner, was admitted during the morning to our emergency ward suffering from a choking episode. Physical examination showed a chronically ill-looking man with a body temperature of 36.5°C, respiratory frequency of 20 breaths/minute, pulse rate of 123 beats/minute, and blood pressure of 181/118 mmHg. Acute hypoxemic respiratory failure and pulseless electroactivity developed soon after admission. He received intubated mechanical ventilation and cardiopulmonary resuscitation, which successfully revived vital signs. A second physical examination uncovered a bilateral and coarse breathing sound and no palpable rib fracture. Laboratory evaluation of the peripheral blood revealed the following: WBC count, 16600/uL, with segments, 91%; hematocrit, 45.3%; and platelet count, 179x10^9/uL. A post-resuscitation chest X-ray (CXR) (Figure 1a) indicated optimal position pneumonia in the left lower lobe with no evidence of rib fracture. The follow-up CXR after 3 days of CPR still showed left lower lung pneumonia, with no evidence of pleural effusion (Figure 1b). Due to persistent drowsiness 7 days following resuscitation, and despite the lack of neurological signs, we performed a brain computed tomogram, which revealed multiple infarctions. On the advice of the attending neurologist, we administered nadroparine 3800 IU q12h, aspirin 100 mg qd, and dipyridamole 25 mg tid to treat the thromboembolic event. The vital signs

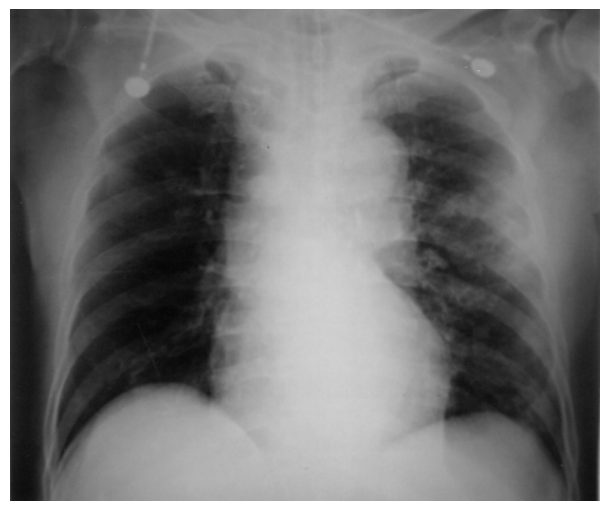

Fig. 1a. Chest radiograph shows pneumonia in the left lower lobe with no evidence of rib fractures after cardiopulmonary resuscitation.

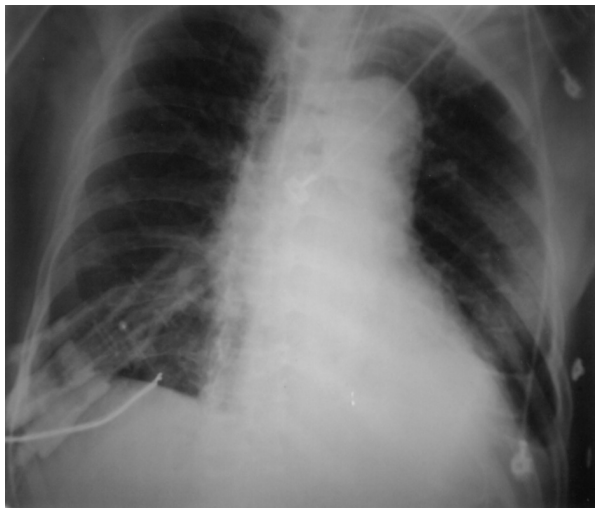

Fig. 1b. Chest radiography after 3 days of CPR shows pneumonia in the left lower lobe, without significant pleural effusion.

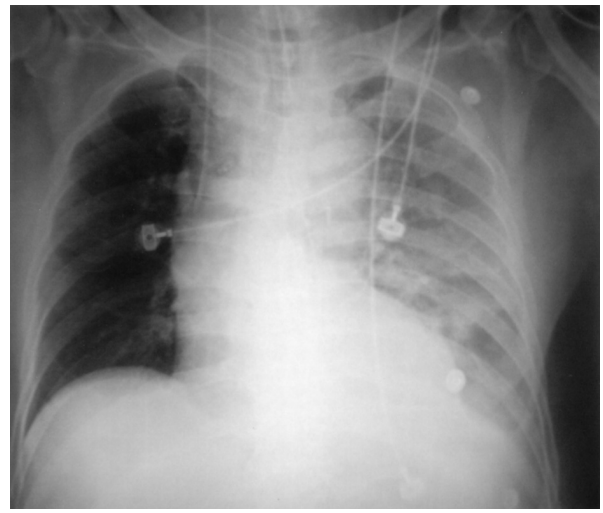

Fig. 2. Chest radiograph after 6 days' administration of aspirin, LMWH and dipyridamole shows left pleural effusion.

were stable without an obvious change in blood pressure for 6 days. Progressive ecchymosis on the left forearm developed, and hematocrit decreased from 40.3% on day 4 and to 21.6% on day 6 after administering antiplatelet drugs and anticoagulants. The patient's platelet count was 214000/uL, and the chest radiograph (Figure 2) showed left pleural effusion. The emergency thoracocentesis of the left chest revealed bloody pleural effusion. The analysis of the pleural effusion revealed a hematocrit level of 12.5%, an RBC count of 1210000/uL, and a WBC count of 1212/uL, with a differential count of 25% neutrophils, 6% lymphocytes, and 69% monocytes. A measure of blood hematocrit taken the same day indicated a level of 21.6%. Gram's stain and culture results for the pleural effusion were negative.

We immediately discontinued the use of nadroparine, aspirin and dipyridamole. Blood transfusion and tube thoracostomy with closed drainage were performed. The left pleural effusion resolved and never re-accumulated.

Discussion

We report our experience with a patient who developed complicated hemothorax 6 days following treatment with a combination of aspirin, dipyridamole and nadroparine. To our knowledge, no report has been published to date describing this rare nadroparine complication. The fact that this complication was observed without the presence of radiographically-obvious rib fractures makes it even more unusual.

During resuscitation, while chest compression risks can be minimized by proper hand positioning, complications can occur even when chest compression is performed properly. Such complications can include rib fractures, fracture of the sternum, separation of the ribs from the sternum, pneumothorax, hemothorax, lung contusion, laceration of the liver and spleen, and fat embolism [11].

Hemothorax associated with rib fractures usually follows within hours of experiencing a trauma, with a delay in presentation ranging from 18 hours to 6 days (mean: 3.06 days) [9]. A delay

in presentation of more than 7 days, as in our case, is extremely rare. Only about 50% of rib fractures are detectable upon examination of plain posteroanterior chest films. However, most can be detected during a physical examination [12]. In our patient, there was no finding of rib fractures during the physical examination. Trauma following CPR has been documented in numerous studies [13]. Autopsies of 705 patients who died after in-hospital CPR demonstrated rib fractures (32%), sternal fractures (21%), anterior mediastinal hemorrhages (18%), hemopericardium (8%), cardiac or great vessel ruptures (4%), pneumothorax (3%), hemothorax (1%), liver lacerations (2%), and other abdominal injuries (1%) [13]. Since neither the radiographic studies (Figures 1a and 1b) nor the physical examination detected rib fractures in our case, traumatic hemothorax caused by CPR was excluded. In a large scale randomized, placebo-controlled, double-blind trial comparing aspirin, dipyridamole and their combination in the prevention of secondary stroke, aspirin alone (8.2%) or combined with dipyridamole (8.7%) caused more frequent bleeding events than either the placebo (4.5%) or dipyridamole alone (4.7%) [14]. Dipyridamole alone did not result in significantly more bleeding events than those experienced with placebos. The bleeding was most commonly reported as epistasis, proctorrhagia, melena, hematuria, hematemesis, and purpura, but no hemothorax has been reported.

Patients with acute ischemic stroke presenting within 48 hours of symptom onset should be given aspirin (160 to 325 mg/day) to reduce stroke mortality and decrease morbidity, and LMWH may be considered for deep vein thrombosis prophylaxis in at-risk patients with acute ischemic stroke [15]. The International Stroke Trial, which randomized patients with acute ischemic stroke to treatment with aspirin (300 mg), subcutaneous unfractionated heparin (5000U bid or 12500U bid), or both, indicated a higher risk of extracranial bleeding in the unfractionated heparin plus aspirin group as compared to the aspirin only group [16]. Nadroparine, compared to unfractionated heparin, has a lower rate of occurrence of major bleeding [5]. The concurrent use of aspirin, dipyridamole and nadroparine, as in our case, may lead to major bleeding [14, 17].

Complicated hemothorax associated with aspirin, dipyridamole, and heparin following bony thoracic injury is theoretically possible, but has not been reported in the literature. In this case, we suspected that the use of nadroparine, aspirin, and dipyridamole resulted in the appearance of a massive hemothorax weeks later, which calls attention to the importance of a careful administration of anticoagulants for conditions such as acute myocardial infarction and brain infarction.

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心肺復甦術及以 Aspirin 、 Dipyridamole 、 Nadroparine 治療腦梗塞之後所造成的延遲性血胸—病例報告

朱建民　吳黃平　謝文斌 *　花仲涇

一位七十五歲男性病患因嗆到而被送到基隆長庚醫院急診室。在施行心肺復甦術後，此病患成功被救回。接下來所拍攝的胸部 X 光片顯示除左側肺炎外，並無肋骨骨折。在施行心肺復甦術後，此病患七天仍未清醒。神經內科醫師診斷為腦梗塞，於是我們給予 Aspirin 、 Dipyridamole 、 Nadroparine 治療。六天後，左前臂出現瘀斑，產生左側血胸，紅血球比容計下降到 21.6% ，需要胸管引流及輸血。抗凝血藥物立刻被停止使用，而血胸也不再發生。對於合併使用 Aspirin 、 Dipyridamole 、 Nadroparine 的病患，必須考慮併發血胸的可能性。*(胸腔醫學 **2006; 21: 376-381**)*

關鍵詞：血胸， nadroparine

基隆長庚紀念醫院　胸腔內科，* 長庚大學醫學院　內科暨呼吸照護學系
索取抽印本請聯絡：花仲涇醫師，基隆長庚紀念醫院　胸腔內科，基隆市麥金路 222 號

Squamous Papilloma and Papillomatosis of the Airway — A Report of 3 Cases

Kang-Cheng Su, Chong-Chen Lu, Reury-Perng Perng

Squamous papillomatosis of the airway is an uncommon disease. One of its common characteristic features is the frequent recurrence and extension of the warty growth of the lesions. Squamous papilloma is rare. It may occur in the upper to lower airway, and is usually seen in male adults who smoke. Complete resection of the lesions is the key to preventing their spread and recurrence. Airway obstruction and malignant transformation are the most severe complications with frequent recurrence. We report 3 cases with airway involvement. Case 1, a 45-year-old female, was diagnosed to have a solitary squamous papilloma in the trachea. She underwent complete resection of the tumor, and has enjoyed an event-free life in the 14 months following treatment, up to this writing. Case 2, a 16-year-old girl, and Case 3, a 52-year-old male, had suffered from recurrent laryngeal papillomatosis since childhood, and underwent tracheostomy to keep the airway patent, within 1 and 2 years, respectively, after the onset of the disease. Case 3 developed squamous cell carcinoma 48 years after the onset of the disease. We discuss the cases and also review the relevant literature. ***(Thorac Med 2006; 21: 382-391)***

Key words: squamous papillomatosis, recurrent respiratory papillomatosis, solitary squamous papilloma, human papillomavirus

Introduction

Squamous papillomatosis (SP) in the airway is an uncommon disease with a characteristic warty growth. It may grow on any part of the body, including the skin, the breast, the aerodigestive tract, the genitourinary tract, etc. In children, laryngeal SP is the most common benign tumor in the upper airway. The most important etiology of SP is the human papillomavirus (HPV) family, and contact transmission is the most likely route. One of its notorious features is frequent recurrence, developing as a juvenile onset recurrent respiratory papillomatosis (JORRP) in children, and adult onset recurrent respiratory papillomatosis (AORRP) in adults. It may subsequently invade the tracheobronchial tree and even the pulmonary parenchyma. In contrast, squamous papilloma is a rare benign tumor in the airway and always seen in adults. It usually occurs as a solitary tumor and may be distributed from the larynx to the lung. It affects mainly middle-aged male smokers and is occasionally associated with HPV infection. The key to treating both papillo-

Department of Chest Medicine, Taipei-Veterans General Hospital, Taipei, Taiwan, R.O.C.
Address reprint requests to: Dr. Chong-Chen Lu, Department of Chest Medicine, Taipei-Veterans General Hospital, 201, Sec.2, Shih-Pai Road, Taipei City 112, Taiwan, R.O.C.

matosis and solitary papilloma is complete resection of the lesions. We herein report 3 cases with airway involvement and discuss their different outcomes.

Case Reports

Case 1

A 45-year-old woman, a non-smoker, had suffered from progressive exertional dyspnea for 3 months when she visited our clinic for help. Physical examinations and chest radiograph (CXR) revealed negative findings. To rule out the possibility of asthma, she received a pulmonary function test which disclosed the pattern of a suspicious fixed upper airway obstruction (Figure 1). Actual forced expiratory volume in the first second (FEV_1) and forced expiratory capacity (FVC) were 1.75 liters and 2.41 liters, respectively, equal to 72%. Then, bronchoscopy disclosed an ulcerative tumor in the trachea, about 2 cm below the vocal cord (Figure 2, 3). The pathological report of the transbronchoscopic biopsy revealed squamous papilloma, composed of a papillary proliferation of the squamous epithelium with heavy acute inflammation. So she underwent a segmental resection of the tracheal tumor, about 1.5 cm in length, with end-to-end anastomosis. At 14 months after the operation, no recurrence had been identified.

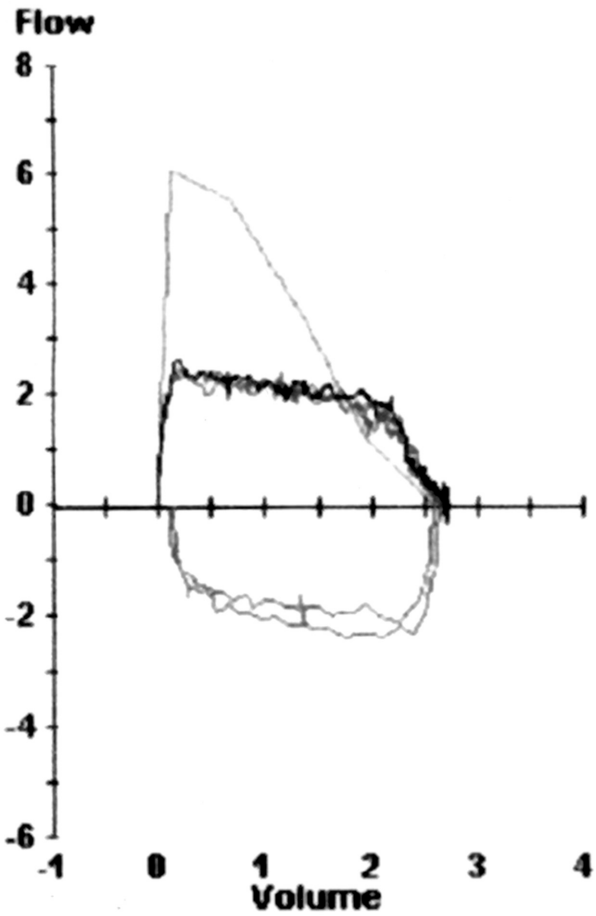

Fig. 1. The flow-volume curve disclosing a limitation of both inspiratory and expiratory flow, which was suggestive of fixed upper airway obstruction.

Case 2

A 16-year-old girl, with no history of smoking, had suffered from weak crying sounds since

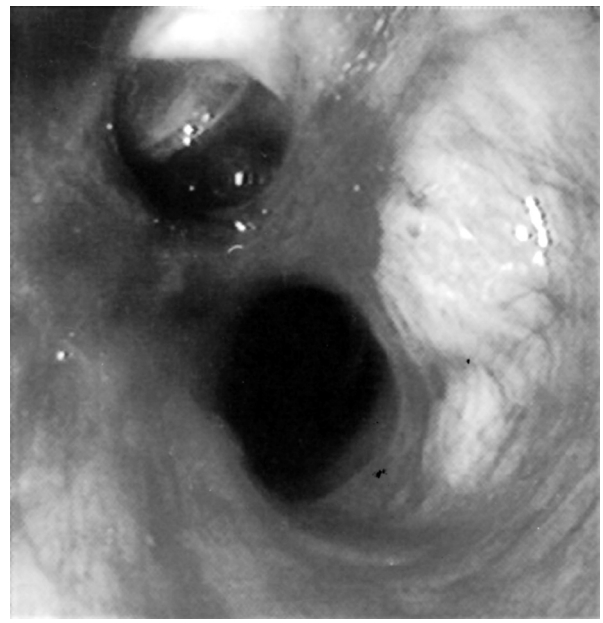

Fig. 2. The bronchoscopic finding revealing an ulcerative wound with narrowing of the trachea about 2 cm below the vocal cord.

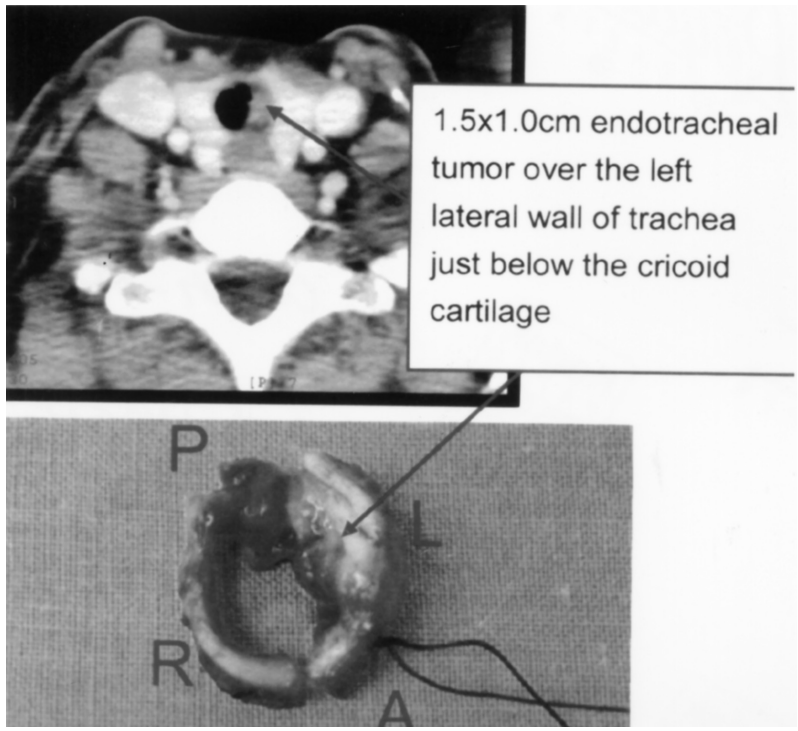

Fig. 3. Chest CT showing an endotracheal tumor on the left lateral tracheal wall, resulting in narrowing of the upper tracheal lumen (upper panel). A section of the tracheal lesion after surgical resection (lower panel).

the age of 10 months. She visited an ear, nose, and throat clinic and laryngeal SP was diagnosed. At the age of 3 years, she underwent tracheostomy because of frequent recurrence of the tumor with upper airway obstruction, despite frequent microscopic laryngeal surgery (MLS) plus carbon dioxide (CO_2) laser ablation. At the age of 16 years, she received a partial laryngectomy because of wound infection and bleeding after MLS. At pre-puberty, she received an average of 5.9 CO_2 laser ablations per year. In her puberty, she underwent about 1.8 CO_2 laser ablations per year. No malignant change had been identified up to her being lost to follow-up at the age of 16 years.

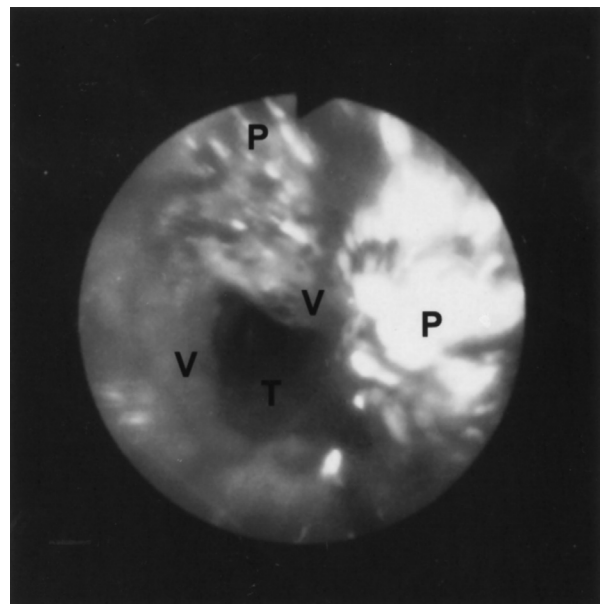

Fig. 4. The bronchoscopic finding of laryngeal papillomatosis: P- Cauliflower-like warty growths protruding upward just above the right vocal cord; T- tracheal lumen; V- vocal cords.

Case 3

At the age of 4, a 52-year-old male was diagnosed with laryngeal SP (Figure 4). A tracheos-

tomy was initially performed for this patient at the age of 5, because of an upper airway obstruction. In the following years, the tracheostomy tube was removed and re-inserted several times. At the age of 16, the tracheostomy tube was removed because of little recurrence. He had a short-term light smoking history as a young adult, but has not smoked for the past few decades. Between the ages of 32 and 42, he used 5-FU (fluorouracil) aerospray. During this period, he enjoyed an almost event-free life, except 1 episode of laser ablation for laryngeal papillomatosis at the age of 39. At the age of 42, he suffered from pneumonia and discontinued 5-FU therapy. About 5 months later, an emergency tracheostomy was performed again because of a recurrence of the laryngeal papillomatosis with upper airway obstruction. He received CO_2 laser ablation for the laryngeal papillomatosis. Bronchoscopy disclosed small nodular eruptions about 1 cm in length in the middle trachea. Brushing cytology was negative for malignancy. A permanent tracheostomy was indicated. CXR disclosed a small nodule about 2.5 cm in diameter in the right lower lung field. At 45 years of age, the patient was admitted again to undergo CO_2 laser ablation for laryngeal recurrence. CXR disclosed a slight enlargement of the RLL nodules. Sputum cytology was negative for malignancy. Bronchoscopic biopsy was suggested to exclude lung involvement, but the patient hesitated. He then became lost to follow-up. At the age of 50, an Nd-Yag (Neodymium-doped Yttrium aluminum garnet) laser was employed to vaporize the warty growth lesions in the stenotic area of the lower trachea. About 3 months later, arytenoidectomy with laryngeal reconstruction and CO_2 laser ablation were performed because of bleeding and diffuse growth of the papilloma in the larynx. In addition, multiple pulmonary nodules and masses about 2 to 3 cm in diameter were seen in the bilateral lower lung fields (Figure 5). Chest computed tomography (CT) revealed that some of the cavitary lesions were thin-walled. SP with lung involvement was suspected at that time. The pathological report of the excisional biopsy of the larynx disclosed squamous papillomas without evidence of malignant transformation. Further investigation was advised to exclude malignant transformation of the tracheal and pulmonary lesions, but the patient hesitated again. At the age of 51, he visited our clinic due to tracheal stenosis, and an Nd-Yag laser was employed again to vaporize the granulation tissue in the middle trachea. At the age of 52, he was admitted because of weakness of the left forearm. CXR revealed a collapse of the right lower lobe (RLL) and multiple pulmonary masses (Figure 6). Bronchoscopy revealed an endotracheal tumor with an irregular and hypervascular surface, which was subject to

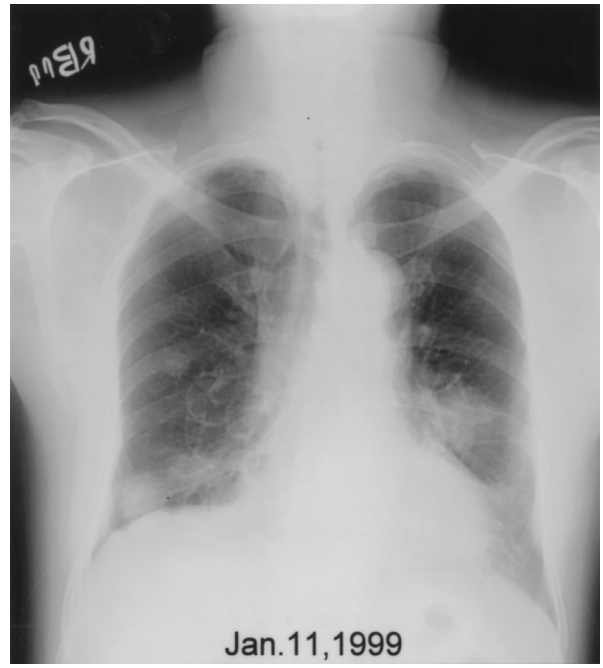

Fig. 5. The CXR showing multiple nodular lesions with variable sizes in the bilateral lung fields.

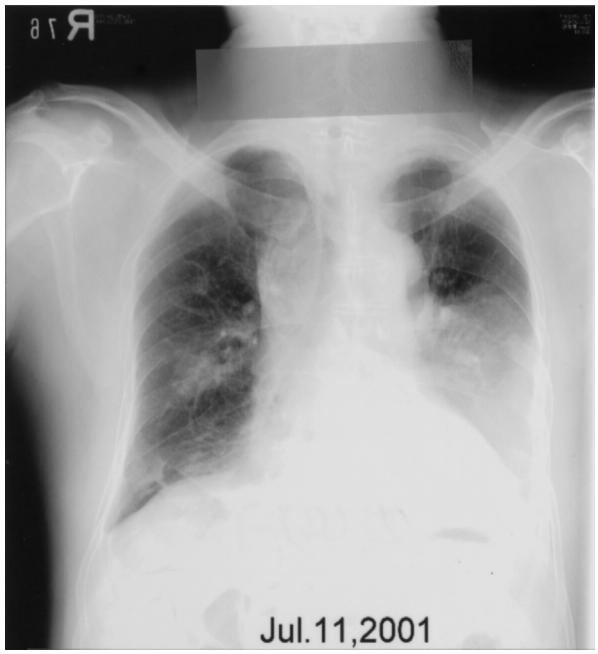

Fig. 6. About 6 months later, the CXR disclosed progression of the lung lesions and collapse of LLL.

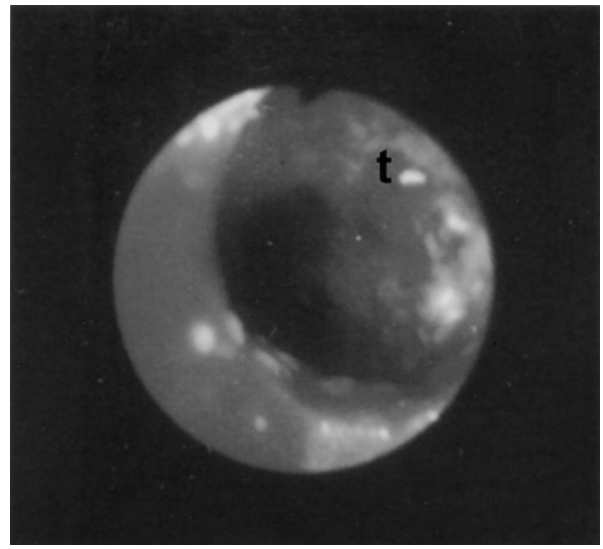

Fig. 7. The bronchoscopic finding revealing a hypervascular, endobronchial mass with an irregular surface (t).

contact bleeding (Figure 7), and resulted in stenosis of the trachea. Bronchoscopic biopsy of the tracheal tumor, and left lower lung mass aspiration, disclosed SCCA. Chest CT showed extensive mediastinal and abdominal lymphadenopathy and multiple nodules and mass lesions in the bilateral lung fields. SCCA with mediastinal and abdominal lymph node and bilateral lung metastasis were suspected. A whole body bone scan revealed multiple bony metastases, including the upper T-spine and left 6th and 8th ribs, and compression of the C7 spine. Radiotherapy with a total of 30 Gy in 12 fractions was performed for the C-spine and upper T-spine area. Because of the patient's poor performance, chemotherapy was not employed. He was discharged and received supportive care. Unfortunately, he was admitted again 1 month later and expired because of pneumonia with septic shock.

Discussion

SP is the most common benign tumor of the larynx in children, and may spread to affect the tracheobronchial tree. In contrast, solitary squamous papilloma (SSP) in the tracheobronchial tree is rare, occurring in middle-aged persons most commonly. Both diseases are benign and histologically similar. Naka and associates reviewed 56 cases of solitary tracheobronchial squamous papilloma and stated that male patients were affected about 4.5 times more than females. Previously, cigarette smoking had been thought to be the most important etiologic factor. Naka also demonstrated that about 9% of papilloma arose in the trachea, 5.3% in a main bronchus, and 73.2% in a lobar bronchus [1]. Unlike viral papillomatosis, these tumors are only occasionally associated with human papillomavirus infection. Endoscopic removal is usually feasible.

Solitary papillomas are associated with dysplasia, carcinoma in situ, or invasive carcinoma in up to one-third of the cases [2]. One case report presented a 30-year-old male smoker with solitary bronchial papilloma who suffered from recurrence 2 months after Nd-Yad laser, and was free of recurrence for 2 years after sleeve resection of the tumor [3]. Despite the lack of a significant difference in the event-free rate between bronchoscopic and surgical management [1], surgical resection is the superior choice because of the relatively high risk of hidden malignancy and the limitation of the bronchoscopic approach to the tumors.

Recurrent respiratory papillomatosis (RRP) is the most common benign tumor of the upper airway in young children. The lesions are sessile or stalked papillary growths lined with flattened squamous epithelium. RRP may occur at any age; however, there is a bimodal age distribution in which the first peak occurs at less than 5 years old, and another peak between 20 and 30 years old, but it rarely presents in patients more than 60 years old. The incidence of JORRP and AORRP in the United States was 4.3 and 1.8 per 100,000 people, respectively [4]. JORRP affects girls and boys in equal proportion, whereas AORRP affects slightly more males [5]. JORRP is more common and more severe than AORRP, and is usually caused by exposure to HPV during the peripartum period. In contrast, AORRP is acquired by HPV transmitted via sexual contact, or by indirect contact with ano-genital lesions. Kashima *et al*. proposed the classic triad of increased risks for JORRP as being first-born, vaginally delivered, and the infant of a teenage mother [6]. Bauman and Smith reported that 50% of mothers of affected children have a history of prior HPV infection [7]. Cesarean delivery in order to prevent JORRP is controversial. In a young woman with her first pregnancy and current condylomata, cesarean delivery should be considered [8]. RRP is caused mainly by HPV-6 and HPV-11, and rarely by HPV-16 and HPV-18. HPV-11 associated RRP is more severe and has a greater propensity for distal pulmonary spreading. In HPV-11 associated JORRP, about 70% of patients require tracheostomy, compared with fewer than 20% of patients with HPV-6 associated JORRP [9].

RRP appears to have a predilection for areas where there is a junction of squamous-cilliary epithelium, such as the nasopharyngeal area, the laryngeal surface of the epiglottis, and tracheostomy sites. The clinical presentations include weak crying sounds, hoarseness, chronic cough, dyspnea, stridor, choking, a foreign body sensation, and a failure to thrive. Direct laryngoscopic or bronchoscopic observation and biopsy are necessary for diagnosis. Children may present symptoms for as long as 1 year before diagnosis. In JORRP, each patient undergoes 4.4 surgical procedures per year on average, and more than 20 procedures in a lifetime. About 10% to 15% of children with JORRP ultimately require tracheostomy, usually during their first 2 years of life [10]. Tracheostomy in AORRP is less frequent, but repeated surgical procedures are almost inevitable, sometimes as often as every few weeks. Karmer and associates compared 532 patients with laryngeal papillomatosis, and documented that the trachea and bronchi were involved in about 5% of patients, and pulmonary invasion in less than 1% of patients. In addition, there is controversy as to whether pulmonary foci represent tracheobronchial dissemination of fragmented portions of papilloma or multifocal viral infection [11].

With involvement distal to the larynx, remission is less common and occurrence more fre-

quent in adults. Recurrence of the disease may appear after years of remission. Malignant degeneration may hide within the lesions of recurrent papillomatosis. Without early diagnosis and resection, distal spreading and metastasis of the cancer cells may occur. Adults are more likely than children to develop both an extension of the tumor to the lower respiratory tract and malignant transformation. It is unusual to encounter multiple papillomas in the tracheaobronchial tree in the absence of laryngeal disease.

Pulmonary papillomatosis occurs only in patients with laryngeal disease requiring tracheostomy, but the mechanism is uncertain. With pulmonary dissemination, multiple, small, sharply circumscribed nodules are seen. With growth, cavities may develop, with thin walls, 2-3 mm in thickness, and with or without an air-fluid level. In contrast to the spontaneous resolution of laryngeal papillomatosis in children, pulmonary lesions progress gradually and relentlessly, and may undergo malignant change into squamous cell carcinoma (SCCA). No cases of pulmonary cysts regressing spontaneously have been reported [12]. The rate of occurrence of carcinoma from a papilloma is 7.8%, and is not unusual in patients who smoke or who have received irradiation or chemotherapy. Cigarette smoking, bleomycin therapy, and radiation treatment of involved areas could be important co-factors in malignant transformation [13]. HPV-16 and HPV-18 are mostly associated with malignant transformation. The sites of malignant change in cases of JORRP usually involve the bronchial or pulmonary parenchyma, while the larynx is the usual site in AORRP. Go and associates reviewed 7 cases of RRP with malignant transformation. They reported that the average age of patients with JORRP and AORRP were 3 years and 31 years, respectively. The average age of onset of transformation to SCCA was 28 years. Three of the 7 patients had tracheal extension and 5 patients were tracheotomy-dependent. Four of the 7 patients developed SCCA of the lung and 3 patients developed laryngeal SCCA. There was no consistent histologic progression from squamous papilloma to papilloma with dysplasia. The overexpression of p53 protein was variable in each of the 5 patients. Five patients were positive for HPV infection, but 2 were negative. Spontaneous transformation of RRP to SCCA is not characterized by a histologic progression through dysplasia over time. Transformation can result in the loss of HPV expression. These cancers may be very difficult to diagnose, histologically and clinically, early in the course of the transformation of the disease [14].

The main goal of treatment is to relieve airway obstruction. Surgical resection, if possible, is the primary method. Treatment includes repeated debulking of the warty growths by laser therapy. CO_2 laser ablation is the most common therapy because it effects minimal hemostasis and thermal damage to the surrounding tissues. In 1980, topical chemotherapy with the antimetabolite 5-FU was used as an adjunct to surgical laser excision of squamous papillomas arising in the larynx and in the tracheobronchial tree. Use of 5-FU was associated with inhibition of papilloma regrowth in 75% of patients. No obviously toxic adverse effects were noted. The major limitation to drug effectiveness is the requirement of its frequent administration [15]. However, 5-FU is no longer used. Alpha-interferon appears to slow the rate of growth [16]. Some anti-viral agents, such as cidofovir and acyclovir, both systemic and intralesional, also may slow the rate of growth. Photodynamic therapy was reported to reduce the growth rate. No curative treatment is available except surgical resection [4]. Some

studies have reported that JORRP might enter remission after puberty.

The characteristics of our 3 cases are listed in Table 1. Case 1 was a female non-smoker. Despite the bronchoscopic biopsy showing benign SSP, surgical resection was performed because of the possibility of a hidden malignancy, the subsequent recurrence, and significant limitation of daily activity. We could not determine if this was associated with HPV infection, due to the lack of HPV identification in the excised specimen. If HPV exists, recurrence and hidden malignancy are more likely. This patient had a good prognosis, and was event-free 14 months after treatment. In cases 2 and 3, laryngeal RRP was active and frequently recurred. Both cases underwent tracheostomy within 2 years. Since puberty, recurrence has regressed. In case 3, the tracheostomy tube was removed at age 16. After a remission of about 3 decades, the trachea was invaded, at 42 years of age, with an increasing frequency of recurrence. Despite tracheal invasion with a negative brushing cytology, bronchoscopic biopsy showed SCCA 10 years later. A RLL nodule was first noted at the age of 42, but 8 years later, multiple pulmonary nodules with thin-walled cavities developed. Pulmonary dissemination was more favored than primary lung cancer. Chemotherapy-associated malignant transformation in RRP was documented only with bleomycin. 5-FU was able to alleviate recurrence without significant adverse effects. Biopsy should have been done to rule out malignancy at that time, but the patient refused. Unfortunately, SCCA was proved by bronchoscopic biopsy of the trachea. A period of about 8 to 10 years transpired from the first tracheal invasion and RLL nodule to the malignant transformation. After relative remission for 3 decades, tracheal invasion, tracheostomy, and pulmonary nodules were the hints of

Table 1. Characteristics of the 3 cases

	Age /Sex	Diagnosis	Age of onset	Initial presentation	Site of lesions	Time from diagnosis to tracheostomy	Treatment	Outcome
Case 1	45/F*	SSP*	45 years	Dyspnea on exertion	Upper trachea	NIL	Surgical resection	No recurrence for up to 14 months
Case 2	16/F*	JORRP*	3 months	Weak crying sound	Larynx, trachea, bronchial tree	2 years	MLS*+CO_2* laser; laryngectomy	Tracheostomy, laryngectomy, with recurrence
Case 3	52/M*	JORRP*	4 years	Voice change	Larynx, trachea, lung	1 year	MLS*+CO_2* laser; arytenoidectomy with laryngeal reconstruction; R/T* for spinal metastasis	Tracheostomy, arytenoidectomy, SCCA* of the lung with metastasis to multiple sites

* Abbreviation: F- female; M- male; SSP- solitary squamous papilloma; JORRP- juvenile onset recurrent respiratory papillomatosis; MLS- microscopic laryngeal surgery; CO_2- carbon dioxide; R/T- radiotherapy; SCCA- squamous cell carcinoma

disease activation and subsequent pulmonary dissemination. More aggressive treatment, such as adjuvant therapy, more frequent follow-up, and laser ablation should be administered because pulmonary invasion usually progresses relentlessly, with the risk of malignant change. Our cases had no evidence of HPV typing. Viral typing seems to be a better prognostic indicator than grading of dysplasia or the age relationship [17]. The disease outcome is diverse, and there is no rule that can predict it. We conclude that for patients with squamous papilloma and papillomatosis in the airway, surgical resection is the mainstay of treatment. HPV typing should be done because it may be a prognostic factor. For long-term laryngeal papillomatosis with tracheobronchial and pulmonary involvement, more aggressive treatment and frequent follow-up are necessary to keep the airway patent and to detect malignant transformation early on.

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呼吸道鱗狀上皮乳突瘤—病例報告

蘇剛正　盧崇正　彭瑞鵬

多發性鱗狀上皮乳突瘤症在上呼吸道是一種常見於小孩的呼吸道良性腫瘤，好患於喉部，其病原為人類乳突狀病毒家族。此病的常見特徵之一就是疣狀生長的病兆常會頻繁的復發以及往外擴散。而單一之鱗狀上皮乳突瘤則罕見，從上呼吸道至下呼吸道皆有可能發生，抽菸為主要誘發因子，好發於抽菸之成人男性，只有少數病例與人類乳突狀病毒感染相關。手術將病灶處完全切除是預防擴散及復發的重要關鍵。如果病灶一直復發，最嚴重的後遺症就是造成呼吸道阻塞及病灶轉變為惡性。我們報告三個病例，一個為發生於氣管之單一乳突瘤，兩個為喉部復發性乳突瘤症合併上呼吸道阻塞，其中一位在發病 48 年後發生惡性轉變。同時我們回顧文獻並提出討論。*(胸腔醫學 **2006; 21: 382-391**)*

關鍵詞：鱗狀上皮乳突瘤，復發性呼吸道乳頭狀瘤症，人類乳頭狀病毒

台北榮民總醫院　胸腔部
索取抽印本請聯絡：盧崇正醫師，台北榮民總醫院　胸腔部，112 台北市北投區石牌路二段 201 號