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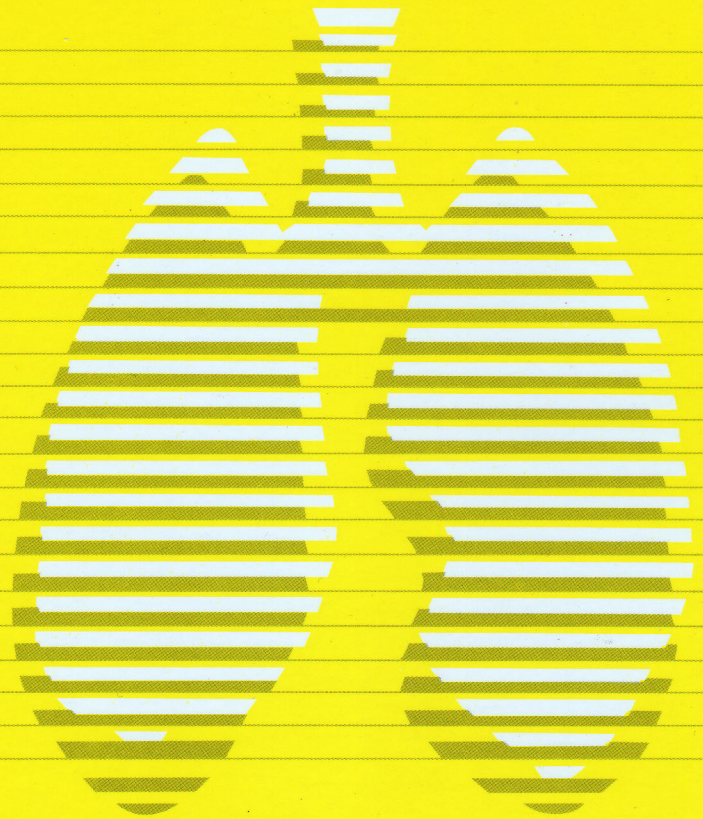

台灣胸腔暨重症加護醫學會

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原著

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Orginial Articles

Case Reports

Higher Percentage of Stage 1 Sleep Predicts Excessive Daytime Sleepiness in Middle-Aged Obstructive Sleep Apnea Males

Yu-Ting Chou*, Yu-Ching Lin*,**, Chin-Kuo Lin*, Chia-Hao Chang***, Cheng-Ta Yang****, Ying-Huang Tsai*,**, Ju-Fang Chang*, Tsung-Ming Yang*

Introduction: The etiologies of excessive daytime sleepiness (EDS) in obstructive sleep apnea (OSA) remain uncertain. We found that the percentage of stage 1 sleep is an important predictor of excessive daytime sleepiness (EDS) in middle-aged OSA males.

Materials and Methods: We retrospectively reviewed the polysomnography (PSG) results of 363 middle-aged OSA patients. A total of 50 patients were enrolled in the final analyses. Patients with an Epworth Sleepiness Scale (ESS) score equal to or more than 20 comprised the EDS group. Patients with an ESS score equal to or less than 4 were included in the non-EDS group. We compared the PSG results between these 2 groups of patients to survey for possible predictors of EDS in middle-aged OSA males.

Results: Patients in the EDS group had a higher respiratory arousal index, total arousal index, and percentage of stage 1 sleep. In addition, both the stage 2 sleep and slow wave sleep percentages were lower in the EDS group, compared with that in the non-EDS group. Logistic regression analysis showed that a higher percentage of stage 1 sleep is an independent predictor of EDS in middle-aged OSA males.

Conclusions: A higher percentage of stage 1 sleep is an important predictor of EDS in middle-aged OSA males. ***(Thorac Med 2011; 26: 179-186)***

Key words: hypersomnia, obstructive sleep apnea, polysomnography, sleep stages

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction that are often followed by hypoxemia and/or sleep fragmentation [1]. Currently, the major diagnostic tool for OSA is polysomnography (PSG), which detects many biophysiological changes that occur during sleep [1]. Excessive daytime sleepiness (EDS) is a common symptom in patients with OSA, and increases the risk of traffic- and occupation-related ac-

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cidents, and other safety-related issues [1]. About 17-35% of patients with sleep disordered breathing reported EDS. This is not only an issue for the safety of the patients themselves, but also for innocent bystanders. The estimated annual costs of OSA-related traffic accidents in the United States are USD15.9 billion, and around 1,400 people die because of these accidents each year [2]. Several investigators have attempted to discover possible predictors or etiologies of EDS in OSA patients. Some studies showed that hypoxemia resulted in EDS in OSA patients [3-4]. On the other hand, other studies indicated that sleep fragmentation is the major determinant of EDS in OSA patients [5-6].

Hypoxemia and sleep fragmentation were found in all OSA patients. However, only 17-35% of OSA patients reported EDS [7-8]. In addition, more than 6% of OSA patients reported residual EDS after adequate continuous positive airway pressure (CPAP) treatment [9]. These 2 findings suggest that, in addition to hypoxemia and sleep fragmentation, there might be other etiologies of EDS in OSA patients. However, the cause of EDS remains uncertain, and currently, there is no reliable predictor of EDS in OSA patients.

In this study, we compared the PSG results of middle-aged OSA males with or without EDS to investigate the predictor of EDS in this group of patients.

Materials and Methods

Patient enrollment

This study was approved by the Research and Ethics Committee of the Chang Gung Memorial Hospital (CGMH) in Chiayi, Taiwan. We retrospectively reviewed PSG results in our hospital between September 2005 and August 2007. Patients who met the following inclusion criteria were screened: (1) male gender; (2) age between 20 and 65 years; (3) apnea hypopnea index (AHI) more than 5. A Chinese-language version of the Epworth Sleepiness Scale (ESS) was used for subjective EDS assessment [10]. In order to clearly show the difference between groups, only patients with extreme ESS scores in our population (5-10% of subjects in the highest and lowest ESS score distributions) were selected for analyses (Figure 1). Patients with ESS scores equal to or less than 4 and equal to or more than 20 were grouped into the non-EDS and EDS groups, respectively. Exclusion criteria were: (1) ESS between 5 and 19; (2) heart failure; (3) renal failure; (4) chronic obstructive pulmonary disease (COPD); (5) liver cirrhosis; (6) post-stroke; (7) other diseases that might interfere with the ESS results.

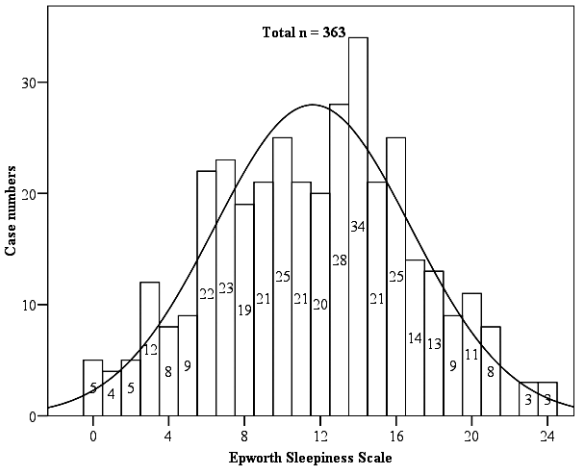

Fig. 1. Distribution of Epworth Sleepiness Scale scores in patients. A total of 363 middle-aged males with OSA met the inclusion criteria. Twenty-five (6.9%) patients had ESS scores equal to or more than 20 (EDS group), and 34 (9.4%) had ESS scores between 0 and 4 (non-EDS group). EDS, excessive daytime sleepiness.

Polysomnography

All patients in this study received hospital-

based PSG using standard techniques and criteria for scoring and recording obstructive apnea/hypopnea events and arousals from sleep [11]. Sleep stages were scored according to the criteria of Rechtschaffen and Kales [12]. Thoracoabdominal movements were detected by respiratory inductance plethysmography, and arterial oxyhemoglobin was evaluated by oximetry. A desaturation episode was defined as a > 3% drop in oxygen saturation (SaO_2), which was induced by an obstructive apnea/hypopnea event. Arousals were classified as respiratory arousals (occurring within 3 seconds following an apnea or hypopnea event), limb movement-related arousal, and spontaneous arousal [13]. PSG variables, including gender, age, body mass index (BMI), ESS score, AHI, desaturation index (DI), percentages of sleep stages 1 to 4 and rapid eye movement (REM), sleep latency, sleep efficiency, mean SaO_2, minimum SaO_2, and respiratory arousal index and total arousal index, were recorded. Sleep latency was defined as the period of time from lights off to the first 30 seconds of stage 1 (sleep onset). Sleep efficiency was defined as the night sleep duration expressed as the percentage of total sleep time in bed. AHI was the number of obstructive apnea/hypopnea events per hour of total sleep time, DI was the number of desaturation episodes per hour of total sleep time, the respiratory arousal index was the number of respiratory arousal episodes per hour of total sleep time, and the total arousal index was the number of every type of arousal event per hour of total sleep time. BMI was defined as weight (kg) divided by height squared (m^2). We compared the difference in these PSG variables between the EDS and the non-EDS group.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Mann-Whitney U tests were used to compare variables between the non-EDS and EDS groups. In order to exclude confounding factors, logistic regression analysis (forward, conditional) was performed to analyze the effects of age, BMI, AHI, DI, respiratory arousal index, total arousal index, sleep efficiency, total sleep time, and percentages of stage 1, stage 2, slow wave sleep (SWS, defined as stage 3+4), and REM. All tests were two-tailed. A p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

The subjects included 363 males whose ages ranged from 20 to 65 years and who were diagnosed as having OSA by PSG in our hospital. The distribution of the subjects' ESS scores is shown in Figure 1. Five patients in the non-EDS group (3 with a history of stroke, 1 who was undergoing an insomnia survey, and 1 who was currently under CPAP therapy) and 4 patients in the EDS group (1 who had heart failure, 1 with ESRD, and 2 with a history of stroke) met the exclusion criteria for conditions that might influence EDS and were thus excluded. Finally, a total of 50 patients were enrolled for analysis in the study: 21 (42%) patients who had an ESS of more than 20 comprised the EDS group, and 29 (58%) who had an ESS of less than 4 were included in the non-EDS group (Figure 2).

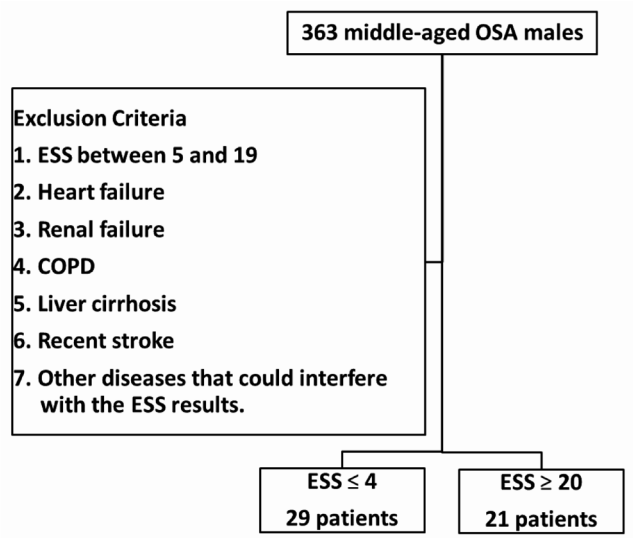

Fig. 2. Diagram showing the enrollment of patients. A total of 50 middle-aged males with OSA were enrolled in this study: 21 were included in the EDS group, and 29 comprised the non-EDS group. OSA, obstructive sleep apnea; ESS, Epworth Sleepiness Scale; COPD, chronic obstructive pulmonary disease; EDS, excessive daytime sleepiness.

Polysomnography results between the EDS and non-EDS groups

As shown in Table 1, there was no significant difference in age and BMI between the EDS and non-EDS groups. Both groups had similar total sleep time, sleep efficiency, sleep latency, stage 1+2 percentages, and REM stage percentages. The EDS patients had higher AHI and DI, although without statistical significance. The mean SaO_2 and minimal SaO_2 were slightly lower in the EDS group than in the non-EDS group, but there was no statistical significance. The EDS patients had a significantly higher respiratory arousal index and total arousal index, a higher percentage of stage 1 sleep, and a lower percentage of stage 2 sleep and SWS.

Logistic regression analysis was performed to evaluate the independent predictor of EDS in this study. The Hosmer and Lemeshow Goodness-of-fit test showed that the logistic model fits well ($p = 0.17$), and the power was 84% at a significance level of 0.05. Logistic regression showed that the percentage of stage 1 sleep only was an independent predictor of EDS in middle-aged male OSA patients (odds ratio = 1.05, 95% confidence interval = 1.01-1.10; $p < 0.01$).

Discussion

In this study, we found that patients in the EDS group had a higher respiratory arousal index, total arousal index, and percentage of sleep stage 1 and 2 than patients in the non-EDS group. We also found that patients in the EDS group had a lower percentage of SWS than patients in the non-EDS group. There was no statistically significant difference in mean oxygen saturation and minimum oxygen saturation between the EDS and non-EDS groups. For middle-aged males with OSA, a higher percentage of stage 1 sleep was the only independent predictor of EDS.

The causes of EDS in OSA patients remain controversial. Colt *et al*. and Miliauskas *et al*. suggested that sleep fragmentation, but not nocturnal hypoxemia, was the major cause of EDS in OSA patients [5-6]. However, Roure *et al*. indicated that sleep apnea and sleep disruption were not the primary determinants of EDS [14]. Mediano *et al*. reported that nocturnal hypoxemia was the major determinant of EDS in patients with OSA [3], and Yagi *et al*. showed that both hypoxemia and sleep fragmentation were important factors of EDS in patients with OSA [15]. Many studies have used the percentage of stage 1+2, instead of the percentages of individual sleep stages, to compare the difference between EDS and non-EDS groups.

Table 1. Comparisons of characteristics and polysomnographic variables between non-EDS and EDS patients

	Non-EDS (n=29)	EDS (n=21)	*p*-value
Age (year)	44.9 ± 10.5	49.3 ± 8.1	0.14
BMI (kg/m^2)	28.1 ± 4.5	29.8 ± 7.1	0.35
Total sleep time (minute)	289.3 ± 48.5	297.1 ± 45.9	0.65
Sleep efficiency (%)	81.8 ± 10.6	81.4 ± 10.4	0.98
Sleep latency (minute)	16.7 ± 13.4	11.2 ± 9.5	0.13
AHI (/hour)	49.7 ± 39.9	71.6 ± 50.2	0.17
DI (/hour)	33.2 ± 25.4	50.9 ± 35.1	0.07
Respiratory arousal index (/hour)	13.7 ± 14.9	28.7 ± 23.3	0.03*
Total arousal index (/hour)	22.1 ± 14.2	35.0 ± 19.4	0.02*
Mean SaO_2 (%)	94.1 ± 2.2	92.1 ± 4.2	0.14
Minimum SaO_2 (%)	76.8 ± 8.9	72.6 ± 12.0	0.25
Sleep stage 1 (%)	27.9 ± 12.7	40.5 ± 18.7	0.02*
Sleep stage 2 (%)	42.3 ± 15.8	40.0 ± 16.3	0.03*
Sleep stage 1+2 (%)	70.2 ± 9.3	71.4 ± 9.0	0.61
SWS	1.9 ± 4.2	0.1 ± 0.2	0.03*
Sleep REM stage	9.8 ± 5.9	9.9 ± 4.5	0.87

* $p < 0.05$; Data are presented as mean ± standard deviation; BMI, body mass index; AHI, apnea-hypopnea index; DI, desaturation index; SaO_2, oxygen saturation; SWS, slow wave sleep; REM, rapid eye movement.

Mediano *et al*. reported that there was no difference in the percentages of stage 1+2 sleep and SWS between EDS and non-EDS patients [3], but Roure *et al*. showed that EDS patients had lower percentages of stage 1+2 sleep and higher stage 3+4 sleep [14]. Our results showed severer sleep fragmentation, lower percentages of stage 2 sleep and SWS, and a higher percentage of stage 1 sleep in the EDS group. However, we found that only the percentage of stage 1 sleep was an independent predictor of EDS in middle-aged OSA males. Wang *et al*. indicated that both the ESS score and percentage of stage 1 sleep were higher in OSA patients with heart failure than in non-OSA heart failure patients, but without statistical significance [16]. In addition, a higher percentage of stage 1 sleep (11.3 ± 6.6 % vs. 7.44 ± 4.2%) was found in systemic lupus erythematosus patients with disabling tiredness than in healthy controls [17].

Whether there are any causal relationships between high percentages of stage 1 sleep and EDS in OSA patients is still unknown. Carskadon and Dement indicated that a higher percentage of stage 1 sleep is a common sign of severely disrupted sleep [18]. One of the functions of non-REM sleep is to restore energy by minimizing energy expenditure [19]. Kuboyama *et al*. found that cerebral blood flow velocity is higher in stage 1 than stage 2 sleep [20]. According to flow-metabolism coupling theory, a higher cerebral blood flow indicates higher O_2 consumption, glucose uptake and metabolic rate, and thus less resting of the brain. In addition, transitions from instability to stability in the cardiovascular and respiratory systems were

found from stage 1 sleep to SWS [21]. These studies suggested that energy expenditure is higher in stage 1 sleep than in other non-REM stages, and that a high percentage of stage 1 sleep may be the cause of EDS in OSA patients. A previous study also showed that higher percentages of stage 1+2 sleep were found in OSA patients, and that CPAP treatment shifts stages 1+2 sleep to SWS sleep and is usually associated with an improvement in EDS [6]. Further studies comparing the percentage of stage 1 sleep and EDS in OSA patients before and after CPAP treatment might help to elucidate the actual relationship between stage 1 sleep and EDS.

There are some limitations to this study. First, the study was focused on subjective EDS, and only the ESS score was used for EDS evaluation. No objective evidence could support the EDS findings for our patients. Therefore, to overcome this limitation to as great an extent as possible, only patients who reported they were very sleepy (ESS scores between 20 and 24) and nearly not sleepy (ESS scores between 0 and 4) were enrolled in this study. Second, micro-arousal was not scored in this study, and this could result in underestimating the effect of arousal on EDS [22].

In conclusion, this is the first study to report that a higher percentage of stage 1 sleep is strongly associated with EDS and might be an important determinant of EDS in middle-aged male OSA patients. Our results warrant further study of OSA patients under CPAP treatment, with or without residual EDS, to confirm the causal relationship between a higher percentage of stage 1 sleep and EDS. Treatments that shift stage 1 sleep to deeper stages may be considered for patient protocols in managing OSA.

Acknowledgement

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高比例之第一期睡眠是中年男性阻塞性睡眠呼吸中止症患者白天嗜睡之預測因子

周育廷* 林裕清*,** 林進國* 張家豪*** 楊政達**** 蔡熒煌*,**
張薷方* 楊聰明*

背景：造成阻塞性睡眠呼吸中止症病患白天過度嗜睡的主要原因目前仍未定論。在我們的研究中，我們發現高比例之第一期睡眠是中年男性阻塞性睡眠呼吸中止症患者白天嗜睡之預測因子。

方法：我們收集2005年9月至2007年8月嘉義長庚紀念醫院中年男性阻塞性睡眠呼吸中止症病患之多頻道睡眠檢查報告。一共有50位病人的資料符合收入條件，其中Epworth睏睡度量表（Epworth sleepiness scale, ESS）分數等於或大於20分之患者被分為白天過度嗜睡（EDS）組，而ESS分數小於4的患者則被分為非白天過度嗜睡（Non-EDS）組，我們比較者兩組睡眠檢查結果之差異，以找出中年男性阻塞性睡眠呼吸中止症患者是否會有白天過度嗜睡之預測因子。

結果：將EDS組與Non-EDS組做比較，我們發現EDS組有較高的呼吸性覺醒指數（respiratory arousal index）以及總覺醒指數（total arousal index），較高比例的第一期睡眠（stage 1 sleep）、較低比例的第二期睡眠（stage 2 sleep），以及較低比例的慢波期睡眠（slow wave sleep）。經由邏輯回歸分析（logistic regression）結果，我們發現高比例的stage 1 sleep是決定病患是否會有白天過度嗜睡的唯一獨立預測因子（OR=1.052, 95% confidence interval=1.011-1.096; $p = 0.013$）。

結論：高比例的stage 1 sleep是中年男性阻塞性睡眠呼吸中止症病患是否會有白天過度嗜睡的主要決定因子。*(胸腔醫學* ***2011; 26: 179-186)***

關鍵詞：過度嗜睡，阻塞性睡眠呼吸中止症，多頻道睡眠檢查，睡眠分期

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Influence of Intensive Care-Acquired Hypernatremia on the Short-term Mortality of Mechanically Ventilated Patients

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Background: ICU-acquired hypernatremia (IAH) is reported to be strongly associated with mortality, and mechanical ventilation (MV) is a risk factor for IAH. However, the incidence of IAH and its impact on ICU mortality among mechanically ventilated patients are unknown.

Methods: A retrospective observational study was conducted in a respiratory ICU from December 2008 to December 2009. Patients receiving MV were evaluated. The outcome measurements were the occurrence of IAH and 28-day ICU mortality.

Results: Of 161 patients enrolled, 30 (19%) had IAH. Patients with IAH had a higher APACHE II score at admission, lower oxygenation status and longer duration of MV in the ICU compared to those without. In a multivariate logistic regression analysis, IAH was independently associated with 28-day ICU mortality (odds ratio 6.756, 95% confidence interval 1.745-26.164, p=0.006) after adjustment for the APACHE II score at admission, acute kidney injury at admission and a Do Not Resuscitate order.

Conclusions: IAH is common among critically ill patients requiring MV and is independently associated with ICU mortality in this patient population. ***(Thorac Med 2011; 26: 187-194)***

Key words: ICU-acquired hypernatremia, mechanical ventilation, ICU mortality

Introduction

Hypernatremia is a common event in the ICU. In recent studies defining hypernatremia as a serum sodium level of ≥145 meq/L or 149 meq/L, the incidence of ICU-acquired hypernatremia (IAH) in patients ranged between 7% and 26% [1-3]. IAH is also reported to be an independent risk factor for mortality among general ICU patients [2-5].

According to some recent studies, risk factors for IAH included greater disease severity, increased serum creatinine, septic shock and mechanical ventilation (MV) use at ICU admission [1-5]. Mechanically ventilated patients may develop IAH because of diuretic treatment

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or restricted access to free water.

Although mechanically ventilated patients are at an increased risk for IAH, the impact of IAH on the ICU outcome of these patients has not been examined. Therefore, the aim of this study was to (1) identify the incidence and risk factors of IAH in critically ill patients requiring MV, and (2) estimate the impact of IAH on short-term ICU mortality in this specific patient population.

Methodology

This retrospective observational cohort study was conducted in the respiratory therapy care unit (a 35-bed respiratory ICU) of Taipei Veterans General Hospital, a tertiary medical center in northern Taiwan. All patients who received invasive MV between December 2008 and December 2009 were reviewed. Patients were excluded (1) if they were admitted for weaning from prolonged MV with a preadmission MV duration exceeding 72 hrs, (2) if they were readmitted to the ICU, (3) if they had advanced malignancy at a terminal stage and (4) if they had hypernatremia upon ICU admission.

Data Gathering and Measurements

The following information was collected through a careful chart review. First, the patient's age, gender, underlying disease, Do Not Resuscitate (DNR) order, APACHE (acute physiology and chronic health evaluation) II scores [6], reasons for the initiation of MV, biomarkers, and clinical events including acute kidney injury (AKI) at ICU admission were recorded. During the ICU stay, IAH was identified and the date of its onset as well as its duration was also recorded. Finally, the number of MV days before ICU discharge, successful weaning from MV, the length of ICU stay and ICU mortality were also collected. The outcome measures were the occurrence of IAH before day 28 and mortality in the ICU within 28 days.

Definition

Hypernatremia was defined as a serum sodium level exceeding 147 meq/L. This measurement was based on the normal reference range of serum sodium in our hospital. Patients were considered to have IAH when the initially normal serum sodium level rose above 147 meq/L during the course of the ICU stay. AKI at admission was defined as a 50% or greater increase in serum creatinine from the premorbid baseline level or a urine output <0.5 ml/kg/hour for a least 6 hours according to the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease) criteria [7].

Statistical analysis

The study patients were divided into 2 groups: those with IAH and those without. The results are expressed as the means ± standard deviations (SD), medians with interquartile ranges (IQRs), or n (%), as appropriate. We used independent *t* tests (Student's *t* test) and Mann-Whitney U tests to compare continuous variables when the distribution was normal and not normal, respectively. We used the χ^2 test or Fisher's exact test to compare percentages, as appropriate.

Then, univariate logistic regression analysis was performed to determine the factors associated with 28-day ICU mortality. We used the timeframe of 28 days because it was previously introduced in 2 studies of IAH [1,5], and only 6.3% observed IAH episodes occurred after day 28 in this study. Variables presenting a sig-

nificant association with 28-day ICU mortality (p<0.05) were entered into multivariate logistic regression analysis in order to determine factors independently associated with 28-day ICU mortality. Odds ratio (OR) and 95% confidence interval (CI) were calculated. These analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, version 18.0).

Results

Study Patients

During the 13-month study period, 161 patients were enrolled (Figure 1). The mean age of the enrolled patients was 78.4 (± 12.5) years and 74% of them were male. The mean APACHE II score at ICU admission was 18.3 (± 5.1) and the median duration of ICU stay was 16 days, with an IQR of 11-27 days. The 28-day ICU mortality rate of the study population was 8% (n=13).

Incidence of IAH

Thirty patients (19%) acquired hypernatremia before day 28 of their ICU stay. Among them, 1/3 (n=10) experienced more than 1 episode. The onset of the first IAH episode was on day 9 (IQR, 4 to 14 days) with a median duration of 3 days (IQR, 1 to 6 days). The prevalence of IAH is shown in Figure 2.

Risk factors for IAH and patient outcome

The characteristics and outcomes of patients with and without IAH are listed in Table 1. Patients with IAH had a significantly greater disease severity and poorer oxygenation status at ICU admission, and they experienced more

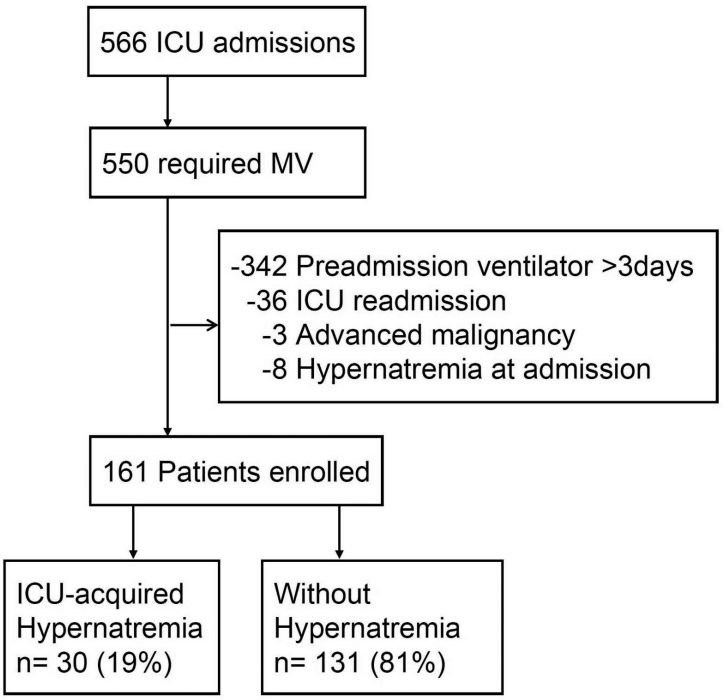

Fig. 1. Flowchart of the study

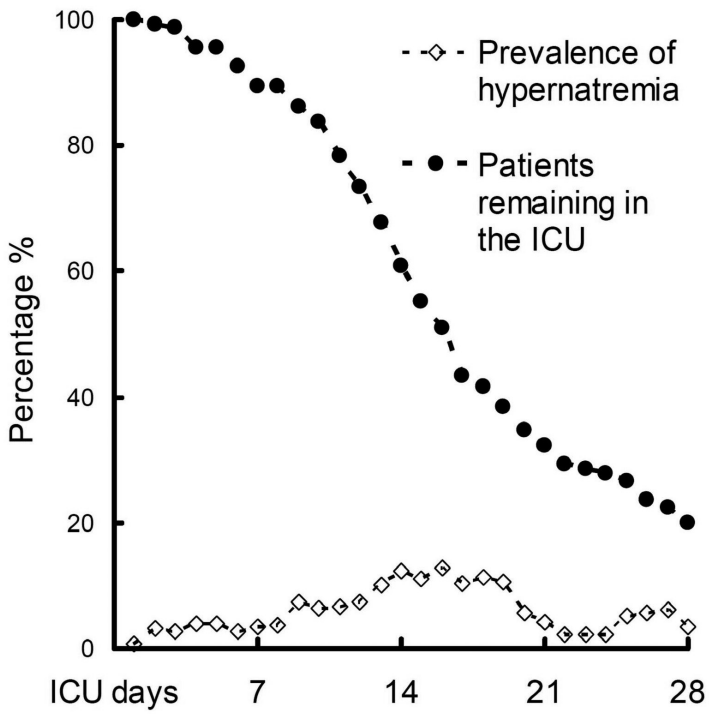

Fig. 2. Daily prevalence of ICU-acquired hypernatremia and percentage of patients that remained in the ICU from admission until day 28

MV days (22 vs. 11 days; p=0.001) and a higher ratio of unsuccessful weaning from MV during their ICU stay than those without IAH (43% vs. 11%; p<0.001). In addition, patients with IAH before day 28 had a higher 28-day ICU mortality compared with those without IAH (27% vs. 4%; p=0.001).

Impact of IAH on ICU mortality

Univariate logistic regression analysis revealed a statistically significant association of IAH with 28-day ICU mortality, as seen in Table 2. In addition, the APACHE II score at ICU admission, AKI at ICU admission and DNR order had a statistically significant association with 28-day ICU mortality in the univariate regression model. In the multivariate logistic regression model, IAH was independently associated with an increased probability of mortality (OR 6.756, 95% CI 1.745-26.164, p=0.006) after adjustment for the DNR order, APACHE II score and AKI at ICU admission, as seen in Table 3.

Discussion

In this study, we investigated an ICU population that required MV use and found that IAH is a common event in this specific patient group. Moreover, we found that IAH is significantly associated with a longer duration of MV use and unsuccessful weaning, and is also an independent risk factor for 28-day ICU mortality in this patient population.

The incidence and duration of IAH among ICU patients requiring MV in our study were in

Table 1. Characteristics and outcomes of patients with or without ICU-acquired hypernatremi

Variables	ICU-acquired hypernatremia (n=30)	Without hypernatremia (n=131)	*p* Value
Age (years)	79 ± 12	78 ± 13	0.882
Male gender	25 (83)	94 (72)	0.193
Underlying disease			
COPD	9 (30)	61 (47)	0.099
Heart failure	6 (20)	31 (24)	0.667
Diabetes mellitus	15 (50)	49 (37)	0.204
Chronic kidney disease	3 (10)	27 (21)	0.178
Cerebrovascular accident	12 (40)	36 (27)	0.176
APACHE II score at admission	21 ± 6	18 ± 5	0.001
Reason for ventilator support			
COPD acute exacerbation	6 (20)	42 (32)	0.193
Acute pulmonary edema	7 (23)	27 (21)	0.742
Sepsis	12 (40)	37 (28)	0.207
Others	5 (17)	25 (19)	0.759
Biomarkers and events at admission			
PaO_2/FiO_2	135 ± 88	210 ± 135	0.004
Serum creatinine, mg/dL	1.8 ± 1.4	1.7 ± 1.6	0.228
Serum sodium, meq/L	137 ± 8	135 ± 8	0.168
Acute kidney injury at admission	7 (23)	23 (18)	0.464
Do Not Resuscitate order	9 (30)	18 (14)	0.023
Outcome			
MV days before discharge	20 (12-30)	11 (6-18)	0.001
Unsuccessful weaning	13 (43)	15 (11)	<0.001
ICU length of stay, days	20 (13-31)	16 (11-26)	0.067
28-day ICU mortality	8 (27)	5 (4)	<0.001

Continuous data expressed as mean ± SD or median (IQR) and categorical data expressed as number (%). Abbreviations: COPD, chronic obstructive pulmonary disease; PaO_2/FiO_2, PaO_2/fraction of inspired oxygen; MV, mechanical ventilation.

line with those of recent studies of general ICU patients [1-5]. However, compared with those reports, the time to onset of the first IAH episode was relatively late among our patients (day 9 vs. days 1-5) and the percentage of those who experienced more than 1 episode of IAH was higher than in previous reports (33% vs. 15%).

The factors associated with the development of IAH in our study were not only the underlying disease severity but also a poor oxygenation status at admission and greater number of MV days before ICU discharge. Ill patients with poor oxygenation and MV may undergo conservative fluid management with or without diuretic treatment, which may lead to potential free water loss with consequent hypernatremia.

Table 2. Summary of univariate analysis revealing the possible factors associated with 28-day ICU mortality

Variables	Odds ratio	95% confidence interval	*p* Value
Age (years)	1.077	0.990-1.172	0.086
Male gender	2.037	0.432-9.595	0.368
Underlying disease			
COPD	0.552	0.163-1.873	0.341
Heart failure	0.587	0.124-2.776	0.502
Diabetes mellitus	1.863	0.596-5.821	0.285
Chronic kidney disease	0.779	0.163-3.715	0.754
Cerebrovascular accident	0.687	0.180-2.614	0.582
APACHE II score at admission	1.214	1.088-1.354	0.001
Reason for ventilator support			
COPD acute exacerbation	0.179	0.023-1.418	0.103
Acute pulmonary edema	1.748	0.504-6.066	0.379
Sepsis	2.994	0.935-9.276	0.065
Others	0.373	0.047-2.996	0.345
Biomarkers and events at admission			
PaO_2/FiO_2	0.995	0.989-1.001	0.090
Serum creatinine, mg/dL	1.128	0.843-1.508	0.418
Serum sodium, meq/L	1.095	0.980-1.223	0.108
Acute kidney injury	6.341	1.953-20.585	0.002
Do Not Resuscitate order	3.494	1.046-11.671	0.042
ICU-acquired hypernatremia	9.164	2.745-30.596	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; PaO_2/FiO_2, PaO_2/fraction of inspired oxygen.

Furthermore, patients at risk of IAH may need prolonged MV for their poor oxygenation and severe disease status. IAH itself may lead to consciousness disturbance, weakness and hemodynamic instability, which may further result in difficult weaning and longer MV duration.

Our study results showed that IAH is independently associated with 28-day ICU mortality among patients receiving MV and this finding has not been reported in the related literature. This study not only adds to the growing body of literature on the impact of hypernatremia in critically ill patients but also highlights the characteristics of IAH in mechanically ventilated patients. We must not neglect the rising serum sodium levels in this patient population and should recognize patients at risk of IAH so as to prevent associated ICU mortality.

There are certain limitations to this study. First, this is a single ICU study of a relatively small sample size. Second, because our study is retrospective, the etiology of IAH could not be established. Future research should be carried out on the etiology of IAH in mechanically ventilated patients. Third, our patients were relatively older because our hospital is a tertiary referral center primarily for the care of veterans. Thus, our findings need to be confirmed in

Table 3. Results of multivariate logistical regression analysis to determine the influence of ICU-acquired hypernatremia on 28-day ICU mortality

Variables	Odds ratio	95% confidence interval	*p* Value
ICU-acquired hypernatremia	6.756	1.745-26.164	0.006
APACHE II score at admission	1.143	1.010-1.293	0.035
Acute kidney injury at admission	4.680	1.187-18.444	0.027
Do Not Resuscitate order	2.427	0.606-9.723	0.211

the future using a younger patient population.

In conclusion, IAH is common in critically ill patients requiring MV and is independently associated with 28-day ICU mortality. In this patient population, the risk factors for IAH were greater disease severity, poor oxygenation at admission and longer MV duration before ICU discharge. Thus, physicians should be able to use these indicators to identify patients with an increased risk of IAH and prevent IAH-associated mortality in this patient population.

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加護照護發生之高血鈉對呼吸器病患短期死亡率之影響

潘聖衛　連德正　陳燕溫　余文光　柯信國　王家弘

前言：加護照護發生之高血鈉與病患死亡率有很高的相關性，使用呼吸器則是加護病房發生高血鈉的危險因子之一。然而在使用呼吸器的病患身上，加護病房高血鈉的發生率及其對死亡的影響尚無研究報告。

方法：本文為呼吸治療加護病房之回溯性研究，納入使用呼吸器的病患，測量加護病房高血鈉的發生率及28天之加護病房死亡率。

結果：共收案161人，其中有30人（19%）在加護病房期間發生高血鈉，這些發生加護病房高血鈉的病人在進入加護病房時有較高的APACHE II分數、較低的血氧濃度及在加護病房中有較長的呼吸器使用天數。在多重迴歸分析中發現，校正了住入加護病房之APACHE II分數、急性腎損傷及拒絕心肺復醒術因子後，加護病房高血鈉與28天之加護病房死亡率確有獨立的相關性（勝算比6.756、95%信心區間為1.745-26.164、p=0.006）。

結論：加護照護發生之高血鈉在使用呼吸器的重症病患身上是常見的，而且加護病房高血鈉與這類病患之死亡率有獨立的相關性。*(胸腔醫學* ***2011; 26: 187-194****)*

關鍵詞：加護照護發生之高血鈉，呼吸器，加護病房死亡率

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Pyogenic Lung Abscess in a Patient with Wegener's Granulomatosis: A Case Report

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Wegener's granulomatosis is a progressive autoimmune vasculitis affecting multiple systems, and a wide variety of lesions may be seen in the lung. Because the disease is treated with immunosuppressants, patients are also at high risk of infection, particularly pneumonia. A 52-year-old woman with bilateral cavitating lung lesions was diagnosed with Wegener's granulomatosis. Her disease responded well to high-dose steroids and cyclophosphamide, after which she was maintained with azathioprine and low-dose prednisolone. Eight months after diagnosis, she presented with fever, and her chest x-ray showed air-fluid levels in residual cavitary lesions. Methicillin-resistant *Staphylococcus aureus* was cultured from the bronchoalveolar lavage fluid. With treatment, the patient recovered from the lung abscesses. A careful review of lung imaging studies is essential to distinguish between underlying Wegener's granulomatosis lung lesions and superimposed infection. ***(Thorac Med 2011; 26: 195-201)***

Key words: lung abscess, Wegener's granulomatosis, methicillin-resistant *Staphylococcus aureus*

Introduction

Wegener's granulomatosis (WG), an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, is a progressive inflammatory autoimmune disease characterized by inflammation and necrosis of the small blood vessels. The classic clinical pattern is a triad involving the upper airways, lungs and kidneys, with pulmonary involvement occurring in 85% of patients [1]. Radiographic studies commonly show bilateral nodular pulmonary infiltrates, ground glass infiltrates from alveolar hemorrhage, and thin- and thick-walled cavities. Since the vasculitis is treated with immunosuppressants, patients with WG are at increased risk of infection. Interpreting lesions seen on chest x-ray is therefore often difficult. We present the case of a woman with WG with striking radiologic findings attributable to her disease and then to a secondary infection.

Case Report

A 52-year-old woman had progressive hearing loss, fever, productive cough, and a sudden

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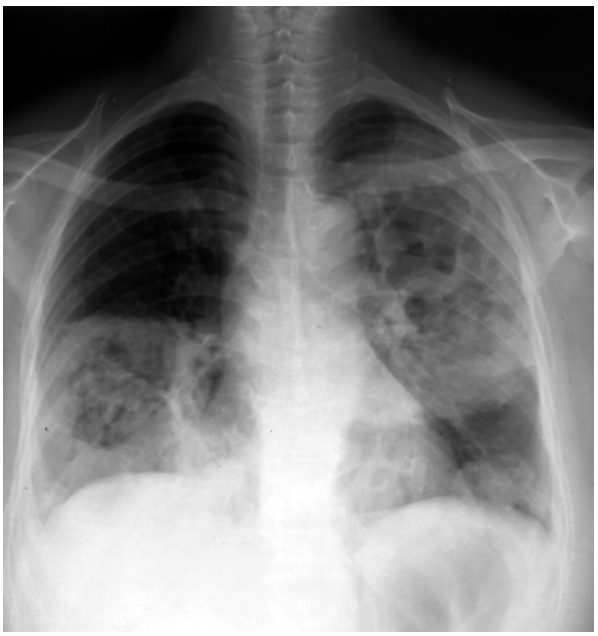
decrease in urine output. Bilateral acute otitis media was diagnosed, with audiometry showing bilateral severe sensorineural hearing impairment. Her chest film and computed tomography (Figure 1) revealed extensive opacities in the left upper and right lower lobe, with central cavitation. Urinalysis revealed microscopic hematuria and granular casts. A test for serum cytoplasmic-antineutrophil cytoplasmic antibody was positive. Pathological examination of tissue from a thoracoscopic wedge biopsy of the left lower lobe revealed granulomatous inflammation, geographic necrosis, microabscesses, and vasculitis -- a picture compatible with WG.



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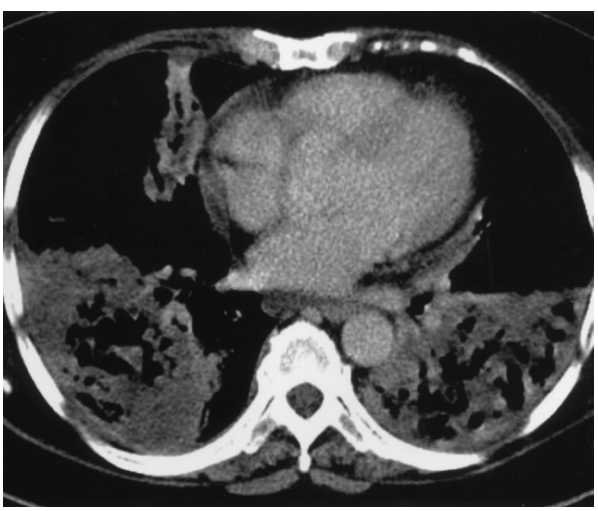


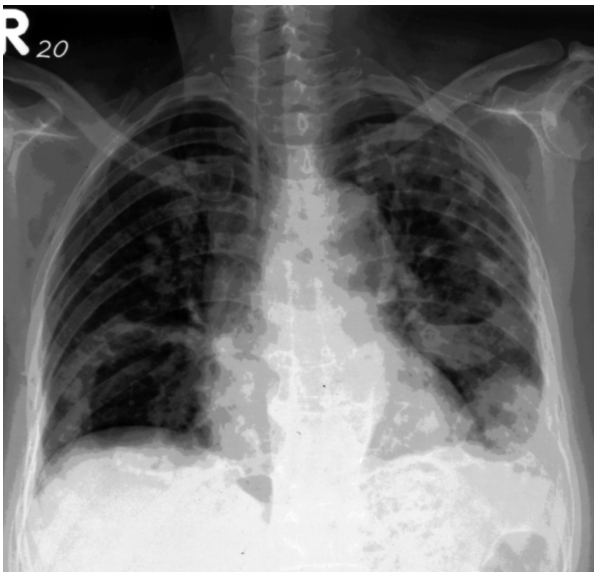
(B)

Fig. 1. Chest film (A) and computed tomography (B), with extensive opacities in the left upper and right lower lobe containing central cavitation.

The patient was initially treated with intravenous methylprednisolone 500 mg for 3 days, followed by prednisolone 1 mg/kg and oral cyclophosphamide 2 mg/kg daily. After 1 month, the chest film revealed partial resolution of the consolidation and cavities bilaterally. Her hearing also improved. After 4 months, her chest film showed residual thin-wall cysts (Figure 2). She subsequently developed toxic epidermal necrolysis attributed to the cyclophosphamide, which was therefore discontinued. Daily azathioprine 1 mg/kg was added to ongoing low-dose prednisolone as maintenance therapy.

Eight months after diagnosis, she again developed fever. A chest film and computed tomography (Figure 3A, 3B) revealed multiple cavities with air-fluid levels. On bronchoscopy, there was diffuse hyperemia of the airway mucosa and granulomatous plaques; blood was seen coming from the right lower lobe. Bronchoalveolar lavage fluid from the right lower lobe cavity grew more than 10^6 colony-forming units per ml of methicillin-resistant *Staphylococcus aureus* (MRSA). Lung abscesses were diagnosed, and teicoplanin was administered for 7 days, followed by a 14-day-course of vancomycin. A follow-up chest film (Figure 3C) 1 month later revealed resolution of the air-fluid levels.

Nine months after the WG diagnosis, the patient's antineutrophil cytoplasmic antibody



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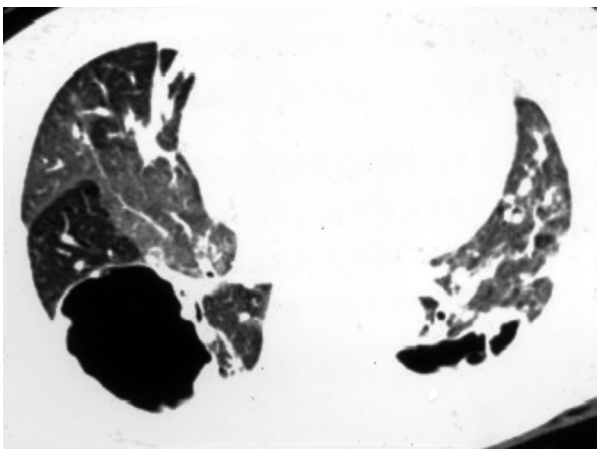


(B)

Fig. 2. Follow-up chest film (A) and computed tomography (B) after 4 months of immunosuppressive treatment; there is marked improvement, but residual thin-walled cysts are present.

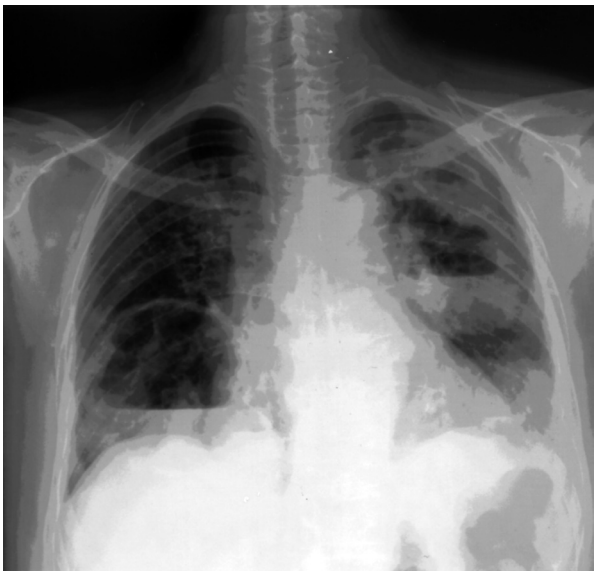
was still weakly positive. Therefore, she was kept on azathioprine and prednisolone. Subsequently, she developed intermittent fever and exertional dyspnea and the chest film revealed pulmonary edema; echocardiography demonstrated left atrial and ventricular enlargement with diastolic dysfunction, suggestive of dilated cardiomyopathy (DCM). A coronary angiogram revealed only insignificant coronary artery disease. An angiotensin-converting enzyme inhibitor and β-blockade were administered with resolution of her dyspnea and pulmonary edema.

In the following year, she developed a urinary tract infection with *Escherichia coli* and vancomycin-resistant enterococcus, an infection that again was successfully treated. However, 21 months after diagnosis, she died in an out-of-hospital cardiac arrest.

Discussion

This case illustrates the risk of opportunistic infections, particularly in the lung, in patients with WG that are undergoing chronic immunosuppressive therapy, highlighting the importance of careful interpretation of imaging studies. New lesions on a chest film might be the result of the underlying disease, a superimposed infection, or even malignancy. Our patient developed MRSA lung abscesses in cavitary lesions originally caused by WG. The clue to this diagnosis was the new air-fluid levels seen when she presented with fever; culture of the bronchoalveolar lavage fluid identified the pathogen.

Active WG in the lungs can mimic pneumonia, septic emboli, and metastases [2]. Granulomatous nodules may occur in a centrilobular distribution, mimicking tuberculosis, hypersensitivity pneumonitis, or an acute viral, bacterial, or fungal pneumonia. Cavitation occurs in approximately 25% of nodules larger than 2 cm, with cavity walls that may be thin, thick, or nodular. A lung cavity, regardless of the underlying disease causing it, may become secondarily infected, signaled by new air-fluid levels, as seen in our patient's images.



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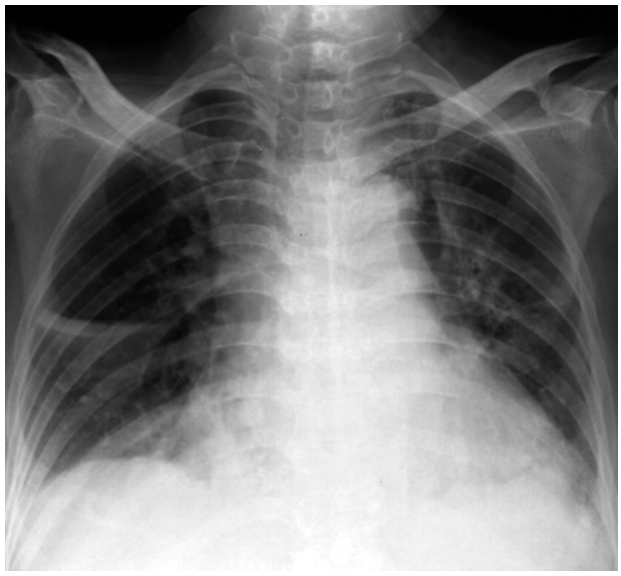

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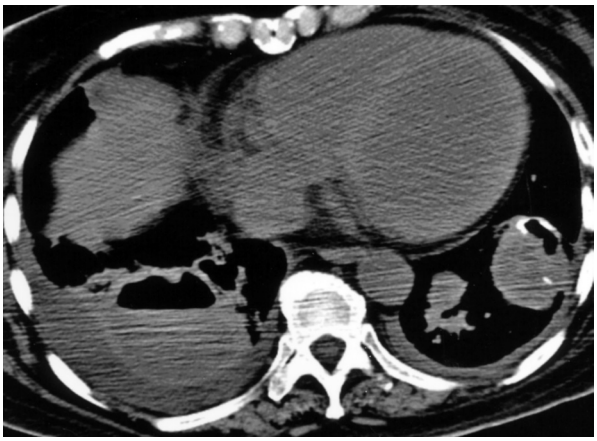

(B)

Fig. 3. (A) Chest film with multiple air-fluid levels suggesting lung abscess; (B) computed tomography with an air-fluid level in the right lower lobe; (C) chest film after antibiotic treatment showing resolution of the air-fluid levels.

While a lung abscess such as our patient had might in theory be caused by any number of pathogens, staphylococcal disease is quite common in patients with WG, who have an abnormally high incidence of a nasal carriage of *S. aureus*. A study from The Netherlands suggested that such colonization was associated with a higher rate of relapse of the underlying vasculitis [3]. Richter *et al*. cultured bronchoalveolar lavage fluid from patients with WG, idiopathic pulmonary fibrosis, and normal controls, and found that *S. aureus* was significantly more likely to grow in the fluid from patients with WG, particularly when they were in remission or relapse [4]. The predilection of *S. aureus* for the lower airways of patients with WG is probably multifactorial, and related, for example, to structural changes in lungs damaged by the disease, to an immunodeficiency secondary both to therapy for WG and possibly to defective host innate immunity, and to the virulence of *S. aureus*. Our patient was chronically immunosup-

pressed because of the azathioprine and prednisolone given to treat her WG, and she had a large cavity in her right lower lobe caused by the vasculitis. Despite infection with a resistant organism, she was successfully treated and recovered well from this particular complication.

Infection is an important cause of death for patients with WG, reportedly accounting for 3% to 12% of deaths in patients followed for a mean of 7 to 10 years. Even if not fatal, infections are associated with significant morbidity. Pneumonia is particularly common. Reported infection rates have ranged from 12% to 72% [5-7], although it must be noted that the highest rate of 72% was published in 1998, in an older study by Hoffman *et al*. [6], and it may reflect the prolonged use of cyclophosphamide. Since then, there have been changes in immunosuppressive regimens in the induction-maintenance strategy to reduce cumulative exposure to cyclophosphamide. In a more recent study, where azathioprine and methotrexate were considered as alternative agents for the maintenance therapy of ANCA-associated vasculitis, the infection rate was 36.5% [8]. As always, the challenge with such disorders is to balance the benefits of immunosuppression in controlling the underlying disease with the deleterious side effects of such treatment.

Our patient had an out-of-hospital cardiac arrest and could not be resuscitated. She was known to have cardiomyopathy, tentatively attributed to her WG. The small and medium vessel vasculitides may affect the myocardium, valves, pericardium, and coronary arteries [9]. If the heart muscle is affected by vasculitis, particularly in patients with WG, the interventricular septum is the most commonly affected site. Death due to fulminant heart failure or arrhythmia, however, appears to be uncommon [10]. Patients with active small vessel vasculitis have also been found to be at increased risk for venous thromboembolic disease [11]. While the exact cause of her death is unclear, it is worth noting that despite our patient's WG and chronic immunosuppressive treatment, she survived 2 serious infections with resistant organisms because of prompt diagnosis and appropriate treatment.

In conclusion, because WG is a multisystem disease, patients are likely to require multidisciplinary care by specialists with expertise in each of the systems that may be involved, either by complications associated with the disease itself or with its treatment. It is vital to distinguish between a relapse of the disease and infection, especially in patients with extensive lung involvement. This requires a meticulous review of imaging studies as well as careful attention to the differential diagnosis.

Acknowledgments

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韋格納肉芽腫合併肺膿瘍：病例報告

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韋格納肉芽腫是一種影響多重器官的漸進性自體免疫血管炎。在肺部可以看到各式各樣的表現。因為病患需要使用免疫抑制劑作治療，是感染的高危險群，特別容易有肺炎產生。一個52歲的女性病患，肺部兩側有數個厚壁開洞，診斷為韋格納肉芽腫，對高劑量類固醇及cyclophosphamide反應良好，之後持續用低劑量類固醇及azathioprine治療。診斷後八個月發燒並在原本開洞處呈現多個air-fluid level。支氣管肺泡沖洗液培養出Methicillin抗藥性金黃色葡萄球菌，經抗生素治療後顯著改善。這讓我們了解在韋格納肉芽腫病患的肺部影像必須仔細鑑別診斷是疾病原本表現還是續發性感染發生。*(胸腔醫學* ***2011; 26: 195-201)***

關鍵詞：肺膿瘍，韋格納氏肉芽腫，Methicillin抗藥性金黃色葡萄球菌

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Paradoxical Vocal Cord Motion in a Patient with Post-extubation Stridor

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Post-extubation stridor frequently causes weaning failure in mechanically ventilated patients. The most common causes of post-extubation stridor are vocal cord edema and paralysis. Paradoxical vocal fold motion (PVFM) is a laryngeal disorder characterized by inappropriate adduction of the vocal cords during inspiration, expiration, or both. Clinically, this disorder is often misdiagnosed as an asthma attack but rarely is it associated with post-extubation stridor. A 62-year-old man with vocal cord paralysis and acute respiratory failure developed post-extubation stridor and was identified as having PVFM. We present the typical findings on bronchoscopy. The characteristic patterns of spirometry, including notching and a flattened or truncated flow-volume loop, are also described. ***(Thorac Med 2011; 26: 202-207)***

Key words: extubation, paradoxical vocal fold motion, spirometry, stridor, vocal cord dysfunction

Introduction

Post-extubation stridor is not uncommon as a complication during mechanical ventilator support, and frequently causes weaning failure. Subsequent intubation is usually followed by ventilator-associated pneumonia and other morbidities. The most common causes of post-extubation stridor are vocal cord edema or paresis/paralysis. Other etiologies, such as laryngospasm and arytenoid dislocation, have been occasionally reported.

Paradoxical vocal fold motion (PVFM), also known as vocal cord dysfunction or Munchausen's stridor, is a laryngeal disorder characterized by inappropriate adduction of the vocal cords during inspiration, expiration, or both. Most studies on PVFM have reported a preponderance of females and those at a younger age [1-4]. PVFM can be triggered by a variety of conditions, including exercise, psychological stress, post-nasal dripping, irritants, laryngopharyngeal reflux, laryngeal dystonia, post-thyroidectomy, and medication (anesthesia or neuroleptic) [4-6]. Patients with PVFM are commonly misdiagnosed as having asthma and receive unnecessary medication [2, 7]. PVFM is rarely associated with post-extubation stridor. The etiologies of post-extubation stridor in patients that have been mechanically ventilated in

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medical intensive care units were reviewed.

Case Report

A 62-year-old man previously diagnosed with vocal cord paralysis due to complications of thyroidectomy was identified as having PVFM. We herein present the bronchoscopic findings and spirometry pattern of this unusual disorder.

This patient was known to have papillary carcinoma of the thyroid 5 years prior to this admission and has post-operation hoarseness. He visited the emergency room of this hospital due to exacerbation of dyspnea and was intubated for ventilator support. After controlling the infection, he was extubated. Post-extubation stridor was found, and he was supported with a non-invasive positive pressure ventilator (NIPPV). The patient underwent bronchoscopy via the right nostril for upper airway evaluation.

Bilateral vocal cord paralysis was noted with narrowing of the glottis chink. The true vocal cords were not swollen. Under tidal volume respiration, the patient had typical paradoxical false vocal fold motion contrary to the direction of the true cords, in other words, mid-inspiratory vocal cord adduction and simultaneous false vocal fold abduction during inspiration (Figure 1A) and true cord abduction accompanied with false vocal fold adduction during expiration (Figure 1B). When the patient was on forced

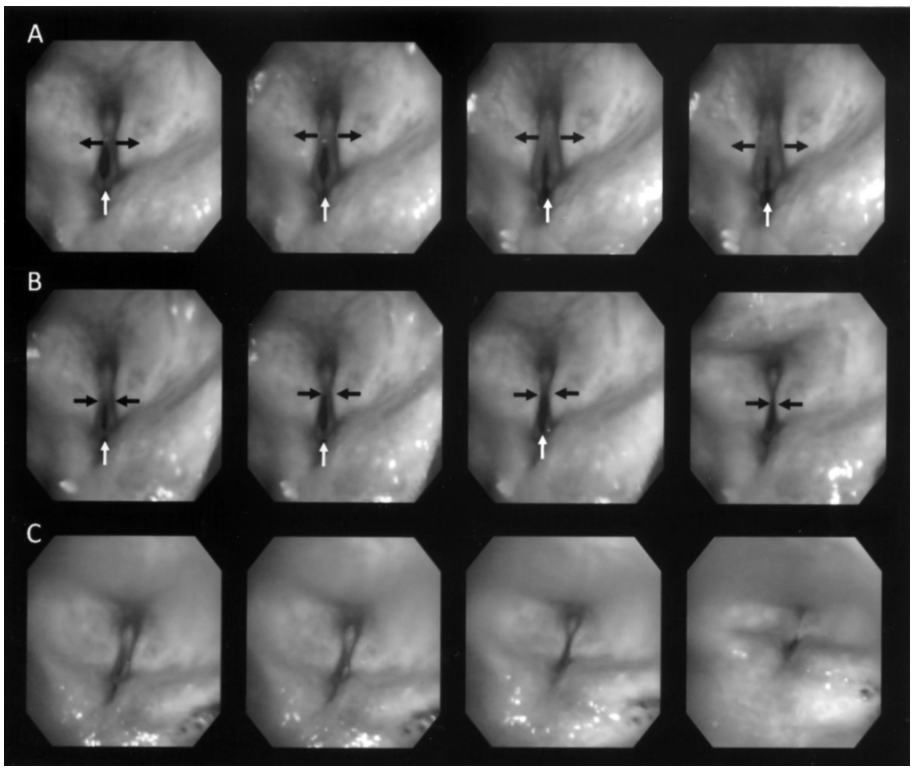

Fig. 1. Bronchoscopic Findings of Paradoxical Vocal Fold Motion.
A. During the inspiratory phase of tidal volume breathing, the true vocal cords (white arrow) approximated each other while the false vocal cords (black arrows) moved apart. B. In contrast, during the expiratory phase of tidal volume breathing, the direction of the motion of the true vocal cords was abduction accompanied with false vocal fold adduction. C. On a forceful inspiration maneuver, the periglottic structures prolapsed paradoxically into the glottis opening and caused almost total airway obstruction during the mid- to late-inspiration phase.

inspiration, the prolapse of periglottic structures into the glottis airway observed in the mid- to late- inspiratory phase correlated clinically with inspiratory stridor (Figure 1C).

Spirometry revealed notching or trembling of flow-volume loops with variable inspiratory curves, including a flattened or truncated pattern (Figure 2). A typical fixed upper airway obstruction pattern in the flow-volume curve actually resulted from the co-existence of vocal cord paralysis and PVFM (Figure 2, right panel). We compared the spirometry with previous ones, which showed extra-thoracic upper airway obstruction when the patient had vocal cord palsy, but no PVFM. The increase in upper airway narrowing in the latest test came from functional derrangement rather than irreversible anatomical destruction (Figure 3).

On follow-up 5 days later, we observed that the post-extubated patient had recovered from the PVFM, and that this was associated with clinical improvement in stridor and hoarseness. Subsequently, he was weaned from NIPPV.

Discussion

Despite the fact that PVFM has been described for more than 100 years and that dozens of terms have been used to describe it [8-9], the overall incidence in the general population or subpopulation is unknown [1] and the pathophysiologic explanation remains controversial [1, 9-10]. The patient was identified to have PVFM unexpectedly while surveying the etiologies of post-extubation stridor. Most cases of PVFM that developed after extubation were attributed to the side effects of anesthesia-related agents, such as phenothiazine or thiopental [6]. However, this patient had no relevant medication history. Actually, PVFM is rare in endotracheal tube-extubated patients without anesthesia, as in our case review, and only 1 out of more than 50 patients was diagnosed with this disorder. The mechanism might require an ex-

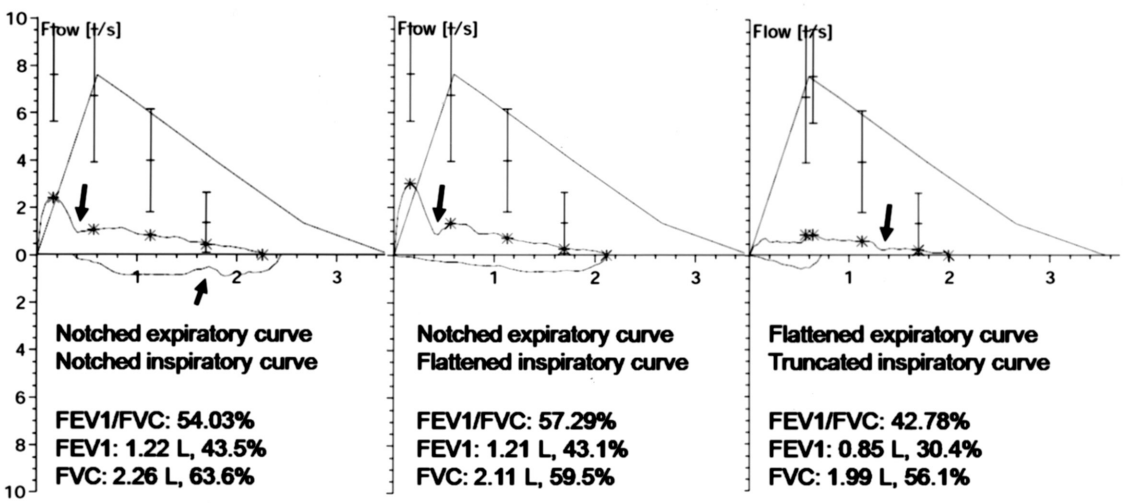

Fig. 2. Successive Flow-Volume Curves in Paradoxical Vocal Fold Motion

Three successive flow-volume curve attempts showed variable patterns, including notching (arrows), flattening, or truncation of expiratory and/or inspiratory curves. Notice the typical pattern of fixed upper airway obstruction in the right panel, which indeed resulted from a combination of structural and functional narrowing due to PVFM.

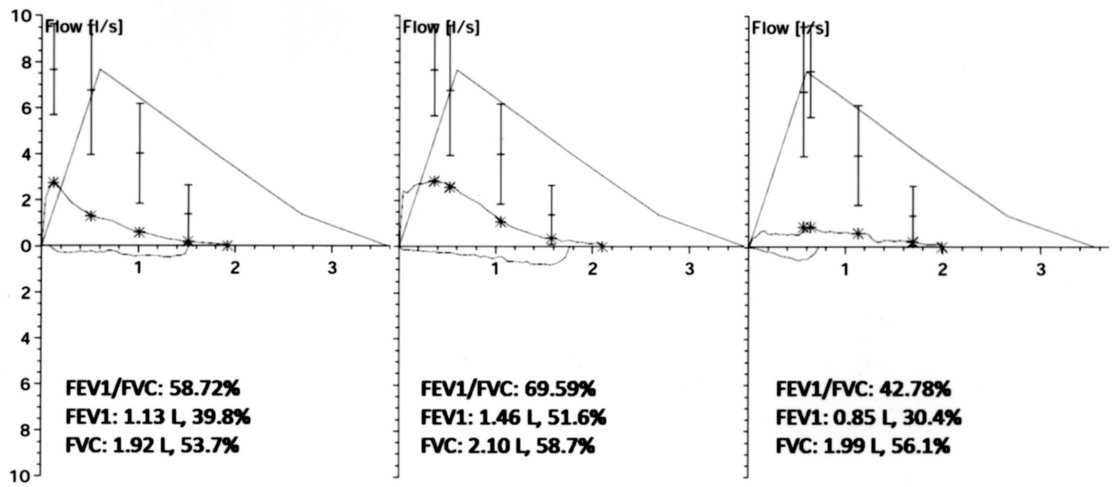

Fig. 3. Vocal Cord Paralysis and Dysfunction
Flow-volume curves in the patient with vocal cord paralysis and varying degrees of PVFM months to years apart. The left panel: pure vocal cord paresis, a pattern of extrathoracic upper airway obstruction. The middle panel: mixed with moderate PVFM. The right panel: with severe PVFM, and prolapse of periglottic structures into the glottis airway.

planation other than medication.

The normal functions of the larynx include airway protection, respiration, and phonation. For the purpose of protection, the glottic closure reflex, mediated by the superior laryngeal, recurrent laryngeal, and vagal nerves, needs to activate 3 levels of cooperation, including adducting of aryepiglottic folds toward the midline of the glottic chink, adducting of the true vocal cords, and then adducting of the false vocal folds [1]. Aberrant nerve conduction triggered by some precipitating factors such as post-nasal dripping, anesthesia, or neuroleptic agents may contribute to PVFM.

Two cases of PVFM developing after thyroidectomy have been reported [5]. The authors attributed the PVFM secondarily to the negative pressure developed during inspiration together with a Venturi effect related to airflow. This situation is very similar to that of our patient. However, as shown in Figure 1C, our patient also manifestated a severe form of PVFM with total prolapse of the periglottic structures into the glottic airway in the mid- to late-inspiratory phase. This was not related to thyroidectomy, as the innervation of the periglottic structures was mediated by the superior laryngeal nerve rather than the recurrent laryngeal nerve. Although the Venturi effect may enhance the paradoxical movement of the vocal cords during inspiration [5], the prolapse of the periglottic structure should not occur if the function of the superior laryngeal nerve is intact. We thought that some local irritation such as microaspiration might be present to cause the disturbance of the glottic closure reflex. Fortunately, the dysfunction seemed to be temporary once this patient was extubated.

The standard diagnostic tool for PVFM is the laryngoscopy or bronchoscopy. In this case, we demonstrated some valuable clues from the standard flow-volume curves leading to the diagnosis of PVFM. Typically, the paradoxical motion of the vocal cords would cause an

unstable flow limitation after mid-inspiration or the expiratory phase, and thus form a repeatable notching or trembling pattern in the flow-volume loop. In successive attempts, the maximal flow also varied because of various degrees of vocal cord adduction during inspiration. In severe dysfunction, a truncated inspiratory flow curve would be observed, reflecting the development of periglottic structural prolapse.

Conclusions

Spirometry is a noninvasive tool used to diagnose PVFM by showing typical flow-volume loop patterns. PVFM is a rare and reversible cause of post-extubation stridor.

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因聲帶異常運動造成的拔管後喘鳴

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拔管後的喘鳴常造成呼吸器脫離的失敗，最常造成的原因是聲帶的水腫及麻痺。聲帶異常運動（paradoxical vocal fold motion）是由於吸氣或呼氣時，負責聲帶內收的肌肉不正常活動所引起。臨床上常被誤診為氣喘發作等其他問題。本病例是一位62歲男性，因聲帶麻痺及急性呼吸衰竭而入院，拔管後發生喘鳴。

藉由支氣管鏡檢查及特殊典型的肺功能量計圖形而確定診斷為聲帶異常運動。*(胸腔醫學* ***2011; 26: 202-207****)*

關鍵詞：拔管，聲帶異常運動，肺功能量計，聲帶功能異常

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Fatal Septicemia Due to *Bacillus cereus* in a Patient with Chronic Obstructive Pulmonary Disease — Case Report

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Bacillus cereus isolates have generally been considered to be a contaminant or harmless pathogen. Fatal *Bacillus cereus* septicemia has been reported occasionally in immunocompromised patients. Recently, there have been reports of fatal cases of septicemia in healthy adults. Herein, we report a patient who developed fulminant and fatal *Bacillus cereus* septicemia 2 days after discharge from a hospital where he had undergone short-term therapy with low-dose corticosteroids for acute exacerbation of chronic obstructive pulmonary disease (COPD). ***(Thorac Med 2011; 26: 208-213)***

Key words: *Bacillus cereus*, COPD, septicemia

Introduction

Infections due to *Bacillus cereus* (*B. cereus*) are of 2 categories: (i) food poisoning-related gastrointestinal infections, characterized by toxin-induced emesis and diarrhea; (ii) systemic (bacteremia) or localized infections (central nervous system and respiratory tract) [1]. Although *B. cereus* used to be considered a contaminant when isolated from clinical specimens, it has been reported to cause fatal septicemia in immunocompromised patients, such as solid organ/umbilical cord blood transplant recipients, or patients with hematological malignancies [2-4]. Recent reports have documented fulminant pneumonia and bacteremia due to *B. cereus* in previously healthy persons, with clinical presentations similar to those of pulmonary anthrax caused by *Bacillus anthracis* (*B. anthracis*). Some of the isolated strains of *B. cereus* contained *B. anthracis* genes [5-6]. In this report, we describe an unusual case of fulminant septicemia due to *B. cereus* in an immunocompetent patient who had been discharged recently from our institution after recovering from an acute exacerbation of chronic obstructive pulmonary disease (COPD).

Case Report

A 77-year-old male businessman with a history of hypertension and benign prostate hy-

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pertrophy visited our outpatient department because of wheezing dyspnea, purulent sputum and voiding discomfort for 7 days. He had a smoking history of 40 packs per year. Physical examination revealed cyanotic fingers, bilateral grade 3 wheezes and respiratory distress. A radiograph of the chest showed hyperinflation without a pneumonic patch. Abnormal laboratory test results included C-reactive protein, 10.94 mg/dl; blood urea nitrogen (BUN), 82 mg/dl; creatinine, 3.2 mg/dl; and albumin, 2.3 g/dl. His white blood cell count (WBC) was 9770 cells/mm^3. One hour later, his condition had progressed to severe respiratory distress that required mechanical ventilation. Under the impression of COPD with acute exacerbation and post-renal obstruction-related acute renal failure, the patient was treated with inhaled bronchodilators, intravenous hydrocortisone 100 mg every 6 hours, ampicillin 1 g/sulbactam 0.5 g every 6 hours, adequate hydration and Foley catheter insertion. On day 3, he deliberately extubated himself, and on day 5, he was transferred to the general ward. On day 7, his renal function improved (BUN, 31 mg/dl, and creatinine, 1.4 mg/dl). Two sets of blood culture were negative for pathogens. The central venous catheter and Foley catheter were also removed. The dose of prednisolone was tapered to 20 mg daily. On day 11, he resumed normal daily activity. He was discharged with oral prednisolone 10 mg daily. During hospitalization, he had no diarrhea, abdominal pain or fever.

Fifty-four hours after discharge, at 9:47 p.m., he was rushed to the emergency room because of chills and dyspnea for 6 hours. His blood pressure was 99/56 mmHg, pulse rate was 114/minute, and respiratory rate, 26/minute. The Glasgow coma scale showed $E_4V_6M_5$. He no longer had wheezes or purulent sputum. Abnormal laboratory results included: WBC count, 410 cells/mm^3 with 48% neutrophils and 44% lymphocytes; platelet count, $82x10^3$ cell/mm^3; C-reactive protein, 10.8 mg/dl; BUN, 29 mg/dl; and creatinine, 2.7 mg/dl. Arterial blood gas analysis in room air showed PaO_2 82 mmHg, $PaCO_2$ 16.5 mmHg, HCO_3^- 13.6 mmol/L and pH 7.520. At 10:45 p.m., his pulse rate was up to 171/minute and respiratory rate was 39/minute. By 11:22 p.m. he was intubated; intravenous piperacillin 2 g, tazobactam 0.25 g and isepamicin (an aminoglycoside) 400 mg therapy was initiated. A radiograph of the chest showed a faint patch in the left lower lung field adjacent to the cardiac border (Figure 1). At 11:45 p.m., he became comatose and developed shock refractory to the treatment of fluid challenge, dopamine, norepinephrine and hydrocortisone injection. Persistent bloody sputum was sucked via the endotracheal tube. He succumbed at 00:43 a.m., less than 4 hours after the initial presentation to the emergency

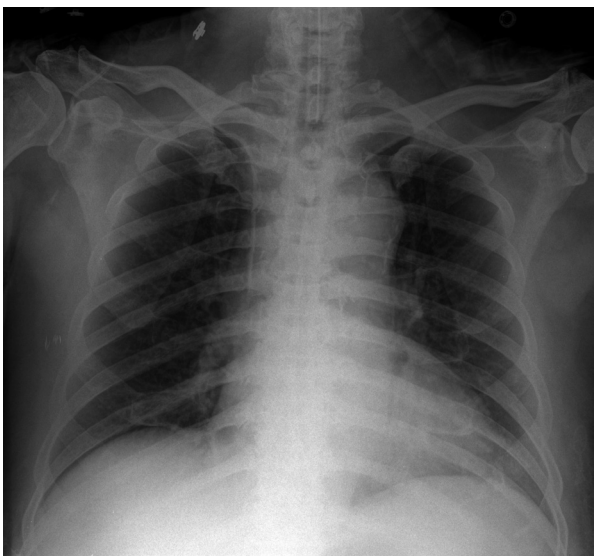

Fig. 1. Chest radiograph shows a faint patch in the left lower lung field adjacent to the cardiac border.

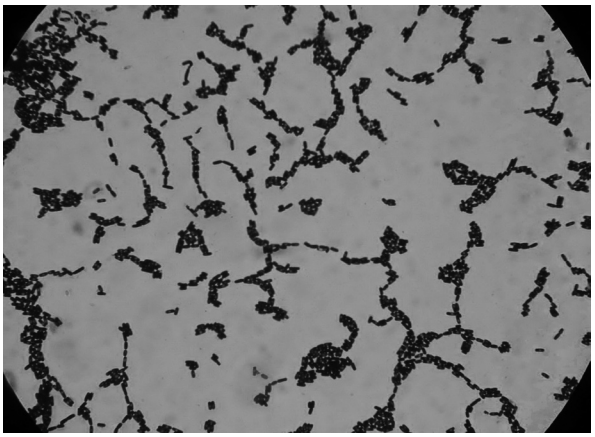

Fig. 2. Photomicrography of Gram-positive bacilli from a cultured colony that was identified to be *B. cereus*.

department. Two days later, 2 sets of blood culture yielded *B. cereus* (Figure 2). Both isolates revealed susceptibility to gentamicin, amikacin, ciprofloxacin and vancomycin, and resistance to penicillin, oxacillin, cefazolin and ceftriaxone.

Discussion

B. cereus is a Gram-positive rod that is widely distributed in the environment. It can be difficult to determine the significance of *B. cereus* isolated from clinical specimens, and it was often considered a contaminant in isolation [15]. However, *B. cereus* can cause severe infections in immunocompromised patients [2-4], and has also been reported to cause fulminant pneumonia and septicemia in healthy persons [5-6].

The case reported herein is of interest because the infection occurred in a previously healthy person who developed fulminant septicemia caused by *B. cereus* after recovery from acute exacerbation of COPD. The isolation of *B. cereus* in 2 different sets of blood cultures excluded the possibility of an environmental contamination [13]. *B. cereus* has been reported to cause nosocomial outbreaks among immunosuppressed patients through contaminated linen [8], catheter tips [9-10], steamed towels [11] and ventilation equipment [12]. In *B. cereus* bacteremia, the most common portal of entry is an intravascular catheter, because *B. cereus* can produce biofilms which play a major role in attachment to catheters, and afford protection for growth on inert surfaces [10]. However, the central venous catheter of our patient had been removed 10 days before the development of septicemia. And, since there were no symptoms of food-borne illness, oral ingestion was an unlikely route of inoculation. Due to the history of ventilator support in our case, which was followed 6 days post-extubation by the onset of *B. cereus* septicemia, the potential for a nosocomial source of infection could not be excluded.

The use of corticosterioids may have increased this patient's vulnerability to *B. cereus* infection. Systemic corticosteroid is a standard treatment for the acute exacerbation of COPD [14]. Reported rates of secondary infection did not differ significantly among 2 groups of COPD patients with acute exacerbation receiving a placebo or corticosterioids for 2 weeks [14]. Our case had received standard corticosteroids for less than 2 weeks.

Similar to previously reported cases with pulmonary infection caused by *B. cereus* [5-6], our patient presented to the emergency room with chills, dyspnea, leukopenia, thrombocytopenia, impaired renal function and a rapid progression of the infection. Hemoptysis is a common presentation in previously reported cases [5]. Although our patient did not complain of hemoptysis initially, persistent bloody endotracheal aspirates were found after intubation. According to the autopsy case report by Avashia *et al*. [5], the cause of hemoptysis could be

necrotizing pneumonia. The patient's thrombocytopenia probably contributed to the bloody aspirates.

In most cases of *B. cereus* infection, isolates are resistant to penicillin, oxacillin and cephalosporins due to the production of ß-lactamase. The combination of clavulanic acid and ticarcillin does not increase activity against *B. cereus*. Drug sensitivity test results in our case were compatible with previous findings [7], and showed sensitivity to aminoglycosides, vancomycin and ciproxin. Our patient received piperacillin and an aminoglycoside immediately after presenting to our emergency room. So, why was the patient's septicemia so fulminant and refractory to antimicrobial therapy that contained an aminoglycoside? Recent reports have documented that *B. cereus*, which harbored *B. anthracis* virulence genes, was identified as the causative agent of severe pneumonia and fulminant septicemia in metalworkers [5]. We did not perform studies to detect anthrax toxin genes in the isolates of our patient, but could not exclude this possibility.

For patients who have received systemic glucocorticoids, *B. cereus* isolated from blood may be a fatal pathogen, and should not be considered an environmental contaminant. Clinicians must give serious consideration to the significance of a *B. cereus* isolate from a clinical specimen, even in patients who are not immunocompromised.

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慢性阻塞性肺病急性發作後併發仙人掌桿菌敗血症——病例報告

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仙人掌桿菌，又稱蠟狀芽胞桿菌，廣泛地分布於土壤中，可造成食品中毒。先前的病例報告指出仙人掌桿菌造成的敗血症總是發生在免疫功能低下的族群，但是近來發現，仙人掌桿菌也可能在非免疫低下甚至健康的成年人中造成嚴重的感染。在此，我們報告一位罹患慢性阻塞性肺病合併呼吸衰竭的患者，在接受全身性類固醇治療急性發作並康復出院後併發嚴重的仙人掌桿菌敗血症的案例。*(胸腔醫學 **2011; 26: 208-213**)*

關鍵詞：仙人掌桿菌，敗血症，慢性阻塞性肺病

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Recurrent Pleural Effusion in a Patient with Multiple Myeloma: A Case Report

Min-Ying Tsun, Yu-Chun Lin*, Chung-Kan Peng

Multiple myeloma (MM) is a malignant clonal neoplasm of plasma cells of B-lymphocyte origin. It can present with symptoms related to intramedullary involvement, such as low back pain or spinal compression fractures, or symptoms related to extramedullary involvement of the nasal cavity, lung, pleura, thoracic wall, central nervous system, lymph nodes, liver, spleen, skin, and eyes. Patients with MM may present with a pleural effusion, or pleural effusion may develop during the disease course; however, myelomatous pleural effusion is rare. We herein present a patient with IgG lambda light chain type MM who presented with a right-side pleural effusion with an absence of monoclonal plasma cells on cytological examination of the effusion. The patient received 2 courses of chemotherapy and the effusion resolved; however, 4 months later, it recurred and myelomatous pleural effusion was confirmed by the demonstration of monoclonal protein and atypical plasma cells in the pleural fluid. ***(Thorac Med 2011; 26: 214-218)***

Key words: multiple myeloma, myelomatous pleural effusion, recurrent pleural effusion

Introduction

Multiple myeloma (MM) is a neoplasm of clonal B-lymphocyte plasma cells of unknown etiology. It accounts for approximately 1% of all malignant diseases, and about 10% of hematologic malignancies [1-2]. The common clinical presentations are fatigue and bone pain (back or ribs) with or without associated fractures or infection; however, patients can be totally asymptomatic or present with life-threatening symptoms. The hallmark of MM is the detection in blood and/or urine of a monoclonal protein, M protein, produced by the abnormal plasma cells. Approximately 6% of MM patients present with a pleural effusion; however, myelomatous pleural effusion (MPE) is rare.

Case Report

An 85-year-old female was seen with the complaint of back pain for 2 months. Laboratory testing revealed pancytopenia, elevated serum immunoglobulin G (IgG) and lambda

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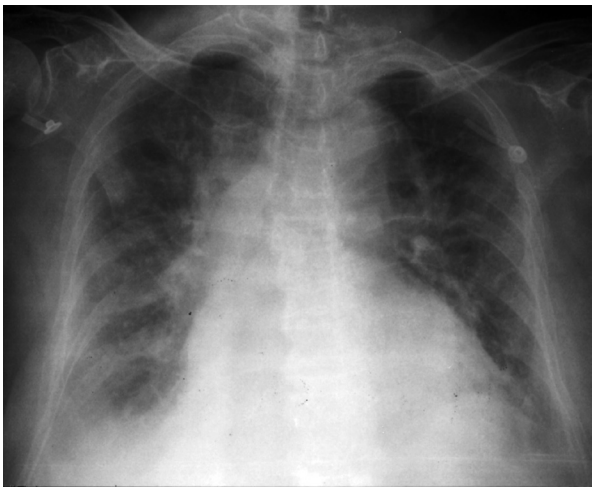

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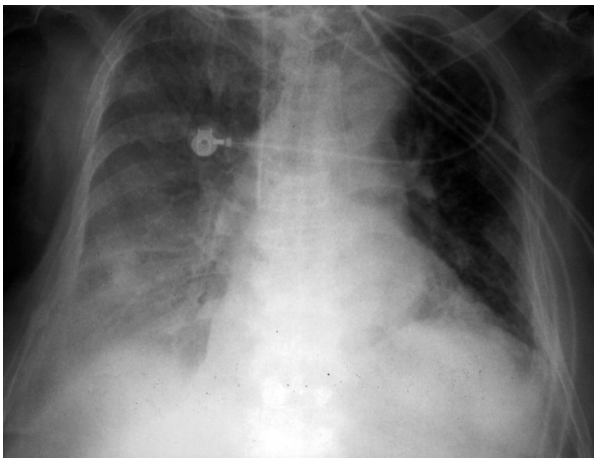
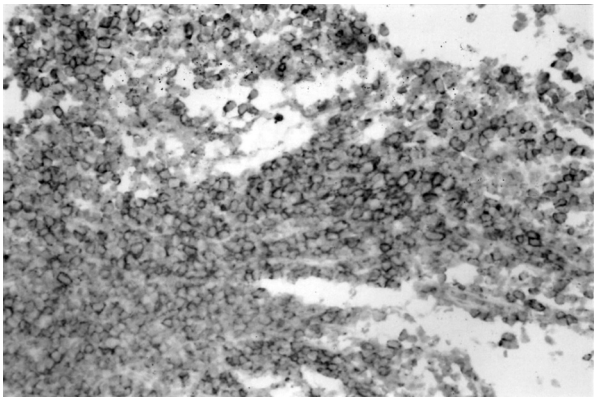


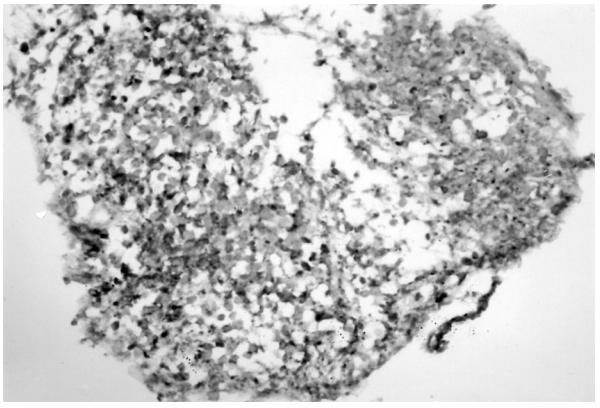
(B)

Fig. 1. (A) Chest radiograph showing right-side pleural effusion. (B) Recurrent pleural effusion was seen 4 months after completion of chemotherapy.

light chain; immunoglobulins IgA, IgM, IgE and kappa light chain were normal. Urine was negative for kappa and lambda light chains. Chest radiograph revealed a right-side pleural effusion (Figure 1A). Diagnostic thoracentesis revealed straw-colored fluid; no plasma cells were seen on microscopic examination. Magnetic resonance imaging (MRI) of the spine revealed multiple compression fractures, suggestive of spinal metastases. Vertebroplasty was performed, and histopathological examination of the tissue revealed plasma cell myeloma with lambda monoclonality (Figure 2A, B). Thus, a diagnosis of MM, IgG lambda type was made. She received 2 cycles of chemotherapy consisting of bortezomib, thalidomide, and prednisolone, and subsequently the disease appeared to be well controlled. Chest radiograph revealed resolution of the pleural effusion and she was discharged. Approximately 4 months later, she experienced severe dyspnea. She was hospitalized and a chest radiograph again revealed right-side pleural effusion (Figure 1B). Diagnostic thoracentesis was performed, which re-



(A)



(B)

Fig. 2. Immunochemistry staining of vertebral tissue was (A) CD 138 positive and (B) lambda positive.

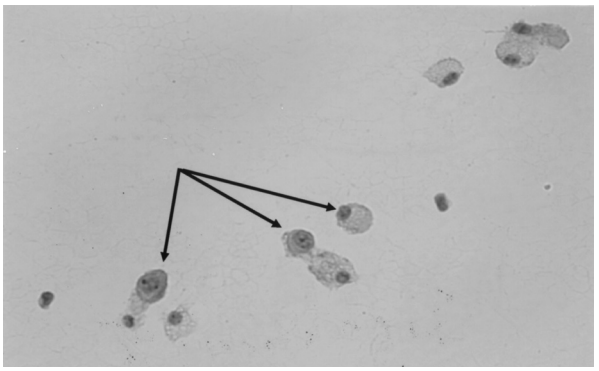


Fig. 3. Cytological examination of the pleural effusion revealed numerous abnormal plasma cells (arrow) (Papanicolaou stain, x400).

vealed bloody fluid with plasma cells (Figure 3). In addition, M peak protein, IgG type lambda light chain, and monoclonal cells were found on electrophoresis of both the pleural effusion and plasma (Figure 4A, B). She died 1 month later due to nosocomial pneumonia with respiratory failure.

Discussion

Involvement of serous cavities in patients with MM is uncommon [3, 6-7]. Only approximately 6% of MM patients present with a pleural effusion [3]. Several possible causes of this pleural effusion have been reported. Congestive heart failure is the most common cause of pleural effusion in MM patients because of amyloid deposition in the pericardium. Other etiologies include pulmonary embolism, chronic renal failure, secondary neoplasm, and pleural myelomatous involvement [3-4]. Pleural involvement in MM often develops from a lesion in the rib or vertebra. MPE occurs in < 1% of MM patients [3, 5], and the reported survival is about 4 months [1]. Diagnosis of MPE is based on (1) demonstration of a monoclonal protein in pleural fluid using electrophoresis; (2) detection of atypical plasma cells in the pleural fluid; and (3) histological confirmation from a pleural biopsy specimen or autopsy. In our case, MPE was diagnosed by the demonstration of a monoclonal protein and atypical plasma cells in the pleural fluid. A pleural biopsy was not performed for our patient because of thrombocytopenia. Approximately 80% of MPEs are due to IgA MM, perhaps as a result of its major tendency to invade extraosseous structures. Kim *et al*. [1] reported that IgG MM was the most common isotype associated with MPE. In his review of 85 MM patients with MPEs, no recurrent pleural effusion was reported. It is interesting that our patient presented with a recurrent right-side pleural effusion with different findings on examination of the fluid.

In conclusion, MPE is rare in MM patients. However, our patient with IgG lambda light chain type MM initially presented with a right-side non-MPE pleural effusion. The pleural effusion resolved with chemotherapy at the beginning, but recurred later in the course of the disease, and repeat thoracentesis confirmed the diagnosis of MPE. MPE is a poor prognostic factor for MM patients.

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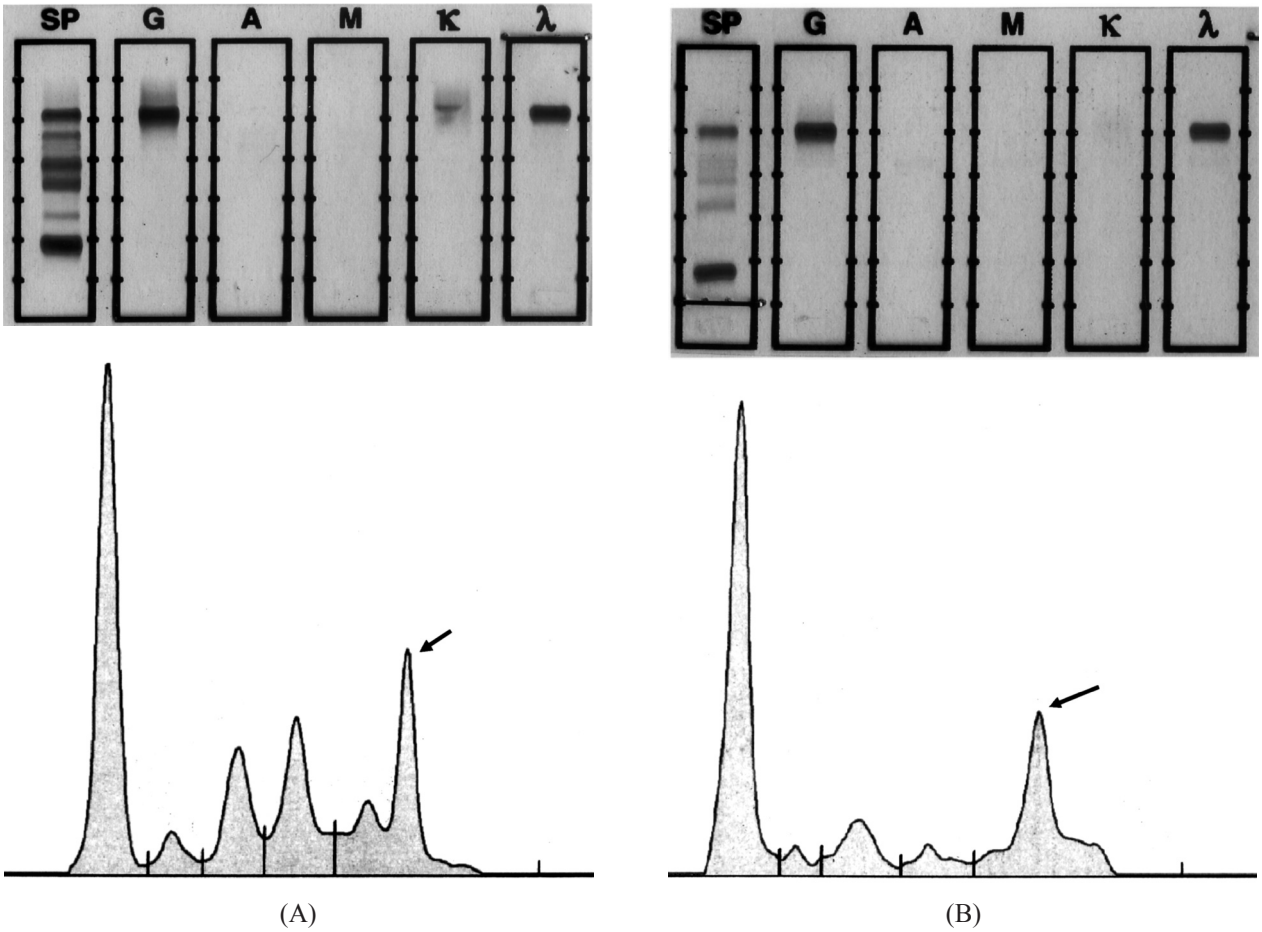

Fig. 4. (A) Serum protein electrophoresis revealed an M spike (arrow). Immunofixation electrophoresis demonstrated a lambda monoclonal protein. (B) pleural effusion electrophoresis revealed an M spike (arrow). Immunofixation electrophoresis demonstrated a lambda monoclonal protein.

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多發性骨髓瘤併反覆肋膜積液—病例報告

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有個85歲的女性病人，因長期下背痛至骨科門診求診及服用口服止痛劑。但未獲得改善，並建議住院做詳細檢查。脊椎核磁共振攝影發現有多處壓破性骨折及疑似骨轉移的病兆，並接受外科手術。病理組織確定為多發性骨髓瘤，同時胸部X光也診斷出右側肋膜積液尚未發現不正常細胞。不幸過了四個月，病人因呼吸急促再次入院，發現同側肋膜積液。同時發現漿細胞也證實了多發性骨髓瘤合併惡性胸水。多發性骨髓瘤合併惡性胸水並不多見。目前英文文獻中約90例，從未提報多發性骨髓瘤併反覆肋膜積液案例。*(胸腔醫學* ***2011; 26: 214-218)***

關鍵詞：多發性骨髓瘤，反覆肋膜積液，惡性胸水

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Rifampin-induced Henoch-Schönlein Purpura in Pulmonary Tuberculosis

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A 53-year-old man was admitted due to active pulmonary tuberculosis, and, while on standard quadruple anti-tuberculosis therapy, developed a rare severe vasculitis involving the skin, kidney, and gastrointestinal mucosa. Skin and renal biopsies identified Henoch-Schönlein purpura (HSP). The cutaneous and gastrointestinal symptoms improved after rifampin was discontinued. The interaction between rifampin and HSP was confirmed by histology and drug re-challenge. Although the mechanism of rifampin-induced HSP remains unclear, immune complex deposition in the skin and renal tissues are important pathological findings. Once vasculitis and the associated symptoms are present, rifampin-induced HSP should be considered, along with prompt discontinuation of the rifampin. ***(Thorac Med 2011; 26: 219-224)***

Key words: rifampin, Henoch-Schönlein purpura, vasculitis

Introduction

Pulmonary tuberculosis (TB) is one of the world's most widespread diseases. Although the adverse effects of anti-TB therapy are well documented, vasculitis associated with anti-TB medications has seldom been reported [1]. We describe herein an extraordinary case of pulmonary TB that led to the development of a rapidly progressive vasculitis with a diffuse petechial rash on the trunk and extremities, as well as gastrointestinal bleeding and renal disturbances, while on standard quadruple anti-TB therapy. Based on the pathological findings as confirmed by cutaneous and renal biopsies, as well as the time line of the symptoms' improvement after the withdrawal of rifampin, we identified the diagnosis as rifampin-induced Henoch-Schönlein purpura (HSP). We concluded that the vasculitis was probably an immunological reaction to rifampin, accompanied by the production of antibodies and the formation of immune complexes [2-5].

Case Report

A 53-year-old man presented to our hospital with a productive cough and body weight loss

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for 1 month. He had a history of diabetes mellitus without regular medical control for 8 years. The physical examination was unremarkable except for rhonchi in the right upper lung field upon chest auscultation. CXR showed patchy consolidation with cavitation of the right upper lobe and small, patchy infiltration of the right lower lung field, suggestive of pulmonary TB (Figure 1). Laboratory examinations revealed WBC 12×10^9/L (16% lymphocytes); platelet count 267×10^9/L; blood urea nitrogen (BUN) 32 mg/dl; creatinine (Cr) 1.4 mg/dl; glucose 432 mg/dl; and albumin 3.1 g/dl. The sputum acid-fast bacilli (AFB) smear revealed numerous acid-fast bacilli. Consequently, he was given standard quadruple anti-TB therapy, including isoniazid (300 mg), rifampin (600 mg), pyrazinamide (1500 mg), and ethambutol (800 mg). The sputum culture identified *Myobacterium tuberculosis* 1 month later. However, after the 6th week of anti-tuberculosis therapy, skin lesions and progressively palpable purpura appeared on the trunk and extremities (Figure 2A). He simultaneously developed a mucus-like bloody stool and renal function deterioration (BUN 88 mg/dl; Cr 7.6 mg/dl). Due to a suspicion that the skin rashes and renal function problems were associated with the medications, we substituted moxifloxacin (400 mg) for the isoniazid and rifampin. The patient subsequently underwent skin and renal biopsies, and the morphology of the skin biopsy showed leukocytoclastic vasculitis (Figure 2C). The renal pathological biopsy showed focal segmental necrotizing glomerulonephritis (Figure 3A) intermixed with acute interstitial nephritis (Figure 3B), and the immunofluorescence studies indicated immunoglobulin A (IgA) (Figure 3C) and complement 3 (C3) deposition (Figure 3D). Except for a low C3 level of 83 mg/dl (normal range 90-180 mg/dl), all of the other laboratory examinations were normal, including antinuclear antibody, rheumatoid factor, and anti-neutrophil cytoplasmic antibody. Based on the clinical features and pathological findings, HSP was diagnosed. The skin lesions and gastrointestinal bleeding resolved within 1 week after discontinuing isoniazid and rifampin (Figure 2B). However, renal function remained impaired (BUN 64 mg/dl; Cr 5.1 mg/dl) and the patient received regular hemodialysis. Isoniazid was re-introduced 3 weeks later due to numerous acid-fast bacilli and no further clinical progression was observed. Consequently, he was treated with isoniazid, ethambutol, pyrazinamide, and moxifloxacin without the recurrence of skin purpura and gastrointestinal bleeding. Unfortunately, he died because of hospital-acquired *Klebsiella pneumoniae* pneumonia and septicemia 2 months later.

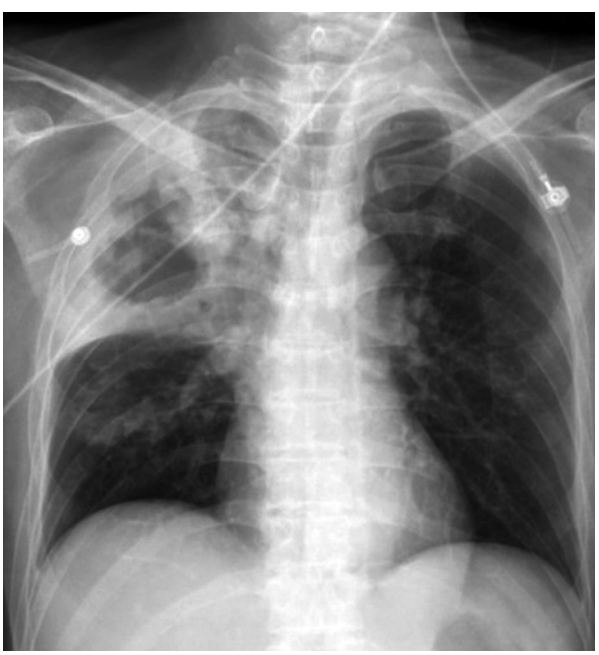
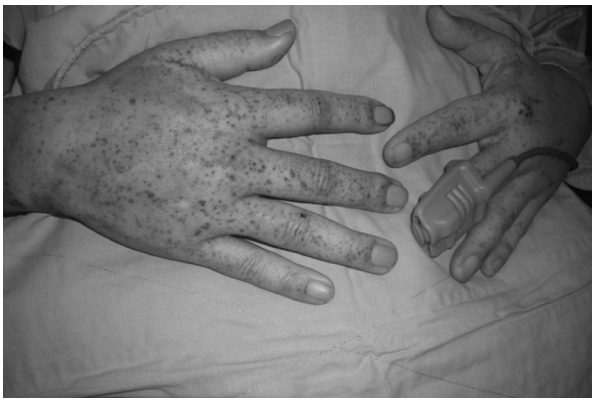


Fig. 1. Patchy consolidation with cavitation of the right upper lung field and small patchy infiltration of the right lower lung field.



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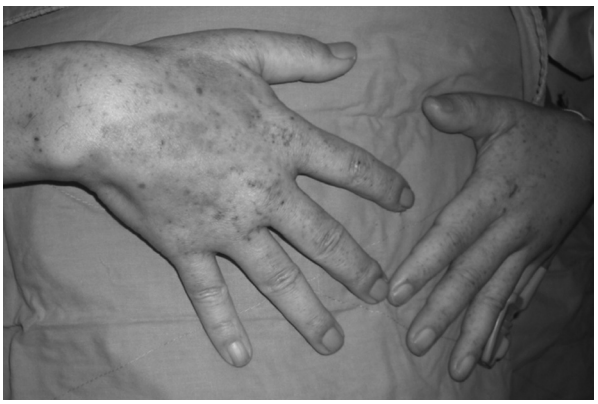

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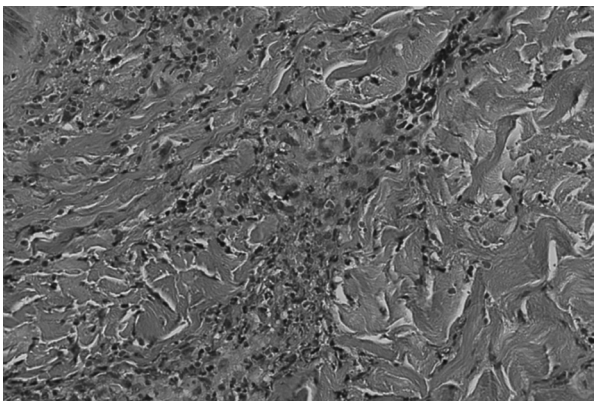

(C)

Fig. 2. Rapidly progressive vasculitis with a diffuse petechial rash (Fig. 2A) and skin lesion improvement within 1 week of discontinuing rifampin (Fig. 2B). The skin biopsy showed leukocytoclastic vasculitis characterized by fibrinoid necrosis of the blood vessels and intense inflammation (Fig. 2C, H&E, 400x).

Discussion

We describe a rare case of severe vasculitis involving the skin, kidney, and gastrointestinal mucosa that developed while on anti-TB therapy. The diagnosis of HSP was confirmed by histology and drug re-challenge. In light of the clearly causative clinical manifestations, such as the rapid resolution of the skin lesions and gastrointestinal bleeding after the withdrawal of the isoniazid and rifampin, and the absence of further clinical progression after the isoniazid re-challenge, there seemed little doubt that the patient's vasculitis was related to the rifampin therapy. HSP, also called anaphylactoid purpura, is a form of systemic small-vessel vasculitis deposition of immune complexes. IgA is the antibody class most often involved in these immunological reactions, and the presence of IgA in the affected tissue strongly supports the diagnosis. HSP is usually seen in children, presenting with palpable purpura, arthralgias, glomerulonephritis, abdominal pain, and/or gastrointestinal bleeding [6]. Our patient was an extremely rare case of adult-onset HSP related to rifampin therapy, presenting with typical clinical features as corroborated by the histopathological and immunofluorescence findings. The interaction of vasculitis and TB was first described in 1967: there are 2 general types of pulmonary TB-related vasculitis: 1) leukocytoclastic vasculitis (a manifestation of pulmonary TB), and 2) anti-TB medication-associated vasculitis (particularly rifampin therapy) [7-8]. Leukocytoclastic vasculitis results from a direct deposition of TB bacilli. By contrast, anti-TB medication-associated vasculitis can not identify microorganisms in hypersensitivity vasculitis, and may result from the deposition of immune complexes [8]. Our patient was a case of hypersensitivity vas-

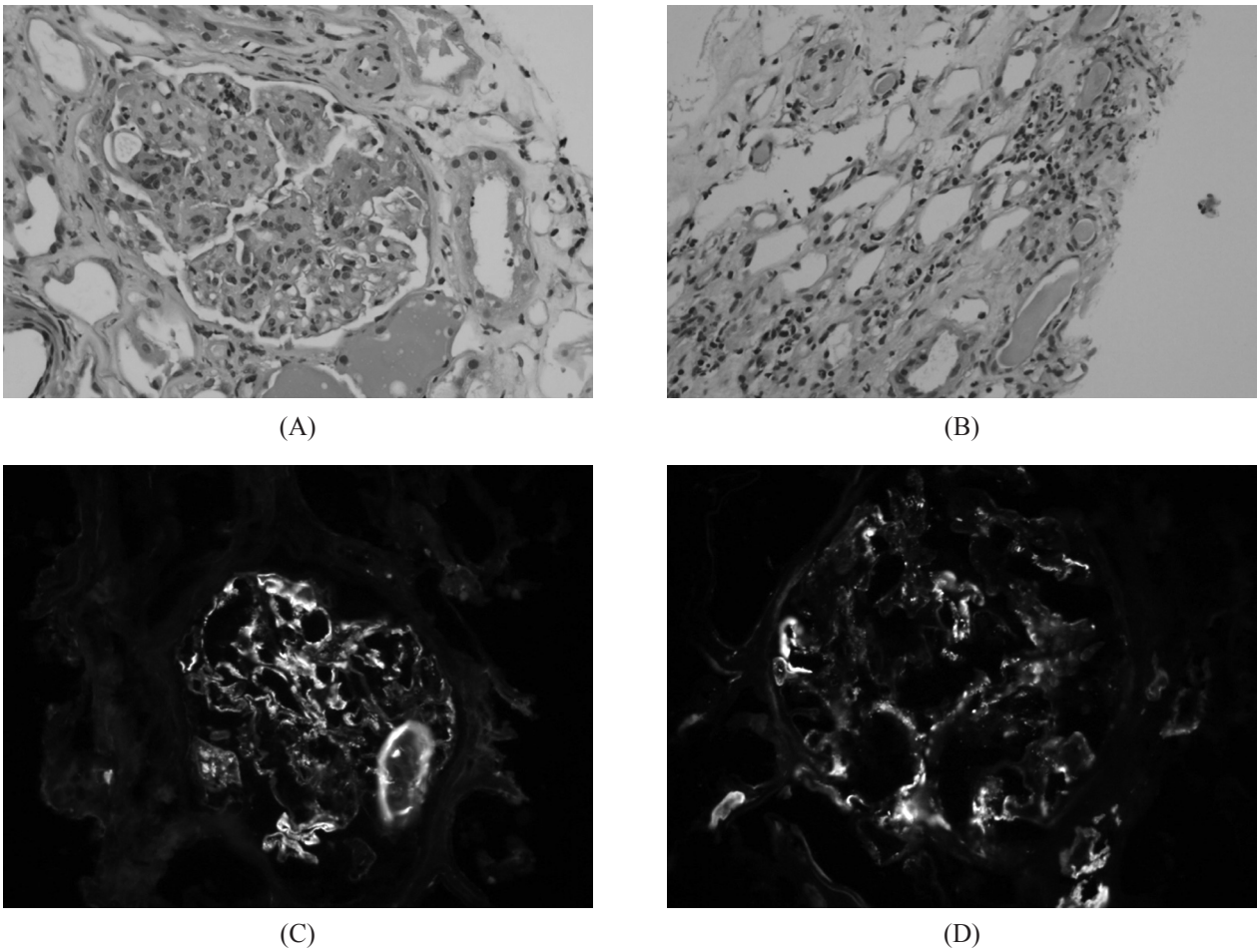

Fig. 3. The renal biopsy showed diffuse endocapillary proliferation and focal segmental necrotizing glomerulonephritis (Fig. 3A, H&E, 400x) intermixed with acute interstitial nephritis (Fig. 3B, H&E, 400x). Immunofluorescence studies presented IgA staining (Fig. 3C, 400x) and C3 complement deposition (Fig. 3D, 400x) in the mesangial regions and glomerular capillary walls.

culitis because of the deposition of immune complexes without microorganisms. The possibility of the patient having TB-related vasculitis was unlikely since the vasculitic symptoms developed after 6 weeks of anti-TB medication. Risk factors for severe adverse anti-TB medication reactions include older age, female gender, diabetes mellitus, a history of hepatitis, and a previous history of anti-TB therapy [8]. Our patient had the risk factor of poorly controlled diabetes mellitus. Several studies have described a relationship between rifampin and vasculitis, and the skin lesions of rifampin-induced vasculitis typically improve upon withdrawal of the medication [3-4]. The mechanism linking rifampin and vasculitis has not been documented. Several cases of rifampin-related renal involvement have also been reported, and the conclusion was that rifampin was a triggering factor for the autoimmune response of glomerulonephritis via the deposition of immune complexes [9-11]. Accordingly, the cutaneous vasculitis and the presence of IgA and C3 deposition in the renal biopsy indicated that

there had been immunological reactions resulting in rifampin-induced antibody production and immune complex formation. Also, a high percentage (30-40%) of patients with HSP with renal involvement will progress to chronic renal failure requiring dialysis, or even death [12-13]. Although the mechanism of rifampin-induced HSP remains unclear, immune complex depositions in the skin and renal tissues are important pathological findings. Although rarely seen, rifampin should be considered a potential cause of HSP, and should be promptly discontinued. Further studies are needed to elucidate the mechanism of the combination of pulmonary TB, anti-TB medication and HSP.

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肺結核使用利肺寧引起過敏性紫斑症

王漢彬　黃瑋琛　趙載光*　彭萬誠

一位53歲男性因為活動性肺結核住院，當給予標準四項抗結核藥物治療時，在皮膚、腎臟和腸胃黏膜產生了罕見且嚴重的血管炎。皮膚和腎臟切片檢查證實是過敏性紫斑症（Henoch-Schönlein purpura）。在利肺寧（rifampin）停用後，皮膚和腸胃道的症狀明顯改善。藉由組織學和藥物再激發反應，證明了利肺寧和過敏性紫斑症的關係。雖然利肺寧引起的過敏性紫斑症機轉不明，但免疫複合物沉積在皮膚和腎臟組織是個很重要的病理發現。當血管炎及相關的症狀都出現時，利肺寧引起的過敏性紫斑症應予以考慮，併同時停用利肺寧。*(胸腔醫學* ***2011; 26: 219-224)***

關鍵詞：利肺寧，過敏性紫斑症，血管炎

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Tunneled Hemodialysis Catheter-related Tuberculous Chest Wall Abscess — A Case Report

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Patients with chronic renal failure have an increased risk of tuberculosis, and a higher incidence of extrapulmonary tuberculosis than the general population. Among extrapulmonary tuberculosis cases, chest wall tuberculosis is far less frequently encountered, and reports of dialyzed patients with tuberculosis of the chest wall are even rarer.

This case is that of a 51-year-old female patient with chronic renal failure but no history of previous tuberculosis, who presented with right upper quadrant abdominal pain and low grade fever. Bilateral neck and intra-abdominal lymphadenopathy and liver nodules were found on physical examination. However, she refused further invasive studies. She then underwent maintenance hemodialysis through a newly indwelled tunneled catheter in the right subclavian area due to uremia. Eight months later, swelling of the chest wall around the tunneled hemodialysis catheter route with abscess formation was detected, and the bilateral neck lymph nodes were greatly enlarged; abscess debridement of the chest wall and neck lymph nodes biopsy were performed, and caseating granulomas were identified. Later, *Mycobacterium tuberculosis* grew in the cultures. After a 6-month standard anti-tuberculosis treatment, her chest wall abscess, lymphadenopathy, and liver and pulmonary nodules all resolved.

To the best of our knowledge, no case of tunneled hemodialysis catheter-related chest wall tuberculosis has been reported in Taiwan. Physicians should maintain a high degree of suspicion of tuberculous chest wall abscess in dialyzed patients with an unresolved chest wall wound or abscess, despite antibiotics treatment. ***(Thorac Med 2011; 26: 225-232)***

Key words: tunneled hemodialysis catheter, chest wall, tuberculosis, end-stage renal disease

Introduction

Tuberculosis (TB) is an important global health problem. Immunocompromised patients, such as those with end-stage renal disease (ESRD) receiving hemodialysis, have an increased risk of developing TB infection [1]. Dialyzed patients have a TB infection rate ranging from 5-25% worldwide, and among those patients, a 6.9- to 52.5-fold increased incidence of TB infection compared to the general population has also been reported [2]. Extrapulmo-

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nary TB is much more common in patients with ESRD (varying from 38% to more than 80%) [1, 3], compared to the general population, in which extrapulmonary TB accounts for 4.5% of all cases of TB [1]. Although extrapulmonary TB is common in patients with ESRD, few cases of TB of the chest wall in dialyzed patients have so far been reported [4-5]. In this report, we describe a patient with ESRD who was diagnosed with tuberculous abscess on a tunneled hemodialysis catheter site in the chest wall, and also had evidence of neck and intra-abdominal tuberculous lymphadenopathy and pulmonary TB.

Case Report

A 51-year-old woman with a history of stage 5 chronic kidney disease (according to the guidelines of the Kidney Disease Outcomes Quality Initiative (KDOQI)), was admitted to the hospital in December 2008 with the complaints of right upper quadrant (RUQ) abdominal pain, poor appetite and low grade fever off and on for 1 week. Bilateral neck lymphadenopathy was also revealed in the physical examination. She had no pulmonary symptoms, such as productive cough or hemoptysis. No abnormality was found in her chest plain film. Abdominal sonography revealed multiple liver nodules. Abdominal computed tomography (CT) demonstrated multiple hypodense nodules in the liver and multiple enlarged para-aortic and paracaval lymph nodes (Figure 1A). The patient then received an upper gastrointestinal endoscopy and colonoscopy because of suspected liver metastasis, but no specific finding was observed. She refused to undergo any other invasive study, including neck lymph nodes biopsy. Since the patient had developed uremic symptoms, she underwent a tunneled catheter insertion in the right subclavian vein for regular hemodialysis.

Eight months later, the chest wall around the tunneled hemodialysis catheter route swelled and erythematous change developed. We also found that her bilateral neck lymphadenopathy was persistent and had become enlarged during an 8-month period (Figure 1B). CT also revealed multiple nodular lesions in the bilateral lungs (Figure 1C) and enlarged intra-

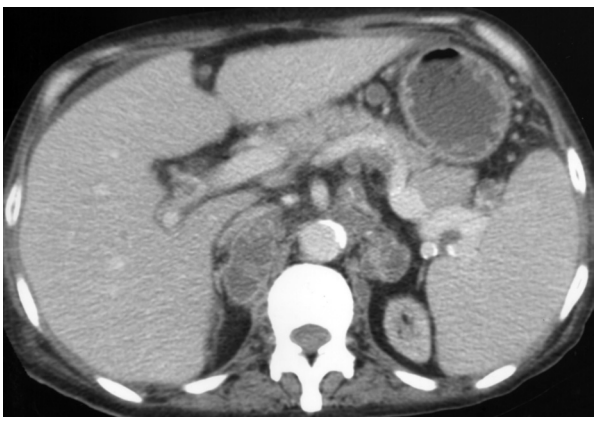

Fig. 1A. Abdomen CT with contrast: multiple enlarged para-aortic lymph nodes (January 3, 2009)

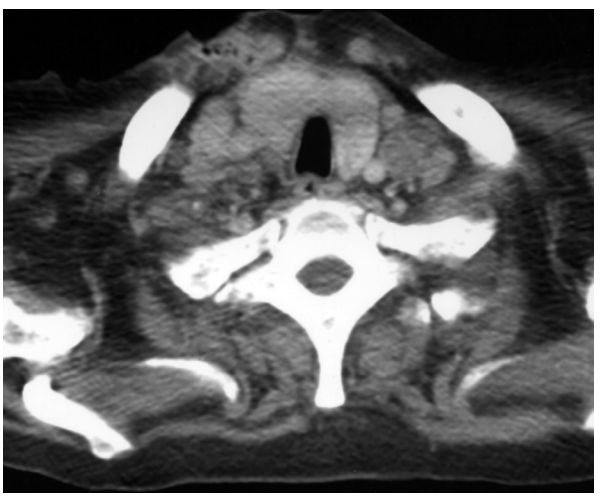

Fig. 1B. Neck CT with contrast: necrotic lymph nodes in the bilateral subclavian area (September 7, 2009)

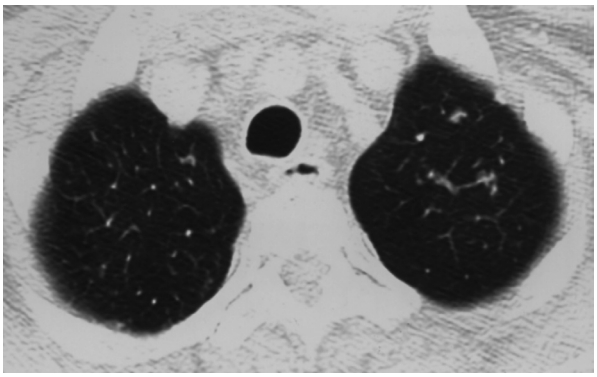

Fig. 1C. Chest CT, lung window: bilateral pulmonary nodular lesions, bilateral upper lobes (September 7, 2009)

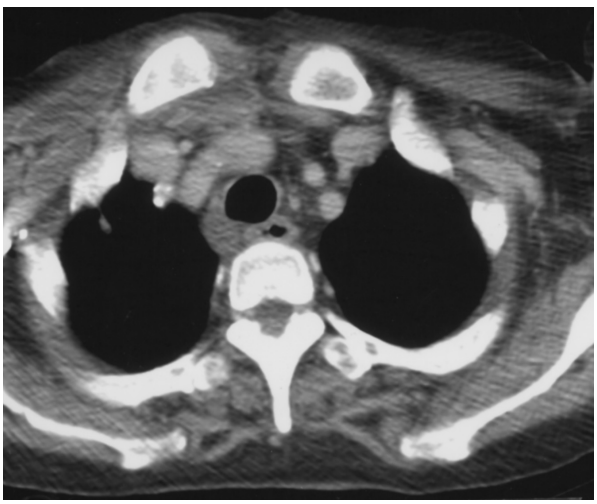

Fig. 1D. Chest CT with contrast: right anterior subclavian region of the chest wall with loculated fluid beneath the pectus muscle, suspected abscess formation (September 7, 2009)

abdominal lymphadenopathy. The tunneled hemodialysis catheter was then removed, followed by debriding of the abscess in the right subclavian area of the chest wall (Figure 1D). Bacterial culture of pus revealed no organism, and acid-fast bacilli stain of pus showed negative. An empirical antibiotic, vancomycin, was prescribed to treat the patient, but purulent discharge persisted. The pathologic report of the debrided specimen from the chest wall abscess depicted granulomatous inflammation with caseous necrotic tissue (Figure 2). Malignancy was excluded by a biopsy of the bilateral neck lymph nodes, and granulomatous inflammation with caseation necrosis was then demonstrated. Results of mycobacterial culture of the chest wall abscess and biopsy specimen of the bilateral neck lymph nodes showed growth of *Mycobacterium tuberculosis* that was sensitive to first-line anti-TB drugs. Her sputum was negative for acid-fast bacilli stain and the mycobacterial culture of sputum also showed no growth. Based on this confirmation, the patient was then diagnosed with tuberculous abscess of the chest wall and tuberculous lymphadenitis. A standard anti-TB regimen was initiated for 6 months. After the completion of treatment, the right side chest wall wound healed (Figure 3D), and the enlarged bilateral neck lymph nodes regressed (Figure 3B). Further evaluation with CT demonstrated no pulmonary nodules (Figure 3C), no liver nodules, and no intra-abdominal lymphadenopathy (Figure 3A). The patient remained in good health after completing standard TB treatment.

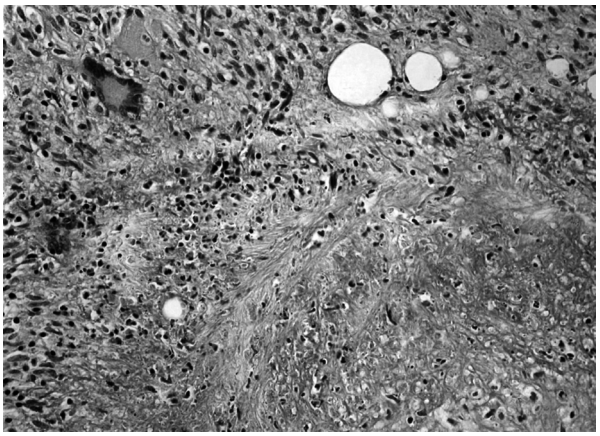

Fig. 2. Subclavian area of the right chest wall: caseation necrosis, necrotic soft tissue and granulomatous inflammation in soft tissue composed of granulation tissue, necrotic material and many Langhans' multinucleated giant cells

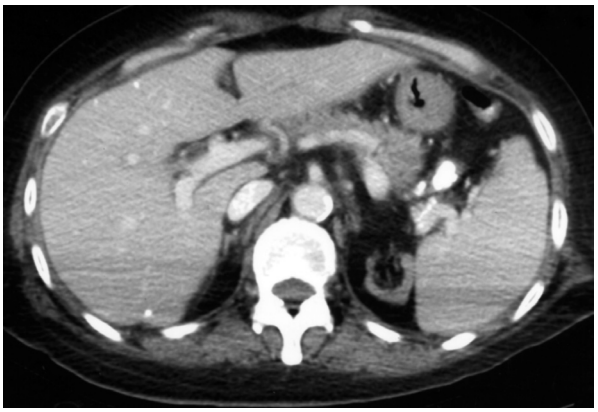

Fig. 3A. Abdomen CT with contrast: resolution of multiple liver nodules, and regression of para-aortic lymphadenopathy (January 10, 2011)

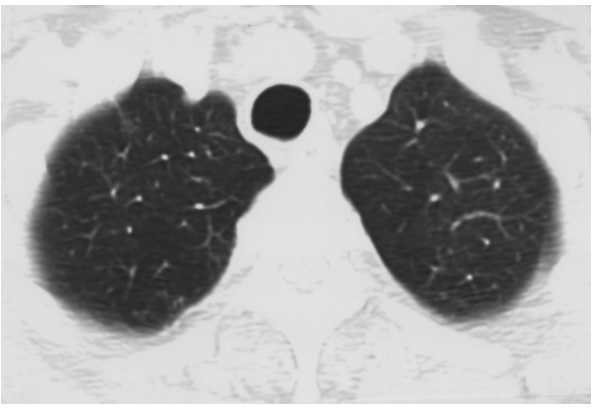

Fig. 3C. Chest CT, lung window: resolution of bilateral pulmonary nodules (January 10, 2011)

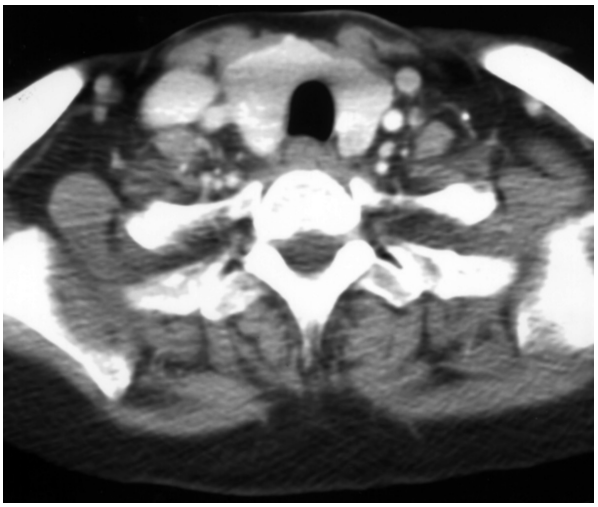

Fig. 3B. Neck CT with contrast: regression of bilateral neck lymphadenopathy (January 10, 2011)

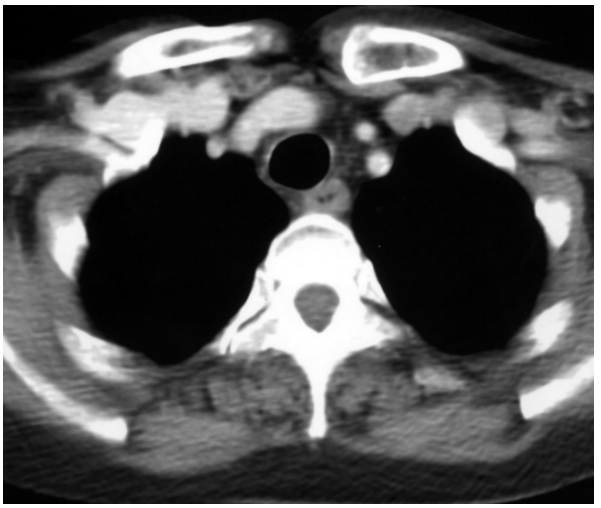

Fig. 3D. Chest CT with contrast: healed chest wall wound in the right anterior subclavian region (January 10, 2011)

Discussion

Immunocompromised patients, such as those with human immunodeficiency virus infection or with ESRD requiring dialysis, have an increased risk of developing TB [1]. According to the United States Renal Data System (USRDS) Annual Data Report, Taiwan has the highest incidence and prevalence rates of ESRD in the world [6]. In consideration of Taiwan's high prevalence of TB and ESRD, we believe more attention should be given to related issues.

The increased incidence of TB in dialysis patients was first reported in 1974, and has been a medical concern since that time [7]. The incidence of TB in these patients is several times higher than that in the general population [8]. Because of the impaired cellular immunity associated with uremia and exacerbated by dialysis, the risk of developing active TB after primary infection is increased [2-3, 8]. Frequent hospital admissions or visits, older age, diabetes mel-

litus, low body mass index and use of immunosuppressive drugs are other factors contributing to the higher prevalence of TB in these patients [2]. Several studies reported a high frequency of cases of TB discovered in the first year of dialysis [1]. The symptoms of TB in ESRD patients are insidious and non-specific, and mimic uremic symptoms, such as anorexia, fever and weight loss, so delayed diagnosis may occur [1, 3]. The localization is often extrapulmonary and occurs in 38-80% of dialysis patients with TB [1, 3]. Physicians should be aware of TB in ESRD patients with an unusual presentation and localization [1-3].

According to the Taiwan Tuberculosis Control Report, in 2007, 802 cases (5.3%) of extrapulmonary TB were found among 15,126 new and relapse cases [9]. Lymph nodes (24.8%) were noted as the most common extrapulmonary sites, followed by sites at the bones and joints, genitourinary tract, meninges, pleural effusion, abdomen, skin and eyes [10]. However, according to 2 studies from Taiwan, lymphadenopathy was not the most common presentation of extrapulmonary TB in patients with ESRD under dialysis [8, 11]. Fang and colleagues reported extrapulmonary TB was noted in 32 patients out of 62 dialyzed patients with active TB (51.6%). The peritoneum (31.2%, 10/32) and pleural cavity (25%, 8/32) were the 2 most common organs involved [8]. In another study, Chung *et al*. reported 17 of 2208 hemodialysis patients had been diagnosed with extrapulmonary TB, accounting for 55.5% of the total TB population. The peritoneum (35.3%, 6/17) and cervical lymph nodes (17.6%, 3/17) were the 2 most preferred sites [11]. But most reports from around the world have revealed that the most common extrapulmonary involvement site in dialysis patients was the lymph node [1, 3].

Tuberculous abscess of the chest wall is an uncommon manifestation of extrapulmonary TB. In our case, the patient had tunneled hemodialysis catheter-related tuberculous abscess of the chest wall. TB of the chest wall constitutes 1% to 5% of all cases of musculoskeletal TB, which occurs in 1% to 3% of TB cases overall [12]. TB of the chest wall may result from direct inoculation from underlying pleural or pulmonary lesions, direct extension from lymphadenitis of the chest wall, or more commonly, from hematogenous dissemination from a quiescent tuberculous focus without active pulmonary disease [13]. Many patients are reported to have concomitant active pulmonary TB, ranging from 14.7% to 62.5% of the cases in some series, or have a past history of TB [13]. The symptoms are indolent and difficult to discover. Destruction of bone adjacent to the chest wall tuberculous abscess is a common finding, but not always seen [14]. CT scan is a useful and ideal tool for the evaluation of tuberculous chest wall lesions, the extent of soft tissue collections, intrathoracic adenopathy and bone erosion [14].

The diagnosis of TB necessitates the finding of typical caseating granuloma on biopsy, or the growth of tubercle bacilli from the culture of the biopsy material or tissue, so some invasive tissue biopsy procedures are necessary if clinical presentations are highly suspected [1, 8].

Treatment for extrapulmonary TB involving sites other than the meninges in ESRD patients is recommended for 6 months, and for the meninges, a 9 to 12-month regimen is suggested [15]. For the management of tuberculous chest wall abscess, many series have reported that medical treatment alone is not suitable for complete treatment, and the authors recommended a combination of medical and surgical manage-

ment, including abscess excision and adjacent bone resections to eradicate all the infected tissue and to prevent recurrence [13].

Most patients reported as being diagnosed with tuberculous abscess of the chest wall were immunocompetent [12-13, 16]. A very limited number of cases of patients undergoing hemodialysis and developing tuberculous chest wall abscess have been reported [4-5]. However, there has been no report of tuberculous abscess presenting on the tunneled hemodialysis catheter site on the chest wall. Malik and colleagues reviewed 330 patients undergoing dialysis (including hemodialysis and peritoneal dialysis); TB was found in 48 patients, and 1 of them had an infraclavicular chest wall cold abscess [5].

Our case was that of an ESRD patient undergoing regular hemodialysis, who was found to have extrapulmonary TB in simultaneously different locations, including tuberculous chest wall abscess on a tunneled hemodialysis catheter site, neck and intra-abdominal lymphadenitis, pulmonary TB, and suspected TB involving the liver. Our patient's symptoms were very insidious, making an early diagnosis difficult. She also had no previous history of TB, which increases the risk of extrapulmonary TB in hemodialysis patients. The 8-month delay in this patient's diagnosis of tuberculous lymphadenitis might have been due to the patient's refusal of biopsy of the neck lymph nodes. Fortunately, her tuberculous abscess of the chest wall did not involve the ribs or cause adjacent bone erosion. Finally, her anti-TB treatment course was well managed and there has been no recurrence up to this writing.

In conclusion, tuberculous chest wall abscess occurring at a tunneled hemodialysis catheter site, as in our patient with ESRD, is rare and no case has been reported in Taiwan. The symptoms and signs of extrapulmonoary TB in dialyzed patients are insidious in onset and not specific. Prompt diagnosis and treatment are important to prevent serious complications, and can reduce mortality and morbidity, thus improving the patient's outcome. Finally, physicians should maintain a high index of suspicion of tuberculous chest wall abscess in dialyzed patients with an unresolved chest wall wound or abscess, despite antibiotics treatment.

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血液透析導管相關之胸壁結核性膿瘍—病例報告

胡亭宇　白冠壬　張宗豪*　陳志榮**　余明治

慢性腎衰竭的病人有較高危險性得到結核病，此族群的病人也比一般人有更高之肺外結核發生率。胸壁結核更是少見的肺外結核，在洗腎的病人只有少數文獻報告過。

我們在此報告一位未曾有結核病紀錄的51歲慢性腎衰竭女性病人因右上腹痛及微燒就醫。檢查時發現頸部及腹腔內淋巴腫大，並有肝內結節，但她拒絕更進一步侵入性檢查。因為尿毒症她接受右鎖骨靜脈血液透析導管置入，並開始長期的血液透析。八個月後，洗腎導管周圍胸壁紅腫化膿且頸部淋巴結更加腫大。經右胸壁膿瘍清創及頸部淋巴結切片後，清創之組織及淋巴結切片標本之病理報告證實為結核菌感染且兩者組織培養均長出結核菌。經六個月標準抗結核病藥物治療後，胸壁膿瘍痊癒，頸部及腹部淋巴結、肝內及肺內結節皆消失。

就我們所知，血液透析導管相關的胸壁結核性膿瘍病例報告非常少，在台灣也未曾被報告過。藉此病例經驗，對於洗腎病人有久未癒合或對抗生素治療無反應的病灶，更要提高警覺有胸壁結核的可能性。*(胸腔醫學* ***2011; 26: 225-232)***

關鍵詞：血液透析導管，胸壁，結核，末期腎衰竭

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Huge Chest Wall Mass Caused by Brown Tumor — A Case Report

Ching-Yuan Lin, Chun-Shih Chin, Cheng-Ming Peng*, Jeng-Yuan Hsu

A chest wall mass with night bone pain and body weight loss may be highly malignant. Brown tumors are benign and rare chest manifestations of hyperparathyroidism that may mimic cancer metastasis. Herein, we present a rare case of a huge brown tumor on the right chest wall with chest bone pain at night as the presenting symptom of primary hyperparathyroidism. After right parathyroidectomy, the right chest wall mass gradually shrank, as displayed on follow-up chest X-rays and nuclear parathyroid scans. The pathology report showed parathyroid carcinoma. ***(Thorac Med 2011; 26: 233-239)***

Key words: brown tumor, metastasis, primary hyperparathyroidism

Introduction

A brown tumor is a benign and rare clinical entity caused by lack of treatment of primary, secondary and tertiary hyperparathyroidism [1-2]. Brown tumors are not neoplasms, and are alternatively called osteitis fibrosa cystica. Osteitis fibrosa cystica is associated with hyperparathyroidism, and was first described in 1950. Brown tumors may occur in the ribs, pelvis, and extremities. Elevated serum calcium levels, alkaline phosphatase and low phosphate are noted mostly in primary hyperparathyroidism [3]. This condition is caused by chronic excess excretion of parathyroid hormone and leads to an imbalance of osteoclastic and osteoblastic activity in the fibrous stromal matrix in multiple skeletal lesions. However, multiple bone lesions with hypercalcemia and poor appetite are easily misdiagnosed as paraneoplastic syndrome in carcinoma with squamous origin, such as lung, esophagus, head and neck cancer [4-8]. Differentiating between brown tumors and malignancies with multiple bone metastases is a major challenge.

Case Report

A 43-year-old man, who denied any systemic disease, presented with bilateral lower leg pain of 6 months' duration. He did not have a history of trauma. The bilateral lower leg pain was constant and dull, not related to ambulation, and became aggravated at night. One

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month later, constant, dull pain at the right chest wall was noted. The chest bone pain developed insidiously, especially at night, without radiation, local tenderness, cold sweating or trauma. However, loss of appetite and a body weight loss of around 20 kg in 6 months were also noted.

Initially, he visited a local hospital for help and a chest X-ray showed a huge right-side lobular chest wall mass (Figure 1A). Chest computed tomography (CT) disclosed a right chest wall mass with eroded ribs (Figure 1B). Bilateral renal stones were also noted. Painkillers were prescribed, but they did not have an acceptable effect. He then came to our neurology outpatient department (OPD) for a second opinion. Electromyography and nerve conduction velocity tests of the lower limbs showed no abnormal findings. He was then referred to our chest medicine OPD. After a review of the chest CT and X-ray, the general impressions were carcinoma with chest wall metastases, plasmacytoma and primary bone tumor. He was subsequently admitted for further evaluation.

Physical examination showed no palpable chest mass, but local tenderness was noted at the right posterior chest wall. Laboratory data showed hemoglobulin 11.3 g/dl (normal range for men: 12.3-18.3 g/dl), albumin 4.1 g/dl (normal: 3.5-5.0 g/dl), total protein 6.7 g/dl (normal: 6.0-8.0 g/dl), elevated serum total calcium 20.3 mg/dl (normal: 8.4-10.2 mg/dl), plasma-free calcium 10.42 mg% (normal: 4.36-5.2 mg%), creatinine 3.2 mg/dl (normal: 0.7-1.4 mg/dl), phosphate 3.9 mg/dl (normal: 2.5-4.5 mg/dl), intact parathyroid hormone 3246 pg/ml (normal: 12-72 pg/ml) and alkaline phosphatase 1,360 U/L (normal: 50-190 U/L). A technetium-99m methylenediphosphonate (Tc-99m MDP) bone scan showed elevated MDP uptake at the posterior aspect of the right 5th, 6th, and 9th costochondral junctions, distal portions of the bilateral tibias and both heels (Figure 2). Renal osteodystrophy and multiple

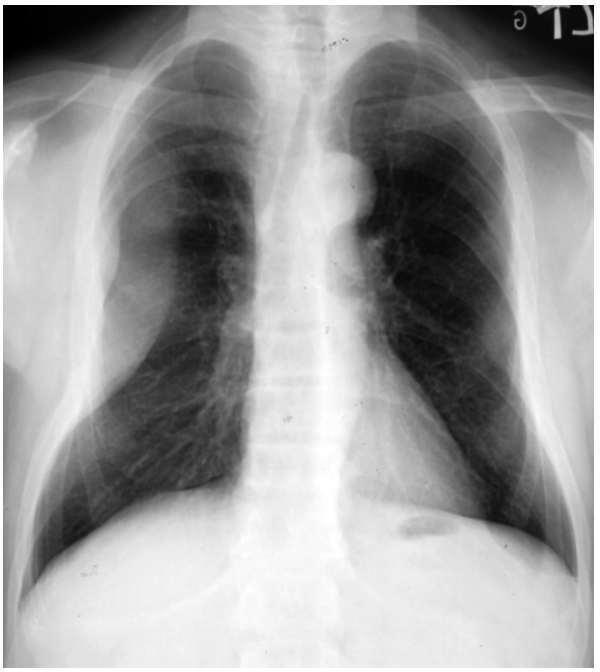

Fig. 1A. Chest X-ray showed a lobulated mass on the right chest wall.

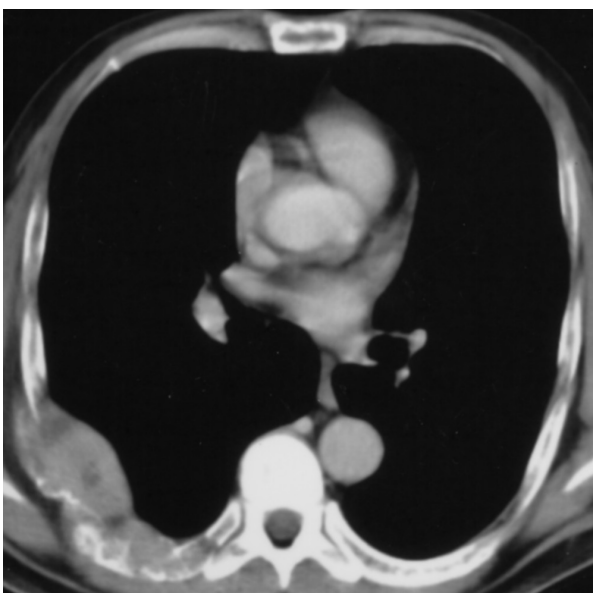

Fig. 1B. Chest CT showed a right chest wall mass with eroded ribs.

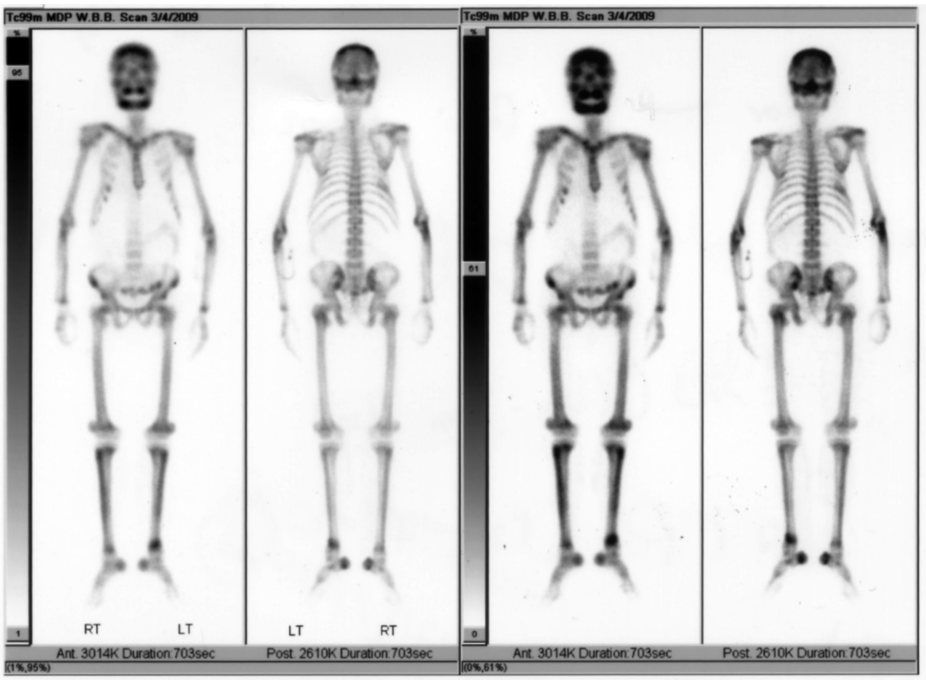

Fig. 2. Whole body bone scan showed increased uptake at the right 5th, 6th, and 9th costochondral junctions, distal portions of the bilateral tibias and both heels.

bone metastases were the most common differential diagnoses, based on the whole body bone scan. A right chest wall ultrasound-guided cutting biopsy was performed and the pathologic results showed oval polygonal mononuclear cells admixed with numerous large, osteoclast-like giant cells. There was also bony tissue and spindle cells with new bone formation and old hemorrhage. No malignant tumor cells were seen in this specimen (Figure 3). The differential diagnoses were fibrous dysplasia, giant cell tumor, and aneurysmal bone cyst based on the pathologic results. Owing to the clinical condition of hypercalcemia, the alternative impression of brown tumor was highly suspected. A nuclear parathyroid image showed Tc-99m methoxyisobutylisonitrile (Tc-99m MIBI) uptake at the right thyroid bed, possibly due to delayed washout of Tc-99m MIBI in the right parathyroid tissue and right chest wall area (Figure 4).

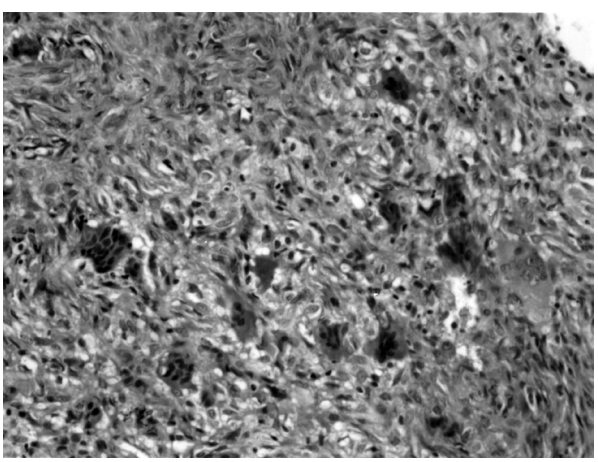

Fig. 3. Pathologic examination showed oval polygonal mononuclear cells admixed with numerous large, osteoclast-like giant cells, new bone formation and old hemorrhage (hematoxylin and eosin stain, 400x).

After serial examinations, a right parathyroid tumor with right chest wall brown tumor was suspected. Right parathyroidectomy was performed and a circumscribed tumor, 5.0×3.5×3.0

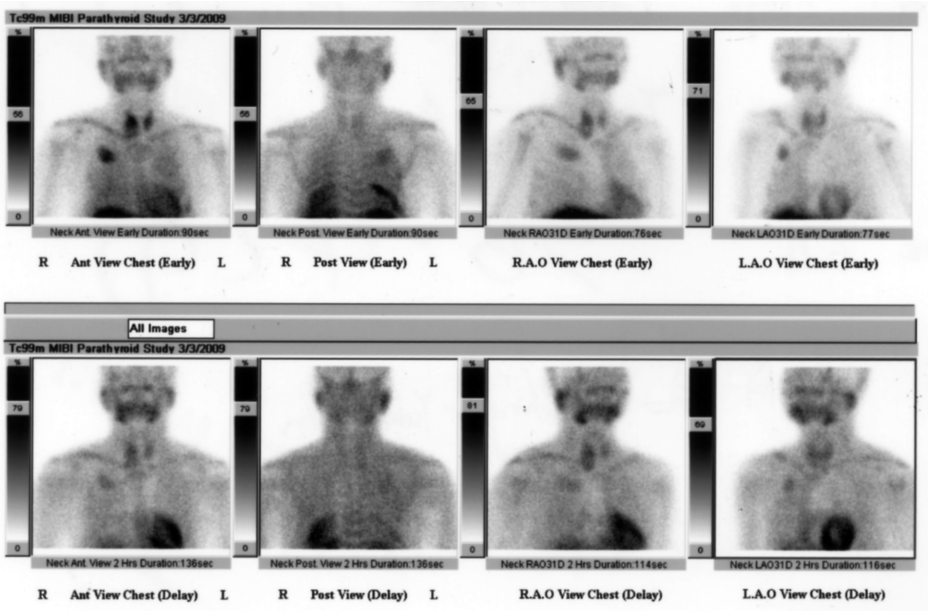

Fig. 4. Parathyroid Tc-99m MIBI image showed increased uptake in right parathyroid tissue and the right chest wall area.

cm in size and 38.28 gm in weight located at the right lower neck, was found. The pathology report showed parathyroid carcinoma with extensive angiolymphatic tumor thrombi. The serum total calcium decreased to 9.0 mg/dl and the intact parathyroid hormone level decreased to 7.89 pg/ml within 1 week after operation. The right chest wall mass shrank gradually, as shown on follow-up chest X-rays. A subsequent parathyroid Tc-99m MIBI scan showed no thyroid bed uptake and decreased right chest wall uptake.

Discussion

Primary hyperparathyroidism is reported to be caused by a solitary adenoma in 80-85% of cases, multiple adenomas in 5%, parathyroid dysplasia in 15%, and parathyroid carcinoma in less than 1-5% [5, 9-10]. Secondary hyperparathyroidism is associated with renal osteodystrophy in the terminal stage of renal failure [11-12]. Brown tumors caused by chronic excess excretion of parathyroid hormone lead to an imbalance of osteoclastic and osteoblastic activity in the fibrous stromal matrix in multiple skeletal lesions. The brown coloration is owing to hemosiderin deposition. Symptoms due to brown tumors are rarely noted. The most common symptoms are hypercalcemia-related and some of them cause pain due to kidney stones, polyuria, poor intake, and stupor [13]. Patients with this condition should be referred to the oncology department for further evaluation [14]. Biochemical examinations, complete imaging and histological studies are needed to disclose the possible existence of primary hyperparathyroidism. Brown tumors and giant cell tumors of the bone have the same radiologic and histological features [15] and differentiation between the 2 diagnoses is dependent upon evaluation of serum biochemistry.

Tc-99m MIBI scanning of the parathyroid gland is highly sensitive and is used preopera-

tively to evaluate the location of parathyroid tumors. Tc-99m MIBI scanning offers greater accuracy than that obtained with ultrasound, CT or magnetic resonance imaging (MRI) [16] and also offers a high degree of accuracy for localizing severe primary hyperparathyroidism [17]. Ectopic and residual parathyroid glands can be detected after parathyroidectomy. Brown tumors increased the signal uptake in Tc-99m MIBI images [18], and this decreased after treatment of hyperparathyroidism [18-19].

The treatment of brown tumors depends mainly on resecting the source of primary hyperparathyroidism. Successful parathyroidectomy that decreases the level of parathyroid hormone usually leads to steady regression of brown tumors [3, 19-20].

Herein, we described a patient with right parathyroid carcinoma, complicated with a hyperparathyroidism-related chest wall brown tumor and hypercalcemia. These conditions subsided after parathyroidectomy, and the right chest wall mass shrank gradually.

Brown tumors are benign lesions; however, the hypercalcemia-related symptoms are similar to those of paraneoplastic syndrome. A complete history, biochemical tests, imaging, and histological examinations are needed to make a definitive diagnosis, and hyperparathyroidism-related brown tumors should be included in the differential diagnosis.

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棕色瘤造成的巨大胸壁腫塊—病歷報告

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胸壁腫塊合併夜間骨痛和體重減輕則惡性腫瘤的可能性很高。棕色瘤是一種副甲狀腺亢進所造成的良性狀況，在胸腔的表現並不多見，一般容易被誤認為腫瘤轉移。我們報告一個病例：原發性副甲狀腺機能亢進引發的右側巨大胸壁棕色瘤合併夜晚明顯胸骨疼痛的症狀。經右側副甲狀腺手術切除後，在後續追蹤的胸腔X光和核醫副甲狀腺掃描，右側胸壁的腫瘤逐漸縮小。病理報告證實為副甲狀腺癌。*(胸腔醫學* ***2011; 26: 233-239)***

關鍵詞：棕色瘤，轉移，原發性副甲狀腺機能亢進

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