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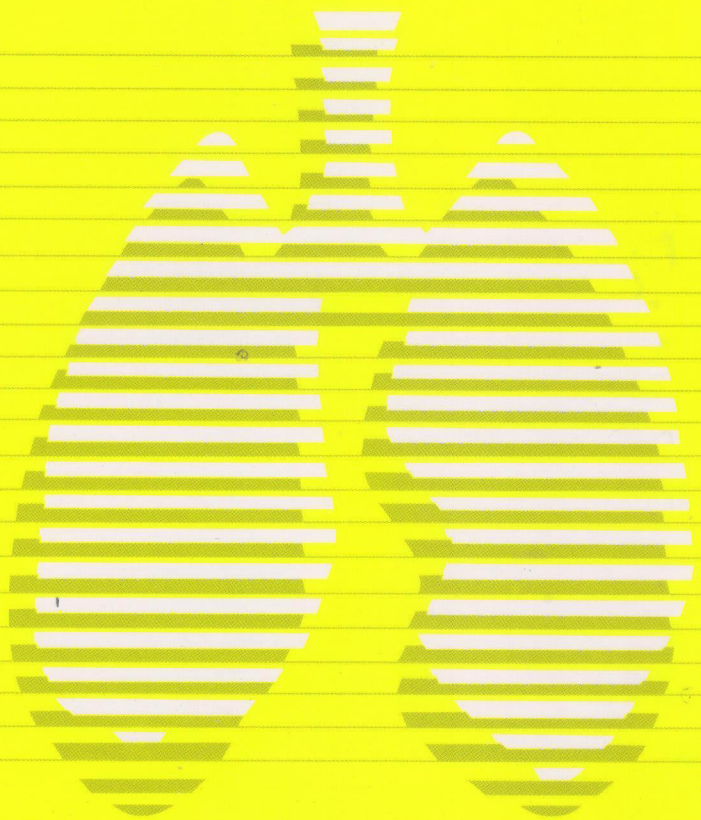

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Orginial Articles

Case Reports

One-year Experience with Unplanned Extubation in Adult Intensive Care Units

Chin-Ming Chen*,**, Wen-Liang Yu*,**, Khee-Siang Chan*, Kuei-Ling Tseng***, Kuo-Chen Cheng*,***,****

Introduction: Unplanned extubation (UE) is a frequent complication following endotracheal intubation, and can increase intensive care unit (ICU) and hospital expenditure. We attempted to investigate the incidence, outcome and predictive factors of patients who failed UE (reintubation within 48 hours) in the adult ICUs of a medical center in Taiwan.

Methods: We reviewed the medical records of patients who experienced UE in intensive care units from July 1, 2004 to June 30, 2005. There were 102 intensive care beds and a total of 3639 admissions with mechanical ventilation via endotracheal tube or tracheostomy. The primary endpoint was factors predicting failed UE, and the second goal was the outcome of failed UE compared with successful UE.

Results: One hundred and fifty-two episodes of UE occurred during the study period, representing 4.2% of mechanically ventilated patients. There were 73 episodes of failed UE (48.0%) and 24 patients (15.8%) died during hospitalization. Using multivariate analyses, the 3 risk factors of Glasgow Coma Scales (GCS) scores <10, pulmonary causes of intubation, and accidental extubation significantly predicted failed UE. The outcomes of the failed UE patients included: longer stays in the ICU and hospital, and higher hospital costs and mortality.

Conclusion: Patients with failed UE suffered a poor prognosis, and increased hospital expenses, and mortality. The predictors of failed UE included GCS<10, pulmonary causes of intubation and accidental extubation. To provide safe patient care, the physicians should consider the risk factors of failed UE and its potential association with adverse events. ***(Thorac Med 2008; 23: 393-404)***

Key words: endotracheal intubation, mechanical ventilation, re-intubation, unplanned extubation

Introduction

Most patients in intensive care units (ICU) are intubated and ventilated, thus exposing them to a considerable level of potential complications. Unplanned extubation (UE) of patients is a frequent event complicating endotracheal intubation, and has an incidence of 1.0-22.5%

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in the literature [1-20]. Morbidity rates of 5% to 28% for UE complications have been reported [5], most UE complications have resulted in serious respiratory and cardiovascular consequences, such as aspiration pneumonia, bronchospasm, hypotension, and tachyarrhythmias; the most profound events can lead to cardiopulmonary arrest and death [3, 18]. UE results in prolonged mechanical ventilation, longer ICU and hospital stay, and increased need for chronic care, but it is not necessarily associated with increased mortality, when compared with matched controls [4-5]. The increased hospital expenditures are due exclusively to patients who failed to tolerate UE.

Published reports reveal a re-intubation rate which varies from 37~76% after UE [1-2, 4-5, 7, 14, 16]. Considering the low re-intubation rate in some studies, earlier weaning and an extubation protocol should be introduced [6]. In addition, the factors predicting re-intubation in the ICUs of established centers have been studied, and include pneumonia as a cause of respiratory failure [16], a higher acute physiological and chronic health evaluation (APACHE II) score [9], a higher pre-extubation FiO_2 level [6, 9, 19], a lower PaO_2/FiO_2 ratio [9, 14], full ventilator support before UE [7, 14], higher pre-extubation minute volume [10], and accidental extubation [1, 6, 14]. The objectives of this study were to identify the predictive factors for re-intubation and to determine the outcome of patients with UE in our ICUs, which are rarely highlighted in Taiwan.

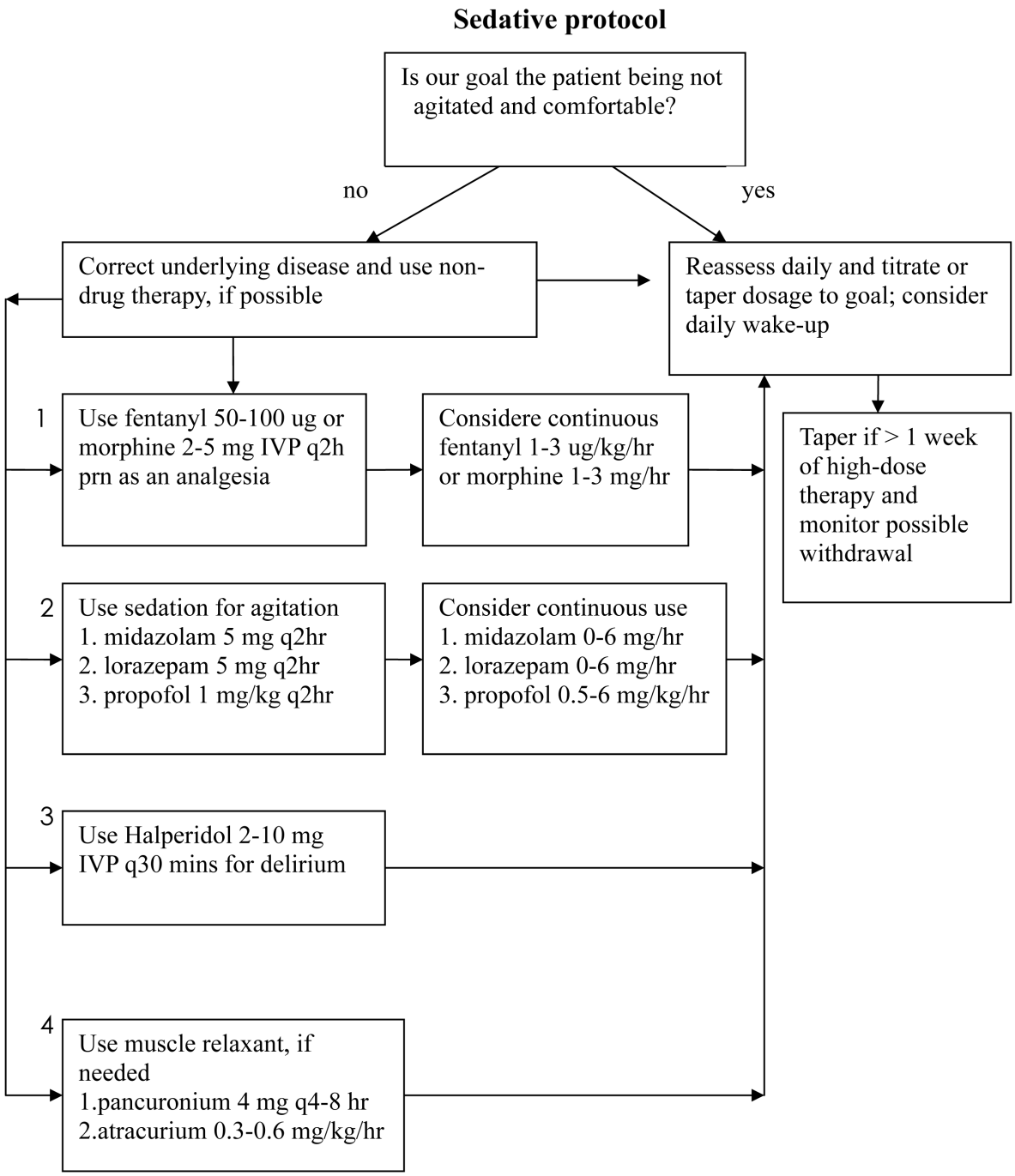
Methods

Study design and patient selection

We collected patients who had experience UE, and retrospectively reviewed their medical records from July 1, 2004 to June 30, 2005 in Chi Mei Medical Center. There were 102 intensive care beds distributed among 9 ICUs, accepting patients over 18 years of age. The ICU staffs included in-charge intensivists, respiratory therapists, clinical nurse specialists, clinical dietitians, clinical pharmacists, and residents who provided 24-hr coverage in-unit. The nursing staff worked 3 shifts at the commencement of the surveys. The morning shift was 08:00-16:00, the late shift 16:00-0:00 and the night shift 0:00-08:00. Each shift had the same workload with patient-to-nursing staff ratios of 2:1~2.5:1. There were also no differences in nursing experience between each shift.

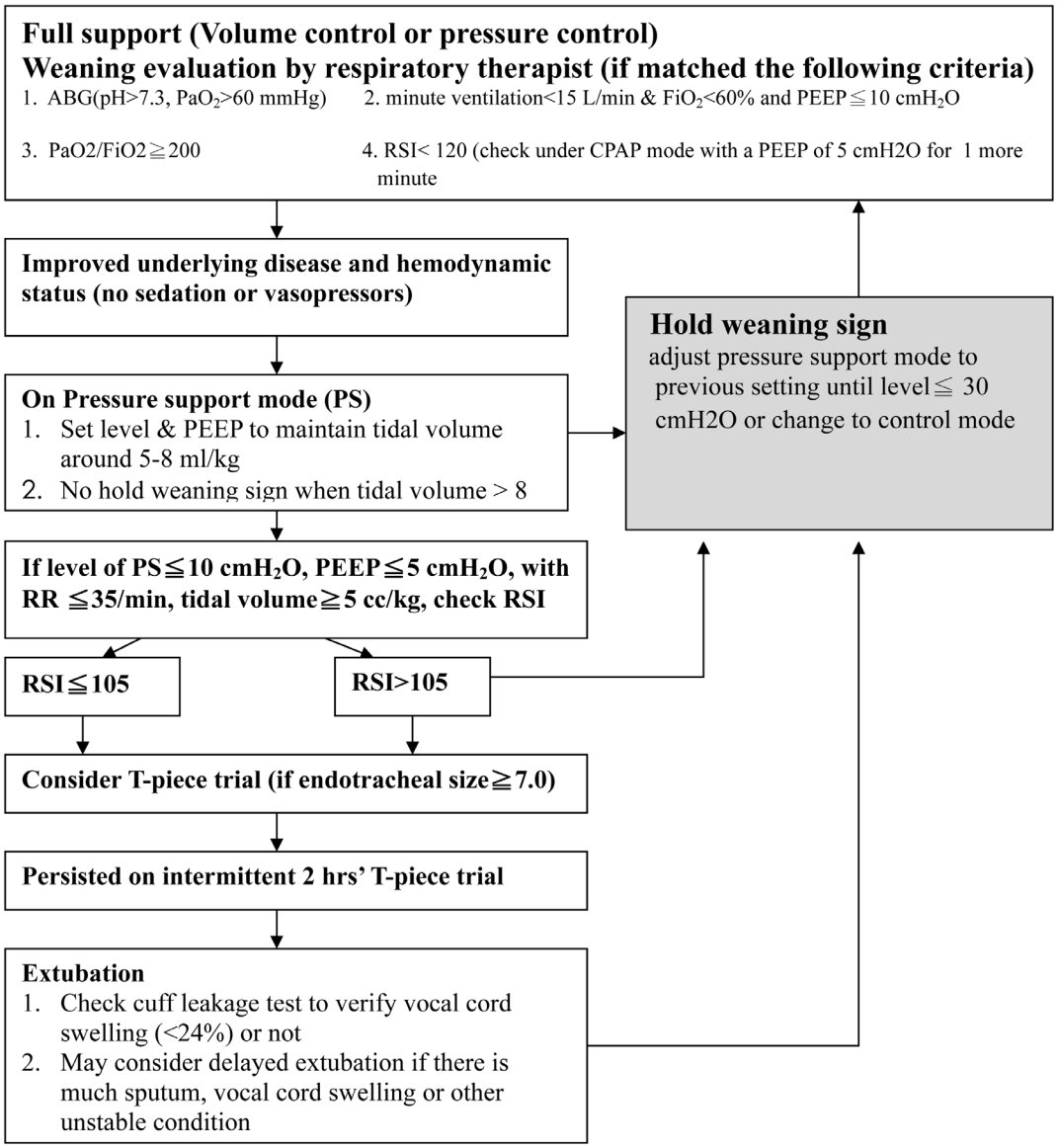
For the study period, 3639 admissions with mechanical ventilation via endotracheal tube or tracheostomy were included. Endotracheal tubes were secured with 1.25 cm elastic adhesive tape or cloth tape, both circled behind the head and secured directly to the tube. If a patient was prescribed and receiving benzodiazepines, opiates, or both, then that patient was considered to be receiving sedation. These agents were used for patients who were agitated, based on the clinical assessment of the attending physicians and the sedative protocol presented in Appendix 1. Nurses restrained patients following consultation with the physician primarily on the subjective assessment of a patient's level of agitation and/or persistent failure to obey instructions. The methods included chest, arm and hand restraints. A weaning protocol was also performed, as in Appendix 2.

UE was defined as deliberate removal of an endotracheal tube by a patient or accidental removal of an endotracheal tube during nursing care or patient transport. Patients with unplanned extubation were subdivided into failure and success groups based on whether or not re-



Appendix 1

intubation was required within 48 hours of extubation. In all cases, the decision to re-intubate was made by a physician in attendance, and was based on clinical indicators of respiratory failure, such as refractory hypoxemia and hemodynamic change.



Appendix 2 Acute Weaning & Extubation Protocol

Measurements

The following data were retrospectively collected: (1) demographic and clinical variables, including: age, gender, cause of intubation (pulmonary origin, such as pneumonia, obstructive airway disease and pulmonary edema; or extra-pulmonary origin, such as hypoventilation, extra-pulmonary sepsis and post-operation), cause of re-intubation (excessive secretion, upper airway obstruction, encephalopathy, oxygenation failure and hemodynamic instability), time between intubation and UE, UE time (daytime was from 8:00 am to 4:00 pm; nighttime, from 4:00 pm to 8:00 am), self-extubation or accidental, and ICU location (medical or surgical); (2) severity calculated by clinical

nurse specialists on ICU admission, including APACHE II, therapeutic intervention scoring system (TISS) and Glasgow Coma Score (GCS); GCS was calculated as 15 if a intubated patient is clear-consciousness and is estimated to talk after extubation; (3) latest data before extubation, such as: vital signs, arterial blood gas, ventilator settings, weaning trial or not (weaning trial defined as a pressure support mode ventilator with a level ≤14 cmH_2O), agitation or not, and the use of sedation and physical restraints or not; (4) outcome measurement, including ICU and hospital stays, total hospital costs, and hospital, ICU and 28-day mortality. The primary endpoint was factors predicting failed UE, and the second endpoint was the outcome of failed UE compared with successful UE.

Statistical analysis

Mean values, standard deviations, and group sizes were used to summarize the results for continuous variables. The differences between failed and successful UEs were examined first by univariate analysis with a nonparametric rank test (Mann-Whitney U test) and a chi-square test. A p value of <0.05 was considered statistically significant. Predetermined variables, or those significantly associated with successful extubation in univariate analysis (p<0.05), were tested for interaction with multiple logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Statistical analysis of the data was done with SPSS 13.0 for Windows (SPSS, Inc., Chicago, Illinois).

Results

One hundred and fifty-two episodes of UE (140 patients; and 12 patients experiencing repeated UE) occurred during the study period, representing 4.2% of all admissions with mechanical ventilation. The average age of the group was 62.2 ± 17.7 years, with a male predominance (102/152, 67.1%). Eighty-one episodes (53.3%) occurred in the medical ICU and 68 episodes were intubations due to pulmonary causes (44.7%). There were 73 episodes of failed UE (48.0% of all UEs), of which more than half (41/73, 56.2%) necessitated prompt re-intubation within 1 hour. Most episodes (78.9% of all UEs) were self-extubations. Tables 1 and 2 list the demographic, clinical and laboratory variables associated with the different UE groups; the causes of intubation and re-intubation are shown in Table 3.

The predictors of failed UE included lower GCS (12.7 ± 3.4 vs. 14.4 ± 1.8, p=0.001), GCS <10 (26.8% vs. 5.2%, p<0.001), medical origins (64.4% vs. 43.0%, p=0.007), pulmonary causes of intubation (61.6% vs. 29.1%, p<0.001), and accidental extubation (31.5% vs. 11.4%, p= 0.002) (Table 1). The latest data before extubation were similar between the different UE groups (Table 2). Using multivariate analyses, the significant predictors for failed UE were GCS<10 (OR 8.009, 95% CI 2.314~27.722, p=0.001), pulmonary cause of intubation (OR 5.396, 95% CI 2.500~11.646, p<0.001) and accidental extubation (OR 3.039, 95% CI 1.123~ 8.225, p=0.029) (Table 4).

Twenty-four patients (15.8%) died during hospitalization. The average stays in the ICU and hospital were 13.4 ± 9.2 and 32.4 ± 21.8 days, respectively. Compared to those with successful UE, the outcome of patients with failed UE revealed a longer ICU period (17.1 ± 9.9 vs. 9.9 ± 7.1 days, p<0.001), a longer hospital stay (38.3 ± 22.8 vs. 26.9 ± 19.4 days, p=0.001), higher hospital costs [18,842 ± 10,327 vs. 9,506

Table 1. The demographic and clinical variables of the different UE groups

Items	All (n=152)	Successful (n=79)	Failed (n=73)	*p* value
Age	62.2 ± 17.7 (23~92)	60.3 ± 18.2	64.2 ± 17.0	0.174
Gender				0.114
male	102 (67.1%)	57 (72.2%)	45 (61.6%)	
female	50 (32.9%)	22 (27.8%)	28 (38.4%)	
APACHE II score	15.9 ± 8.4 (0~39)	14.8 ± 8.3	17.0 ± 8.5	0.182
TISS	29.2 ± 8.6 (12~55)	28.3 ± 7.2	30.1 ± 9.8	0.237
Glasgow Coma Scales	13.6 ± 2.8 (4~15)	14.4 ± 1.8	12.7 ± 3.4	0.001
Glasgow Coma Scales<10	23 (15.1%)	4 (5.2%)	19 (26.8%)	<0.001
Intubation cause				<0.001
Pulmonary cause	68 (44.7%)	23 (29.1%)	45 (61.6%)	
Extra-pulmonary cause	84 (55.3%)	56 (70.9%)	28 (38.4%)	
Time of mechanical ventilation before UE(hrs)	109.3 ± 118.3 (1.0~660.0)	93.1 ± 88.5	126.8 ± 42.4	0.085
UE time*				0.478
Day time	59 (38.8%)	30 (38.0%)	29 (39.7%)	
Night time	93 (61.2%)	49 (62.0%)	44 (60.3%)	
Extubation manner				0.002
Self-extubation	120 (78.9%)	70 (88.6%)	50 (68.5%)	
Accidental extubation	32 (21.1%)	9 (11.4%)	23 (31.5%)	
ICU location				0.007
Medical ICU	81 (53.3%)	34 (43.0%)	47 (64.4%)	
Surgical ICU	71 (46.7%)	45 (57.0%)	26 (35.6%)	

Expressed as mean ± SD (range) or n (%)

*UE time (day time is 8:00 am to 4:00 pm; night time is 4:00 pm to 8:00 am)

± 8,612 US Dollars (USD), $p<0.001$] and higher hospital mortality rates (21.9% vs. 10.1%, $p=0.038$), but ICU or 28-day mortality did not reach statistical significance (Table 5).

Discussion

The findings of our study were consistent with those of previous studies in terms of the incidence of UE, the rate of failed UE, and the mortality of patients with failed UE. The incidence of UE in our ICUs was 4.2%, comparable to that (1.0-22.5%) reported in the literature [1-20]. Our rate of failed UE at 48.0% was similar to the reported rate of 37-76% [1-2, 4-5, 7, 14, 16]. Failed UE had a significantly higher hospital mortality than successful UE (21.9% vs. 10.1%), but not ICU and 28-day mortalities. This was evidenced in previous studies, with higher hospital mortalities in patients who failed to tolerate UE (25-57%) than in those who succeeded (0-21%) [1, 3-4, 9, 14, 17, 19]. Though it has been reported that UE patients did not differ in hospital mortality when compared to matched control subjects [4-5], increased lengths of stay in hospitals and ICUs and other expenditures for UE patients were still highlighted [4-5, 17]. These were due exclusively to

Table 2. The most recent data before extubation of the different UE groups

Items	All (n=152)	Successful (n=79)	Failed (n=73)	*p* value
Mean arterial pressure (mmHg)	94.9 ± 17.8 (59.3~142)	97.0 ± 15.6	94.8 ± 15.2	0.398
Heart rate (beats/min)	95.2 ± 18.1 (54~135)	93.2 ± 17.0	96.8 ± 18.5	0.204
Respiratory rate (per min)	18.8 ± 5.1 (8~38)	18.3 ± 4.8	19.2 ± 5.4	0.291
pH	7.45 ± 0.06 (7.25~7.62)	7.45 ± 0.07	7.45 ± 0.06	0.676
PaO_2 (mmHg)	107.0 ± 43.3 (54.3~417)	111.5 ± 50.3	102.2 ± 33.9	0.195
FiO_2 (%)	32 ± 8 (25~70)	31 ± 5	33 ± 10	0.154
PaO_2/FiO_2 (mmHg)	305.9 ± 92.0 (111.5~552.4)	311.6 ± 88.3	299.9 ± 96.1	0.448
$PaCO_2$ (mmHg)	35.8 ± 6.9 (12.7~54.5)	36.0 ± 6.5	35.6 ± 7.3	0.775
Minute volume (L/min)	9.3 ± 2.9 (4.2~19.2)	8.9 ± 2.5	9.7 ± 3.3	0.080
Tidal volume (mL)	499.2 ± 132.1 (142.2~880)	505.3 ± 123.6	492.6 ± 141.3	0.556
PEEP (cmH_2O)	5.3 ± 1.8 (0~12)	5.0 ± 1.4	5.5 ± 2.1	0.080
Weaning trial*				0.111
Yes	81 (53.3%)	44 (55.7%)	37 (50.7%)	
No	71 (46.7%)	35 (44.3%)	36 (49.3%)	
Agitation				0.291
Yes	58 (38.2%)	28 (35.4%)	30 (41.1%)	
No	94 (61.8%)	51 (64.6%)	43 (58.9%)	
Sedation or/and physical restraint				0.428
Yes	100 (65.8%)	53 (67.1%)	47 (64.4%)	
No	52 (34.2%)	26 (32.9%)	26 (35.6%)	

Expressed as mean ± SD (range) or n (%)

*weaning trial defined as a pressure support mode ventilator with a level ≤14 cmH_2O; not weaning trial defined as pressure support mode ventilator with a level >14 cmH_2O, pressure control mode or volume control mode

the proportion of patients who failed to tolerate UE, as mentioned in our study (Table 5). As an invasive procedure, re-intubation may independently correlate with an adverse outcome, due to the potential complications of cardiac arrest, cardiac arrhythmias, and aspiration pneumonia [3, 18]. Studies conducted by Epstein and Esteban *et al*. have shown that patients reintubated within 12 hours of planned extubation had a lower mortality than those reintubated later [19, 21]. Rapid re-intubation may reduce the risk of death, significant organ damage can still occur with delayed re-intubation. This is accompanied with the expense of unnecessary delay in recovery and prolonged ICU care and hospitalization. We recommend that early identification of patients after failed UE and the early re-institution of ventilatory support, which can potentially reduce the increased mortality and morbidity associated with extubation failure, as described by Epstein and Esteban *et al.* [19, 21].

Since UE is abrupt, unpredictable, and not totally preventable, it is important to identify the clinical and laboratory parameters of patients that suggest a high risk for re-intubation. Multivariate analysis demonstrated that three factors were significantly correlated to re-intubation: a lower level of consciousness as evaluated by GCS<10 (OR, 8.009), pulmonary cause of intubation (OR, 5.396) and accidental

Table 3. Causes of intubation and re-intubation of all UE patients

Causes of intubation	n=152
pulmonary origin	
Airway obstruction	9 (5.9%)
Pneumonia	28 (18.4%)
Pulmonary edema	22 (14.5%)
COPD	9 (5.9%)
extra-pulmonary origin	
Hypoventilation	32 (21.1%)
Sepsis	20 (13.2%)
Post-operation	32 (21.1%)
Causes of re-intubation	n=73
Excessive secretions	20 (27.4%)
Upper airway obstruction	7 (9.6%)
Oxygenation failure	16 (21.9%)
Encephalopathy	15 (20.5%)
Hemodynamic instability	15 (20.5%)

extubation (OR, 3.039). Our results were similar to those reported by Cheveron and Listello *et al*., in that less alert patients were associated with a risk of re-intubation [1, 14]. Moons reported that a higher GCS level was a high risk for patients with deliberate self-extubation, as compared with non-UE patients (12 vs. 4, $p<0.001$) [20]; hence, an adequate level of sedation resulting in diminished consciousness was required in patients who were still in need of complete support by mechanical ventilation. But, when UE occurred and re-intubation was not immediately necessary, the presence of an alert level of consciousness appeared to prevent re-intubation. In addition, we found that respiratory failure due to pulmonary causes (such as airway obstruction, pneumonia, pulmonary edema, and COPD) was another important factor in re-intubation after UE, similar to the report of Chen *et al*. [16]. Respiratory failure due to extra-pulmonary causes (such as hypoventilation due to brain stroke, sepsis, and post-operative status) was associated a rapid response to effective therapy, while those with pulmonary causes required more recovery time, even with aggressive treatment. In fact, we found all UE patients were on relatively low FiO_2 (around 30%) and excellent PaO_2/FiO_2 (around 300 mmHg), but 48% of them needed re-intubation. Table 3 shows that more than half of patients with re-intubation (43/73, 58%) had excessive secretion, upper airway obstruction or oxygenation failure at the time of extubation, and we found that most (38/43, 88.4%) were patients with a pulmonary origin at initial intubation. Thus, pulmonary cause of intubation was the other important factor of failed UE. In addition, Cheveron and Razek *et al*. showed that accidental extubation was a predictor of re-intubation after UE [1, 6, 14]. Also, in our study, 21.1% of the UE were accidental with 71.9% (23/32) requiring reintubation, matching results from previous work. We believe that when UE does not occur accidentally during nursing care or patient transport, re-intubation is frequently not required (70/120, 58.3%).

Patients who stayed in surgical ICUs were often reported to experience a lower UE rate and subsequent re-intubation rate than those who were confined to medical ICUs [2, 6, 10, 14]. Listello *et al*. reported that the rate of failed UE for surgical ICU patients (14%) was less than that for medical ICU patients (66%). Razek et al. showed that the frequency of UE was 4.9% in a traumatic ICU, whereas 36% of UE patients required re-intubation, and 85% did not require re-intubation while being actively weaned from ventilatory support. Our study also revealed a statistically significantly lower failed UE rate in surgical patients than in medical patients, using univariate analysis (35.6% vs. 64.4%). In multivariate analysis, surgical origin was not a meaningful predictor of failed

Table 4. Predictors of failed UE, using multivariate analyses

Item	B value	Odds ratio	95% CI	*p* value
Glasgow Coma Scales<10	2.081	8.009	2.314~27.722	0.001*
Pulmonary cause of intubation	1.686	5.396	2.500~11.646	<0.001*
Accidental extubation	1.112	3.039	1.123~8.225	0.029*

CI: confidence interval

*p<0.05 (statistically significant)

Table 5. The outcome of the different UE groups

Items	All (n=152)	Successful (n=79)	Failed (n=73)	*p* value
ICU mortality	10 (6.6%)	3 (3.8%)	7 (9.6%)	0.150
28-day mortality	16 (10.5%)	7 (8.9%)	9 (12.3%)	0.486
In-hospital mortality	24 (15.8%)	8 (10.1%)	16 (21.9%)	0.038*
ICU days	13.4 ± 9.2 (0~46)	9.9 ± 7.1	17.1 ± 9.9	<0.001*
Hospital days	32.4 ± 21.8 (2~118)	26.9 ± 19.4	38.3 ± 22.8	0.001*
Cost of hospitalization (USD)†	13,654 ± 10,460 (1,455~52,061)	9,506 ± 8,612	18,842 ± 10,327	<0.001*

Expressed as mean ± SD (range) or n (%)

*p<0.05 (statistically significant)

† USD: US dollars

UE, and we found no advantage of successful UE while patients were on weaning trial. We found most surgical patients were intubated due to extra-pulmonary causes, which may explain why the real independent predictor of failed UE was pulmonary causes of intubation, rather than surgical causes or being under a weaning trial.

Of these non-re-intubated patients in our study, more than half (55.7%) were under a weaning trial, and UE shortened the stay. These findings suggest that some patients might have delayed liberation from mechanical ventilation. Patients who can achieve their own spontaneous ventilation should be identified earlier to prompt extubation. Practicing weaning protocols to screen and initiate extubation has been shown to be effective [21]. As weaning protocols have been performed in the medical ICU since 2003, we found that some extubation was delayed by the surgeons. This may also explain why surgical patients had a higher percentage of successful UE than medical patients (57% vs. 43%); all surgical patients with successful UE seemed to have their extubation delayed and did not require re-intubation.

Agitation and delirium are frequent problems of patients confined to ICUs. Sensory overloads, fear, pain, sleep deprivation, thirst, inability to communicate, and lack of analgesia or sedation may also be precipitating factors. The presence of agitation may serve as a predictor of UE [12], and the appropriate use of adequate sedation and physical restraints may decrease UE [15]. Agitation was present in 38.2% of our UE population, while the proportion of all UE patients to use sedation

or physical restraints was 65.8%. Our results are in accordance with findings in other reports that show UE can still occur in patients who are treated with sedation or physical restraints [8, 22]. However, agitated patients should be sedated with caution, as over-sedation may result in delayed weaning and prolonged exposure to mechanical ventilation.

Various clinical predictors for failed UE have been reported. Similar to previous studies [1, 6, 9-10, 14], our study found that a tendency to a higher APACHE II or TISS score, a higher pre-extubation FiO_2 level, a lower PaO_2/FiO_2 ratio, and a longer duration of intubation before UE were likely to be found in patients who failed UE. Krinsley *et al*. revealed that age was the only predictor of the need for reintubation (p=0.037), but gender, race, admitting service, and APACHE II scores were excluded from the model. Age and gender did not contribute as predictors of re-intubation after UE in our group. Other clinical parameters, such as vital signs, also seemed not to achieve any statistical significance.

We believe that the increased incidence of UE at night (from the evening to the early morning) is related to the decreased care and attention in the ICU, as there are fewer bed-side rounds of physicians, families visiting, and personnel performing new orders, which all lead to increased attention for high-risk patients. Our study showed that a higher percentage of UEs occurred at night, but this did not contribute as a predictor of failed UE (failed vs. successful UE was 62.0% vs. 60.3%, p=0.478). Our data were similar to that in Coppolo's report [12], but were in contrast to the findings of Tindol *et al*. [2]. The differences suggest that the time of UE occurrence may vary along with conditions in different hospitals, and generalizations should not be made.

Conclusion

In this study, UE occurred in 4.2% of mechanical ventilated patients. Failed UE provided a poor prognosis for higher mortality and increased hospital expenditures. The predictors of failed UE included GCS<10, pulmonary causes of intubation and accidental extubation. To provide safe patient care, physicians should keep in mind the risk factors of failed UE, and its potential association with adverse events. By using the quality improvement process and protocol for regular surveillance, it may be possible for ICU staffs to reduce the incidence of UE.

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成人加護病房非計劃性拔管之一年經驗

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前言：非計劃性拔管（簡稱UE）是插管常見之併發症。UE會增加加護病房及醫院的費用。我們嘗試去探討台灣某一醫學中心之成人加護病房，UE失敗（48小時內重新再插管）的發生率、預後以及其預測因子。

方法：從2004年7月1日到2005年6月30日，我們收集並回顧所有UE病人之各項臨床資料。在102張加護病房病床中，總共有3639人次住院，並經由氣管內管或氣管切開術而使用呼吸器。我們想知道，與UE成功之病人比較，UE失敗之預測因子及其預後。

結果：在這期間共有152人次UE，佔所有使用呼吸器病人的4.2%。其中有73人次UE失敗（48%），及24位病人死亡（15.8%）。經由多變項分析發現，UE失敗者之3個預測因子為格拉斯哥昏迷指數（GCS）<10，肺部原因插管及意外拔管。UE失敗者之預後為：ICU及總住院天數較長，總住院費用以及死亡率均較高。

結論：UE失敗者之預後較差，總住院花費及死亡率高均較高。UE失敗者之預測因子為格拉斯哥昏迷指數（GCS）<10，肺部原因插管及意外拔管。為提供病人安全照顧，醫生必需考慮UE失敗者之因素及可能之併發症。*(胸腔醫學* ***2008; 23: 393-404)***

關鍵詞：氣管插管，呼吸器，再插管，非計劃性拔管

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Effects of Human Neutrophil Elastase on Human Airway Smooth Muscle Cell Functions

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Human neutrophil elastase (HNE), a serine protease, is abundant in chronic inflammatory diseases such as chronic severe asthma. Changes in the airway smooth muscle (ASM) phenotype may play a fundamental role in the pathogenesis of airway remodeling in chronic asthma. The aim of this study was to investigate whether HNE modulates the tumor necrosis factor (TNF) α-induced synthetic function and platelet-derived growth factor (PDGF)-induced migratory functions of ASM. HNE stimulated secretion of regulated on activation, normal T cells expressed and secreted (RANTES), but not interleukin (IL)-6, by human ASM cells. In ASM cells pre-treated with HNE (10 nM) for 2, 4 and 8 h, RANTES and IL-6 secretion by 10 ng/ml TNFα (18 h) were significantly increased with HNE pretreatment (p<0.05, n=3). However, HNE had a partial effect on TNFα-induced intercellular adhesion molecule (ICAM)-1 expression. HNE, but not heat-inactivated HNE, induced a 2.19 ± 0.44-fold increase in ASM cell migration (n=4, p<0.05). Interestingly, HNE had no effect on PDGF-induced ASM cell migration (3.10 ± 0.23 in control cells versus 3.59 ± 0.11 in HNE-treated cells, n=4). Our results show that HNE may play an important role in the pathogenesis of chronic asthma by modulating the synthetic and migratory functions of human ASM cells. ***(Thorac Med 2008; 23: 405-413)***

Key words: human neutrophil elastase, airway smooth muscle, synthesis, migration, asthma

Introduction

Asthma is a chronic inflammatory disease characterized by reversible airway obstruction, inflammation, and structural changes in the bronchi that include epithelial cell denudation, mucus gland hyperplasia, airway smooth muscle (ASM) hypertrophy and hyperplasia [1]. ASM, existing in the trachea and in the bronchial tree up to the terminal bronchioles, plays a pivotal role in modulating bronchomotor tone, but also orchestrates and perpetuates airway inflammation and remodeling [2]. ASM hypertrophy/hyperplasia, an important feature of chronic asthma, represents either a pathologic or an injury-repair response due to chronic

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inflammation [3]. These observations suggest that changes in the ASM phenotype may play a fundamental role in the pathogenesis of airway remodeling in chronic asthma [3-4].

Neutrophils are generally considered to play little role in the asthmatic inflammatory response, unlike the situation in chronic obstructive pulmonary disease (COPD) [5]. Although the precise role of neutrophils in the pathogenesis of asthma is still unclear, recent research indicates that the sequestrated neutrophils in asthmatic airways release transforming growth factor (TGF) ß [6], and are closely associated with the pathogenesis of airway remodeling in asthma. In patients with slow-onset status asthmaticus, neutrophils have been found in increased numbers, with eosinophils predominating, in lung autopsy specimens [7]. Bronchial neutrophilia was found in patients with noninfectious status asthmaticus [8].

Among the neutrophil-derived proteinases, elastase, a serine protease found in the azurophilic granules of the neutrophil, is one such molecule in particular that has received attention as a proteolytic enzyme [9]. Human neutrophil elastase (HNE) has been reported to play an important role in patients with COPD [10]. The level of neurtophil-derived elastase is also elevated in the airway lining fluid in chronic asthmaticus, ranging from 0.1-50 μg/ml [11]. In *in vitro* studies, elastase alone is mitogenic for bronchial smooth muscle cells by increasing cyclin D1 activity through the extracellular signal-regulated kinase (ERK) signaling pathway [12]. Furthermore, elastase upregulates TGF-beta1 gene expression and release in human bronchial smooth muscle cells via the My88/IRAK/NF-kappaB pathway, possibly through activation of Toll-like receptor (TLR)-4 [13].

Previous studies have shown that human ASM is an important source for regulated on activation, normal T cells expressed and secreted (RANTES) and interleukin (IL)-6 secretion in the regulation of airway inflammation [14], and intercellular adhesion molecule (ICAM)-1 expression induced by cytokines plays an important role in T-lymphocyte adhesion in human ASM cells [15]. Cell migration of smooth muscle is also a feature of both airway and pulmonary vascular diseases [16]. However, the role of HNE in the functions of human ASM cells is still not well known. In this study, we investigated the effects of HNE on synthetic and migratory functions of human ASM cells.

Materials & Methods

Human ASM Cell Culture

Human trachea was obtained from lung-transplant donors in accordance with procedures approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania. ASM cells were dissected, purified, and cultured in Ham's F12 medium supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin, and 0.1 mg/ml streptomycin (GIBCO BRL Life Technologies, Grand Island, NY), as described previously [17]. ASM cells in subculture during the second to fifth cell passages were studied. Cultured ASM cells retain native contractile protein expression, as demonstrated by indirect immunofluorescent staining for smooth muscle-specific actin, and retain functional cell-excitation coupling systems, as determined by fura-2 measurements of agonist-induced changes in cytosolic calcium.

HNE was purchased from Elastin Products Company (Owensville, MO). Substract, Suc-Ala-Ala-Pro-Val-pNA was purchased from Bachem (King of Prussia, PA). Unless other-

wise specified, all chemicals used in this study were purchased from Sigma/Aldrich (St. Louis, MO).

Measurement of RANTES and IL-6 Secretion by ASM Cells

Confluent human ASM cells were growth-arrested by incubating the monolayers in Ham's F12 with 0.1% bovine serum albumin (BSA) for 24 h. The concentration of RANTES and IL-6 in the culture medium was determined by enzyme-linked immunosorbent assay (ELISA), as described previously [14]. Human ASM cells were treated with 10 nM HNE for 0 to 8 h for a time-course response. To characterize the HNE involved in RANTES and IL-6 secretion stimulated by tumor necrosis factor (TNF) α, HNE was added for 2, 4, and 8 h, then carefully washed out before the addition of TNFα (10 ng/ml) for 18 h, in order to exclude a possible degrading effect of HNE on secreted cytokines.

Flow Cytometry Analysis

Flow cytometry was performed as described previously, with slight modifications [18]. Briefly, adherent cells were washed with phosphate-buffered saline (PBS), detached by trypsinization (2 min, 37°C) and then washed with Ham's-F12 (10% FCS) media, centrifuged, and transferred to microfuge tubes (1.5 ml). Following incubation with the FITC-conjugated mouse anti-ICAM-1 Ab (10 μg/ml, R&D Systems, Minneapolis, MN) for 1 h at 4°C, the cells were centrifuged and resuspended in cold PBS in microfuge tubes. Samples were then analyzed using an EPICS XL flow cytometer (Coulter, Hialeah, FL). ICAM-1 expression was demonstrated as the increase in mean fluorescence intensity over background. Human ASM cells were pretreated with HNE 10 nM for 2, 4, and 8 h. In order to exclude the degrading effect of HNE on cytokines, HNE was washed out before adding TNFα (10ng/ml) for 18 h.

Migration Assay

To evaluate the migratory effects, we used the Neuro Probe AP48 chemotaxis chamber (Gaithersburg, MD) to measure the migration of cultured human ASM cells, as described previously [16]. Confluent ASM cells, growth-arrested for 48 h in serum-free media, were briefly trypsinized by 0.05% trypsin/0.53 mM ethylenediaminetetraacetic acid, centrifuged at 900 rpm for 10 min, and resuspended in serum-free Ham's F-12 media supplemented with 0.1% BSA. Human ASM cells in a suspension (50,000/50 μl) were added to the upper wells of the Boyden chamber fitted with an 8-μm pore membrane, coated with Vitrogen (100 μg/ml). HNE, boiled HNE and platelet-derived growth factor (PDGF) added to the lower wells acted on ASM cells added to the upper wells. Cells in the Boyden chamber were incubated for 4 h at 37°C in a 5% CO_2 incubator. Nonmigrated cells were scraped off; the membrane was fixed with methanol, stained with a Hemacolor stain set and scanned. Cell migration was analyzed using the Gel-Pro analyzer program (Media Cybernetics, Silver Spring, MD).

Statistics

Data are expressed as the mean ± SEM. One-way analysis of variance (ANOVA) was used to compare mean values of more than 2 experimental groups. If variance among groups was noted, a Bonferroni test was used to determine significant differences between specific points within groups. Some data were also analyzed by Student's *t*-test for paired or unpaired data. A *p*-value of less than 0.05 is considered

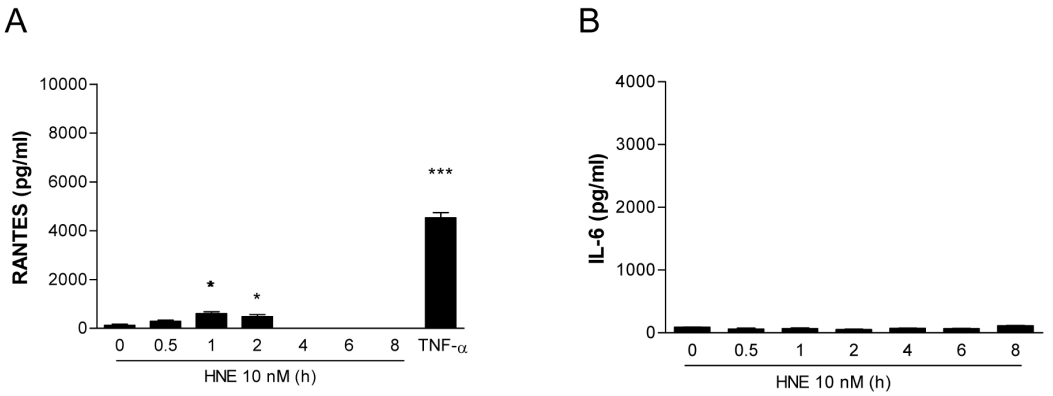

Fig. 1. HNE alone stimulates RANTES, but not IL-6 in human ASM cells. (A) HNE on RANTES production, (B) HNE on IL-6 production. ASM cultures were treated with HNE (10 nM) for 0 to 8 h, and TNFα (10 ng/ml) for 18 h as a control. RANTES and IL-6 protein levels in culture media were subsequently measured by enzyme linked immunosorbent assay (ELISA) in the supernatants. The results are expressed as mean ± SEM of 3 separate experiments. *p<0.05, *** p<0.001

statistically significant.

Results

HNE alone stimulates RANTES, but not IL-6 in human ASM cells

As shown in Figure 1A, HNE induced RANTES secretion in a time-dependent manner, significantly at 1 h (607 ± 74 pg/ml, p<0.001) and 2 h (478 ± 88 pg/ml, p<0.05), and approximately 4-fold and 3-fold more than that of the control (121 ± 48 pg/ml). However, the level of RANTES secretion was lower than that induced by TNFα 10 ng/ml for 18 h (4532 ± 206 pg/ml). In contrast, HNE did not stimulate IL-6 secretion by human ASM cells simultaneously (Figure 1B).

HNE augments TNFα-induced RANTES and IL-6 secretion by human ASM cells

We found that HNE augmented TNFα-induced RANTES and IL-6 production in a time-dependent manner (p<0.05, n=3) (Figure 2A, B). 10 nM HNE for 8 h increased TNFα-induced RANTES by 63% while TNFα-induced IL-6 production was augmented by 44%. These data provide evidence that HNE increases TNFα-induced cytokine production from human ASM cells.

HNE has a partial effect on ICAM-1 expression by human ASM cells

HNE alone did not affect ICAM-1 expression, but slightly augmented TNFα-induced ICAM-1 expression after pretreatment with HNE for 2 and 4 h (p<0.05) (Figure 3). 10 nM HNE for 2 and 4 h slightly increased TNFα-induced ICAM-1, by 9% and 11%, respectively. These data provide evidence that HNE partially affects TNFα-induced ICAM-1 from human ASM cells.

HNE enhances HASM cell migration, but has no effect on PDGF-induced human ASM cell migration.

HNE induced a 2.19 ± 0.44-fold increase

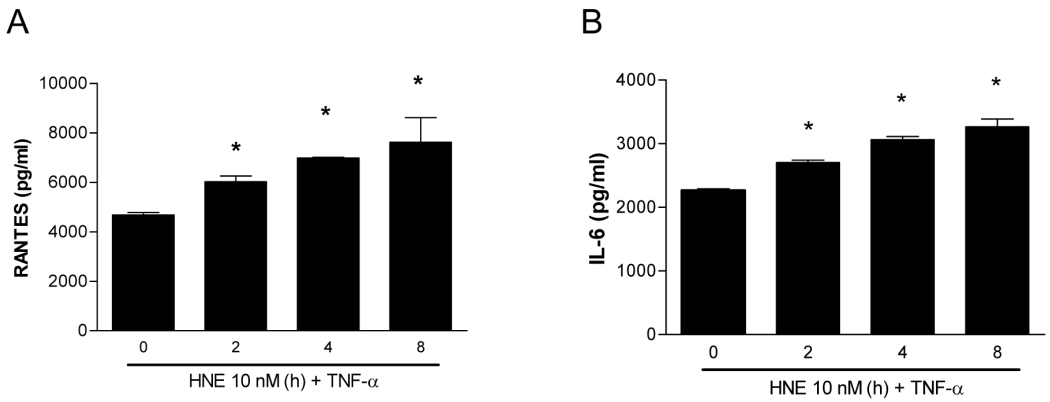

Fig. 2. HNE augments TNFα-induced RANTES and IL-6 secretion by human ASM cells. Cells were pretreated with HNE (10 nM) for 2, 4, and 8 h. Then, HNE was washed out before adding TNFα (10 ng/ml) for 18 h. HNE augmented TNFα-induced RANTES (A) and IL-6 (B) production in a time-dependent manner, significantly after pretreatment with HNE for 2, 4, and 8 h. The results are expressed as mean ± SEM of 3 separate experiments. *p<0.05 compared with TNFα alone.

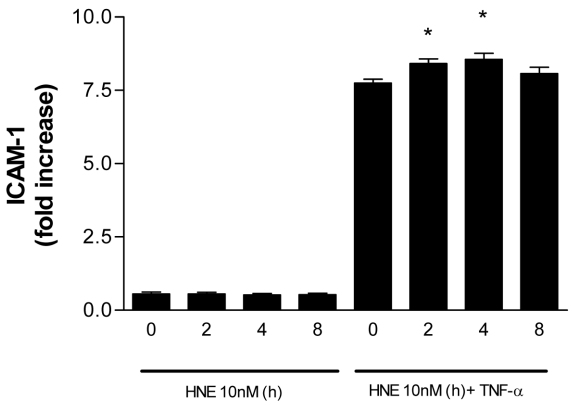

Fig. 3. HNE is partially responsible for mediating TNFα-induced ICAM-1 from human ASM cells. Cells were pretreated with HNE (10 nM) for 2, 4, and 8 h. HNE was then washed out before adding TNFα (10 ng/ml) for 18 h. HNE partially augmented TNFα-induced ICAM-1 expression after pretreatment with HNE for 2 and 4 h.

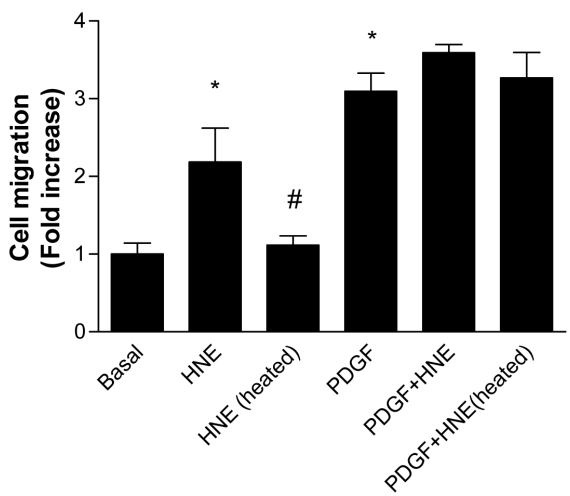

Fig. 4. Effects of HNE on human ASM cell migration. HNE induced a 2.19-fold increase in ASM cell migration, an effect that was lost when the cells were exposed to heat-inactivated HNE. HNE had little effect on PDGF-induced ASM cell migration (3.10 ± 0.23 in control cells versus 3.59 ± 0.11 in HNE-treated cells, n=4). *p<0.05 compared with basal, $^{\#}p$<0.05 compared with HNE alone.

in ASM cell migration (n=4, p<0.05), an effect that was lost when cells were exposed to heat-inactivated HNE. Interestingly, HNE had no effect on plate-derived growth factor (PDGF)-induced ASM cell migration (3.10 ± 0.23 in control cells versus 3.59 ± 0.11 in HNE-treated cells, n=4) (Figure 4). The results indicate that HNE increases non-directional cell movement (chemokinesis), but does not enhance the chemotactic response to PDGF.

Discussion

In the present study, we demonstrated that HNE treatment alone stimulated RANTES secretion, but not IL-6 in human ASM cells. In addition, TNFα-induced IL-6 or RANTES secretion was significantly enhanced by HNE pretreatment. However, HNE had a partial effect on TNFα-induced ICAM-1 expression. Further, HNE induced a 2-fold increase in ASM cell migration, an effect that was lost when cells were exposed to heat-inactivated HNE. HNE had no effect on PDGF-induced ASM cell migration. Taken together, these results suggest that HNE has the ability to modulate the synthetic and migratory functions of ASM, which may be an important player in the pathogenesis of asthma.

In contemporary concepts, it is believed that ASM cells may play a key role in chronic asthma by functioning as a rich source of pro-inflammatory cytokines, chemokines, and growth factors, and express various adhesion molecules [2]. In this study, we found that HNE increases RANTES secretion in resting cells and enhances the RANTES secretion in TNFα-treated ASM cells. In other species, transient exposure of elastase induced the mouse aortic smooth muscle cell production of RANTES [19]. However, in contrast to human bronchial epithelial cell lines, in which neutrophil elastase induces the release of interleukine-6 [20], we found that HNE alone failed to stimulate IL-6 expression, but significantly augmented TNFα-induced IL-6 secretion. In addition, HNE alone did not affect basal, and only slightly increased TNFα-induced ICAM-1 expression. A previous study showed that chymase, a chymotrypsin-like protease, does not affect cytokine-induced ICAM-1 expression in ASM cells [21], suggesting that ICAM-1 expression by protease is stimuli-specific. Taken together, these findings suggest that the differential modulatory effect of elastase on inflammatory genes and adhesion molecules is gene-specific.

The molecular mechanisms by which elastase differentially regulates the expression of inflammatory genes in ASM cells are not yet known and need to be further studied. In previous studies, TNFα stimulated nuclear factor-κB (NF-κB) DNA binding activity in ASM cells [18], and increased mRNA expression and protein levels for IL-6 [22]. Ammit *et al*. demonstrated that TNFα promotes IL-6 gene expression in ASM cells via an NF-κB-dependent pathway [23]. In this study, we showed that HNE treatment alone stimulated RANTES secretion, but not IL-6 in human ASM cells. Therefore, the enhancing effect of HNE on TNFα-induced IL-6 or RANTES secretion suggests the possible involvement of NF-κB-independent pathways. This hypothesis is further supported by the fact that induction of ICAM-1, an NF-κB-dependent gene in ASM cells [18], is unaffected by HNE treatment. Since other transcription factors, such as AP-1 and NF-AT, have been shown to regulate the RANTES gene [23], it is probable that elastase may regulate gene expression by acting on different signaling molecules.

Although there is still no direct evidence showing that ASM cells migrate *in vivo* in the airway, in vitro studies of cultured ASM cells have supported the concept that ASM cells can migrate [16, 24]. Several studies have demonstrated chemotactic responses to PDGF, IL-1ß, TGF-α, TGF-ß, and urokinase, and have delineated some of the major signal transduction pathways involved [24-27]. Using an in vitro model with fibroblast embedded between 2 layers of collagen gel to investigate cell mi-

gration, elastase exposure increased directed fibroblast migration through the extracellular matrix [28]. Digestion of matrix itself, generation of extracellular matrix (ECM) fragments, and activation of metalloprotease proenzymes or inactivating fibroblast-derived anti-proteases may contribute to the HNE-enhanced cell migration [29-30]. In this study, HNE induced a 2-fold increase in ASM cell migration, an effect that was lost when HNE was heat-inactivated. This is the first study to show the effect of HNE on ASM cell migration. Interestingly, HNE had little effect on PDGF-induced ASM cell migration. These data indicate that HNE increases a non-directional cell movement (chemokinesis), but does not enhance the chemotactic response to PDGF. In this migration assay model, the pore membrane used for ASM cell migration was coated with collagen, so degradation of the matrix may be contributory to the increase of ASM cell migration in response to HNE. Further evaluation of the relationship between ASM and ECM may be needed to clarify the mechanism by which proteases regulate ASM cell migration.

In summary, HNE, a serine protease found in the azurophilic granules of the neutrophil, is abundant in chronic inflammatory diseases such as asthma and COPD. In this study, HNE differentially regulated proinflammatory mediators and ICAM-1 expression. Interestingly, HNE induced an increase in ASM cells migration, but had no effect on PDGF-induced ASM cell migration, indicating that HNE induces non-directional cell movement (chemokinesis), but does not enhance the chemotaxis to PDGF. Taken together, these results show that HNE can modulate the synthetic and migratory functions of human ASM cells and may play an important role in the pathogenesis of chronic inflammatory airway diseases.

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人類嗜中性白血球彈性酵素對呼吸道平滑肌功能的作用

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人類嗜中性白血球彈性酵素（Human neutrophil elastase）是一種絲胺酸蛋白酶（Serine protease），富含於像嚴重慢性氣喘之類的慢性呼吸道發炎疾病。呼吸道平滑肌（Airway smooth muscle）的不同表型變化在慢性氣喘的呼吸道重塑（Airway remodeling）過程中扮演著十分重要的角色。這篇研究的主要目的是探討人類嗜中性白血球彈性酵素是否能夠調節腫瘤壞死因子（TNF-α）刺激的合成（Synthetic）功能和血小板衍生生長因子（PDGF）引導的移動（Migratory）功能。結果顯示人類嗜中性白血球彈性酵素能刺激呼吸道平滑肌分泌調節RANTES，但沒有改變IL-6。當呼吸道平滑肌經過人類嗜中性白血球彈性酵素分別處理二至八小時後，再使用10 ng/ml 的腫瘤壞死因子刺激，RANTES和IL-6分泌是有意義的隨著人類嗜中性白血球彈性酵素前處理的時間而增加（p<0.05, n=3）。然而，人類嗜中性白血球彈性酵素對於腫瘤壞死因子引導的細胞間黏連分子（ICAM）-1表現僅有部分的效果。人類嗜中性白血球彈性酵素對於呼吸道平滑肌細胞移動有2.19 ± 0.44倍的增加（p<0.05, n=4），但是熱抑制的人類嗜中性白血球彈性酵素卻沒有如此現象。有趣的是，人類嗜中性白血球彈性酵素對於血小板衍生生長因子引導的呼吸道平滑肌移動並沒有作用（控制組細胞3.10 ± 0.23，人類嗜中性白血球彈性酵素處理過的細胞 3.59 ± 0.11，n=4）。我們的研究顯示，人類嗜中性白血球彈性酵素藉由調節人類呼吸道平滑肌細胞的合成與移動功能，可能在慢性氣喘的致病機轉中扮演著重要的角色。*(胸腔醫學* ***2008; 23: 405-413)***

關鍵詞：人類嗜中性白血球彈性酵素，呼吸道平滑肌，合成，移動

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Acute Respiratory Failure in Two Pregnant Women during Tocolytic Treatment: Two Case Reports

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Acute respiratory failure due to pulmonary complications or acute respiratory distress syndrome (ARDS) is a life-threatening condition during pregnancy. The incidence of pulmonary edema is 24% in all critical illnesses associated with pregnancy. The causes are numerous, having both cardiogenic and non-cardiogenic origins, and include sepsis, tocolytic agents, and preeclampsia. The mortality rate could be as high as 23% in patients with ARDS. We report 2 patients with acute pulmonary complications during the 2nd trimester of pregnancy: 1 patient was diagnosed with tocolytic-associated pulmonary edema, and the other had septicemia-related ARDS. Both of them had received prolonged tocolytic treatment presenting with dyspnea, fever, and hemodynamic instability, and required invasive ventilation; they both received fluid and vasopressor management guided by a pulmonary artery catheter and the best supportive care. The 2 patients survived and were weaned from the mechanical ventilator successfully during their stay at the intensive care unit (ICU). Their babies survived, although 1 was delivered in the ICU on the 4th day due to precipitated labor. In this case, the mother and her baby required long-term rehabilitation after discharge. ***(Thorac Med 2008; 23: 414-420)***

Key words: tocolytic treatment, acute respiratory failure, pulmonary edema, acute respiratory distress syndrome

Introduction

Acute respiratory failure is a critical condition for both the fetus and the mother, and pulmonary edema has contributed to 24% of intensive care unit (ICU) admissions during pregnancy. Pulmonary edema was generally classified as cardiogenic and non-cardiogenic, depending on hydrostatic pressure and vascular permeability [1-3]. Tocolytic therapy is a factor commonly contributing to acute pulmonary edema under several conditions, including preeclampsia, infection, and fluid overload. Fifteen percent of pregnant women receiving multiple regimens of tocolytics developed acute pulmonary edema and 15% of that number required invasive ventilation [1]. Acute respiratory distress syndrome (ARDS) has occurred in 16-70 cases per 100,000 pregnant women [4]. The mortality of ARDS is 23% in antepartum and

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50% in postpartum mothers [5]. We report 2 pregnancies with acute respiratory failure due to acute pulmonary edema related to tocolytic treatment and ARDS.

Case Reports

Case 1

A 28-year-old healthy woman with 19 weeks of gestational age was admitted for frequent preterm uterine contraction. A ritodrine infusion was administrated intravenously, with a gradual dose increase from 153 μg/min to 220 μg/min over a 3-week period. Magnesium sulfate was added at the 3rd week of treatment, due to the inadequate tocolytic effect of ritodrine. Her vital signs were normal, but her weight increased from 42 kilograms (kg) to 48 kg. Fever developed about 3 days before ICU admission. Progressive shortness of breath and orthopnea occurred 1 day after fever onset. Tachypnea, spiking fever, tachycardia, and oxygen desaturation developed on the day of ICU admission. She was ill, febrile, and hyperhidrotic-looking. Her blood pressure (BP) was 118/71 mmHg, heart rate (HR) 122 beats per minute, respiratory rate (RR) 24 breaths per minute, and body temperature (BT) 39.8°C. Physical examination disclosed bilateral basal lung crackles, engorgement of the external jugular vein, pitting edema in both legs, and a puffy face. There was a positive fluid balance. Chest X-ray (CXR) revealed bilateral basal lung infiltrates with an air-bronchogram (Figure 1a). The hemogram revealed hemoglobin (Hb) 9.4 g/dl, a leukocyte count of 20,000/mm^3 with neutrophils 94%, and a platelet count of 88,000/mm^3. Abnormal serum data were C-reactive protein (CRP) 24 mg/dl, albumin 2.6 mg/dl, sodium 126 mEq/L, and potassium 3.2 mEq/L. Urinalysis revealed no pyuria or proteinuria. There was no significant cough, sputum, or chest pain.

Initially, she was put on non-invasive positive pressure ventilation (NIPPV) in the ICU. Data from the pulmonary artery catheter (PAC) showed pulmonary capillary wedge pressure (PCWP) of 20 mmHg, central venous pressure (CVP) 14 mmHg, cardiac index (CI) 6.55 l/min/m^2, and systemic vascular resistance index (SVRI) 1050 dyne•sec/cm^5/m^2. Acute pulmonary edema was suspected. A sudden onset of oxygen desaturation was noted 4 hours after NIPPV, and she was intubated with mechanical ventilation (MV). Arterial blood gas (ABG) data before intubation was pH 7.42, $PaCO_2$ 37 mmHg, PaO_2 41.9 mmHg, HCO_3 23.5 mEq/L, and SaO_2 78.9%. The initial MV settings were pressure control ventilation, with an oxygen fraction (FiO_2) of 1.0, positive end expiratory pressure (PEEP) 10 cmH_2O, and tidal volume (Vt) 460 ml. The ABG after MV was pH 7.39, $PaCO_2$ 31.1 mmHg, PaO_2 72.9 mmHg, HCO_3 18.6 mEq/L, and SaO_2 95%.

We gave her furosemide, ranging from 20-60 mg daily, intravenously. Meropenem was administrated for her bacteremia with *Enterobacter cloacae*. The MV demand began decreasing and bilateral basal lung infiltrates on CXR resolved gradually after 4 days of treatment (Figure 1b). Her vital signs also improved. ABG after extubation was pH 7.44, $PaCO_2$ 38.8 mmHg, PaO_2 131 mmHg, HCO_3 26.1 mEq/L, and SaO_2 99% under FiO_2 0.4. She left the ICU without respiratory distress and delivered a healthy baby at full term.

Case 2

The second case was a 24-year-old previously healthy woman, with 20 weeks of gestational age. She was admitted for tocolytic

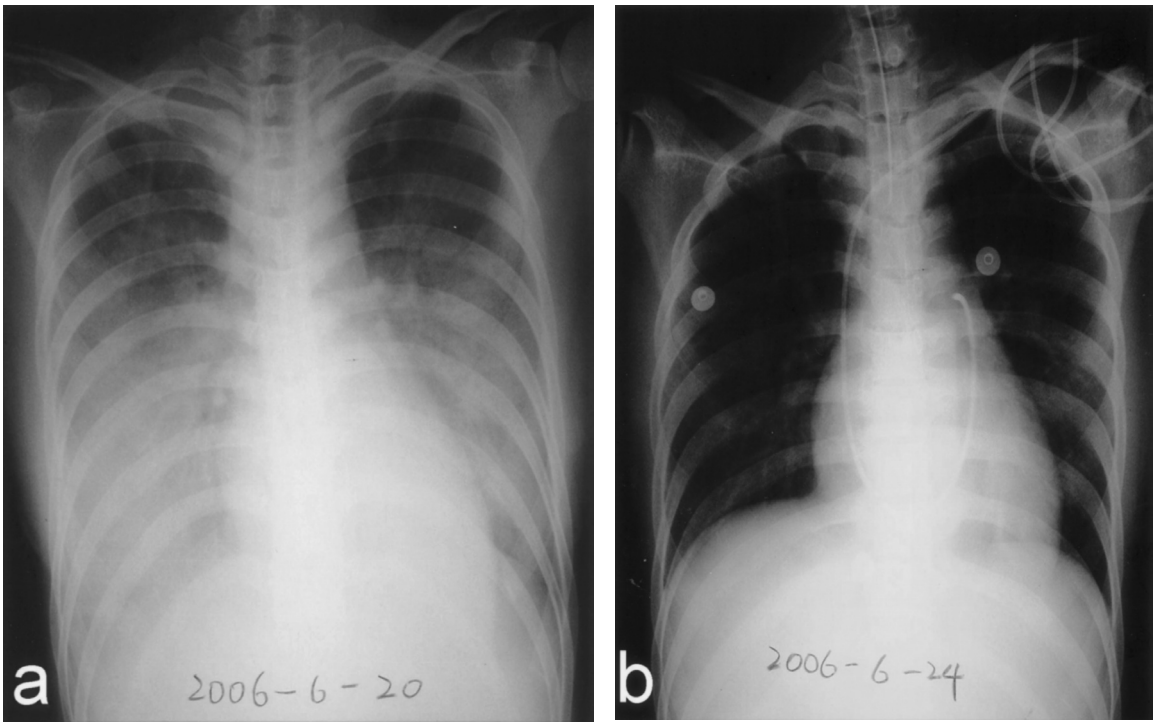

Fig. 1. Chest radiograph of the first case. The patient had bilateral pulmonary infiltrates on arrival (a) and pulmonary edema was diagnosed by PAC. Pulmonary edema was resolved 4 days after furosemide injection (b).

therapy. Ritodrine was escalated from 88 μg/min to 220 μg/min because of frequent uterine contractures, and magnesium sulfate infusion was also prescribed. Prolonged tocolytics were infused for 6 weeks due to an unstable condition.

During the 7th week of admission, she developed fever and complained of non-productive cough. Shortness of breath and hypotension became prominent in the following 2 days. Her blood pressure dropped (85/42 mmHg), and was associated with tachycardia (140 beats per minute), tachypnea (RR 44 breaths per minute), and high fever (39.3^{o}C). She was then transferred to the ICU due to hemodynamic instability. On arriving, physical examination revealed respiratory distress with bilateral basal lung crackles, but no recognizable heart murmur or leg edema The ABG was pH 7.42, $PaCO_2$ 25.1 mmHg, PaO_2 59.9 mmHg, HCO_3 16.9 mEq/L, and SaO_2 92.1% under oxygen mask FiO_2 1.0. The hemogram was Hb 10.9 g/dl, leukocyte count 14,000/mm^3 with band forms 11%, neutrophils 85%, and a platelet count of 67,000/mm^3. Of the laboratory data, only CRP 4.6 mg/dl and hypokalemia (2.6 mEq/L) were contributory. Urinalysis revealed neither pyuria nor proteinuria. Bilateral lung infiltrates were seen on serial CXRs (Figure 2a).

She was intubated and received MV with FiO_2 1.0, PEEP 10 cmH_2O, 18 breaths per minute, and a Vt 500 ml setting under an assist/control mode. Dopamine was infused for blood pressure maintenance, and then a PAC was inserted and yielded PCWP 13 mmHg, CVP 13 mmHg, CI 6.6 l/min/m^2, and SVRI 665 dyne•sec/cm^5/m^2. ARDS due to septic shock was suspected. Dopamine was tapered rapidly

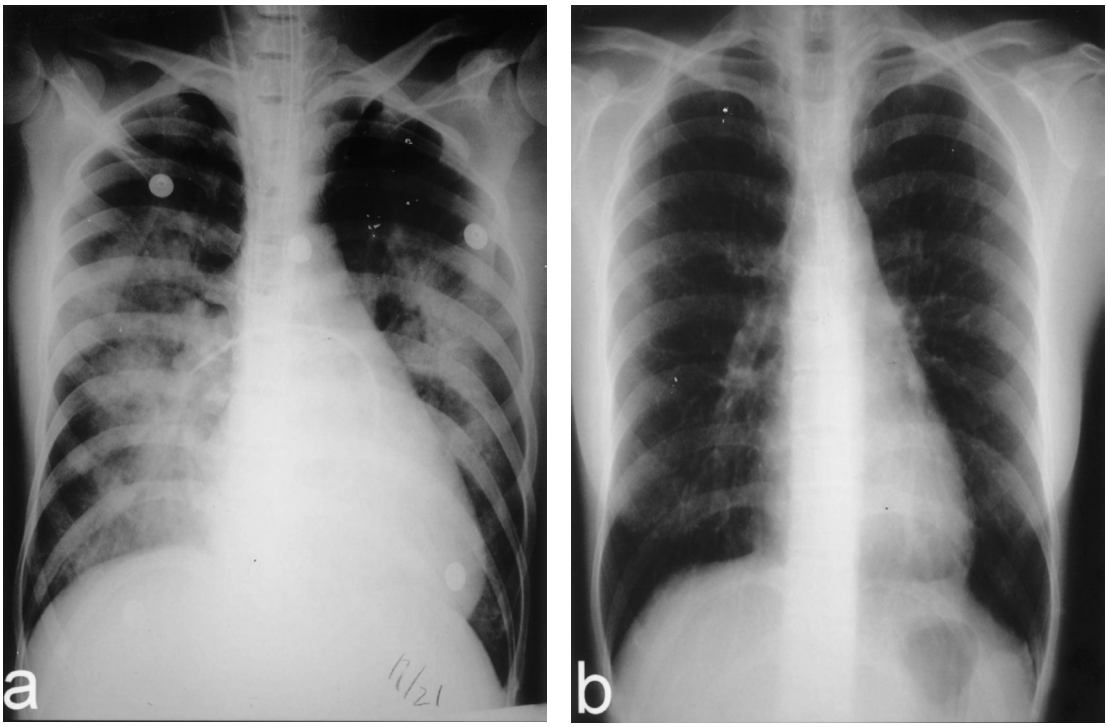

Fig. 2. Chest radiograph of the second patient. Bilateral pulmonary infiltrates were presented initially (a) and were diagnosed as ARDS by PAC. Pulmonary infiltrates had resolved 6 weeks after treatment (b).

after adequate hydration. During her 4th ICU day, abrupt vaginal bleeding was recognized by the nurse and the gynecologist was called to evaluate whether the precipitated labor was inevitable. Because of the emergency, a 1,562-g fetus was delivered at bedside. After delivery, her condition improved gradually. On the 12th ICU day, she was extubated and transferred to the general ward.

During her ICU stay, and because of delayed resolution of the pulmonary infiltrates on the follow-up CXR, a chest computed tomography was arranged and showed a bilateral inflammatory process with fibrolinear infiltrates (Figure 3). The infiltrates were considered to be the fibroproliferative plaque of ARDS. Hydrocortisone (300 mg per day) was administrated for 2 weeks, and then was tapered gradually. She showed steady improvement and was followed up regularly at the outpatient department. Her CXR revealed resolution of the pulmonary infiltrates during the follow-up (Figure 2b). Six

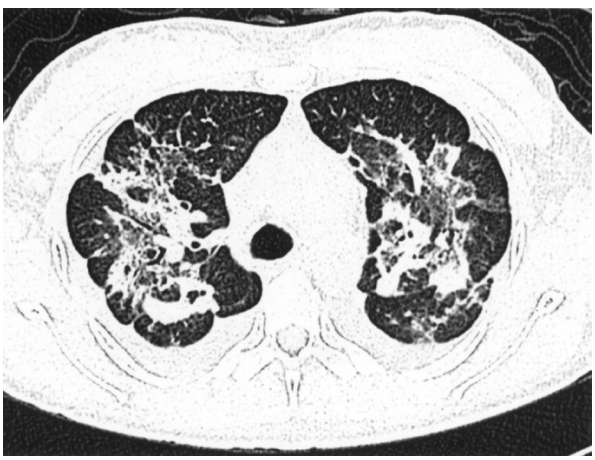

Fig. 3. Chest computed tomography of the second patient revealed a bilateral inflammatory process with parenchymal fibrolinear infiltrates in the lung window. These features were similar to the fibroproliferative plaque of ARDS.

months later, her pulmonary function test had returned to an almost normal level. The final diagnosis of this case was sepsis-related ARDS during pregnancy.

Discussion

The causes of pulmonary edema or ARDS in pregnant patients are mainly classified into 4 categories, including cardiogenic, pregnancy-related, septic, or pulmonary [6]. Tocolytic therapy, fluid overload, preexisting heart disease or cardiomyopathy, obstetric sepsis or aspiration pneumonia, and preeclampsia are the leading causes of cardiopulmonary complications during pregnancy [7-8]. Pregnant women are prone to pulmonary edema because of hypervolemia, higher cardiac output, higher heart rate, and decreased pulmonary and systemic vascular resistance [6, 9].

Tocolytics are frequently administrated for the prevention of preterm labor. These agents included ß-sympathomimetics (ritodrin), calcium channel blockade (nifedipine), magnesium sulfate, ethanol, and non-steroidal anti-inflammatory drugs (indomethacin) [10]. Bandi *et al*. [8] reported 25% of patients with pulmonary edema during pregnancy had received tocolytics before the disease onset. Tocolytic-related pulmonary edema often appeared within 48 hours of treatment and usually resolved rapidly, within 24 hours after diuretics use [9]. Prolonged and multiple regimens of tocolytics treatment with maternal infection may worsen the edema [11-12].

Management of tocolytic-related pulmonary edema includes etiology workup, hemodynamic monitoring and support, diuretics, and morphine. Our first patient had received prolonged tocolytic treatment and gained weight (6 kg in 3 weeks) before deterioration. Pulmonary edema occurred during an episode of infection and responded rapidly to fluid management. These features were compatible with the diagnosis of tocolytic-related pulmonary edema precipitated by infection.

The leading causes of ARDS during pregnancy include obstetric or non-obstetric sepsis, preeclampsia, and aspiration pneumonia. Fat and amniotic fluid emboli may also contribute [4, 11]. The maternal mortality rate of ARDS during pregnancy is 39%, and the fetal death rate is 23% [13]. Multiple organ failure is the main reason for maternal death [4].

The treatment for ARDS in pregnant women is not different from that of the general population [14]. The etiology workup, supportive care, mechanical ventilation support, and fetal monitoring are critical to patient survival. Early delivery for fetus safety should be considered if there is no benefit to continuing the pregnancy [2, 7]. Our second patient had a presentation similar to the first, but experienced a different course. Her profound shock and persistent pulmonary infiltrates did not respond to fluid management because of severe sepsis and ARDS. In spite of the precipitated labor, she survived during her ICU stay after aggressive antibiotics treatment and protective lung ventilation. Her lung function returned to nearly normal 6 months later, as with other ARDS patients [15]. Her baby survived the prolonged neonate ICU stay and was discharged requiring long-term rehabilitation. This suggests that pregnant ARDS patients should not be managed in the same way as other ARDS patients, but further research is needed.

In conclusion, acute pulmonary edema is not uncommon during tocolytic treatment. The principles of treatment are correct diagnosis,

infection control, fluid balance, and respiratory support. Workups for underlying cardiovascular disease, infection, pulmonary thromboembolism, and ARDS are necessary when there is no response to initial treatment after 24 hours.

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安胎孕婦併發急性呼吸衰竭—兩例病例報告

朱聖棻　郭秋萍　王玠仁　吳健樑

安胎孕婦的肺水腫在懷孕婦人危症中佔約四分之一。其中如果合併急性呼吸窘迫症，死亡率更高達23%。造成肺水腫的原因分為心因性及非心因性，包括感染、安胎藥物、子癇前症、及體液過量。我們報告分別是因安胎藥物及感染合併急性呼吸窘迫症引發急性肺水腫及呼吸衰竭的孕婦，在侵入性呼吸器的支持下，以肺動脈導管指引給予升壓劑及利尿劑治療改善，最後脫離呼吸器並拔管成功的兩個病例。*(胸腔醫學* ***2008; 23: 414-420)***

關鍵詞：安胎治療，急性呼吸衰竭，肺水腫，急性呼吸窘迫症

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Relapsing Polychondritis Complicated by Trachea-bronchial Stenosis: A Case Report and Literature Review

Cheng-Chien Tsai*, Chong-Chen Lu*, ***, Guang-Ming Shiao*, ***,
De-Feng Huang**, ***

Relapsing polychondritis is an autoimmune disease of the cartilage. The most common manifestations are scleritis, and chondritis of the ear and nose. If the disease is not treated well, inflammation of the cartilage in the trachea or bronchi may occur and develop into a rare life-threatening complication with severe airway narrowing, obstruction, or sudden onset of airway collapse. As the clinical manifestations of relapsing polychondritis do not usually present simultaneously, this disease is easily subjected to misdiagnosis or delayed diagnosis. We herein report a 24-year-old patient who was initially afflicted with chondritis of the ear lobes and scleritis, but was eventually complicated with severe tracheal and bronchial stenosis 6 months after inadequate immunotherapy. Computed tomography studies of the airway showed severe narrowing in the sub-glottic area (70% stenosis) and moderate narrowing in the trachea and bronchi. The affected cartilage of the trachea was also found to be swollen. After being treated with high-dose glucocorticosteroid and immunosuppressant drugs (azathioprine) for 1 month, the ear chondritis and scleritis were well controlled, but the airway stenosis remained unchanged and required surgery to prevent airway obstruction. We think that increased awareness of this disease may help us to diagnose it earlier and treat it more promptly, so as to prevent airway stenosis. ***(Thorac Med 2008; 23: 421-427)***

Key words: relapsing polychondritis, sub-glottic stenosis, traheo-bronchial stenosis

Introduction

Relapsing polychondritis (RP) is a rare autoimmune disease characterized by recurrent cartilage inflammation in many systems [1-2]; the incidence is estimated to be 3.5 cases per million in Caucasians [3-4]. About 25% to 35% of patients with RP have a concomitant disease, such as vasculitides, rheumatoid arthritis, systemic lupus erythematosus (SLE), primary Sjogren's syndrome, etc. Any type of cartilage can be involved in this disease, including the elastic cartilage of the ears and nose, hyaline cartilage of the peripheral joints, fibro-cartilage

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of the axial bones, and cartilage of the respiratory tract, in which the major collagen involved is type II collagen fiber [5]. This disorder can also involve the non-cartilaginous structures, such as the sclera, conjunctiva, heart, blood vessels and inner ear. The exact etiology remains unknown. The most common clinical presentations are auricular chondritis, nasal chondritis, and arthritis, but rarely is there respiratory tract involvement [1]. Auricular chondritis is not life-threatening; however, if the respiratory tract is involved, the disorder will become serious and have a poor prognosis. The most common manifestation of respiratory tract involvement is sub-glottic stenosis. Tracheo-bronchial stenosis is rarely reported. We herein report a case of relapsing polychondritis eventually complicated with severe stenosis from the upper airway to the bronchi. Literature concerning respiratory tract involvement in this disorder will be reviewed.

Case Report

A 24-year-old male was admitted to Taipei Veterans General Hospital because of hoarseness, chronic cough and dyspnea on exertion on 4 May 2007. Relapsing polychondritis had been diagnosed 1 1/2 years previously, based on the evidence of bilateral scleritis and chondritis of the left ear at another medical center in Taiwan. The patient was started with prednisolone (60 mg/day) alone for the first 12 days, and shifted to azathioprine alone thereafter, because he was very nervous about the long-term side effects of glucocorticosteroid. He did not take the medication regularly. Right auricular chondritis and hoarseness developed 1 year later. On admission, stridor in the neck and coarse breathing sounds in the left lower lung field were heard. Both ears were deformed with a cauliflower appearance and severe scleritis of both eyes was noted, as well. The hearing function was intact at that time. Laboratory tests showed that the complete blood count, SMAC, anti-nuclear antibody (ANA), serum immunoglobulin level, rheumatoid factor (RF), and HLA-B27 were all within normal limits. The blood erythrocyte sediment rate (ESR) level was very high (103 ml/hr). Serum HBsAg was positive, but anti-hepatitis C antibody was negative.

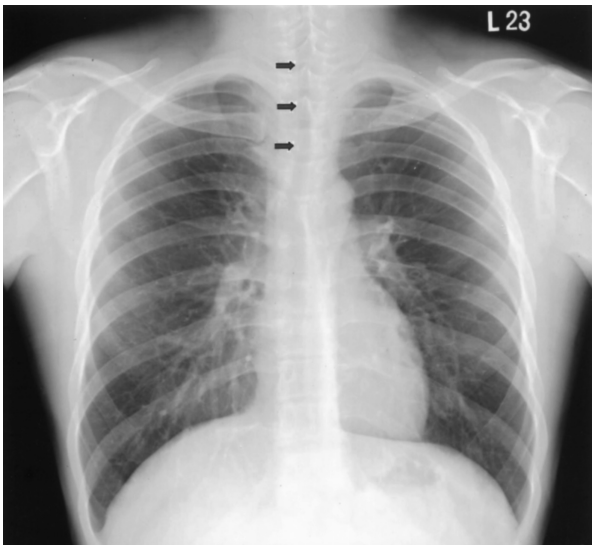

Fig. 1. Chest X-ray discloses narrowing of the tracheal and bronchial air column. (Arrow head)

The conventional chest X-ray (CxR) study was unremarkable, except for narrowing in the upper trachea and bronchi (Figure 1). Pulmonary function test (PFT) disclosed airway obstruction and a severe increase in airway resistance. Chest computed tomography (CT) scan with 3-dimensional (3-D) reconstruction revealed thickening of the anterior and lateral walls of the trachea and bronchus. The whole trachea (below the vocal cord), right main bronchus, left main bronchus, and right intermediate main bronchus were involved (Figure 2, 3 and 4). After admission, he was treated initially with

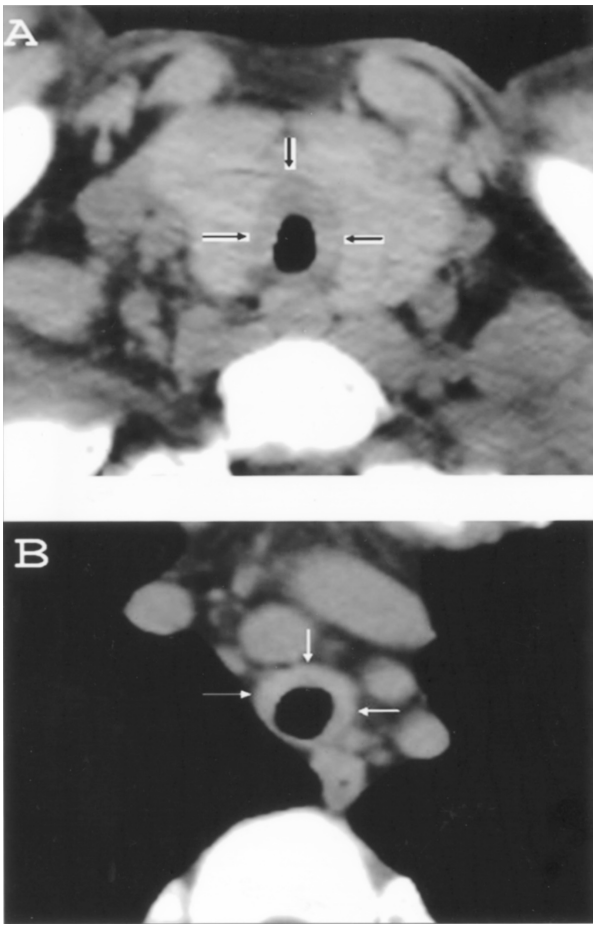

Fig. 2. Mediastinal window of the chest CT scan shows narrowing of the trachea and smooth swelling of the tracheal wall. (Anterior and lateral-cartilaginous portion) (Anterior and lateral cartilaginous portions). A (upper trachea around thyroid), B (area below A)

intravenous methylprednisolone 31 mg 3 times daily. The dose of methylprednisolone was increased to 125 mg 4 times daily in the following 6 days. Since severe sub-glottic stenosis (70% stenosis) was found, pulse therapy with intravenous cyclophosphamide 300 mg once was given 2 weeks later. After treatment, the scleritis and ear chondritis showed good improvement. He also felt more comfortable and the ESR declined (from 103 mm/hr to 8 mm/hr). Thereafter, treatment was maintained with oral methyprednisolone 12 mg twice daily, oral cyclophosphamide 50 mg once daily and oral

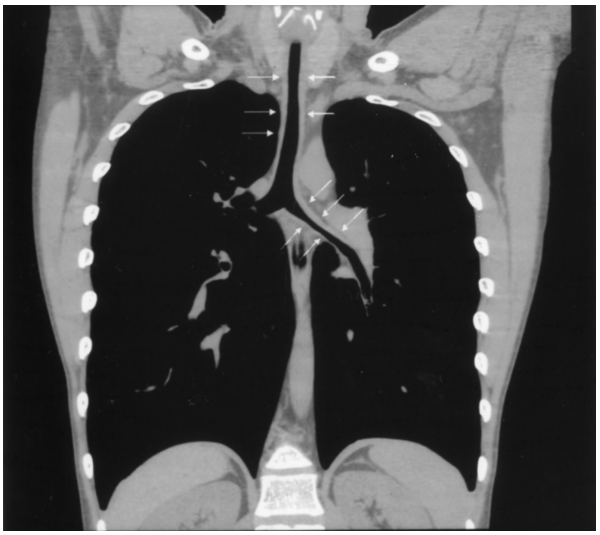

Fig. 3. Coronary section of the chest CT scan discloses diffuse swelling and narrowing of the tracheo-bronchial tree. (Arrows point to the lesions).

azathioprine 50 mg once on alternative days. However, severe stenosis of the upper airway remained, as evidenced by further imaging studies, and the patient had more difficulty breathing days later. He was transferred to the chest surgery department for surgical intervention.

Imaging by 3-D chest CT showed the left main bronchus was the most severely stenotic region of the trachea-bronchial tree (Figures 3 and 4), so the patient received a tracheal stent implantation in the left main bronchus on 26 June 2007. However, dyspnea occurred after extubation just days post-surgery, [airway stenosis with collapsed related.-not clear] Cardio-pulmonary resuscitation (CPR) was performed, and the emergency endotracheal tube was intubated with difficulty due to the collapsed airway. After resuscitation, the vital signs recovered, but he became comatose (E1VtM1). Tracheostomy was performed months later for chronic respiratory care. Unfortunately, he expired due to complications of hospital-acquired pneumonia

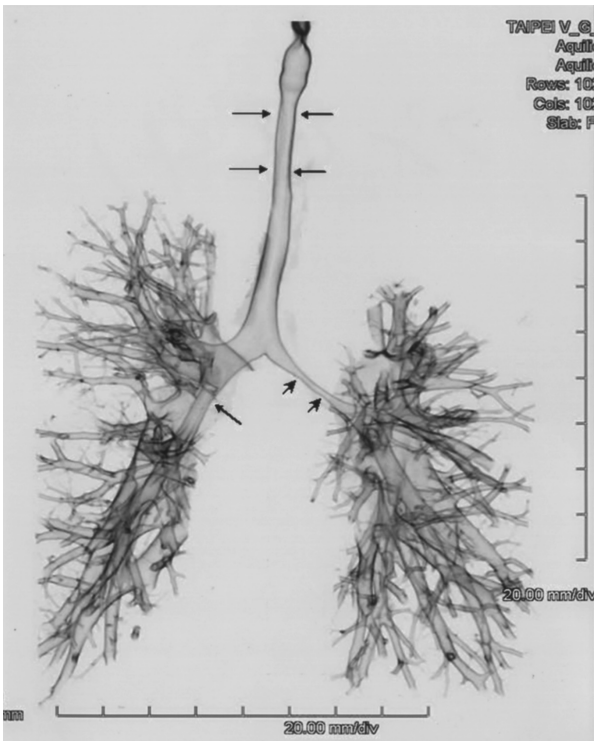

Fig. 4. 3-D reconstruction of the tracheo-bronchial tree shows diffuse narrowing of trachea, right main bronchus, right intermediate main bronchus, and left main bronchus(long arrow), and especially severe narrowing of the left main bronchus(short arrow head).

with sepsis months later.

Discussion

RP is a rare inflammatory disease of cartilaginous structures. The etiology and pathogenesis of this disorder remain unknown, although humoral and cellular immunity abnormalities have been suggested [5, 7-8]. The common presentation of RP is inflammation of the auricular cartilage in the early stage and cauliflower deformity in the chronic stage. Many studies have shown that blood ESR levels are well correlated with disease activity. Our patient initially had high ESR (103 ml/hr), which declined very quickly after immunotherapy. At the same time, the scleritis and ear chondritis improved greatly.

According to the criteria proposed by Damiani and Levine, a diagnosis of RP can be made if any 1 of the following 3 conditions is met: (1) 1 or more of the clinical criteria plus a positive cartilaginous biopsy; (2) 2 or more of the clinical criteria plus response to steroid or dapsone therapy; (3) 3 or more of the clinical criteria alone [10]. The clinical criteria proposed by McAdam, *et al*. are (1) recurrent ear chondritis, (2) non-erosive inflammatory arthritis, (3) nasal chondritis, (4) inflammation of the ocular structures, including scleritis/episcleritis, conjunctivitis, keratitis, and/or uveiitis, (5) laryngeal or tracheal chrondritis, and (6) cochlear and/or vestibular damage manifested by sen-seri-sensori-neural hearing loss, tinnitus and/or vertigo [1]. Our patient was a definite case of RP, fulfilling 3 of the clinical criteria: ear chrondritis, scleritis, and sub-glottic/tracheobronchus stenosis.

Respiratory tract involvement in RP is uncommon in the early stage, but the incidence and severity will increase as the disease progresses; the incidence is 14% in the early stage and about 50-56% during the entire course [1, 8, 14]. Airway narrowing is an indicator of a poor prognosis and poor responsiveness to corticosteroid therapy [1, 9, 11]. Airway narrowing may be asymptomatic in the early stage, but will become symptomatic when a large portion of the airway is involved. Once involved, airway narrowing is usually diffuse, from the upper to the lower airway; in severe cases, sudden collapse of the trachea may occur, causing asphyxia or even death [12]. If only the distal airway is involved, which is rare, the clinical course is usually not life-threatening [13].

There are many modalities to evaluate respiratory involvement in RP, including PFT, bronchoscopic examinations and radiographic

examinations. CxR will show diffuse, rather than segmental, narrowing of the airway. In chest CT studies, diffuse, smooth swelling of the anterior and lateral tracheal walls (cartilaginous portion, C-shaped cartilage), and narrowing in the involved areas of the airway are the most common findings. Computed programming technique-CT with 3-D reconstruction is the best method to demonstrate the extension and severity of airway involvement. PFT usually demonstrates a non-reversible obstructive abnormality, rather than an upper airway obstructive pattern. Bronchoscopic examination is helpful in evaluating the extent of inflammation, but is not performed routinely due to the high risk of severe morbidity [9].

Treatment for RP includes prednisolone, dapsone [15] or methotrexate, cyclophosphamide, azathioprine and anti-tumor necrosis factor blocker [16]. Pulse methylprednisolone therapy has been reported to be effective in acute airway obstruction [17]. Tracheostomy or stent of the respiratory tree may be required if airway stenosis in the sub-glottic area and bronchus develop [12]. Airway stent implantation can preserve the patient's voice, but may cause lethal complications if the implanted stent is displaced or causes a granulomatous formation or massive airway hemorrhage [8, 18]. Once airway stenosis appears, the prognosis is poor. Other negative prognostic factors at the time of diagnosis include old age, anemia, saddle nose deformity, arthritis, tracheo-laryngeal stricture, vasculitis, and microhematuria. Pulmonary infection such as pneumonia is the leading causes of mortality in RP [7].

In this case, despite implanting a tracheabronchial stent in the most severely stenotic area, the left main bronchus, respiratory failure occurred after extubation and CPR was needed. Unfortunately, the patient expired due to the complication of pulmonary infection. The sub-glottic mucosa may easily swell after extubation, and even lead to life-threatening complications of airway collapse. This serves as a reminder that physicians should be attentive to the complication of post-extubation swelling in the sub-glottic mucosa, and perform tracheostomy to maintain an artificial airway, if needed. And it is important to be aware of this disease when the patient presents with recurrent auricular chondritis, nasal chondritis, scleritis/episcleritis, and uveitits, so that early intensive intervention can be performed.

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覆發性多發性軟骨炎（Relapsing Polychondritis）合併氣管—支氣管狹窄之併發症：病例報告及文獻回顧

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覆發性多發性軟骨炎（RP）是一種軟骨的自體免疫性疾病。最常見的表現是鞏膜炎、耳朵和鼻子的軟骨炎。在這種疾病，如果不好好的治療，會發生氣管或支氣管的軟骨炎和罕見的嚴重性氣管狹窄、阻塞的威脅生命的併發症、或突然發生氣管塌陷。因為覆發性多發性軟骨炎的臨床表徵通常不會同時出現，這種疾病容易被主觀的誤診或延遲診斷。我們在這裡報告一位最初以耳朵的軟骨炎和鞏膜炎表現的24歲年輕患者，在接受了6個月不適當的免疫療法後，產生了嚴重氣管和支氣管狹窄。氣道的電腦斷層（CT）研究顯示了在聲門下區域產生了嚴重狹窄（70%狹窄）並且在氣管和支氣管都有中等程度的狹窄。而且受影響的氣管軟骨都腫脹起來。在以高劑量類固醇和免疫抑制藥物（azathioprine）治療1個月後，耳朵的軟骨炎和鞏膜炎都被控制得很好，但氣管狹窄依然沒有變化，而且需要外科開刀來防止氣道堵塞。我們認為如果增加了對這種疾病的了解也許會幫助我們及早診斷和適當的治療；氣管狹窄就會因而被防止產生。*(胸腔醫學* ***2008; 23: 421-427)***

關鍵詞：覆發性多發性軟骨炎（relapsing polychondritis），聲門下狹窄，氣管支氣管狹窄

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Empyema Caused by *Chryseobacterium meningosepticum* Infection: A Case Report

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Chryseobacterium meningosepticum is a Gram-negative bacillus historically associated with meningitis and sepsis in premature neonates. It is an infrequently isolated organism and a rare cause of adult and pleural infections. We reported the first case of thoracic empyema due to *C. meningosepticum*, in a 78-year-old man with transitional cell carcinoma and diabetes mellitus. He developed fever and dyspnea 13 days after bladder surgery, and was intubated due to hypoxic respiratory failure the following day. The chest radiograph revealed pleural effusion and consolidation in the left lower lung field, and thoracentesis obtained turbid fluid. Gram-negative bacilli were visible on staining of the plural fluid, and *C. meningosepticum* was isolated from the sputum, blood and pleural fluid. Thoracic drainage and trimethoprim-sulfamethoxazole therapy were then instituted. A subsequent chest radiograph showed gradual resolution of the empyema. Although it is a rare pathogen, *Chryseobacterium* empyema should be excluded in a dyspneic cancer patient with pleural effusion. ***(Thorac Med 2008; 23: 428-434)***

Key words: *Chryseobacterium meningosepticum*, empyema

Introduction

Chryseobacterium meningosepticum (*C. meningosepticum*), formerly known as *Flavobacterium meningosepticum*, is a Gram-negative rod widely distributed in nature, and rarely causes infection in adults. The organism is resistant to multiple antibiotics and is historically associated with meningitis and sepsis in premature neonates [1]. It is an inhabitant of soil and water and can live in municipal water supplies despite adequate chlorination. It has been recovered from the hospital environment often in conjunction with clusters of clinical isolates [2]; adult infections are usually nosocomial. There are no reports of *C. meningosepticum* causing pleural empyema and lung abscess in the literature. We report the first case of *C. meningosepticum* empyema in a 78-year-old man with transitional cell carcinoma and diabetes mellitus.

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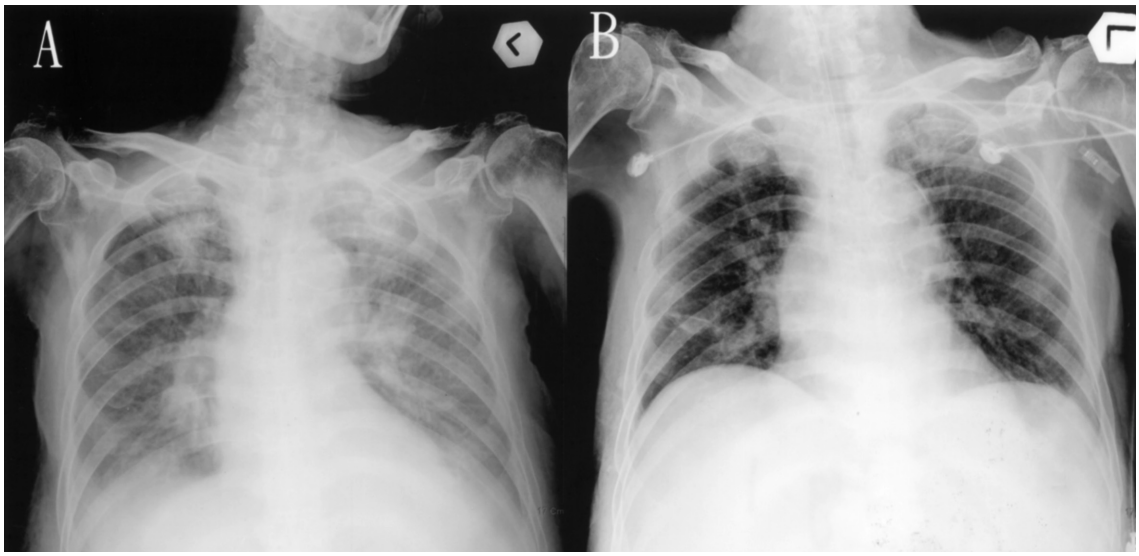

Fig. 1. (A) Chest radiograph at the onset of fever and dyspnea showing bilateral costophrenic angle blunting and bilateral infiltrates, especially in the left lower lung field; (B) Chest radiograph after treatment showed clearing of bilateral lung fields.

Case Report

A 78-year-old man was referred to our hospital with the chief complaint of a sudden onset of hematuria on 25 July 2007. He had a 9-year history of type II diabetes mellitus, with poor diabetic control prior to admission. He was a current smoker, and had consumed 1 pack per day for more than 30 years. He underwent transurethral resection of the bladder tumor, and non-invasive transitional cell carcinoma was diagnosed.

After being admitted for 14 days, and 13 days after bladder surgery, the patient developed fever and progressive dyspnea. Physical examination disclosed a pale and toxic appearance. His temperature was 40°C. His heart rate was 124 beats/min, respiratory rate 28/min, and blood pressure 105/50 mmHg. His body weight was 41 kg, and body height 155 cm. Breathing sounds in the left lower zone of the lung were decreased, with coarse crepitations heard on inspiration. Laboratory investigations revealed a total leucocyte count of 28300/mm^3, with 98% neutrophils, 1% monocytes, and 1% band forms. The level of C-reactive protein was elevated to 15.6 mg/dL, and the blood sugar level was 139 mg/dl. Chest radiograph (Figure 1A) demonstrated bilateral pleural effusions and infiltrates, seen more prominently in the left lower lobe; the patient was treated empirically with imipenem intravenously at a dose of 500 mg every 12 hours.

On the next day, an ultrasound-guided thoracentesis was performed from the left side, obtaining a turbid fluid. As there was no evidence of significant multiloculations in the thoracic sonography, a pig-tail catheter was inserted to drain the empyema. At that time, the arterial blood gases under FiO_2 0.5 were: pH 7.441; PaO_2 64 mmHg; arterial carbon dioxide tension, 35 mmHg; sodium bicarbonate, 24 mEq/l; and oxygen saturation, 90%. He then received intubation with ventilator treatment due to acute hypoxic respiratory failure.

Analysis of the pleural aspirate prior to

antibiotic therapy demonstrated the following results: a WBC count of 700/cmm (N/L=85/5), a pH of 7.0, a glucose concentration of 11 mg/dl, a protein concentration of 6400 mg/dl, and a lactic dehydrogenase (LDH) of >1000 units/l. Gram stain showed few pus cells (white cells) and filamentous Gram-negative bacilli. The pleural fluid specimen was cultured in 5% sheep blood, eosin methylene blue and chocolate agars at 35°C in 5 to 10% CO_2 for 24 to 48 h. Six drops (50 μl each drop) of specimen were inoculated in thioglycolate without an indicator broth enrichment medium. Blood was collected when the patient was febrile, and placed in 3 bottles for culture, with each bottle containing 10 ml of the patient's blood. Blood culture bottles were incubated in a BACTEC 9240 instrument (Becton Dickinson and Company, Sparks, MD). Bacterial growth was detected within 48 hours. The smooth and large colonies grew on all agars after 24 hours. Additional conventional biochemical tests, including oxidase and indole tests, and the API 20NE identification system (bioMerieux, Marcy l'Etoile, France) were used to determine the identities of these colonies. The organism was a nonmotile, oxidase-, and indole-positive Gram-negative bacillus that produced a pale yellow pigment on 5% sheep blood agar (Figure 2). In the API 20NE system, the isolate gave the biotype number 2476304 with a probability of 99.9%, which was interpreted as an "excellent identification." All tests showed that *C. meningosepticum* was present in the pleural fluid and blood cultures. Sputum culture also revealed the same result. A direct antimicrobial sensitivity test was done on Mueller Hinton agar, as well. The isolate was susceptible to trimethoprim-sulfamethoxazole only, and was resistant to all the other antibiotics: ciprofloxacin, levofloxacin, ceftazidime, cefepime, amikacin, gentamicin, imipenem, piperacillin, and piperacillin-tazobactam. Thus, we started oral trimethoprim-sulfamethoxazole (Baktar, sulfamethoxazole 400 mg + trimethoprim 80 mg), 2 tablets 3 times a day, after empyema had been diagnosed for 3 days.

Fig. 2. *Chryseobacterium meningisepticum* produced a pale yellow pigment on 5% sheep blood agar.

The patient's condition improved gradually after local and systemic therapy, and markers of infection returned to normal values. The drainage tube was removed after 6 days, and the endotracheal tube and ventilator were removed after 12 days. Trimethoprim-sulfamethoxasole was maintained for 18 days. The subsequent chest radiograph (Figure 1B) showed resolution of pneumonia and pleural effusion. The patient was discharged in good condition.

Discussion

Anaerobic bacteria are responsible for most cases of lung abscess and pleural empyema. Frequently isolated organisms in this setting

are viridans streptococci, *Pepto streptococcus* spp., and *Fusobacterium nucleatum* [3]. These organisms are part of the normal human flora, with the oropharynx and sinuses being the main sources of infection. *C. meningosepticum* was first reported by King in 1959; while studying unclassified bacteria associated with meningitis in infants, he named the organism that he recovered *Flavobacterium* ("the yellow bacillus") *meningosepticum* ("associated with meningitis and sepsis") [4]. In 1994, it was reclassified in the genus *Chryseobacterium* and was named *C. meningosepticum* [5-6]. It is a nonfermentative, nonmotile, slender, slightly curved, and catalase-, oxidase-, and indole-positive saprophytic Gram-negative aerobic rod not considered part of the normal human flora [7]. *C. meningosepticum* causes disease predominantly in premature newborns and infants. Meningitis and sepsis are the most common clinical presentations [1]. However, *C. meningosepticum* is not a common pathogen in adults [8]. The infection usually occurs in patients with significant underlying diseases, such as malignancies, neutropenia, tuberculosis, aplastic anemia, diabetes, bone marrow and solid organ transplantation, and other immunosuppressive conditions [6, 9-11]. In the hospital environment, the bacterium exists in water systems and wet surfaces and serves as a potential reservoir of infection [8, 12]. Colonization of patients via contaminated medical devices, such as respirators, endotracheal/tracheostomy tubes, mist tents, humidifiers, incubators for newborns, syringes, etc., has been documented [13]. Contaminated surgically implanted devices, such as intravascular catheters and prosthetic valves, have also been reported [14]. In this study, we reported a case of nosocomially acquired *C. meningosepticum* empyema and sepsis in an adult with transitional cell carcinoma and diabetes mellitus. Empyema caused by *C. meningosepticum* is a very unusual infection, even in immunocompromised patients. To our knowledge, this is the first report of primary *C. meningosepticum* empyema in an immunocompromised patient.

There are 2 possible pathways *C. meningosepticum* may take to cause pleural empyema. The first is through aspirated bacteria causing pneumonia and subsequently intruding into the pleural space. The second is through circulating microorganisms invading the pleural space in patients with bacteremia. Our patient developed empyema possibly through both pathways at the same time, because the bacteria were cultured in his sputum, blood, and pleural fluid.

In most of the reported cases, and in our case, *C. meningosepticum* infection was acquired in the hospital [8, 15]. The choice of an effective drug for the empirical treatment of infections due to *C. meningosepticum* is difficult. *Chryseobacterium* spp. is inherently resistant to most antibiotics commonly prescribed for Gram-negative bacterial infections, such as aminoglycosides and extended spectrum beta-lactam antibiotics [16]. However, it is often susceptible to agents generally used for Gram-positive bacteria infections (rifampin, clindamycin, and vancomycin), as well as trimethoprim-sulfamethoxazole and quinolones [17]. Our *C. meningosepticum* strain was susceptible to trimethoprim-sulfamethoxazole, but resistant to quinolones. *C. meningosepticum* is usually resistant to multiple antibiotics. These resistant phenotypes could be explained by the presence of beta-lactamases, including extended-spectrum beta-lactamases and metallo-beta-lactamases [18]. Moreover, discrepancies between the standard agar dilution test and the routinely-used disk diffusion method for susceptibility

patterns have been reported [19]. Treatment failures have also occurred with antibiotics to which the organism was deemed sensitive by disk diffusion. These observations all increase the difficulty of choosing proper antimicrobials. Previous studies have also shown that the combination of vancomycin and rifampin appears to be the most appropriate therapy for *C. meningosepticum* infections [20]. Several other reports, however, showed that vancomycin had poor activity against *C. meningosepticum* isolates [15], probably due to prior exposure to vancomycin in the immunocompromised hosts. Our patient was successfully treated with trimethoprim-sulfamethoxazole.

We have reported a case of empyema and bacteremia due to *C. meningosepticum* in a patient with transitional cell carcinoma and diabetes mellitus that was successfully treated with catheter drainage and trimethoprim-sulfamethoxazole. *C. meningosepticum* is a rare pathogen in adults, but can cause infection in immunocompromised patients with prolonged hospitalization and prior exposure to multiple antibiotics.

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腦膜膿毒金黃桿菌感染造成膿胸—病例報告

柯仰謦　許啟森*　戴孟平

腦膜膿毒金黃桿菌常是造成早產新生兒腦膜炎與敗血症的一種革蘭氏陰性桿菌，但在成人與肋膜感染中較為少見。不過，在身體防禦組織受損與免疫不全患者中，假如革蘭氏染色與細菌培養出現陰性桿菌，還是有可能是腦膜膿毒金黃桿菌感染。我們報告一位78歲男性，診斷為膀胱過渡細胞癌及糖尿病患者，手術後出現呼吸困難，胸部X光片出現左下部份的肺肋膜實質化病變，超音波穿刺則有中量肋膜混濁液。肋膜液革蘭氏染色發現革蘭氏陰性桿菌，痰液、血液、肋膜液培養均長出腦膜膿毒金黃桿菌感染的結果。我們開始使用抗生素撲菌特錠並給予適當引流。之後，膿胸在X光片與臨床上獲得明顯的控制。在這裡，我們提出這樣少見的病例報告，並對既有文獻做一回顧整理。*(胸腔醫學* ***2008; 23: 428-434)***

關鍵詞：腦膜膿毒金黃桿菌感，膿胸

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An Unusual Initial Presentation of Hemothorax due to Melanoma – A Case Report and Literature Review

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Malignant melanoma has the potential for disseminated metastasis, and, almost 90% of patients have pulmonary metastasis. Rare cases have shown isolated malignant pleural effusion. We presented a patient who suffered from progressive dyspnea for more than 10 days, and unilateral massive hemothorax was found. Melanoma was diagnosed via closed pleural biopsy. The patient also had giant congenital melanocytic nevi and extra-mammary Paget's disease, but the primary origin of the melanoma was not identified. We explored the possibility of primary pleural melanoma in this patient by reviewing published articles. Further examinations were needed to establish the hypothesis.

Once metastatic or recurrent melanoma is diagnosed, the prognosis is poor: life expectancy is lesser than 1 year. ***(Thorac Med 2008; 23: 435-440)***

Key words: melanoma, hemothorax, giant congenital melanocytic nevi

Introduction

Melanoma is the most common fatal neoplasm of the skin. Extracutaneous melanomas are rare, and of them, ocular melanoma is the most common type. Primary visceral melanoma is more unusual - it had been documented to occur in the upper airway, lungs, esophagus, gallbladder, liver, rectum, ovary, uterus, cervix, vagina, adrenal gland, and leptomeninx [1-3]. The diagnosis of primary visceral melanoma necessitates the fulfillment both clinical and histological criteria. To our knowledge, the initial diagnosis of melanoma is rarely made by means of pleural biopsy. Herein, we describe a patient with melanoma who had the initial presentation of hemothorax.

Case Report

A 70-year-old gentleman was admitted to our hospital because of progressive dyspnea for more than 10 days. He was a heavy smoker for about 30 years; no mention of chronic cough, chest pain, fever or body weight loss was made. At the time of admission, he was acutely ill-looking. The physical examination revealed a blood pressure value of 136/74 mmHg, a pulse rate of 103 bpm, a body temperature of 36.9°C, and a respiration rate of 24 breaths/min. Respi-

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ratory sounds were decreased in the left middle and lower lung fields, and dullness on percussion in that area was noted. A large-sized congenital nevus, more than 20 cm, extending from the lower back to the upper thighs, was noted. The patient denied any new changes in the congenital nevus, or a past history of excised nevus. In addition, erythematous and exudative plaque had existed in the right scrotal area for more than 10 years. The remainder of the physical examination was unremarkable.

The laboratory studies revealed no obvious abnormality except mild anemia (hemoglobin: 11.8 gm/dl). The chest radiography showed left massive pleural effusion (Figure 1). The computed tomography of the chest revealed left-side pleural effusion and contrast-enhanced nodular thickening of the parietal pleura (Figure 2). We performed thoracentesis in the left hemithorax and bloody fluid was found. Laboratory testing of the pleural fluid revealed the following: the white blood cell count: 525/mm^3 (neutrophils, 24%; lymphocytes, 68%; monocytes, 3%); red blood cell count: 1.3 × 10^6/mm^3; glucose: 76 mg/dl; protein: 5 g/dl; lactate dehydrogenase: 1403 IU/L. The hematocrit of the pleural effusion was 25.8%, and that of the peripheral blood was 37.3%; hemothorax was diagnosed. We arranged a closed pleural biopsy and found some black-pigmented debris on the pleural samples. The patient then underwent thoracostomy to drain hemothorax. Histological analysis of the pleural biopsy specimen confirmed the diagnosis of melanoma. The immunohistochemical stains of the specimen were positive for HMB-45 (Figure 4) and negative for TTF-1, CEA

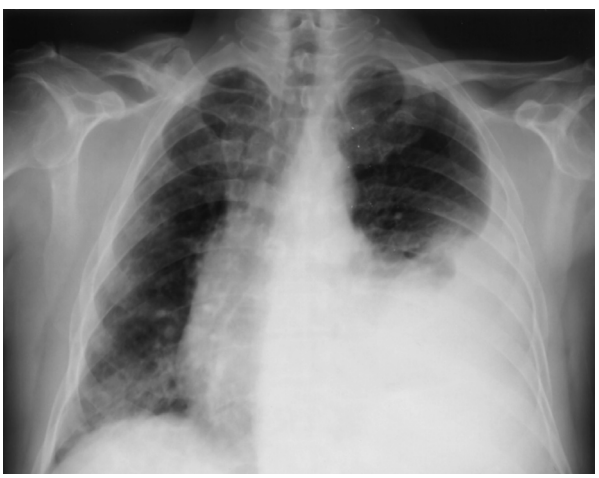
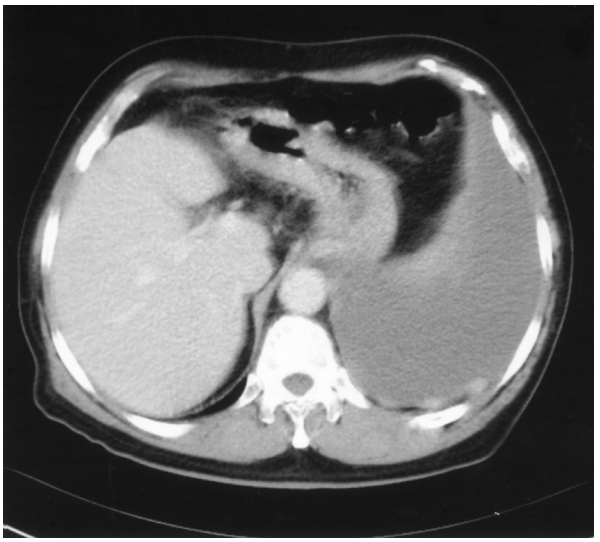


Fig. 1. Posteroanterior chest radiograph demonstrating massive pleural effusion in the left hemothorax resultinged in a deviation of the mediastinum to right side.



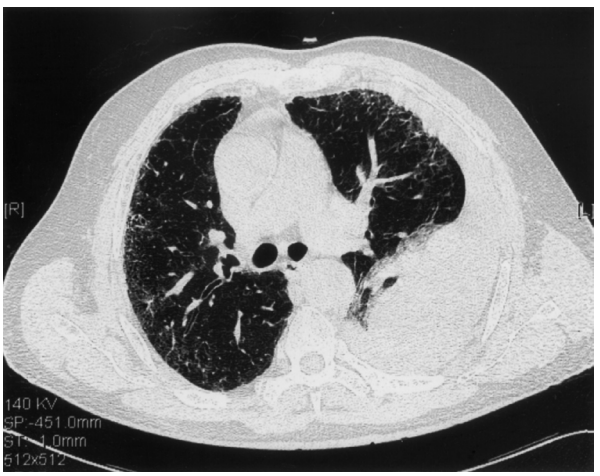


Fig. 2, 3. Computed tomography of the thorax revealing left-sided pleural effusion and nodular thickening of the parietal pleura to the posterior. No pulmonary metastatic lesion was detected.

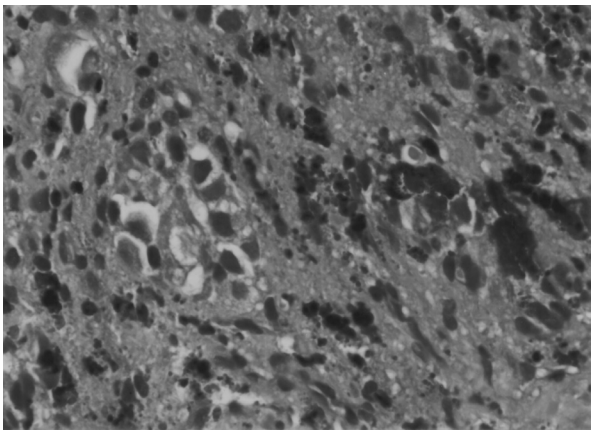


Fig. 4. Pleural biopsy: Hematoxylin and eosin stain showed cancer cell nests with melanin - contain (original magnification × 400).

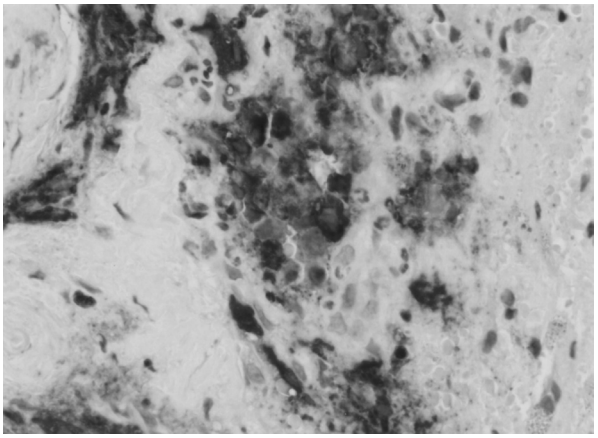


Fig. 5. Pleural biopsy: Immunohistochemical stain showed positive tumor cell staining for HMB-45 (original magnification × 400).

and calretinin. Skin biopsy of the right scrotal lesion was also performed, and the pathologic report showed extra-mammary Paget's disease. The scrotal specimen was negative for HMB-45 staining. Dermatologic and ophthalmologic specialists were consulted to evaluate the possibility of metastatic melanoma, but negative findings were revealed at the primary site of the melanoma. The patient later received pleurodesis with tetracycline. No further anemia was noted during hospitalization. After discharge, the patient went to another hospital for a second opinion.

Discussion

Malignant melanoma has the capacity to metastasize widely and quickly to every organ in the body. The most common metastatic sites are the lung, liver, brain, and bones. Pulmonary involvement occurred in almost all cases of generalized disease [4]. Most patients encountered pleural metastasis combined with pulmonary metastasis, and fewer cases had isolated and unilateral pleural effusion [4]. From descriptions found in published reports, malignant pleural effusions due to melanoma were mostly straw-colored or serosanguineous in appearance and only 2 cases with hemothorax were presented [5-6]. One of the patients underwent thoracoscopy for massive hemothorax, which showed blood oozing from multiple pleural, pericardial, and diaphragmatic implants of metastatic melanoma [5].

There are 2 hypotheses for the occurrence of pleural melanoma. Several investigators have hypothesized that primary visceral melanomas were probably derived from residual melanoblasts [1]. The others hypothesized that spontaneous regression of a previously unknown mucosal melanoma lesion is the explanation for primary pleural melanoma, or called "metastatic pleural melanoma". DasGupta *et al*. suggested that a primary growth on the skin or within the eyes often eluded clinical recognition or regressed spontaneously [7]. It is widely recognized that small primary sites of this disease may be absent after metastasis appeares, due to medical removal, accidental removal or even spontaneous regression. However, our patient denied a prior history of melanoma. This patient's pleural melanoma originated from a

previously unknown mucosal lesion with spontaneous regression; the congenital residual melanoblast cannot be proved or disproved.

Giant congenital melanocytic nevi have the risk of developing melanoma. Giant congenital melanocytic nevi also had an association with leptomeningeal melanosis. William reported 12 well-documented patients with giant pigmented nevi associated with melanocytosis of the brain. The leptomeninges were involved in all of these patients. The cerebellum was the main area of pigmentation, followed by the pons [2]. Several investigators reported cerebral melanomas in associated with leptomeningeal melanosis and giant nevi. None of these patients had demonstrable cutaneous melanomas [2]. Magnetic resonance imaging with gadolinium contrast is the procedure of choice to detect meningeal thickening when cerebral melanosis is suspected [3]. We did not perform a skin biopsy of the congenital melanocytic nevus (although no newly-changed lesion was detected), and the patient hesitated having a skin biopsy it.

The genitalia, perineum, axilla, and external auditory cannels are rich in aprocrine glands, and they are the usual sites of extra-mammary Paget's disease (EMPD). The anatomic location of EMPD plays a role in predicting the risk of associated carcinoma. About 4-7% of patients with genital disease have an associated carcinoma. Because superficial spreading of malignant melanoma is 1 of the differential histological diagnoses of EMPD [8], special stains are necessary to distinguish Paget's disease from melanoma. Immunohistochemical markers S100 and HMB-45 show positive findings in most cases of melanoma. Very occasionally, S100 staining may be positive in extra-mammary disease, but HMB-45 staining does not label Paget's cells. Besides, melanocytes are not labeled with the antibodies commonly used to identify Paget's cells (Cam5.2, anti-EMA, anti-CEA) [8]. The misdiagnosis of the scrotal lesion was less likely in our patient, but further examination of the lower gastrointestinal tract malignancy (e.g., anorectal melanoma) was needed.

In this case, we could not prove that the pleural melanoma arose from a primary lesion or was due to metastasis. The criteria for proving a primary case of pulmonary melanoma, established by Jesen and Egledrof in 1967, were (a) no previously removed skin tumor, (b) no ocular tumors, (c) a solitary specimen from the lung, (d) pleomorphism as an indication of metastasis, (e) no other organ involvement, and (f) autopsy with proof of no other primary organ involvement [9]. Autopsy for a definite diagnosis is rarely accepted in Taiwan. If primary visceral melanoma is suspected, a more complete survey is needed to fulfill criteria similar to those above. Allen and Drash also proposed 3 histologic criteria to help differentiate "primary" pulmonary melanoma from "metastatic" disease. These criteria include (1) junctional change with nesting of malignant cells beneath the bronchial epithelium; (2) invasion of the bronchial epithelium in an area without epithelial ulceration; and (3) demonstration of melanoma beneath the aforementioned described changes [10]; however, such criteria remain to be substantiated [11]. Das Gupta and others reviewed the problems of occult primary lesions in melanoma and suggested that a primary growth on the skin or within the eye often had eluded clinical recognition or had regressed spontaneously [9]. We also face a difficulty in the diagnosis of primary visceral melanoma.

The treatments for melanoma include surgery, chemotherapy, biotherapy (e.g., interferon-alfa, interleukin-2), radiotherapy or a combi-

nation of treatments. The treatment regimen depends on the extent of the disease, the patient's age, and general health. It begins with surgical removal of the melanoma and the surrounding tissue. In patients with a high risk for metastasis, a combination therapy with chemotherapy and biological therapy is needed to spread control. However, the prognosis of metastatic melanoma is poor, despite advanced treatment. Life expectancy is short, less than 1 year (mean, 9 months) in patients with metastatic pulmonary melanoma [12]. Therefore, we explored the possibility of primary pleural melanoma in this patient.

Acknowledgements

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以血胸爲初始表現之惡性黑色素細胞瘤—一病例報告及文獻回顧

曾筱倫　林明憲　薛尊仁*　鄭任勳

惡性黑色素細胞瘤容易有廣泛性全身性轉移之情形，而大約90%的病人表現有肺部轉移。少數病例以單純的惡性胸水、未合併肺部轉移來表現。我們提出一位以漸進性呼吸困難及單側量多之血胸來表現的病人，其肋膜切片報告顯示為惡性黑色素細胞瘤。此病人合併有大型先天性黑痣及外生殖器之乳房外柏哲德氏病（extramammary Paget's disease），但其惡性黑色素細胞瘤之原發位置尚未證實。根據文獻報告，我們試著討論其為原發性肋膜黑色素細胞瘤之可能性，但現有之檢驗報告不足以診斷其原發處，仍需更進一步的影像學檢查、甚至病理檢驗。一旦病人被診斷有轉移性或再發性惡性黑色素細胞瘤，其預後通常不佳，病人的預期存活期將少於一年。*(胸腔醫學* ***2008; 23: 435-440)***

關鍵詞：黑色素細胞瘤，血胸，大型先天性黑痣

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Plexiform von Recklinghausen's Neurofibromatosis with Mediastinal Involvement – A Case Report

Chi-Sheng Chen, Min-Hsi Lin, Huang-Chou Chang*, Shong-Ling Lin**,
Kuo-An Chu, Ruay-Sheng Lai

A 21-year-old male was admitted to our hospital because of an abnormal shadow on chest X-ray (CXR) noted during a routine military health check-up. He was asymptomatic and had no neurologic dysfunction. CXR showed widening of the upper mediastinum. Chest computed tomography scan demonstrated diffuse low-attenuation mass-like lesions on multiple compartments of the mediastinum, with cephalic extension to the lower neck and downward extension to the subdiaphragmatic paraaortic area. Mediastinoscopic biopsy disclosed a plexiform neurofibroma. During 2 years of follow-up, the patient was asymptomatic and stable, based on the radiographic results. We report this rare case of plexiform neurofibromatosis with mediastinal involvement. ***(Thorac Med 2008; 23: 441-446)***

Key words: plexiform neurofibroma, neurofibromatosis

Introduction

Von Recklinghausen's disease is characterized by multiple neurofibromas and cutaneous café-au-lait spots, either with or without a family history. Von Recklinghausen neurofibromatosis is a hamartomatous disorder which primarily involves the ectoderm and mesoderm. The disease can be subdivided into central and peripheral forms. The central form is associated with the presence of intracranial or intraspinal tumors, including neurilemmomas, astrocytomas, meningiomas, and ependymomas. The peripheral form is characterized by the presence of multiple nerve sheath tumors, usually neurofibromas, together with cutaneous lesions and skeletal abnormalities. Neurofibromas may be found in any location, including the mediastinum.

Plexiform neurofibromas are among the most common and debilitating complications of neurofibromatosis type 1 (NF1). Plexiform neurofibromas are subject to transformation into malignant tumors, a complication that is refractory to treatment both because of a paucity of effective therapies for malignant soft tissue sarcomas in general, and because of the delay in diagnosis that results from change in a

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small portion of a large pre-existing tumor. The current mainstay treatment of plexiform neurofibromas is surgical resection, and the major challenges are the timing and means of identification, methods of follow-up, and indications for surgery. In this report, we present a case of plexiform von Recklinghausen's neurofibromatosis with mediastinal involvement.

Case Report

This 21-year-old male was admitted to our hospital because of an abnormal shadow on chest X-ray (CXR) noted at a routine military health check-up. His parents denied having von Recklinghausen's disease. Physical examination revealed numerous café-au-lait spots and nodular cutaneous lesions on his trunk. CXR showed widening of the upper mediastinum (Figure 1). Computed tomography (CT) scans of the chest and abdomen demonstrated diffuse low-attenuation masses in multiple compartments of the mediastinum with cephalic extension to the lower neck and downward extension to the subdiaphagmatic paraaortic area (Figure 2), simulating extensive adenopathy infiltrating throughout the mediastinum and retroperitoneal space (Figure 3). The patient also had subcutaneous neurofibroma (Figure 4). Initially, we thought the problem to be lymphangioma or lymphoma. Mediastinoscopy with biopsy was done to make a definite diagnosis. The pathology of the resected specimen revealed plexiform

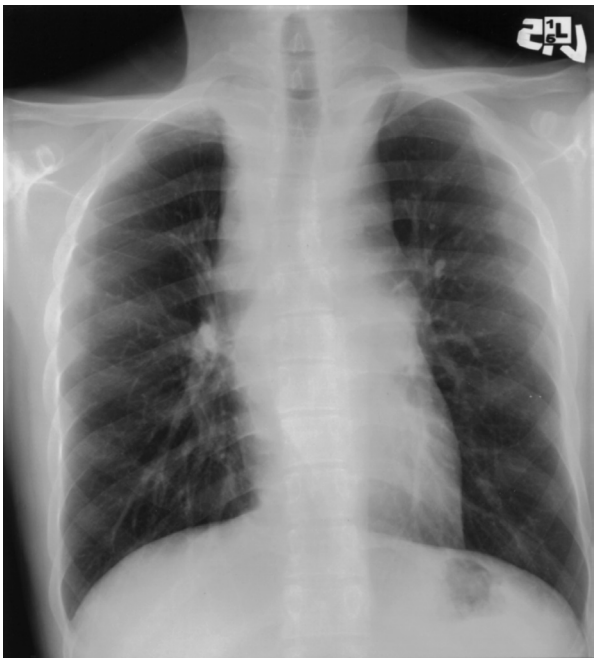

Fig. 1. CXR showing widening of the upper mediastinum

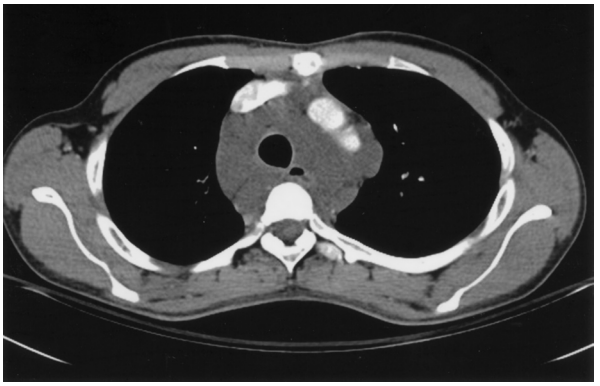

Fig. 2. Intravenous contrast-enhanced chest CT scan demonstrates multiple low-attenuation masses in the upper mediastinum.

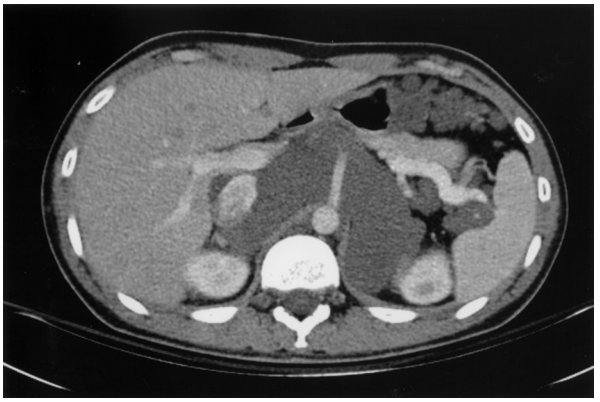

Fig. 3. Intravenous contrast-enhanced abdominal CT scan demonstrates low-attenuation masses simulating extensive celiac adenopathy infiltrating throughout the retroperitoneal space. Multiple low-attenuation masses in the mesentery and splenic hilum are also present.

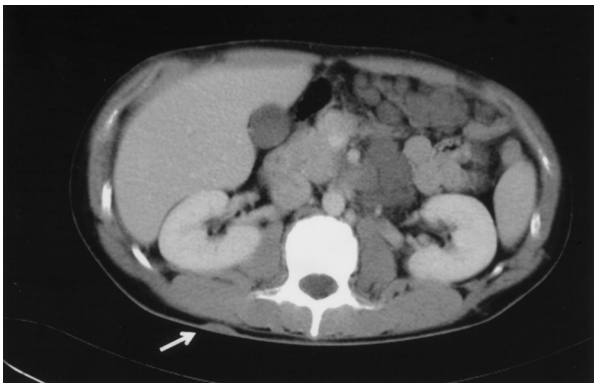

Fig. 4. Intravenous contrast-enhanced abdominal CT scan shows multiple low-attenuation masses in the mesentery and retroperitoneal space. The patient also has a subcutaneous neurofibroma (arrow).

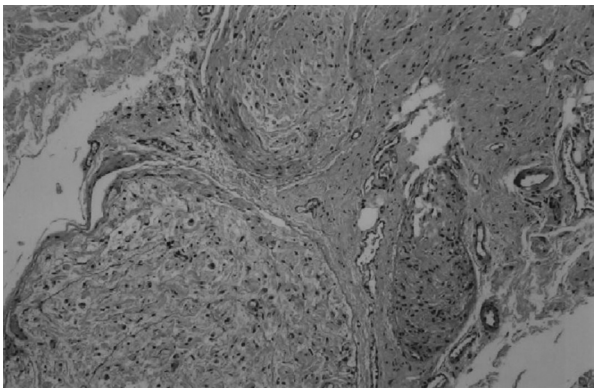

Fig. 5. The pathology of the resected specimen revealed plexiform neurofibroma, composed of a plexiform growth of spindle cells with wavy nuclei embedded in a myxoid stroma (H&E, x100).

neurofibroma, composed of plexiform growth of spindle cells with wavy nuclei embedded in a myxoid stroma (Figure 5). The tumor cells were positive for S-100 staining (Figure 6). The diagnosis was plexiform neurofibromatosis with mediastinal involvement.

Discussion

Mediastinal neurogenic tumors are the most common mediastinal tumors, and are classified as neurilemmoma (schwannoma), ganglioneuroma, and neurofibroma. Neurofibroma accounts for 2-4% of all mediastinal tumors, and neurofibroma with von Recklinghausen's disease is associated with less than 1% of all cases [1-3].

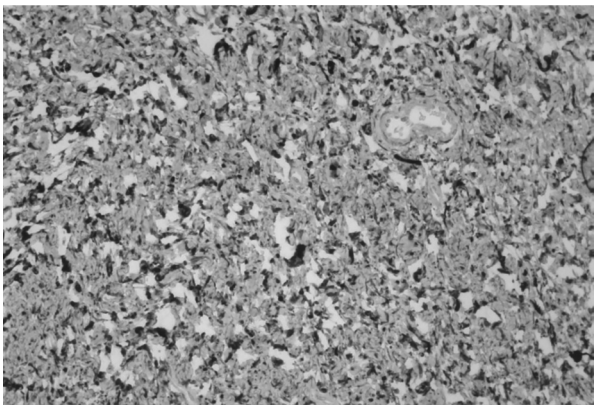

Fig. 6. The tumor cells are positive for S-100 staining (x100).

Neurofibromatosis is a common neurocutaneous disorder, and includes many different forms; NF1 is the most common type, and accounts for at least 85% of patients. NF1 is an autosomal dominant genetic disorder with an incidence of approximately 1 in 3000 individuals [4]. Plexiform neurofibromas are not rare in individuals with NF1. In a population-based study by Huson, 26.7% of individuals had plexiform neurofibromas evident by physical examination [5].

The diagnostic criteria for NF1, as originally established by the National Institutes of Health Consensus Development Conference in 1987 [6], specified that 2 or more of the following be present:

(1) Six or more café-au-lait macules more than 5 mm wide at the greatest diameter in prepubertal individuals and over 15 mm in postpubertal individuals;

(2) Two or more neurofibromas of any type or 1 plexiform neurofibroma;

(3) Freckling in the axillary or inguinal re-

gions;

(4) Optic glioma;

(5) Two or more Lisch nodules (iris hamartomas);

(6) A distinctive osseous lesion such as sphenoid dysplasia or thinning of the long bone cortex, with or without pseudarthrosis;

(7) A 1st-degree relative (parent, siblings, or offspring) with NF1 by the above criteria.

The presence of multiple neurofibromas in this patient fulfilled 2 of the criteria for NF1. He had more than 6 café-au-lait spots and plexiform neurofibromas. He did not have axillary or inguinal freckles, Lisch nodules, skeletal dysplasia, or optic glioma. There was no definitive diagnosis of NF1 in a 1st-degree relative.

Plexiform neurofibromas usually occur in the neck, pelvis, and extremities, but may be seen in any location, including the thorax [7-8]. In the thorax, the sympathetic chains are most commonly involved, but plexiform neurofibromas of the vagus and phrenic nerves are rarely involved [9]. Plexiform neurofibromas appear as a diffuse fusiform enlargement of the peripheral nerves and as multiple masses along the courses of the peripheral nerves [10].

Growth of plexiform neurofibromas can occur at any time in life. Clinical experience, however, suggests that plexiform neurofibromas tend to grow in 2 distinct periods. The first is early childhood; growth may occur rapidly for several years and then stop entirely, or may continue steadily. The second is during times of hormonal changes, most notably during puberty or, in women, during pregnancy [11].

Intrathoracic neurofibromas may have an increased incidence of malignancy when associated with von Recklinghausen's disease [12]. Intrathoracic neurofibroma with von Recklinghausen's disease might have a potential for malignant transformation [13]. The cause of von Recklinghausen's disease is now considered to be mutations in the tumor suppressor gene, namely the NF1 gene, thus suggesting a molecular basis for the malignant transformation of the benign tumors [14].

Treatment of plexiform neurofibromas remains a surgical challenge with no established medical approach. The major dilemma for surgery is optimal timing. Plexiform neurofibromas often grow and invade surrounding tissues during childhood, so it would seem that early surgery might prevent the development of major cosmetic and functional impairment. In a retrospective review of 121 patients who underwent surgery, representing 168 tumors, 94/168 (56%) tumors did not recur after the initial surgery, with a median follow-up of 6.8 years (range 2 months to 24.5 years). Prognostic factors for tumor recurrence were age less than 10 years at the time of initial surgery, presence of residual tumor after surgery, and location of the tumor on the head, neck, or face. Only 14 patients (4.6%) had permanent neurological sequelae, such as sensory loss, paralysis, and cranial nerve palsy, following surgery. As might be expected, tumors that could be completely resected were less likely to recur [15]. This 21-year-old male patient was asymptomatic, without signs of cardiopulmonary compromise or radiographic signs of progression in the 2 years of follow-up. Because of the infiltrative nature of the neurofibroma and the fear of operative mortality, the patient was followed up at our outpatient department regularly.

In conclusion, neurofibromatosis is a common neurocutaneous disorder and includes many different forms. NF1 is the most common type. Plexiform neurofibromas are not rare in individuals with NF1. Plexiform neurofibromas

of the vagus and phrenic nerves are rarely involved in the thorax. With radiographic signs of a widened mediastinum, identification of café-au-lait spots and subcutaneous nodules favors the diagnosis of plexiform neurofibromatosis of the mediastinum, and helps exclude lymphadenopathy caused by lymphoma or metastatic disease. Our case highlights the importance of a detailed physical examination, which may significantly narrow the list of differential diagnoses and allow physicians to do further procedures that lead to a precise diagnosis.

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縱膈腔叢狀神經纖維瘤—病例報告

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一名21歲男性，兵役體檢胸部X光片發現不正常陰影而入院檢查。病患無任何症狀亦無神經學異常。胸部X光片顯示縱膈腔增寬。胸部電腦斷層顯示腫瘤位於縱膈腔，並從頸下延展至橫隔下主動脈旁。經安排縱膈腔鏡手術，病理切片結果為叢狀神經纖維瘤。在兩年的追蹤期間病患沒有特別的症狀並且沒有影像方面的惡化。在此我們報告一位於縱膈腔的叢狀神經纖維瘤罕見病例。*(胸腔醫學* ***2008; 23: 441-446****)*

關鍵詞：叢狀神經纖維瘤，第一型神經纖維瘤

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Chemical Pneumonitis Induced by Cinnabar – A Case Report

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It is not uncommon to use Chinese herb to treat disease in Asian societies. The function of cinnabar (China red) in Chinese herbal medicine is to relieve nervousness and induce mild sedation. We reported a 74-year-old man with acute for 2 days exposure to cinnabar vapor. Acute chemical pneumonitis with respiratory failure developed and progressed to acute respiratory distress syndrome. He was intubated, and mechanical ventilation was applied. After Dimaval [2.3-dimercaptopropane sulfonate (DMPS)] and corticosteroid treatment, the clinical condition deteriorated and the patient died from profound hypoxemia. Literature was reviewed. The necessity of educating people to use China red appropriately for preventing such a tragedy is highlighted. ***(Thorac Med 2008; 23: 447-451)***

Key words: cinnabar, Dimaval, 2.3-dimercaptopropane sulfonate (DMPS), acute respiratory distress syndrome

Introduction

In industrial society, chemical pneumonitis induced by accidental inhalation of mercury vapor has been reported. Acute inhalation of high concentration of mercury vapor can cause pneumonitis that can lead to respiratory failure and death [1-2]. However death via cinnabar vapor inhalation is seldom reported in Asian countries. The Cinnabar is a name applied to mercury sulfate. It is used in Asian countries for medical purposes and is usually taken orally. We report here a case of inhalation of cinnabar vapor and review the literature

Case Report

The 74-year-old man suffered from insomnia for months. Even under sleeping pills, the condition was not improved. Then he accepted friend's suggestion to use cinnabar. The procedure was done in a closed room of his apartment via inhalation of cinnabar vapor 2~3 hours daily for 2 days. He became ill with paroxysmal cough, dyspnea, chest pain, nausea, and vomiting. Condition deteriorated, and he was sent to a local hospital for progressive dyspnea, change conscious, and respiratory failure. The initial arterial blood gas (ABG) at the emergency department in that hospital showed a pH of 7.25,

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a PCO_2 of 22.6 mmHg, a PO_2 of 42.4 mmHg, and a saturation of oxygen of 80%. Intubation was done immediately. He and his family didn't mention the history of cinnabar inhalation. The clinical condition progressed to acute respiratory distress syndrome. All bacteria cultures were negative. The Legionella urinary test, serum tests for *Mycoplasma pneumoniae* antibody, and *Chlamydia pneumoniae* antibody were negative. After hospitalization for one week, the family found the history of cinnabar inhalation in the patient's written notes. The patient was immediately transferred to our hospital for 2, 3-Dimercaptopropane sulfonic acid (DMPS) treatment. The chest X-ray film (Figure 1) on the 7th day after inhalation showed bilateral alveolar infiltration. The laboratory data on our emergency department disclosed urine arsenic: 17.28 μg/g (reference normal range, <120). Zinc: 4199.38 μg/g (reference normal range, 10-700) lead: 6363 μg/g (reference normal range, <7.5) Chromium (Cr): 0.87 μg/g (reference normal range, <9.0) and mercury (Hg): 357.78 μg/g (reference normal range, <5). The serum mercury level was 319.08 μg/l (reference normal range, <20). Chelating agent, DMPS 250 mg and methylprednisolone 62.25 mg twice daily were administered for 7 days. His general condition declined progressively with a widened alveolar-artery oxygen difference ($AaDO_2$). Under the fractional inspired oxygen concentration (FIO_2) with 1, the blood ABG showed a pH of 7.411, a PCO_2 of 60 mmHg, a PO_2 of 50 mmHg, a saturation of oxygen of 78.9%. The $AaDO_2$ was 588 mmHg. Following chest X-ray film showed progressing bilateral increasing alveolar infiltration (Figure 2) on day 14. Despite a decrease in serum mercury concentration (48.3 μg/l) measured on day 12, he still died of profound hypoxemia on the 15th days after inhalation of the cinnabar.

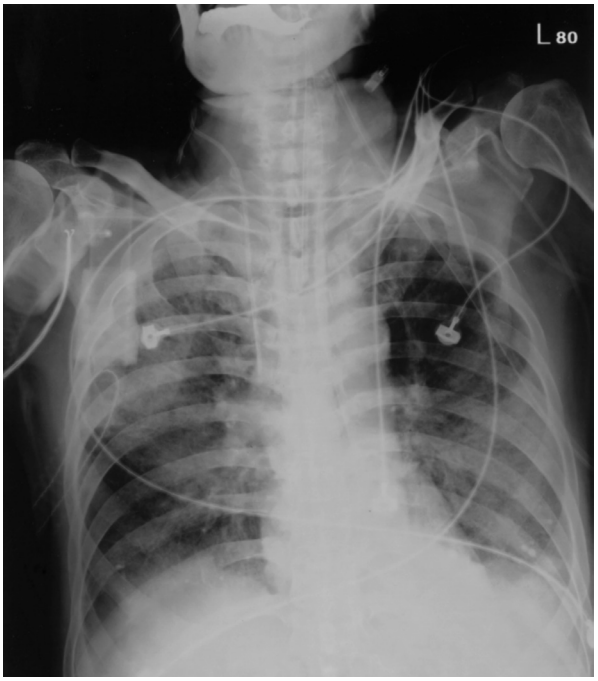

Fig. 1. Chest radiograph taken in emergency room at our hospital revealed bilateral alveolar infiltration without cardiomegaly

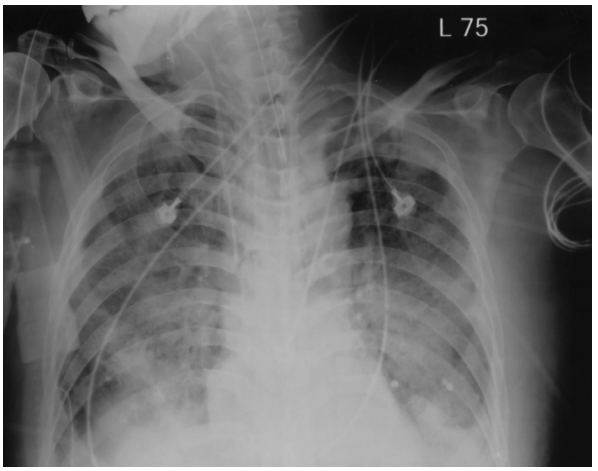

Fig. 2. Chest X-ray film on day 14 showed bilateral diffuse alveolar infiltration without cardiomegaly

Discussion

Acute mercury exposure by inhalation tends

to occur in three settings: industrial accidents, accidents within the home, and association with novice attempts to extract precious metals from mercury amalgam. Chemical pneumonitis following acute exposure to mercury vapor is well described in recent references. Pulmonary toxicity appears related to local irritant effects created by oxidized mercury ions. There may be direct damage to bronchial and parenchymal cells with resultant acute lung injury [3-4].

The evolving clinical course may be divided into three phases. The initial phase is manifested as flu-like illness. The intermediate phase involves a period in which severe multi-organ symptoms may become manifest. The late phase consists of a period when central nervous symptoms persist [5]. The cause of death in all lethal cases is progressive respiratory failure, and the pathologic findings in the lung at autopsy reveal various stages in acute lung injury, similar to those found in the acute respiratory distress syndrome (ARDS) [6].

Although chelating therapy has been shown to decrease serum mercury concentration, review of the literature showed that this has no effect on the progression of acute lung injury. Jaeger *et al*. [7] postulated that lung tissue damage is complete, and that the treatment of serum level with chelating agents has no effect on the reversal of lung damage. In our patient, despite reduction in serum mercury levels with DMPS, there was no reversal in the progression of lung injury and respiratory dysfunction. The role of chelating therapy in acute lung injury induced by acute mercury vapor poisoning needs further investigation. Although the actual fatal level of mercury vapor is unknown, exposure to more than 1-2 mg/m^3 of elemental mercury vapor for a few hours causes acute chemical bronchiolitis and pneumonitis. Two hours after exposure, lung injury appears as hyaline membrane formation, and finally, extensive pulmonary fibrosis occurs. Clinical findings correlate with the duration of exposure, the concentration of mercury and the survival time after exposure [8].

Corticosteroids have been used sporadically and may prevent progression to severe interstitial fibrosis in mildly affected patients [9]. However, the benefit of corticosteroids in reducing pulmonary fibrosis remained unproven [1, 10]. In our patient methylprednisolone was used to suppress the inflammatory process since admission. It did not appear to have been of any benefit. The role of corticosteroid and its optimal timing in the treatment of acute mercury vapor inhalation are uncertain.

In Taiwan, some Chinese herb stores sell the minium (red lead) or materials composed of other metals as cinnabar (China red). People hardly distinguish the cinnabar from minium or other materials. That is why mercury intoxicated people also get lead intoxication, or other metal intoxication. The government put a ban on cinnabar use since 2005. This patient got the cinnabar illegally. It could result in several kinds of metal intoxication.

There is no report about lead toxicity resulting in respiratory distress. However acute zinc fumes from welding could be toxic and cause metal fume fever (fatigue, chills, fever, myalgias, cough, dyspnea, leukocytosis, thirst, metallic taste, salivation), but extremely progress to ARDS. There is only 1 case about diffuse alveolar damage after inhalation of zinc, which is reported in Japan in 2003, and in that case the patient survived after steroid treatment [11]. By the clinical course, the patient should die from mercury

In conclusion, China red is still frequently used in Asian societies. Case report with se-

vere inhalation injury is seldom reported. The necessity of educating people to use China red appropriately for preventing such a tragedy is highlighted.

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吸入硃砂引起急性肺炎—病例報告

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在亞洲社會使用中藥材來治療疾病是很常見的。硃砂在中藥醫學中是用來安神、緩和情緒及幫助睡眠的。我們報告一個病例因使用吸入硃砂蒸氣來治療疾病而引發肺炎，進而導致急性呼吸窘迫症候群。經解毒劑（DMPS）和類固醇使用，仍無法挽救其生命。*(胸腔醫學* ***2008; 23: 447-451)***

關鍵詞：硃砂，肺炎，急性呼吸窘迫症候群，DMPS

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Recurrent Papillary Thyroid Carcinoma with Endobronchial Metastasis

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Thyroid carcinoma is the most common endocrine malignancy, and sometimes invades the regional lymph nodes or metastasizes distally to the lungs, bone and brain. Endobronchial metastasis is rare, and the most common primary malignancies are breast cancer, and colorectal and renal cell carcinoma. Endobronchial metastasis of papillary thyroid cancer is extremely rare, and only a few case reports have been documented.

We came across a patient who had thyroid papillary carcinoma and underwent a right total thyroid lobectomy for papillary thyroid carcinoma 9 years previously. He complained of progressive productive cough with blood-tinged sputum. In addition, a huge right lower lung mass was noted on chest X-ray. Chest computed tomography showed a right lower lobe mass with a heterogeneous enhancement. Bronchoscopy demonstrated an endobronchial mass and the biopsy specimen showed metastatic papillary thyroid carcinoma, proven by immunohistochemical stains. ***(Thorac Med 2008; 23: 452-457)***

Key words: endobronchial metastasis, hemoptysis, recurrence of thyroid papillary carcinoma

Introduction

Endobronchial metastasis (EBM) is defined as metastatic non-pulmonary tumors located at the subsegmental or more proximal central bronchus, observable directly by bronchoscope. EBM of extrapulmonary malignancies has been reported in patients with sarcoma and carcinoma of the breast, tongue, penis, testis, kidney, larynx, pharynx, prostate, ovary, uterus, urethra, pancreas, adrenal gland, colon and rectum, and thyroid gland [1-3].

Thyroid carcinoma is the most common endocrine malignancy and is ranked 1st in mortality among endocrine tumors. The bones, lungs and brain are the most frequent sites of metastasis. EBM of papillary thyroid carcinoma has rarely been reported. We describe a patient who underwent right total thyroid lobectomy for thyroid papillary carcinoma and in whom recurrence developed as an endobronchial mass. We present this rare case and review the literature.

Case Report

A 55-year-old man had been diagnosed

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with papillary thyroid carcinoma in 1998 and underwent a right thyroid total lobectomy at that time. Subsequently, he regularly took TSH suppression therapy with L-thyroxin. He was followed-up at our hospital, and no enlarged cervical lymph nodes or thyroid mass were noted. Then, in 2006, he experienced a progressive productive cough with scanty blood-tinged sputum. One huge lung mass located at his right lower lung field was seen in the chest X-ray. The patient refused to undergo further examination, asked for a second opinion, and then disappeared from the outpatient department (OPD). Unremarkable physical findings and thyroid function tests were reported at that time.

One year and 3 months later, he visited our chest OPD because of hemoptysis. An enlarged right lower lung tumor was seen in his chest X-ray (Figure 1) and chest computed tomography (CT), (Figure 2) compared with the previous X-ray. A Tc-99m-MIBI scan revealed a high uptake in the right pulmonary field, right femoral trochanter, left lower back and left thyroid lobe. The thyroglobulin level was 13068 ng/ml. He underwent a bronchoscopy examination and the orifice of the right lower bronchus was totally occluded by an observed mass (Figure 3). The biopsy specimens revealed metastatic papillary

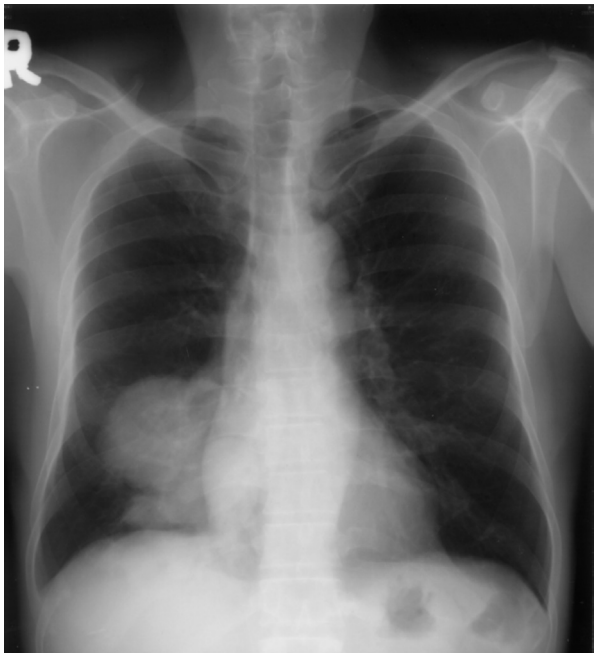

Fig. 1. Round lung masses with smooth margins at the right lower lung field.

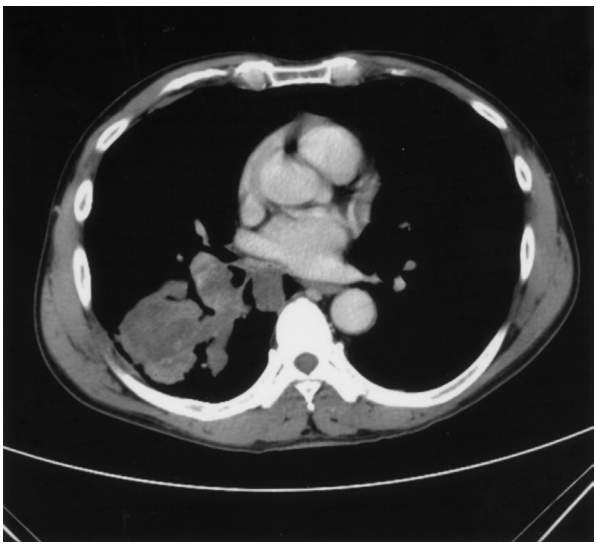

Fig. 2. A heterogeneous enhanced mass occluding the orifice of the right lower lobe bronchus is demonstrated.

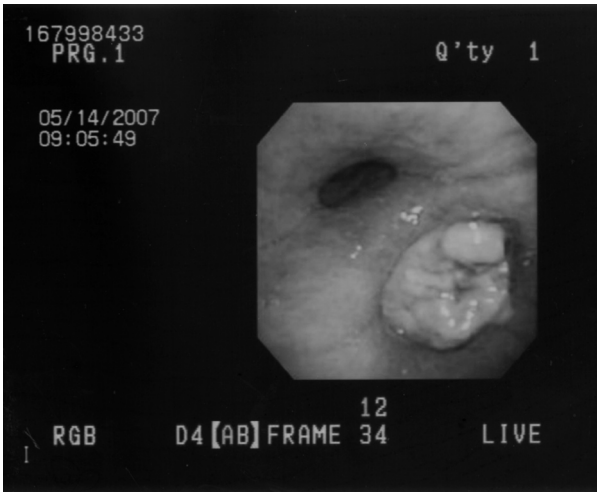

Fig. 3. Total occlusion of the right lower bronchus was observed by bronchoscopy.

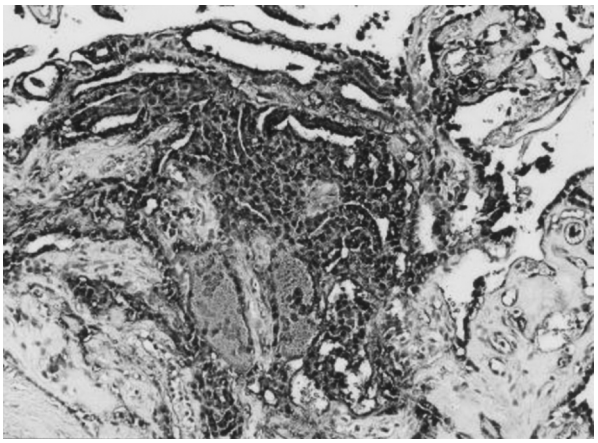

Fig. 4. A transbronchial biopsy specimen showed positive for thyroglobulin. (hematoxylin and eosin: × 100 magnification).

thyroid carcinoma pathologically, and were positive for thyroglobulin (Figure 4) and TTF-1 immunohistochemical stains.

The patient underwent right middle and right lower lobe bilobectomy followed by left total thyroidectomy before I131 ablation therapy. No evidence of malignancy in the residual left thyroid lobe was noted, and the same histological features were discovered in the bilobectomy specimens of the lung. Six months after diagnosis of EBM of papillary thyroid carcinoma, the patient passed away after suffering from bilateral femoral subtrochanter pathological fractures and multiple metastasis to the brain in spite of administration of I131 therapy (200 mCi).

Discussion

EBM is defined as a bronchoscopically visible lesion involving proximal to subsegmental bronchi and with the same histopathological features as extra-thoracic malignancy [1]. EBM from extrathoracic malignancy has been reported in 2-50% of patients with pulmonary metastasis [1-2, 10-11]. The mean recurrence interval, which is the time interval between diagnosis of primary extrathoracic carcinoma and EBM, is 50 months (range 0-300 months) [13]. Distal metastasis from well-differentiated thyroid carcinoma is not uncommon, and metastasis to the lungs, bone, and brain are frequently reported. From 5% to 20% of patients with papillary thyroid carcinoma have pulmonary metastasis [4-5]. However, to the best of our knowledge, only 4 cases of EBM of papillary thyroid carcinoma have been reported [6-9].

The 1-year mortality rate of these thyroid cancer patients after diagnosis of distal metastasis is greater than 50% [16]. In the papillary thyroid cancer subgroup, the interval between distal metastasis to patient death is 2.2 years. The age at diagnosis, postoperative thyroglobulin levels, pathologic type, tumor size and chest X-ray findings play important roles in predicting metastasis of well-differentiated thyroid carcinoma [17].

Papillary thyroid carcinoma is unencapsulated, and up to 80% of patients may have microscopic regional lymph node metastasis. Less frequently, the carcinoma may spread into the lungs through the lymphatics within the thyroid. Four modes of development of EBM have been described by Kiryu *et al*., and include type I, direct metastasis to the bronchus; type II, bronchial invasion by a parenchymal lesion; type III, bronchial invasion by mediastinal or hilar lymph node metastasis; and type IV, peripheral lesions extending along the proximal bronchus [3]. The exact mode of EBM of papillary thyroid cancer is still uncertain.

Symptoms associated with EBM are nonspecific. Coughing is most frequently reported, followed by hemoptysis, dyspnea and chest pain [13]. Approximately 20-62.5% of cases are

asymptomatic [3, 13]. In patients with EBM of thyroid carcinoma, hemoptysis is usually mentioned. [6-7, 9, 14-15]

Metastatic thyroid carcinoma presents various patterns in chest radiography. Hoie et al. categorized these findings into 2 forms [16]: Form I includes miliary X-ray lesions, single or multiple nodules, and normal chest X-ray findings with positive I-131 scintiscan. Rounded macronodular masses, 2 to 30 in number, distributed bilaterally in various sizes, is the most common pattern of form I. Form II includes hilar or mediastinal lymph adenopathy, pleural effusion and pulmonary infiltration . In contrast, Sorensen reported that atelectasis is the most common chest X-ray finding in patients with EBM of extra-thoracic malignancy [13]. Chest X-rays are not recommended routinely in patients with well-differentiated thyroid carcinoma, especially when thyroglobulin is not detectable, and X-ray has been found to have lower sensitivity in the detection of lung metastasis (52%) than I131 whole body scans (64%) and chest CT (82%) [18]. High-resolution CT without contrast is superior to conventional CT, as the iodine content contrast used may decrease I131 uptake in functioning metastasis. However, bronchoscopy is highly sensitive for the detection of EBM [3, 23].

Radioiodine-131 scans and monitoring of serum thyroglobulin levels have been widely used for postoperative screening for metastasis in patients with well-differentiated thyroid carcinoma. Two to 5 mCi of I131 is often used for I131 scans. When distal metastasis is still suspected in I131 scan-negative patients, metastatic lesions may be detected with a higher dose of I131 (100 mCi), Tl-201, Tc99m-MIBI scintigraphy, and FDG PET [20-21].

The therapeutic goal in patients with EBM is to resolve the obstructed bronchial lumen and hemoptysis. Therapeutic procedures, such as intraluminal radiotherapy, photodynamic therapy, bradytherapy, electrocoagulation, cryotherapy, forceps, laser debulking, and stents have been developed, and some patients have had prolonged survival after these palliative treatments [24-26]. Patients with thyroid carcinoma may also benefit from external radiotherapy [14]. I131 therapy should be arranged for I131-accumulating metastasis, which has a better prognosis than low-uptake tumors.

Ulger *et al*. [14] suggests that EBM from extra-thoracic malignancy should not be overlooked when a patient presents with hemoptysis. Underestimated cases of EBM may be disclosed more frequently by bronchoscopy examination, as well as by the application of fluorescence bronchoscopes. The correct diagnosis should be made by all means, because a relatively shorter survival is expected in those with confirmed EBM.

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以支氣管內轉移爲表現之乳突狀甲狀腺癌復發：一病例報告及相關文獻回顧

張永裕　蔡忠榮　黃琬婷*　黃明賢

甲狀腺癌目前仍為最常見的內分泌腫瘤。除可能侵犯局部淋巴結外，亦可轉移至肺、骨骼及腦部。肺外腫瘤合併支氣管內轉移是罕見的，過去被報導最多者為乳癌、大腸結腸癌及腎細胞癌。乳突狀甲狀腺癌合併支氣管內轉移更是很少被報導。

文中我們提出一位乳突狀甲狀腺癌病患於接受右側甲狀腺切除術9年後，因咳嗽併少量嗜血求診，除了胸部X光及電腦斷層顯示的肺腫瘤外，在軟式支氣管鏡檢查中，我們發現腫瘤阻塞右下葉支氣管，經病理切片證實為乳突狀甲狀腺癌併支氣管內轉移。*(胸腔醫學* ***2008; 23: 452-457****)*

關鍵詞：支氣管內轉移，咳血，乳突狀甲狀腺癌復發

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Pulmonary Histoplasmosis in an Immunocompetent Man

Shih-Wei Wu, Wann-Cherng Perng, Chih-Feng Giian, Giian-Wen Chen, Wen-Lin Su

Histoplasmosis is rarely seen in Taiwan and only a limited number of cases have been reported locally. We reported a 37-year-old man, a Myanmar immigrant, with established pulmonary histoplasmosis. No known risk factors, such as AIDS or immunosuppressive therapy, were identified. The patient willingly refused antifungal therapy of uncertain efficacy, which provided the opportunity to observe the evolution of untreated pulmonary histoplasmosis. Furthermore, this case serves as a reminder for clinicians to always consider alternative diagnoses when the clinical course of a disease does not evolve as expected. ***(Thorac Med 2008; 23: 458-463)***

Key words: pulmonary histoplasmosis, antifungal therapy

Introduction

Histoplasmosis is a worldwide infection caused by the fungus *Histoplasma capsulatum*, and the pulmonary manifestation is the most common form. It is traditionally seen in endemic areas, such as the Ohio and Mississippi River valleys in the US, and is rarely recognized clinically in other regions. However, the epidemiology of histoplasmosis has changed in non-endemic areas in recent decades because of the prevalence of HIV and immunosuppressive therapy, which has led to the identification of more aggressive or even disseminated histoplasmosis. The case we present herein is a rare instance of pulmonary histoplasmosis in an otherwise healthy man. It is rarely recognized clinically in Taiwan.

Case Report

A 37-year-old man came to our OPD due to his 1-month history of productive cough. No other constitutional symptoms were mentioned. He is an ethnic Chinese from Myanmar and had immigrated to Taiwan 2 years ago, where he worked as a cook. He denied any remarkable illness, medications or smoking in the past. On physical examination, he was afebrile and had diminished breathing sounds in the right lower lung field. Chest X-ray revealed patchy opacity in the right lower region (Figure 1A). Initially,

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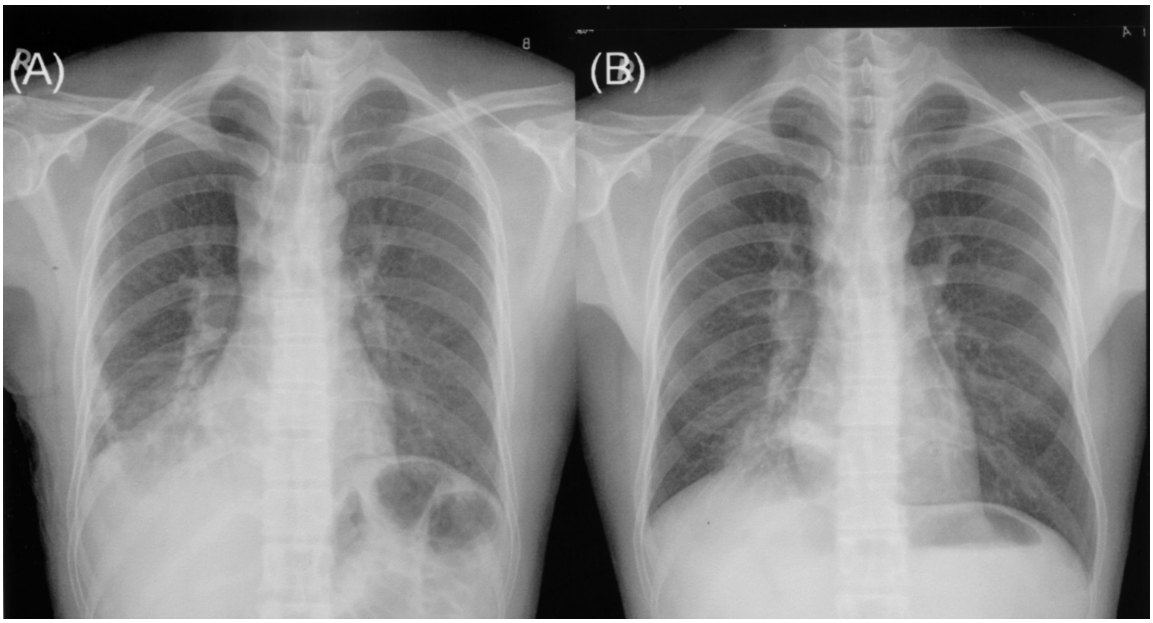

Fig. 1. (A) Patchy infiltration in the RML, RLL and LLL at admission. (B) Improvement of RLL and LLL infiltration 3 months later; the RML lesion was still present.

he was treated as having community-acquired pneumonia and was given a 7-day course of levofloxacin.

During follow-up 1 week later, there was no significant improvement in clinical symptoms or chest X-ray appearance. Neither acid-fast bacilli nor bacteria were identified in the sputum. Subsequently, computed tomography (CT) scan of the chest disclosed a patchy area with a heterogeneous consolidated lesion with fluid-bronchograms in the right lower lobe, and multiple enlarged mediastinal lymph nodes (Figure 2). Laboratory studies showed a leukocyte count of 5.1×10^9/L (61.3% neutrophils, 23.7% lymphocytes in the differential count).

To exclude malignancy, he was admitted for bronchoscopy and possible tissue biopsy. Bronchoscopy revealed a narrow lumen and abundant secretions near the RML and RLL orifices. A specimen was yielded finally via CT-guided lung biopsy, and pulmonary histoplasmosis was diagnosed histopathologically (Figure 3). Due to the unusual manifestation, an HIV screening test was done, with the patient's agreement, and showed a negative result.

After discussing this with the patient and informing him of the current consensus, he refused antifungal medications. Chest X-ray taken 3 months later showed slight resolution of the lesion (Figure 1B). The patient had only a mild cough at that time.

Discussion

Histoplasmosis is the infection caused by the dimorphic fungus *Histoplasma capsulatum*. It has been recognized more than 100 years, and is mostly found in certain areas of the American mainland [1]. Although this infection is highly endemic, it has been reported worldwide. However, the cases in non-endemic areas are exclusively confined to immunocompromised pa-

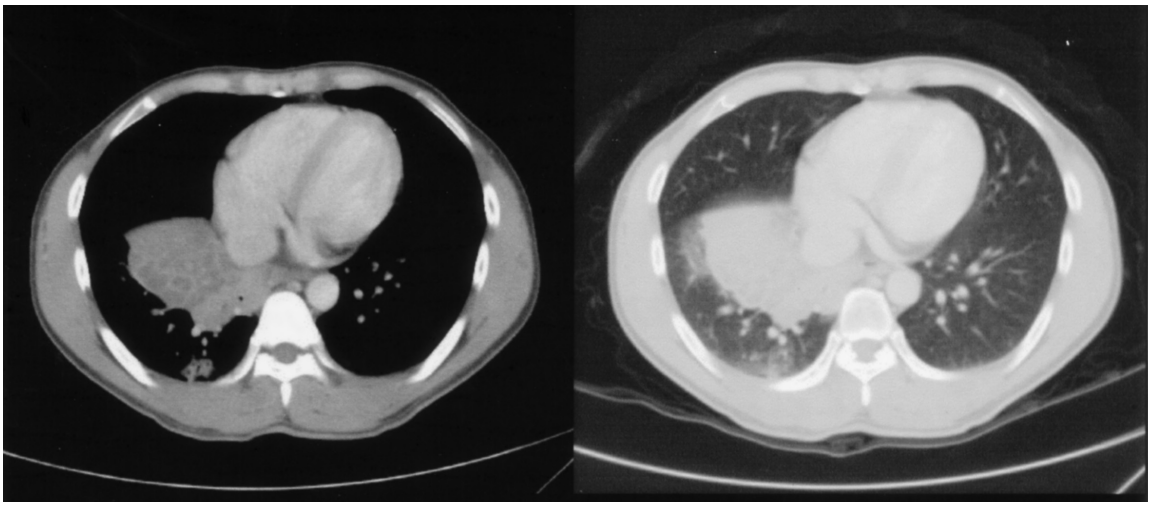

Fig. 2. A patchy area of heterogeneous consolidated lesion with fluid-bronchograms in the RLL and adjacent ground-glass opacity.

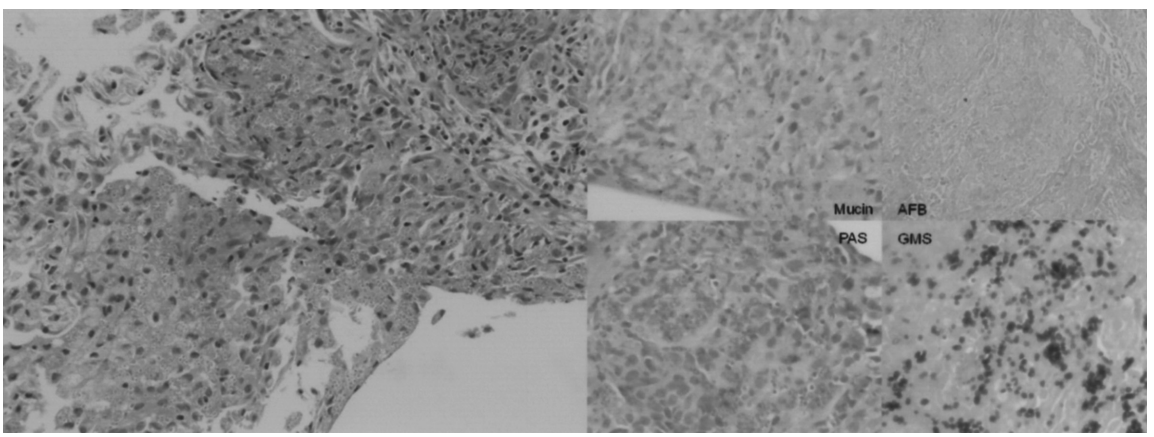

Fig. 3. A picture of chronic pneumonia characterized by granuloma formation, proliferation of epithelioid histiocytes, and many fungal yeast forms in the phagocytes, GMS(+), PAS(+), Mucin(-), AFB(-).

tients, such those with AIDS, those using immunosuppressive agents or steroid, and those with chronic disease [1-2]. In normal persons, only sporadic instances are reported in the literature.

In humans, the fungus is inhaled into the respiratory tract as spores, and then converts to a yeast phase in the lung. The lung is the major pathway of invasion. The defense response against this fungus is dependent on neutrophil, macrophage and lymphocyte-mediated cellular immunity, in sequence. Similar to tuberculosis, the fungus is phagocytosed and circulated by macrophages, but not killed. Most normal persons infected by this fungus appear asymptomatic. When immunity is flawed, the organism becomes pathogenic, resulting in clinical manifestations. The infection ranges from minor self-limited illness to disseminated life-threatening disease, depending on host immunity and the intensity of exposure [3].

The diagnosis of histoplasmosis is based on

fungus culture, serology, antigen detection and histopathological stain [4-5]. Fungus culture is the gold standard for diagnosis, but is limited in clinical practice by the several-week incubation period. Both serology and antigen detection provide a rapid and relatively sensitive method for the detection of histoplasmosis. However, these 2 methods are not readily available in Taiwan. In this case, we used histopathological stain to reach the diagnosis, based on the characteristic appearance of the organism. This method has lower sensitivity, but good specificity when examined by experts [6].

The most comprehensive report of histoplasmosis in Taiwan is that by Hung in 2005 [7], and 2 other cases were reported by Lai in 2006 [8]. Seven cases have been reported in Taiwan, but all of them was found to have multiple comorbidities, such as AIDS or other illness. Not surprisingly, 6 patients died, despite treatment, and only 1 young man with AIDS survived. This case may be the first describing a patient with pulmonary histoplasmosis in Taiwan whose health status was relatively good. The infectious sources of the previously reported cases were mostly from abroad. Similarly, this patient was not indigenous, because he is a Myanmar immigrant. We assume he developed an asymptomatic *Histoplasma capsulatum* infection in the past, which later became latent. Even so, it is still extremely rare for reactivation to occur in a healthy person without known risk factors.

The Infectious Diseases Society of America (IDSA) updated the clinical practice guideline for the management of patients with histoplasmosis in 2007 [9]. It summarized the consensus of antifungal therapy for histoplasmosis. Absolute indications for antifungal therapy included only moderate to severe acute diffuse pulmonary, chronic cavitary pulmonary, disseminated and CNS infection. The necessity of an antifungal regimen is still debated in acute focal pulmonary disease, such as in our case, particularly in those cases with symptoms lasting less than 1 month. In addition, antifungal therapy in cases with symptoms longer than 1 month is suggested, but the efficacy is also uncertain. If treatment is initiated, a course of 6~12 weeks of itraconazole is recommended. So far, no clinical trials have been conducted to compare treated and not-treated groups. In this case, the patient asked for follow-up only, and willingly refused treatment. The gradual improvement of his pulmonary condition provided us a good opportunity to understand its natural course, partially, in a healthy person. Furthermore, it also helps in the decision-making between an uncertain efficacy and the side effects of antifungal treatment. In certain conditions, an intentional delay of antifungal treatment may avert the unnecessary side effects of azole.

Histoplasmosis is an extremely rare entity in Taiwan. However, it should be always kept in mind because of the popularity of intercontinental travel and the presence of numerous Southeast Asian workers in modern society. A comprehensive therapeutic strategy for pulmonary focal histoplasmosis can also be established based on the experience with this case. This case also provides a reminder to clinicians to promptly consider alternative diagnoses when the clinical course of a disease does not evolve as expected.

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在一個免疫力正常男性身上發現的肺組織漿菌病

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在台灣組織漿菌病是非常罕見的，在本土的雜誌中也僅有極少數的病例被報告過。我們在此報告一個最後被診斷為肺組織漿菌病的37歲男性，該病人除了是緬甸移民之外，並沒有其他已知的危險因子，例如AIDS或免疫抑制劑的使用等。由於這樣的肺組織漿菌病其治療效果仍未定，該病人決定不接受抗黴菌藥物治療，這也剛好提供了一個絕佳的機會，讓我們觀察未經治療的肺組織漿菌病其病程進展。再者，這病例也提醒了臨床醫師當疾病的臨床病程或治療不如預期發展時，永遠要想到其他可能的診斷。
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關鍵詞：肺組織漿菌病，抗黴菌藥物治療

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Migration – A Usual Complication of Covered Self-Expandable Metallic Stent with an Unusual Course – Case Report

Yen-Lung Lee*, Jui-Ying Lee*, Hsien-Pin Li*, Shah-Hwa Chou*,**, Eing-Long Kao*,**

The authors report a 46-year-old male with middle-third esophageal cancer and invasion of the left main bronchus who underwent an insertion of a left main bronchial stent (Ultraflex, Boston Scientific, 14 mm×40 mm) to relieve airway stenosis, since the widest portion of the left main bronchus was only 11 mm. After 3 months, left main bronchial stent migration with right main bronchial orifice obstruction was noted on the chest computed tomography and flexible bronchoscopy. Rigid bronchoscopy was performed to remove the migrated stent and a new larger stent was inserted (Ultraflex, Boston Scientific, 16 mm×40 mm). Left main bronchial stent migration with right main bronchial orifice total obstruction is rarely encountered in the literature. Migration rarely occurs 3 months after an initial stent deployment, especially when a larger stent is used. ***(Thorac Med 2008; 23: 464-469)***

Key words: migration, complication, tracheobronchial stent

Introduction

Traditionally, tracheobronchial stenting is considered a palliative procedure for inoperable malignant conditions which cause airway stenosis, since the stent can quickly relieve the critical airway narrowing that causes respiratory distress and life-threatening stridor [1-2]. Although tracheobronchial stenting has some advantages in dealing with these patients, there are still some complications, such as stent migration, complete or partial airway obstruction, halitosis, recurrent respiratory infections, and metal framework fracture leading to airway or vascular perforation [3-4]. Among these complications, stent migration usually occurred within 1 month after deployment [4]. We report a patient with left main bronchial stent migration and right bronchial orifice total obstruction, which occurred 3 months following implantation, and discuss the possible reasons.

Case Report

Middle-third esophageal cancer with left main bronchial invasion was diagnosed in a

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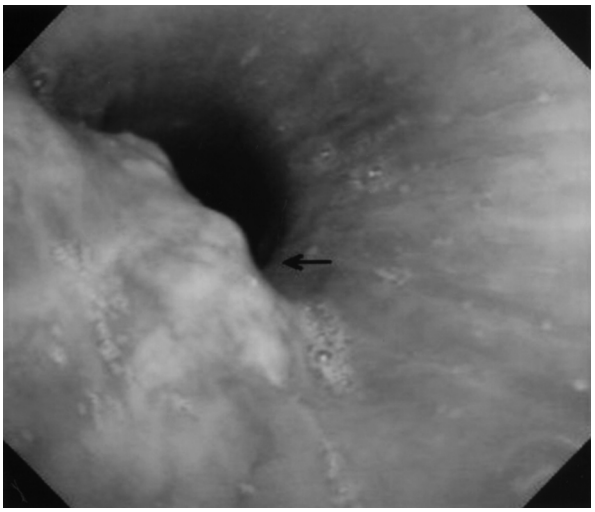

Fig. 1. Middle-third esophageal cancer with left main bronchus invasion (black arrow, flexible bronchoscopic view)

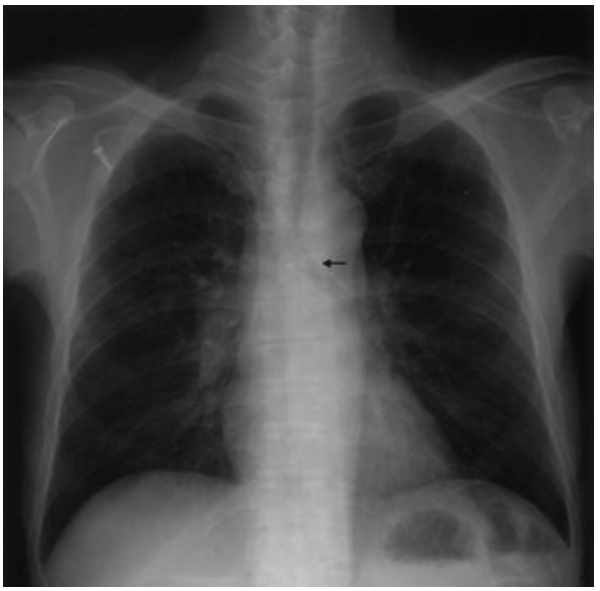

Fig. 2. The left main bronchial stent still had not migrated (black arrow, chest X-ray) 6 weeks after the initial deployment

46-year-old male (figure 1). Initially, he presented at the outpatient department (OPD) with progressive dysphagia, odynophagia and body weight loss, so history-taking, physical examination, and several other examinations such as chest computed tomography (CT), panendoscopy and biopsy, and bronchoscopy were arranged. Due to unresectable T4 esophageal cancer and a left main bronchial diameter of about 11 mm at the widest portion (measured from the chest CT), feeding tube and left main bronchial stent (Ultraflex, Boston Scientific, 14 mm×40 mm) implantation were suggested to the patient for nutritional support and relieving the respiratory distress. Concurrent chemoradiotherapy was used for further treatment.

Chest X-ray at about 6 weeks after initial deployment showed that the left main bronchial stent was still in place and had not migrated. During OPD follow-up about 3 months later, the patient complained of persistent cough and mild but progressive dyspnea. Chest X-ray, chest CT, and flexible bronchoscopy were then used. Bilateral pleural effusion and left main bronchial stent migration with right main bronchus total obstruction were noted (figures 3 and 4), so we suggested the patient receive surgical intervention because of the stent migration. Under endotracheal tube general anesthesia, bilateral tube thoracostomy was performed. Then, rigid

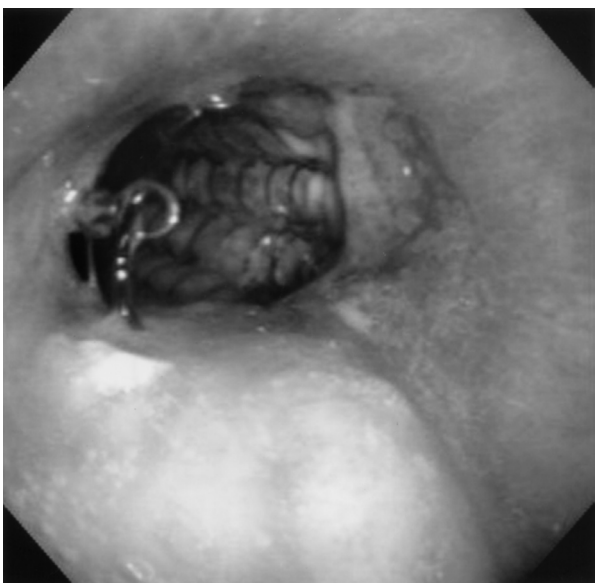

Fig. 3. Left main bronchial stent migration with right main bronchus total obstruction (flexible bronchoscopic view)

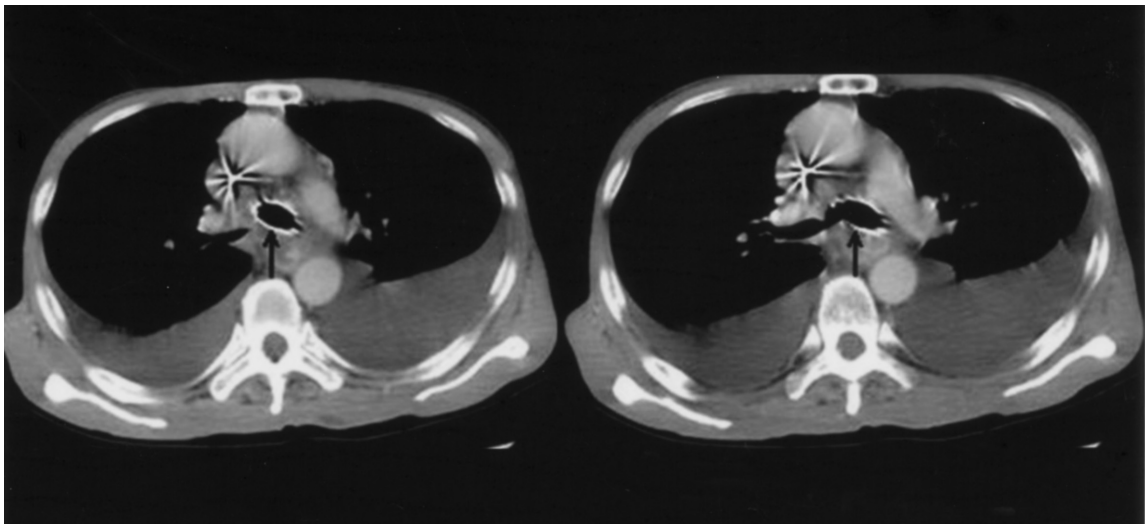

Fig. 4. Enhanced computed tomography of the middle thoracic level shows left main bronchial stent migration with right main bronchus total obstruction (black arrow)

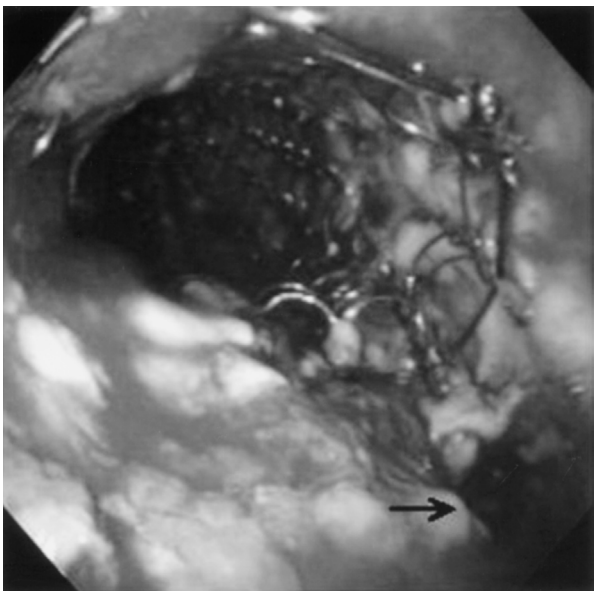

Fig. 5. A larger covered self-expandable metallic stent (Ultraflex, Boston Scientific, 16 mm×40 mm) was reinserted and the right main bronchial orifice can now be seen (black arrow)

bronchoscopy was used to remove the migrated stent. Ventilation and oxygenation were ensured with 100% oxygen delivered by a side port of the rigid bronchoscope. The stent was removed by grasping the circular extraction loop with a rigid alligator forceps. Once the stent was removed, a larger new one (Ultraflex, Boston Scientific, 16 mm×40 mm) was reinserted (figure 5). Dyspnea improved after these procedures, and the patient was discharged after removing the chest tube. Two months after the second operation, the left main stent had not migrated, but the patient died due to terminal-stage esophageal cancer.

Discussion

Patients who have severe central airway obstruction have disabling symptoms of dyspnea, respiratory distress, and obstructive pneumonia. There are many methods, such as photodynamic therapy, stents (self-expandable metal or silicon), thermal laser ablation and brachytherapy that can be used to resolve airway stenosis-related malignant disease that cannot be treated by curative surgery [5]. Among these methods, stents can provide some advantages which the other methods cannot, such as structural airway support without painful surgery, and relief of obstruction due to extrinsic, as well as intrinsic

compression [6]. The benefit of airway stents is particularly seen in the short-term symptomatic improvement and low risk of complication. Stent-related complications will increase the longer the stent is inserted, especially in the long-term treatment of benign conditions [7-8].

Self-expandable metal stents have some advantages compared with silicone stents, such as their ease of delivery, the utilization of flexible bronchoscopy with fluoroscopy under topical anesthesia, the lower rate of stent migration, and the good conformation to distortions or curves within the airway [1]. Uncovered stents can allow granulation ingrowth and prevent migration, but are not suitable in malignancy, since the tumor can undergo ingrowth and obstruct the lumen again. Covered stents (covered by a polymer membrane called Permalume), compared with uncovered stents, have several advantages in preventing tumor and granulation ingrowth and are easier to remove, but still use bare metal portions at each end of the stent to allow stable seating [1].

In this case, we initially chose the Ultraflex (Boston Scientific, 14 mm×40 mm) covered self-expandable metallic stent due to the unresectable T4 esophageal cancer with left main bronchus invasion and a left main bronchial diameter of about 11 mm at the widest portion. However, the stent migrated and obstructed the right main bronchus totally 3 months later. Complications of covered self-expandable metallic stents, such as airway obstruction due to breakage or malpositioning of the stent, perforation, migration, retention of secretions, respiratory infections and overt granulation tissue can occur at different times [2-4, 7, 9]. Lemaire, *et al*. reported the complication rates of tumor ingrowth (4.6%), granulation tissue (2.9%), and migration (2.3%) [2]. The dynamic size of the airway can exert excessive pressure against the airway wall in bronchomalacia, especially with coughing, a short stent, or an undersized stent, and a location at the origin of the right main bronchus with overlap with the larger trachea may contribute to migration [7]. Usually, granulation tissue formation, which can prevent migration, is noted at the bare area of the bilateral ends of the stent about 1 month after deployment [4, 7]. Thus, stent migration usually occurs within 1 month after deployment. In the Lemaire, *et al*. report, 4 cases of stent migration occurred after 30 days, but whether there were contributing factors was not mentioned. If several contributing factors exist, migration, which may occur any time, even after 30 days, should be kept in mind. In our case, no factors contributing to migration, except cough, were noted, hence migration was less likely to occur, especially after 3 months. This patient did not have bronchomalacia. We inserted a relatively wide and long stent (14 mm×40 mm) into the left main bronchus and there was no overlap with the trachea at first. Only a few granulation tissue formations were noted at a bare area 3 months after flexible bronchoscopy. The patient's characteristics, the persistent cough, and the lack of adequate granulation tissue formation at the bare area may have contributed to the stent migration in this patient. Therefore, we performed rigid bronchoscopy to remove the stent and reinserted a larger stent to offer more radial force, and added more medications for cough control [10-12].

In conclusion, tracheobronchial stents provide minimally invasive therapy for inoperable malignant conditions with significant airway obstruction. They can quickly relieve critical airway narrowing that causes respiratory distress and life-threatening stridor. Migration is one

of the most common complications of airway stents, and usually occurs about 1 month after deployment. In this case, left main bronchial stent migration with right bronchus total obstruction was noted 3 months later, even though a larger stent was used. Cough was the only factor noted that may have contributed to the migration. Stent migration should be kept in mind, even after 1 month and with the use of a larger stent.

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移位—常見的氣管自動擴張型金屬支架併發症以少見的方式表現—病例報告

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氣管自動擴張型金屬支架可以快速的撐開狹窄的呼吸道並且改善呼吸困難。但是有許多併發症如位移、部分或完全的呼吸道阻塞、口臭、反覆性呼吸道感染、與其他器官形成廔管及肉芽組織形成等等，會使支架的功能不佳，甚至危及病人的性命。

在此，我們分享了一個四十六歲男性病人胸部中段食道癌併左支氣管侵犯的病人使用氣管自動擴張型金屬支架撐開左支氣管狹窄，之後發生移位情形的處理經驗。在置入比左主支氣管直徑稍大的支架三個月後，發生了呼吸困難的情況，原因是支架移位並且造成右主支氣管阻塞。因此安排硬式支氣管鏡取出原本的支架，並置入一個直徑比原先大的新支架。根據這個病人的經驗，儘管已經使用了較大的支架且置放超過一個月後，支架仍然可能移位。*(胸腔醫學 **2008; 23: 464-469**)*

關鍵詞：移位，併發症，氣管自動擴張型金屬支架

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Unusual Presentation of Right Aberrant Subclavian Artery: Case Report

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Background: Dysphagia due to an aberrant subclavian artery is termed dysphagia lusoria. Although right aberrant subclavian artery is a congenital anomaly, dysphagia lusoria is rare and generally develops during the 4th decade of life. We present a young patient who had had chest pain and mild dysphagia for 3 months. A barium contrast study and computed tomography of chest revealed an aberrant right subclavian artery passing behind the esophagus; Magnetic resonance angiography of the aorta confirmed the diagnosis. Usually, aberrant subclavian artery does not lead to symptoms; however, sometimes dysphagia develops. Barium contrast study of the esophagus will reveal the abnormality. ***(Thorac Med 2008; 23: 470-474)***

Key words: dysphagia, aberrant subclavian artery

Introduction

The lusorian artery is a rare anomaly of the right subclavian artery which passes over the posterior aspect of the esophagus. The term "arteria lusoria" was first described by Bayford in 1794. An abnormal insertion of the right subclavian artery in the aortic arch was found in a 62-year-old woman who died after years of dysphagia [1]. At that time, it was commonly called "dysphagia lusoria". Although aberrant right subclavian artery is a congenital anomaly, dysphagia lusoria is rare and general develops during the 4th decade of life. We present a young patient who had had chest pain and mild dysphagia for 3 months. Barium contrast study of esophagus revealed the abnormality.

Case Report

A 27-year-old female had had chest pain and mild dysphagia for 3 months. She denied any dyspnea, abdominal pain, change in voice, or weakness. Her physical examination was unremarkable, and there were no neurologic deficits. Chest plain film revealed no remarkable findings in both the lung and heart. A barium study of the esophagus revealed external compression in the right lateroposterior aspect of the esophagus (figure 1), and an aberrant right subclavian artery was suspected. Computed tomography (CT) of the chest showed an aberrant

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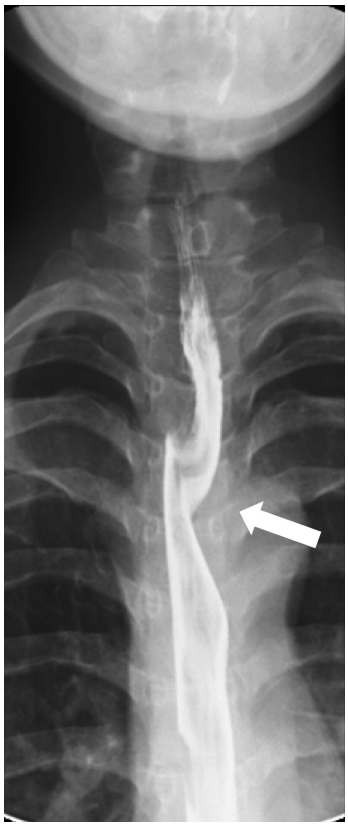

Fig. 1. Esophagogram reveals an external compression in the right lateroposterior aspect of the esophagus (white arrow), consistent with an aberrant subclavian artery at a level about 3 cm above the aortic arch.

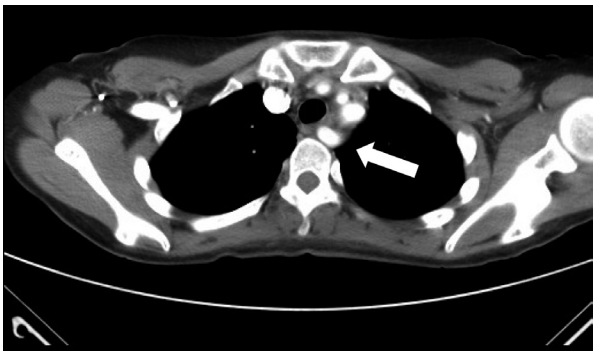

Fig. 2. CT scan of the chest demonstrates an aberrant subclavian artery passing over the posterior aspect of the esophagus (white arrow).

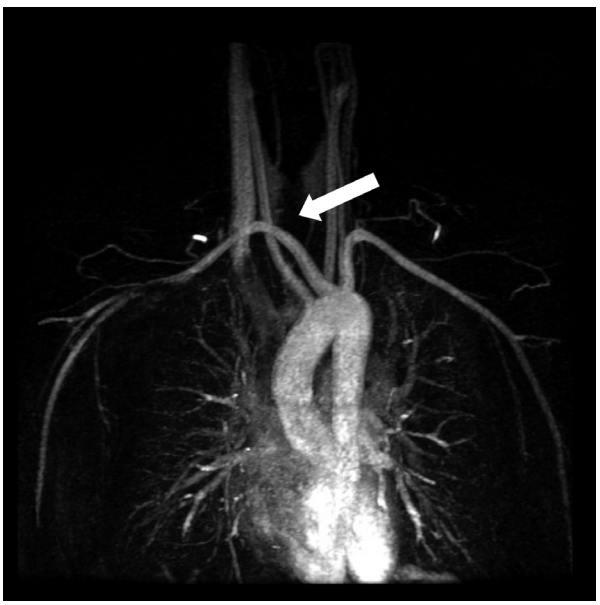

Fig. 3. MR angiography of the aorta and pulmonary artery shows an aberrant right subclavian artery arising from the distal aortic arch, just distal to the orifice of the left subclavian artery (white arrow).

subclavian artery behind the esophagus (figure 2). Magnetic resonance (MR) angiography of the thoracic aorta and pulmonary artery showed an aberrant subclavian artery arising from the distal aortic arch, which was distal to the orifice of the left subclavian artery (figure 3). There were no aneurysms or other associated vascular diseases. Due to the mild symptom of dysphagia, the patient underwent medical treatment and was followed up in the OPD.

Discussion

In the early embryo, the aorta consists of a ventral aorta and 6 paired dorsal aortic roots. As hypothesized by Edwards, this abnormal origin of the right subclavian artery can be explained by the involution of the 4th vascular arch with the right dorsal aorta [2]. The 7th intersegmental artery remains attached to the descending aorta, and eventually becomes the right subclavian artery. This leads to an aberrant artery, which often follows a retro-esophageal course.

Aberrant right subclavian artery is the most

common of the vascular ring anomalies associated with the aortic arch. The incidence of aberrant right subclavian artery is 0.5% to 2% [3-5]. It has a posterior origin from the aorta and usually travels along a retroesophageal course to the right thoracic outlet. Only 10% of adult patients with aberrant right subclavian artery have symptoms, including cough, strider, chest pain and dysphagia; these are usually associated with evident compression of adjacent structures [6]. Dysphagia lusoria generally develops during the 4th decade of life [7]. There are a number of theories on why adult patients with this congenital anomaly become symptomatic. Elongation of the arteries, a high aortic arch caused by aging, and hypertension are possible explanations for the late onset of dysphagia [8]. The development of atherosclerotic changes and aneurysms in the aberrant artery also can cause compressive symptoms.

Diagnostic modalities may vary based on the clinical presentation. The barium esophageal study will reveal a round filling defect in the retroesophageal portion. CT scan and thoracic aortograms will show the anatomy and confirm the diagnosis. New imaging techniques, such as MRI, may contribute to better visualization, especially when an aneurysm is present in the proximal part of the artery [9]. Esophagoscopy can reveal a pulsating mass and exclude malignancy.

The management of patients with right aberrant subclavian artery depends on the severity of symptoms. Mild to moderate symptoms are often treated conservatively. Severely symptomatic patients require surgical intervention. In addition, when the aberrant subclavian artery is responsible for upper limb ischemia or the presence of an aneurysm of the aberrant subclavian artery, whether it is symptomatic or not, this is an indication for surgery. There is no standard surgical approach to the repair of this anomaly. Right and left thoracotomies, cervical incision, median sternotomy, and combinations of these approaches have been used [10]. In the largest series study, Kieffer and colleagues [11], classified patients into 4 groups: Group 1, patients having dysphagia with a non-aneurysmal aberrant right subclavian artery; Group 2, patients with symptomatic occlusive disease of a non-aneurysmal aberrant right subclavian artery; Group 3, patients having aneurysms of the aberrant right subclavian artery with or without symptoms; Group 4, patients with an aberrant right subclavian artery arising from the aortic lesion. The surgical approach to aberrant right subclavian artery must depend on the anatomic condition and routine reconstruction of the aberrant right subclavian artery to avoid ischemic complications in the vertebrobasilar territory or upper extremity [11].

In conclusion, aberrant right subclavian artery rarely causes symptoms. Dysphagia lusoria generally occurs in older adults. In younger patients with the symptoms of dysphagia, the differential diagnosis should include this disease. The barium contrast study of the esophagus will disclose the abnormality.

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罕見的右側異生性鎖骨下動脈：案例報告

莊冠華　黃才旺　程永隆　陳仁智　張宏　李世俊

前言：因為異生性鎖骨下動脈而造成的吞嚥困難稱為dysphagia lusoria。儘管右側異生性鎖骨下動脈是先天性的疾病，造成吞嚥困難的機會是很小的而且通常發生在四十歲左右。

案例報告：我們要呈現的是一位有輕微胸痛及吞嚥困難症狀將近三個月的年輕病患。鋇劑食道顯影及胸部電腦斷層發現十到後方有一異生性鎖骨下動脈，而主動脈核磁共振血管攝影證實了這個準斷。

結論：通常異生性鎖骨下動脈不會導致臨床症狀，但是有時候會發生吞嚥困難。鋇劑食道顯影會發現異常病灶。*(胸腔醫學* ***2008; 23: 470-474)***

關鍵詞：吞嚥困難，異生性鎖骨下動脈

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