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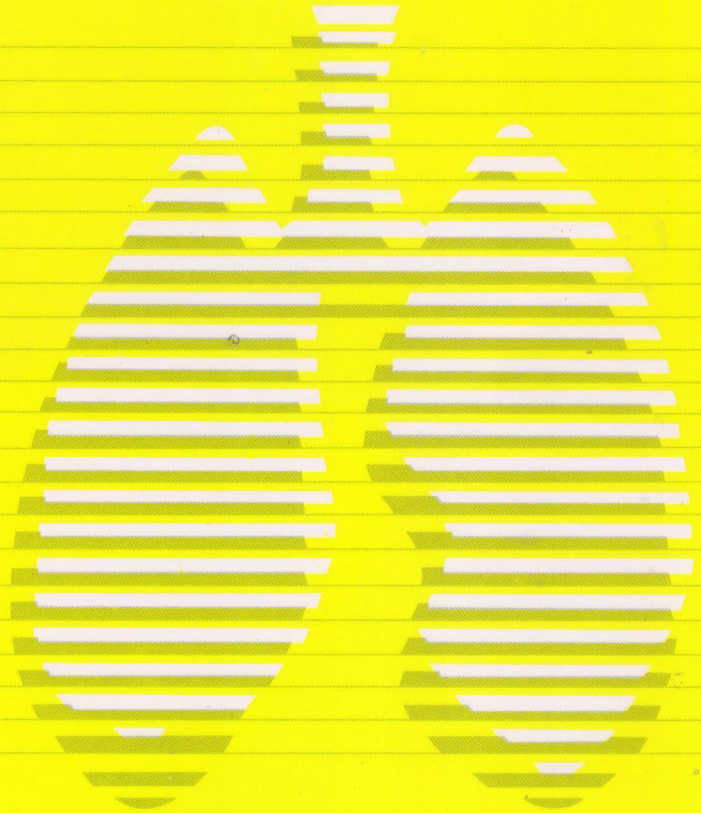

台灣胸腔暨重症加護醫學會

11217 台北市北投區石牌路二段201號

5.No.201, Sec. 2, Shipai Rd., Beitou District,
Taipei City, Taiwan 11217, R.O.C.

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Orginial Articles

Case Reports

Cirrhosis is a Crucial Factor in Mortality and Medical Costs of Acute Respiratory and Renal Failure Patients

Shuo-Chueh Chen, Shih-Ni Chang*, Wei-Erh Cheng, Chih-Yi Chen**, Wu-Huei Hsu, Yu-Chao Lin, Kuo-Liang Chiu***, Shinn-Jye Liang, Yu-Feng Wei****, Jiung-Hsiun Liu*****, Fung-Chang Sung*, Chuen-Ming Shih

Objective: Patients with cirrhosis are at high risk of mortality in Taiwan, especially those with other organ failures. This study focused on determining if cirrhosis is a crucial factor in the mortality and medical costs of acute renal and respiratory failure patients using claims data from the National Health Insurance (NHI) system of Taiwan.

Methods: Using the 2000-2007 NHI claims data for patients with acute respiratory and renal failure, we identified 2,798 patients with liver cirrhosis and 11,192 with no cirrhosis diagnosis. These subjects were frequency matched by sex and age, and co-morbidities, length of stay (LOS) in the hospital, cost, discharge status and impact of cirrhosis on in-hospital mortality were compared between the 2 groups.

Results: Non-cirrhotic patients were more prevalent than patients with the co-morbidities of sepsis, pneumonia, chronic heart/lung disease and diabetes, but the negative impact of cirrhosis on in-hospital mortality was still significant higher after correcting for other factors (OR=2.42, 95% CI=2.17 to 2.70). The cirrhotic patients had higher mortality and against-advice discharge (AAD) rates (83.8%/68.0%, $p<0.0001$), a shorter LOS ($p<0.0001$), and a higher daily cost than those with more than 3 co-morbidities and younger age at hospitalization.

Conclusion: Patients with acute renal and respiratory failure and a diagnosis of cirrhosis are at an elevated risk of in-hospital mortality, AAD, shorter LOS, and higher daily costs during admission. ***(Thorac Med 2012; 27: 199-208)***

Key words: cirrhosis, acute renal failure, acute respiratory failure, mortality, medical cost

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan; *Institute of Environmental Health, China Medical University, College of Public Health, Taichung, Taiwan; **Division of Chest Surgery and Cancer Center, Department of Surgery, China Medical University Hospital, Taichung, Taiwan; ***Division of Chest Medicine, Department of Internal Medicine, Buddhist Tzu-Chi Hospital, Taichung, Taiwan; ****Division of Chest Medicine, E-Da Hospital, Kaohsiung County, Taiwan; *****Division of Nephrology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan

Address reprint requests to: Dr. Chuen-Ming Shih, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung, 404, Taiwan

Introduction

Mortality from liver cirrhosis and hepatoma in Taiwan is among the highest in the world [1]. In 2008, chronic hepatitis and liver cirrhosis caused 4,917 deaths in Taiwan, making it the 8th most common cause of mortality [2]. Hepatitis B virus (HBV) is the leading cause of chronic hepatitis in Asia-Pacific countries, differing from the United States and Europe, and up to 25% of HBV patients eventually die of liver cirrhosis and/or its complications. The prevalence of HBV in the general population in the Asia region is higher than that of HCV, with the highest rates in Taiwan (>10%) and Thailand (>8%) [3]. In Taiwan, 75-80% of patients with chronic liver disease, including cirrhosis, are HBsAg positive, including 34% of patients with cirrhosis and 72% of those with hepatocellular carcinoma [3].

Acute renal failure is a life-threatening condition that frequently complicates advanced liver disease, especially in those with marked hyperbilirubinemia, hyponatremia, elevated liver enzymes, infection, and gastrointestinal (GI) bleeding [4]. Patients with cirrhosis and renal failure are at an elevated risk of complications and fatality, as compared to those without renal failure [4-5]. Most cirrhotic patients die of liver-related causes. More than 1/3 of these patients experience either acute bleeding or infection, usually complicated with acute respiratory failure at the terminal stage [6-7]. The decision to aggressively intervene and use invasive mechanical ventilation in individual cirrhotic patients is controversial, as ventilated cirrhotic patients often progress to multi-organ failure [7]. Patients with mechanical ventilation have a poor prognosis [8-9]. Several studies from the United States and Europe [10-11] have analyzed the outcomes of cirrhosis patients with intensive care at a single tertiary center from different perspectives. To our knowledge, there are still no published data on the prognosis of cirrhotic patients with acute renal and respiratory failure using invasive mechanical ventilation, compared with other major critical diseases without cirrhosis in Taiwan. In this study, we used claims data from the National Health Insurance (NHI) system of Taiwan to investigate whether patients with acute renal and respiratory failure and cirrhosis differed from patients without cirrhosis. We also assessed the hospitalization cost for these patients.

Material and methods

Data sources

This study used the reimbursement claims data of the universal NHI system of Taiwan for the years 2000-2007. The NHI has covered more than 96% of the country's population and contracted with 97% of hospitals and clinics since the end of 1996. The claims data provided the encrypted identification number of each patient and the patient's medical records, containing information on sex, birthday, physicians and hospitals, dates of admission and discharge, the primary admission diagnosis and up to 4 secondary diagnoses, operation procedures (up to 5), discharge disposition and cost by admission. The hospitalization cost components included fees for diagnoses, room and meals, laboratory tests, radiography services, therapeutic treatment, operation, rehabilitation, blood products, hemodialysis, anesthetics, special medical supplies, medications, and other services. The International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) was used to identify the patient's disease.

Study population

We used inpatient claims data for 2000-2007 obtained from the NHI Research Database (NHIRD) to identify patients first admitted for respiratory failure (ICD-9-CM codes 518.81, 518.83 and 518.84) and renal failure (ICD-9-CM codes 584, 585 and 586) to serve as study subjects (n=74,163). Among these patients, we identified 2,798 with liver cirrhosis (ICD-9-CM codes 571.5 and 571.2). Four controls were randomly selected from among the patients without liver cirrhosis for each cirrhosis case, and were frequency matched by distributions of age and sex during the same period.

Key variables of interest

We calculated length of stay (LOS) using the duration between admission and discharge dates. The daily cost of hospitalization was the estimate of the sum of all medical costs divided by LOS. Costs expressed in this study were in Taiwan dollars (US$1 is approximately NT$33 in Taiwanese currency).

Discharge status in the NHIRD is categorized as recovered, transferred to outpatient care, deceased, against-advice discharge (AAD), critical AAD, transferred to another hospital, and others. In Taiwan, the majority of citizens prefer to die at home. It is uncommon for hospitals to discharge critically-ill patients that have suffered from refractory shock, hypoxemia or bradycardia. Therefore, in this study, discharge status was classified into 1 of 3 groups: discharged for outpatient care, deceased or AAD, and other.

Co-morbidities associated with the prognosis of cirrhotic patients were assessed; these included sepsis (ICD-9-CM code 038), pneumonia (003.22, 055.1, 480-482 and 507), chronic obstructive pulmonary disease (COPD) (ICD-9-CM code 491.2, 493.2 and 496), heart failure (ICD-9-CM code 482), old myocardial infarction (ICD-9-CM code 412), acute myocardial infarction (ICD-9-CM code 410), coronary atherosclerosis (ICD-9-CM code 414.0), hepatic coma (ICD-9-CM code 572.2 and 070.2), and diabetes (ICD-9-CM code 250), which commonly cause acute renal and/or respiratory failure.

Statistical analysis

The categorized distributions of age, sex, hospital level, urbanization, and hospitalization characteristics and co-morbidities between patients with (cases) and patients without liver cirrhosis (controls) were examined using the Chi-square test. The distributions of LOS and transfer status at discharge between the cases and controls were compared. The *t*-test was used to examine the differences in average daily care costs between the 2 groups. We used logistic regression to estimate the difference in in-hospital mortality and risk among the cases and controls. A p-value <0.05 was considered statistically significant. All analyses were performed with SAS 9.1 software (SAS institute Inc., Cary, NC).

Results

Subject Characteristics

The demographic characteristics of the study subjects, including 2,798 cases of liver cirrhosis and 11,192 controls without liver cirrhosis, are summarized in Table 1. There were more male than female subjects (67.7% vs. 32.3%). Age and sex were equally distributed in both groups. Compared with the controls, the cases were more likely to receive care at medical centers (46.5% vs. 42.4%, $p<0.0001$)

Table 1. Comparison of demographic characteristics of patients with liver cirrhosis and controls without liver cirrhosis, 2000-2007

Variable	Controls (non-cirrhosis) N=11,192		Cases (cirrhosis†) N=2,798		Total N=13,990		*p*-value‡
	n	(%)	n	(%)	n	(%)	
Sex							1.00
Male	7,575	(67.7)	1,894	(67.7)	9,469	(67.7)	
Female	3,620	(32.3)	904	(32.3)	4,524	(32.3)	
Age, years							1.00
<50	2,891	(25.8)	723	(25.8)	3,614	(25.8)	
50-59	2,032	(18.2)	508	(18.2)	2,540	(18.2)	
60-69	2,300	(20.5)	574	(20.5)	2,874	(20.5)	
70-79	2,612	(23.3)	653	(23.3)	3,265	(23.3)	
≥80	1,360	(12.2)	340	(12.2)	1,700	(12.2)	
Hospital level							<0.0001
Medical center	4,743	(42.4)	1,301	(46.5)	6,044	(43.2)	
Regional hospital	4,095	(36.6)	1,040	(37.2)	5,135	(36.7)	
District hospital	2,357	(21.1)	457	(16.3)	2,814	(20.1)	
Urbanization							<0.0001
Low	641	(5.7)	180	(6.4)	821	(5.9)	
Moderate	2,541	(22.7)	811	(29.0)	3,352	(24.0)	
High	8,013	(71.6)	1,807	(64.6)	9,820	(70.2)	

† All cases and controls were patients with renal and respiratory failure

‡ *t*-test or Chi-square test

and reside in moderately or less urbanized areas (35.4% vs. 28.4%, $p<0.0001$).

A comparison of co-morbidities between the patients with liver cirrhosis and the controls without liver cirrhosis showed that the control group was more likely to have sepsis ($p<0.0001$), pneumonia ($p<0.0001$), COPD ($p<0.0001$), heart failure ($p<0.0001$), old myocardial infarction ($p<0.0001$), acute myocardial infarction ($p<0.0001$), coronary atherosclerosis ($p<0.0001$), and diabetes ($p<0.0001$) (data not shown).

Hospitalization Characteristics

Figure 1 shows that the patients with liver cirrhosis had shorter LOS than the controls, and also higher mortality and AAD than the controls (83.8% vs. 68.0%); i.e., the proportion of discharge or transfer to outpatient care was lower among the cirrhosis patients (15.3% vs. 29.4%, $p<0.0001$) (Figure 2), and with an approximately equivalent distribution between males and females (data not shown).

Hospital Care Costs

Table 2 displays the average daily hospital care costs for the liver cirrhosis patients and controls based on the number of co-morbidities and age. Overall, the average costs were higher for the cirrhosis patients than for the controls, particularly among patients with 0 and ≥3 co-morbidities ($p=0.02$ and 0.006, respectively).

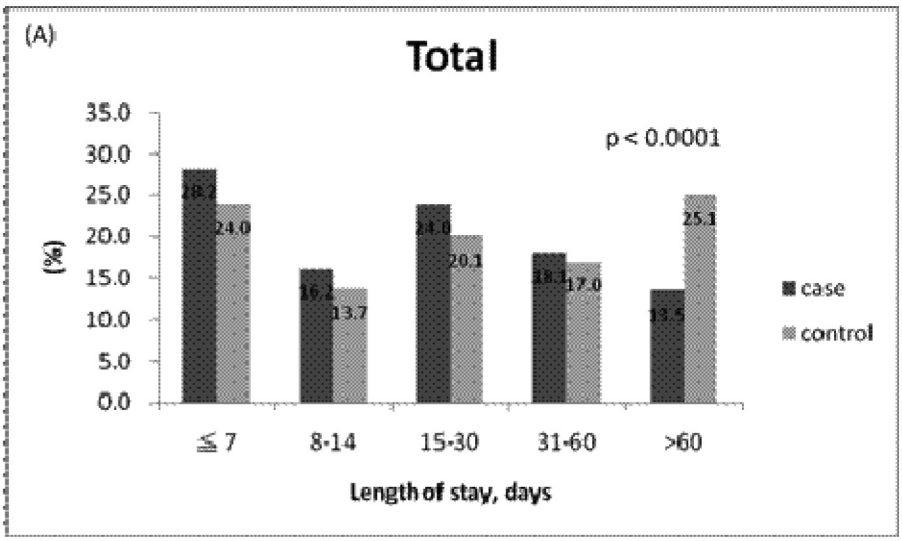

Fig 1. Comparisons of length of stay in the hospital between cases and controls (p<0.0001).

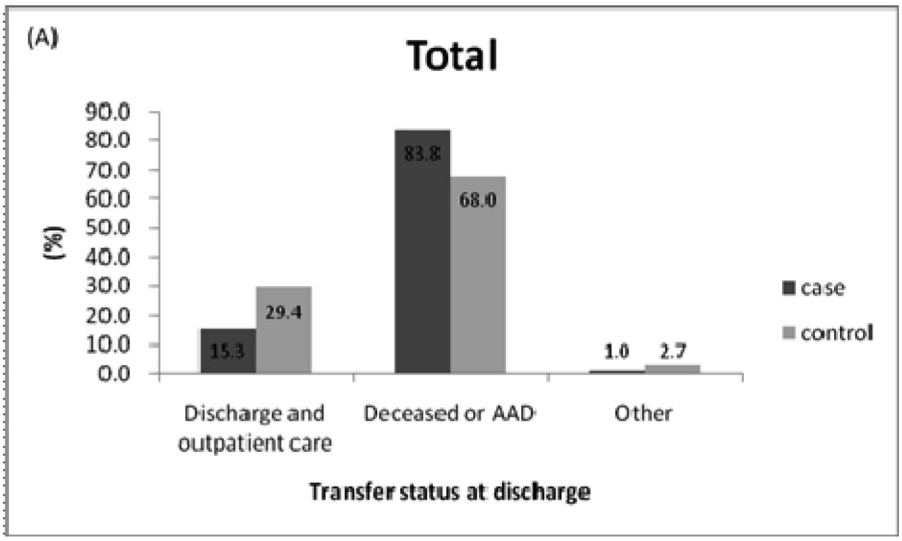

Fig. 2. Comparisons of transfer status at discharge between cases and controls (p<0.0001).

The costs decreased with the increase of age for both the cirrhosis patients and the controls. However, the age-specific costs were significantly higher for the cirrhosis patients and the controls in the younger groups.

Odds ratios of in-hospital mortality

Table 3 presents the odds ratios of in-hospital mortality by socio-demographic status and comorbid disorder. Using multivariate logistic regression analysis, the ORs of in-hospital mortality increased with age. Compared with patients <50 years of age, patients ≥80 years old were at the highest risk (OR=1.92, 95% CI=1.67 to 2.22). Table 3 also shows that risks were higher among male patients than female

Table 2. Average daily hospital care cost (NT$) for patients with liver cirrhosis and controls without cirrhosis by number of comorbidities and age

Variables	Control (non-cirrhosis)			Case (cirrhosis)			*p*-value†
	No.	Mean‡	Median‡	No.	Mean‡	Median‡	
Comorbidity*							
0	2,789	15,432	11,994	1,174	16,653	12,428	0.02
1-2	2,686	13,134	10,524	365	13,757	11,214	0.27
≥3	5,717	13,821	10,735	1,259	14,835	11,745	0.006
Age, years							
<50	2,892	17,345	13,102	723	19,477	14,430	0.003
50-59	2,032	14,883	11,366	508	16,387	13,258	0.017
60-69	2,296	13,409	10,632	574	15,596	11,968	0.0005
70-79	2,612	11,888	9,969	653	12,093	10,242	0.58
≥80	1,360	11,099	9,533	340	11,748	10,097	0.13

† *t*-test

‡ per day cost

patients (OR=1.14, 95% CI=1.05 to 1.24). Moreover, the risk was significantly greater for patients with liver cirrhosis than for those without (OR=2.42, 95% C =2.17 to 2.70).

Discussion

Using the existing NHI database from 2000 to 2007, we documented the significantly negative impact of cirrhosis on patients with acute renal and respiratory failure. The overall rate of mortality and AAD among cirrhotic patients, up to 83.8%, was much greater than that among patients with other major co-morbidities such as sepsis, pneumonia, chronic lung disease, heart disease and diabetes. Although cirrhotic patients were more likely to be admitted to a medical center, in-hospital mortality tended to be lower (OR=0.92, 95% CI=0.83-1.02), after adjusting with multivariate analysis. The negative impact of cirrhosis on in-hospital mortality was also significantly higher after correcting for other factors (OR=2.42, 95% CI=2.17 to 2.70). Cirrhotic patients also had shorter LOS, but higher daily costs during admission, particularly those patients with more than 3 co-morbidities and younger age.

Multiple organ failure was the leading cause of death among patients admitted to the medical ICU, and acute respiratory and renal failure were 2 of the most common occurrences. Because of the high incidence of chronic hepatitis B in Taiwan, decompensated cirrhotic patients commonly need intensive care due to multiple complications, such as esophageal varices bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, and acute respiratory or renal failure [12]. Patients with advanced liver disease admitted to the ICU have a low survival rate, with mortality ranging from 50% to 100% [13-14]. Many studies have shown that respiratory and renal failure increased the mortality rate of advanced liver disease patients admitted to the ICU. In a cohort study from India, mortality among cirrhotic patients with renal failure on admission to the ICU was observed for 30 days, and mechanical ventilator use was found to be significantly related to mortality. The first-

Table 3. Risks of in-hospital mortality in association with demographic characteristics and comorbid disorder

Variables	Univariate		Multivariate	
	OR	(95% CI)	OR†	(95% CI)
Age, years				
<50	1.00	(reference)	1.00	(reference)
50-59	1.15	(1.03-1.29)*	1.18	(1.06-1.32)**
60-69	1.14	(1.03-1.27)*	1.21	(1.08-1.35)**
70-79	1.40	(1.26-1.55)***	1.49	(1.33-1.66)***
≥80	1.80	(1.57-2.06)***	1.92	(1.67-2.22)***
Sex				
Female	1.00	(reference)	1.00	(reference)
Male	1.02	(0.94-1.10)	1.14	(1.05-1.24)**
Hospital level				
Medical center	0.88	(0.80-0.97)*	0.92	(0.83-1.02)
Regional hospital	0.85	(0.74-0.94)**	0.86	(0.78-0.96)**
District hospital	1.00	(reference)	1.00	(reference)
Urbanization				
Low	1.00	(reference)	1.00	(reference)
Moderate	1.16	(0.98-1.36)	1.10	(0.93-1.30)
High	1.11	(1.02-1.22)*	1.08	(0.99-1.18)
Comorbidity				
0	1.00	(reference)	1.00	(reference)
1-2	0.89	(0.80-0.99)*	0.93	(0.84-1.04)
≥3	0.91	(0.84-1.00)*	0.95	(0.87-1.04)
Liver cirrhosis				
No	1.00	(reference)	1.00	(reference)
Yes	2.44	(2.19-2.71)***	2.42	(2.17-2.70)***

† Adjusted for variables in Table 3.

*p<0.05; **p<0.01; ***p<0.0001

day Acute Physiology and Chronic Health Evaluation II (APACHE II) scores and Sequential Organ Failure Assessment (SOFA) scores were good predictors of mortality [15]. Fang *et al*. [16] also reported that in critically ill cirrhotic patients with acute renal failure, the mean arterial pressure, serum bilirubin, respiratory failure and sepsis (MBRS) score was a reliable and easily adopted evaluation tool for short-term prognosis.

The incidence of acute renal failure is high in cirrhotic patients, especially in those admitted to the ICU [8, 14]. Acute renal failure in these patients may be due to pre-renal factors, hepato-renal syndrome, sepsis secondarily, drugs, or renal ischemia [17-18], and these patients appear to have particularly high mortality. In advanced-stage cirrhosis, systemic vascular resistance is markedly reduced and the increased cardiac output cannot compensate, leading to

an underfilling of the arterial circulation. Bacterial translocation from the bowels may also elicit an inflammatory response, with increased production of proinflammatory cytokines and vasodilator factors in the splanchnic area, leading to splanchnic artery dilatation [5]. These are the main mechanisms of renal dysfunction in cirrhotic patients. Endotracheal tube intubation with mechanical ventilation also has been shown to be associated with high ICU mortality rates, ranging from 83% to 95% in patients with cirrhosis [8, 22-23]. The most common reasons for these mortality rates include hepatic encephalopathy, esophageal varices bleeding, massive ascites-related hypoventilation, alcoholism, and septic shock. Only those with a less severe Child-Pugh score (<12 points) had a relatively satisfactory outcome [7].

The increased morbidity and mortality in critically ill cirrhotic patients may be associated with immunologic, mechanical, or pharmacological mechanisms [15]. Abnormalities influence both cell-mediated and humoral immunity. Both C3 complement synthesis in the liver and hepatocyte-diffused fibrosis commonly result in hypocomplementemia. Abnormal T-cell and B-cell functioning caused by malnutrition is related to the dysfunction of albumin synthesis in cirrhotic patients [19]. Decreased intestinal motility, bacterial overgrowth, increased intestinal permeability, and bacterial translocation are seen with the spontaneous bacterial peritonitis observed in multi-organ failure, sepsis, and hemorrhagic shock [20]. Mechanical factors such as the hepatoencephalopathy-related diminished cough function, suppressed respiration, and decreased lung expansion from massive ascites-induced intra-abdominal hypertension may promote respiratory complications. However, an abnormal respiratory cellular function has also been demonstrated in studies of cirrhotic patients, which found an impaired cytokine release from stimulated alveolar macrophages [24] and a reduced alveolar macrophage phagocytic ability [25]. Hepatopulmonary syndrome, resulting in intra-pulmonary shunt, also contributes to the risk of hypoxemic respiratory failure [5]. Finally, the treatment of infections must take into consideration the susceptibility of cirrhotic individuals to drug-related complications due to alterations in drug metabolism and clearance. One common drug-related complication is aminoglycoside nephrotoxicity. Deteriorated coagulopathy and thrombocytopenia from broad-spectrum antibiotics may also occur [26].

In conclusion, patients with acute respiratory and renal failure and cirrhosis are at a significantly more elevated risk of in-hospital mortality and AAD than those complicated with other major co-morbidities, such as chronic lung disease, heart disease, pneumonia, sepsis, or diabetes. A previous study also indicated that the MBRS score is an important short-term prognostic factor in critically ill cirrhotic patients with acute renal failure [16]. The daily cost of medical care for these patients is also higher. This may be due to the delicate and complex function of the liver which fails to induce an alteration of immunologic, mechanical, and pharmacological factors.

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肝硬化爲急性呼吸衰竭及急性腎衰竭病人之死亡率及醫療成本之重要決定因素

陳碩爵　張仕妮 *　程味兒　陳志毅 **　徐武輝　林裕超　邱國梁 ***　梁信杰
魏裕峰 ****　劉炯勳 *****　宋鴻樟 *　施純明

背景：在台灣，慢性肝炎和肝硬化病人死亡率很高，尤其是合併急性呼吸衰竭及急性腎衰竭時。本研究利用健保資料庫分析肝硬化是否為急性呼吸衰竭及急性腎衰竭病人死亡率及醫療成本之重要決定因素。

方法：從 2000 年到 2007 年，我們由健保資料庫找出符合急性呼吸衰竭及急性腎衰竭之病人共 13,990 位，其中有肝硬化者占 2,798 位，無肝硬化者 11,192 位。進一步分析兩組間年齡，性別，合併症，住院天數，醫療成本，出院狀態及在院死亡率之差異，以釐清肝硬化對此類病人之衝擊。

結果：無肝硬化之組別雖然有較多之合併症，包括肺炎，敗血症，慢性心肺疾病及糖尿病，但在校正後發現，肝硬化組仍有較高之在院死亡率（OR=2.42, 95% CI=2.17 to 2.70）。肝硬化組出院狀態有較高之死亡及病危自動出院率（83.8%/68.0%, p<0.0001），較短之住院天數（p<0.0001），以及在較年輕及大於三種以上合併症者之族群每日住院花費較高。

結論：肝硬化病人合併急性呼吸衰竭及急性腎衰竭時，會造成較高之死亡及病危自動出院率，較短之住院天數但較高之每日住院花費。*(胸腔醫學* ***2012; 27: 199-208)***

關鍵詞：肝硬化，急性呼吸衰竭，急性腎衰竭，死亡率，醫療成本

中國醫藥大學附設醫院　內科部　胸腔暨重症系，* 中國醫藥大學　公共衛生學院　環境衛生所
** 中國醫藥大學附設醫院　外科部　胸腔外科暨癌症中心，*** 台中慈濟醫院　胸腔內科，**** 義大醫院　胸腔內科
***** 中國醫藥大學附設醫院　內科部　腎臟科
索取抽印本請聯絡：施純明醫師，中國醫藥大學附設醫院　內科部　胸腔暨重症系，台中市北區育德里育德路 2 號

Risk Factors and Outcomes of Patients with Prolonged Mechanical Ventilation after Successful Weaning

Hung-Cheng Chen*, Meng-Chih Lin*,**, An-Shen Lin*, Chin-Chou Wang*, Yi-Hsi Wang*,**

Prolonged mechanical ventilation (PMV) places a large burden on patients, families, and healthcare resources. Some of these patients are successfully weaned and discharged, but some experience recurrent respiratory failure and undergo reinstitution of mechanical ventilation (MV). The purpose of this paper is to identify the risk factors that lead to reinstitution of MV in patients who have undergone successful weaning, and to evaluate their outcome. From January 2006 to December 2007, 314 patients were successfully weaned in the respiratory care center (RCC) of Chang Gang Memorial Hospital. Patients with reinstitution of MV were compared to patients without reinstitution of MV to identify the risk factors that lead to reinstitution. The observation period was from the day of RCC admission to the day of discharge from the hospital. Of the 314 patients, 133 (42.4%) underwent reinstitution of MV due to recurrent respiratory failure, and 181 (57.6%) were discharged without reinstitution. Patients without tracheostomy (p<0.005) had an increased incidence of reinstitution. Seventeen percent of PMV patients expired during RCC admission and 78 (58.7%) of the 133 patients that received reinstitution of MV expired during hospitalization. The incidence of MV reinstitution after successful weaning is increased in patients without tracheostomy and in those with congestive heart failure as the cause of acute respiratory failure. The prognosis of patients with MV reinstitution is poor. ***(Thorac Med 2012; 27: 209-216)***

Key words: prolonged mechanical ventilation, reinstitution of ventilator

Introduction

Acute respiratory failure (ARF) is the most common reason for patients to be admitted into an intensive care unit (ICU) [1-2]. Approximately 40% of ICU patients receive ventilator support, and the frequency of mechanical ventilation (MV) appears to be increasing. Although most patients are rapidly weaned from ventilator support, up to 20% require several

*Divisions of Pulmonary Medicine, Department of Internal Medicine, Department of Respiratory Therapy, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Taiwan
**Department of Respiratory Care, Chang Gung Institute of Technology, Chiayi, Taiwan
Address reprint requests to: Dr. Yi-Hsi Wang, Division of Pulmonary Medicine, Department of Internal Medicine, Department of Respiratory Therapists, Chang Gung Memorial Hospital, #123, Dapi Road, Niaosong District Kaohsiung City 833, Taiwan, Republic of China

days to weeks to be successfully weaned, and some become ventilator-dependent. Prolonged mechanical ventilation (PMV) is defined as the use of MV for more than 21 days [3-4]. Causes of PMV include systemic factors such as underlying chronic respiratory disease, pathogenesis of ARF, and severity of illness. A multicenter observational study in 23 long-term acute care hospitals encompassing more than 1,400 PMV patients 5 found that the PMV patients often had coexisting non-pulmonary diseases; 54% had cardiac disease and 20% had neurologic disease.

PMV places a large burden on patients, families, and healthcare resources [6-7]. Some patients with PMV are transferred from ICUs to a weaning center that offers a lower level of care, but a reduction in cost. One study reported a USD 4,832,551 saving in patient care costs by transferring 964 patients from ICUs to the chronic ventilator dependent unit [8].

Some of these patients can be weaned effectively when they are transferred to a weaning center. The weaning rate is about 34-60% after they are transferred [9-12]. Some were discharged with a ventilator-dependent status and some expired. Others experience recurrent respiratory failure after successful weaning. Reinstitution of MV in these patients resulted in an increase in the length of hospital stay and, of course, costs. One study reported 17.3% of 255 patients required an additional period of MV for recurrent ARF after successful weaning [13]. However, the risk factors and outcomes of these patients were not mentioned.

In our hospital, patients were transferred from a respiratory care center (RCC) to an ordinary ward after successful weaning. We also found that some of these patients experienced recurrent respiratory failure and underwent reinstitution of MV. Why do some patients experience recurrent respiratory failure? What are the risk factors? The purpose of this study was to evaluate the risk factors of patients with PMV who experienced recurrent respiratory failure after successful weaning and to evaluate the outcome of these patients.

Materials and Methods

Design

We conducted a retrospective study to identify the risk factors that led to the reinstitution of MV.

Patients and Methods

The RCC at Chang Gung Memorial Hospital is a 20-bed unit designed to care for MV patients that are hemodynamically and metabolically stable. The great majority of patients are from 1 of the hospital's ICUs. Patients were transferred to the RCC if they received MV for 21 days with stable vital signs and fractional inspired oxygen of less than 60%.

Demographic data including age, gender, APACHE II score, and Glasgow Coma Score (GCS) were recorded after the patients were transferred to the RCC. Patients received medical care in the RCC, where weaning parameters were measured twice a week and laboratory tests were measured once a week. Physician-directed weaning was performed according to weaning parameters and clinical condition. Weaning parameters included respiratory rate, tidal volume and rapid shallow breathing index (RSBI). Laboratory tests included hemoglobin, BUN, Cr, and albumin. Patients were transferred to an ordinary ward after they had been successfully weaned. The decision to reinstitute ventilator support was made by a physician in

an ordinary ward. Reasons for MV reinstitution were recorded and categorized into 6 groups. Patients with MV reinstitution were compared to patients without MV reinstitution to identify the risk factors that led to reinstitution of the ventilator.

Causes of ARF and recurrent respiratory failure were classified into the following 6 categories: a) acute lung injury/acute respiratory distress syndrome (ALI/ARDS) from various causes, such as pneumonia, sepsis, and trauma; b) chronic obstructive pulmonary disease (COPD): ARF due to acute exacerbation with bronchospasm in patients with known COPD; c) congestive heart failure (CHF): ARF from CHF with or without pulmonary edema; d) neurologic: ARF in patients with a predominant neuromuscular problem, such as a stroke causing an inability to protect the airway, Guillain-Barre syndrome, severe polyneuropathy of critical illness, a high spinal cord injury, and others; e) cardiac or respiratory arrest: patients who underwent cardiopulmonary resuscitation in the hospital; and f) postoperative: ARF in patients after operation [13-14].

Statistical Analysis

All statistical analyses were performed using the SPSS 14.0 software package (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using the chi-square test or Fisher's exact test where appropriate, and continuous variables were compared using the Student t test or Mann-Whitney U test. Results are presented as an absolute number (percentage) or mean (± standard deviation). A two-tailed p value <0.05 was considered significant. Relative Risk (RR) and 95% confidence interval (CI) were also calculated for qualitative variables in univariate analysis.

Results

From January 1, 2006, through December 31, 2007, 581 patients were admitted to the RCC due to prolonged MV; 314 (54%) were weaned successfully, 97 (17%) expired during RCC admission, and 170 (29%) failed to wean and were transferred to the respiratory care ward with ventilator support. Of the 314 patients, 133 (42.4%) underwent reinstitution of MV due to recurrent respiratory failure, and 181 (57.6%) were discharged without reinstitution of MV. The mean time to reinstitution of MV was 15.1 ± 1.83 days. Sixty-two of the 133 patients that underwent reinstitution of MV expired within 3 weeks, and mortality was 46.6%.

There was no significant difference between the 2 groups in terms of age and coma scale. Ninety-eight of the 314 patients received tracheostomy; 29 of the 98 patients underwent reinstitution of the ventilator and 69 did not, revealing a significant difference between these 2 groups (p<0.005). The risk of reinstitution of MV for patients without tracheostomy was 1.54 times that of patients with tracheostomy (RR=1.54, 95% CI=1.1-2.13) (Table 1). The data regarding weaning parameters is shown in Table 2. There was a significant difference between the 2 groups with regard to causes of respiratory failure (Table 3).

The reasons for reinstitution of MV and the times to reinstitution are shown in Table 4. The majority of patients (60/133) underwent reinstitution of MV due to cardiac and respiratory arrest. Fifty-seven (43%) of the 133 patients received reinstitution of MV within 1 week, 34 (25%) within 8-14 days, 19 (14.3%) within 15-21 days, and 23 (17.3%) underwent reinstitution after 3 weeks. Of the 133 patients that received reinstitution of MV, 78 expired during hospital-

Table1. Demographic data of 314 patients who were successfully weaned from MV in the RCC

	Total (%)	No Reinstitution (%)	Reinstitution (%)	*p* value
Patient numbers	314 (100)	181 (57.6)	133 (42.4)	NS
Male/Female	169/145	96/85	73/60	NS
Age	71.8 ± 14.8	70.4 ± 15.6	73.6 ± 13.6	NS
Coma scale	10 ± 4.2	9.6 ± 4.0	10.4 ± 4.4	NS
Patient source				
Medical ICU	231 (73.6)	133 (73.5)	98 (73.7)	NS
Surgical ICU	83 (26.4)	48 (26.5)	35 (26.3)	NS
Tracheostomy	98 (31.2)	69 (38.1)	29 (21.8)	$p<0.005$
APACHE II Score				
Admission	16.7 ± 4.1	16.5 ± 4.0	17.0 ± 4.3	NS
Time to liberation from MV (days)	13.5 ± 7.4	13.5 ± 7.6	13.4 ± 7.1	NS
Time to reinstitution of MV (days)			15.1 ± 1.83	
Length of hospital stay (days)	82.5 ± 52.9	66.6 ± 36.8	104.1 ± 63.0	$p<0.005$

Values are presented as mean ± SD.

APACHE: acute physiology and chronic health evaluation II score

NS: no significant difference

Table 2. Weaning parameters of 314 patients

	Total	No Reinstitution	Reinstitution	*p* values
Respiratory rate (/mins)				
Admission	26.8 ± 7.4	26.6 ± 7.1	27.1 ± 7.9	NS
Discharge	25.9 ± 7.5	26.2 ± 7.7	25.6 ± 7.3	NS
$P_{Imax\ (cm\ H2O)}$				
Admission	24.4 ± 9.9	24.0 ± 9.0	24.9 ± 9.0	NS
Discharge	27.8 ± 9.0	28.1 ± 8.4	27.4 ± 9.9	NS
$P_{Emax\ (cm\ H2O)}$				
Admission	24.4 ± 11.7	23.5 ± 30.3	25.6 ± 13.1	NS
Discharge	26.1 ± 14.1	26.0 ± 12.5	26.3 ± 16.1	NS
Tidal volume (ml)				
Admission	257.7 ± 101.6	262.3 ± 103.5	251.4 ± 99.7	NS
Discharge	269.2 ± 107.4	272.9 ± 100.4	264.1 ± 116.4	NS
RSBI				
Admission	121.4 ± 62.1	117.4 ± 57.8	126.9 ± 67.3	NS
Discharge	116.5 ± 62.9	114.2 ± 61.2	119.7 ± 65.4	NS

Values are presented as mean ± SD.

RSBI: Rapid shallow breathing index

NS: no significant difference

Table 3. The cause of acute respiratory failure in PMV patients with and without reinstitution of MV

Disease group	Total (%)	No Reinstitution (%)	Reinstitution (%)	*p* value
CHF	86 (27.4)	32 (17.7)	54 (40.6)	
Post-operation	65 (20.7)	45 (24.9)	20 (15)	
ARDS/ALI	65 (20.7)	40 (22.1)	25 (18.8)	
Respiratory arrest & cardiac arrest	35 (11.1)	19 (10.5)	16 (12)	
Neurological	33 (10.5)	25 (13.8)	8 (6)	
COPD	30 (9.6)	20 (11)	10 (7.5)	
Total	314 (100)	181 (58)	133 (42)	$p<0.05$

CHF: congestive heart failure by Chi square

ARDS/ALI: Acute lung injury/acute respiratory distress syndrome

COPD: chronic obstructive pulmonary disease

Table 4. Reasons for reinstitution of MV and time to reinstitution

Causes of reinstitution	Time to reinstitution of MV				
	≤7 days	8~14 days	15~21 days	>21 days	Patient numbers (%)
Cardiac and respiratory arrest	29	15	10	6	60 (45.1)
CHF	13	11	5	8	37 (27.8)
Pneumonia /Sepsis	7	5	4	6	22 (16.5)
COPD	6	3	0	3	12 (9)
Neurologic disorder	2	0	0	0	2 (1.5)
Total	57	34	19	23	133

CHF: congestive heart failure

COPD: chronic obstructive pulmonary disease

ization.

Discussion

Tracheostomy is thought to have many benefits over prolonged translaryngeal intubation, including a lower risk of laryngeal injury, and a decrease in the work of breathing, the pressure-time product, airway resistance, peak inspiratory pressure, and intrinsic positive end-expiratory pressure (i.e., auto-PEEP), all of which facilitate weaning from MV [15-16], improve patient comfort, and facilitate airway hygiene. In our study, 29 of 133 patients that received tracheostomy underwent a reinstitution of MV (21.8%). There was a significant difference between the patients that received tracheostomy and those that did not. The risk of reinstitution of MV for patients without tracheostomy was 1.54 times that of patients with tracheostomy. Therefore, we can suppose that tracheostomy is important and lowers the incidence of MV reinstitution in PMV patients after successful weaning. This is possibly due to the improvement in bronchial hygiene of patients with tracheostomy. We also noted that 170 (29%) of 581 patients were ventilator-dependent and 100 (58.8%) of 170 ventilator-dependent patients received tracheostomy in our hospital. About 44.1% (70/170) of these patients did not un-

dergo tracheostomy. The incidence of ventilator dependence may be reduced if we enhance the use of trachestomy.

Of 255 reported patients, 17.3% required an additional period of MV for recurrent ARF after successful weaning [17]. In our series, 133 (42.3%) of 314 patients experienced recurrent respiratory failure and received reinstitution of MV. The incidence of MV reinstitution, therefore, was higher in our series. In the report cited above, 112 of 383 patients were placed on PMV due to postoperative respiratory failure. This PMV rate is higher than in our series and may be the reason why the incidence of reinstitution of MV was higher in our series.

In another report of 250 patients with a minimum of 10 days of ventilator support, the patients with postoperative or neurologic disease as the cause of respiratory failure were found to have the highest survival rate, and those with cardiac and/or pulmonary disease had the worst prognosis [18]. We had similar results in our series.

Maximum inspiratory pressure decreases with age -- but does age have an important effect on the outcome of patients with MV? This issue has been debated in several reports [19-21]. Weaning parameters, especially RSBI, have been proposed to identify patients ready for weaning. However, many patients with an RSBI less than 100 cannot pass a spontaneous breathing trial. Forty-two of 289 intubated patients in another report required reintubation for failed extubation. A comparison of the weaning parameters of patients who failed extubation and patients who were successfully extubated showed no significant difference in tidal volume, P_{Imax}, RSBI and respiratory rate [22]. Since the weaning parameters did not show a significant difference between the 2 groups, we may conclude that they cannot differentiate patients who need reinstitution of MV from those who do not.

There are a number of important limitations in our study. First, this was a retrospective review of all patients transferred to a single unit within a 2-year period. The unit was hospital-based; hence, size and staff may differ from non-hospital-based units. There was also a lack of the contemporaneous control data. Control for confounding factors was limited to those factors that were recognized and measured, and adjustment for unknown factors was not possible. In addition, both the time to liberation from MV and the length of hospital stay in the group with MV reinstitution was increased, possible due to the aggravation of underlying disease (including malignancy, CHF, and acute kidney injury). Further prospective study is needed for identification of the predisposing risks factors.

Conclusions

Tracheostomy can reduce the incidence of MV reinstitution in patients with successful weaning from the ventilator, and is important in patients with PMV. ARF due to CHF is a risk factor that increases the incidence of MV reinstitution after successful weaning. The prognosis of patients with reinstitution of MV is poor.

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長期機械通氣病人在成功脫離呼吸器後再放置呼吸器的危險因子及預後

陳泓丞 * 林孟志 *,** 林安伸 * 王金洲 * 王逸熙 *,**

背景及方法：長期機械通氣（PMV）的病人常造成家屬和醫療資源一大負擔。這其中一些病人能成功脫離出院，但也有些人重覆發生呼吸衰竭並再使用呼吸器。本文目的在要找出在成功脫離呼吸器患者中再放置呼吸器的危險因素。高雄長庚紀念醫院呼吸照護中心（RCC）在 2006 到 2007 年內有 314 例成功脫離呼吸器。回顧病歷中的年齡，性別，急性生理及慢性健康評估Ⅱ評分（APACHE II 評分），格拉斯哥昏迷評分（GCS），導致急性呼吸衰竭（ARF）原因和脫離呼吸器相關參數，包括呼吸頻率，潮氣量和淺快呼吸指數（RSBI）。研究觀察期從病人入住 RCC 開始至病人出院為止。

結果：314 例中有 133 例（42.4%）因反覆呼吸衰竭再度接受機械通氣。181（57.6%）於出院時無使用機械通氣。這兩組之間在年齡，性別，APACH II 評分和相關脫離呼吸參數並沒有顯著差異。脫離呼吸器期間無氣管切開患者（p 值 <0.05）則再放置呼吸器的發生率是增加的。17% 長期機械通氣（PMV）的病人在住院期間死亡，133 例在接受重置呼吸器患者中有 78 位（58.7%）在住院期間死亡。

結論：病人成功脫離呼吸器的患者中，無接受氣管切開術患者和急性呼吸衰竭原因是充血性心臟衰竭皆是重置呼吸器的危險因素。再放置呼吸器患者的預後是不佳的。*(胸腔醫學* ***2012; 27: 209-216)***

關鍵詞：長期機械通氣，再放置呼吸器

* 長庚紀念醫院高雄醫學中心　內科部　呼吸胸腔科及呼吸治療科，** 長庚技術學院嘉義分部　呼吸治療系
索取抽印本請聯絡：王逸熙醫師，高雄長庚紀念醫院　內科部　胸腔科，高雄市鳥松區大埤路 123 號

Gastric Metastasis as the First Sign of Tumor Recurrence after Lung Cancer Resection — Case Report

Wei-Min Tsai, Jiunn-Min Shieh, Shian-Chin Ko

Although distant dissemination is commonly encountered in patients with lung cancer, gastrointestinal metastasis is rarely diagnosed in clinical practice. Recent reports suggest that gastrointestinal metastasis of lung cancer may be more frequent than previously thought, because it is rarely symptomatic. When present, the symptoms related to gastrointestinal metastasis are not specific and the diagnosis is often delayed. However, gastrointestinal metastasis can cause life-threatening complications such as massive hemorrhage, intestinal obstruction or perforation of the hollow organ, which necessitate surgical intervention. Computed tomography (CT) may be helpful for the diagnosis of gastrointestinal metastasis, but the definite diagnosis is dependent on endoscopic or surgical biopsy. The existence of gastrointestinal metastasis is an important marker of advanced disease, which indicates a poor prognosis. We present a case of gastric metastasis of lung cancer, which presented as the first sign of tumor recurrence after a lobectomy that was performed more than 3 years before. Clinicians should take gastrointestinal metastasis into consideration when there are unexplained gastrointestinal symptoms, such as those not associated with chemotherapy or radiotherapy, in patients with lung cancer. ***(Thorac Med 2012; 27: 217-222)***

Key words: gastrointestinal metastasis, lung cancer

Introduction

Lung cancer is one of the leading causes of cancer death worldwide. The prognosis of lung cancer is generally poor because the disease is often advanced due to extensive local invasion or distant dissemination at the time of initial diagnosis. Approximately 1/2 of patients with lung cancer have distant metastases at presentation [1]. The common sites of metastasis include bone, brain, liver, adrenal glands and collateral lung.

Gastrointestinal metastasis is rarely encountered in patients with lung cancer in clinical practice. Since patients with gastrointestinal metastasis seldom have symptoms related to the gastrointestinal system, it is rarely diagnosed during the patient's lifetime. However, it was reported that up to 11.9% of patients that died of lung cancer had gastrointestinal metas-

Division of Chest Medicine, Department of Internal Medicine, Chi Mei Medical Center, Tainan City, Taiwan
Address reprint requests to: Dr. Shian-Chin Ko, Division of Chest Medicine, Department of Internal Medicine, Chi Mei Medical Center, No.901, Zhonghua Rd., Yongkang Dist., Tainan City 710, Taiwan (R.O.C.)

tases confirmed by autopsy [2]. Lung cancer with gastrointestinal metastasis may be more frequent than previously thought. We report a rare case of gastric metastasis developing after surgical resection of lung cancer and review the associated literature.

Case Report

A 67-year-old man, a heavy smoker of 45 packs per year, initially presented to our hospital in July 2006 with the chief complaint of chronic cough. Chest radiography and computed tomography (CT) showed a cavitary lung tumor in the right upper lobe. The patient underwent lobectomy and regional lymph node dissection. The resected tumor was 3.0 × 2.5 × 2.5 cm at the greatest diameter. Histological examination showed squamous cell carcinoma with hilar lymph node metastasis in 1 location. The pathological stage was pT1N1M0, stage IIA.

Two months after the operation, the patient received adjuvant radiotherapy of 6,120 cGy to the mediastinum. However, severe bilateral radiation pneumonitis developed immediately after mediastinal irradiation. The radiation-induced lung injury was controlled successfully with systemic corticosteroid, but severe fibrosis and volume reduction in the right upper lung field were the significant sequelae. After radiotherapy, the patient was regularly followed at outpatient clinics and led a disease-free life for more than 3 years.

Three years and 4 months after the operation, the patient began to suffer from anorexia and intermittent epigastric dull pain. Melena and body weight loss were also noted thereafter. He was admitted for detailed investigation. Occult blood was found in the stool. The hemoglobin level decreased from 10.3 to 7.9 g/dL in 2 weeks. Localized gastric wall thickening in the lesser curvature of the stomach was found incidentally on the follow-up chest CT images (Figure 1). Under the impression of peptic ulcers with hemorrhage, he underwent esophagogastroduodenoscopy (EGD). EGD showed an irregular volcano-like ulcer, about 1 cm in size, with an elevated margin at the lesser curvature of the stomach. The ulcerative base was coated with a heaped-up coffee ground-like substance. Multiple tiny ulcers were also noted at the duodenal bulb. Endoscopic biopsy of the gastric ulcer showed squamous cell carcinoma (Figure 2). In the immuno¬histochemical analysis, the tumor cells expressed CK5/6 and P63, but not CK7 or CK20, a phenotype similar to that of the specimen taken by lobectomy 3 years before. These findings indicated a metastatic squamous cell carcinoma from the lung rather than a primary gastric cancer.

After distant metastasis was diagnosed, the patient received 6 courses of systemic palliative chemotherapy with cisplatin 60 mg/M^2 and docetaxel 60 mg/M^2 every 3 weeks. However,

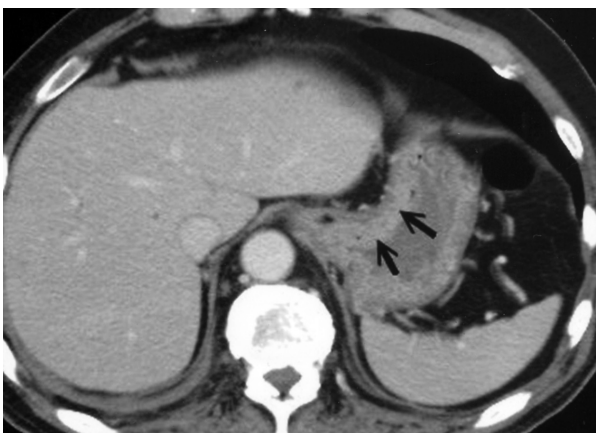

Fig. 1. CT scan: More than 3 years after tumor resection, the CT scan showed gastric wall thickening in the lesser curvature of the stomach (black arrows).

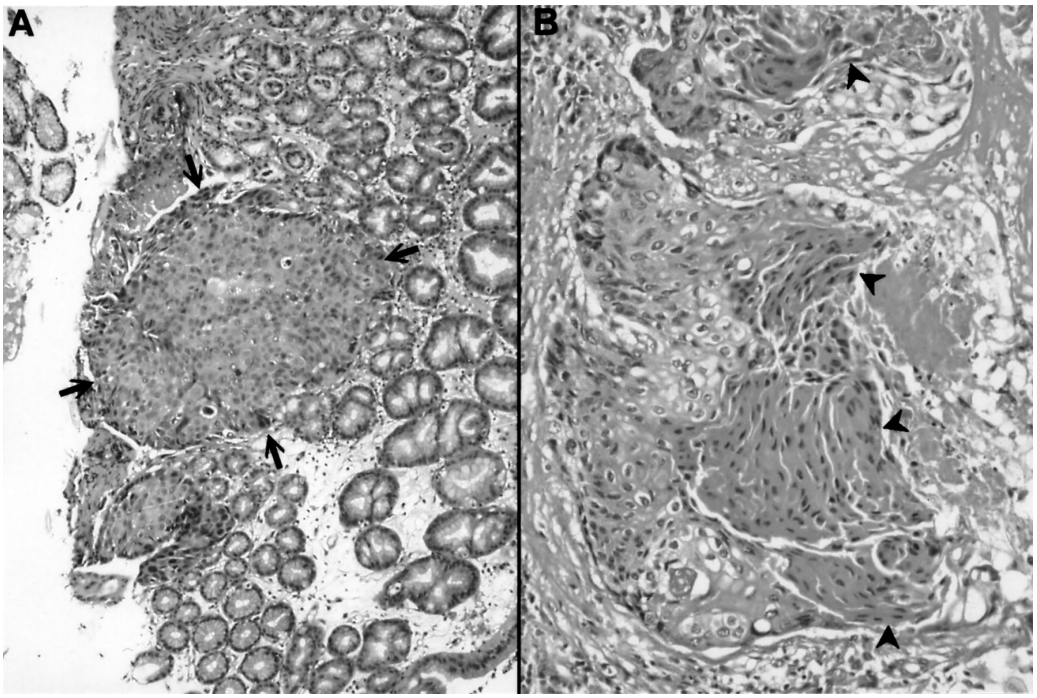

Fig. 2. Microscopic photograph: (A) There were several small tumor nests (black arrows) within the submucosa of a gastric mucosal fragment. The tumor cells were polygonal and had pink cytoplasm. (hematoxylin & eosin stain, x100); (B) The tumor cells were cohesive with eosinophilic cytoplasm and focal dyskeratosis (arrowheads) compatible with squamous cell carcinoma. (hematoxylin & eosin stain, x400)

another tumor developed in the left upper lobe during chemotherapy. The patient succumbed to lung abscess in the left upper lobe and sepsis 4 years and 7 months after lung cancer resection.

Discussion

Although distant metastases are frequently found in patients with lung cancer, gastrointestinal metastases are rarely diagnosed during the patient's lifetime. Most cases are detected at autopsy because they are rarely symptomatic [3]. Gastrointestinal metastases of lung cancer may be more common than previously thought. Yoshimoto *et al*. found that 11.9% of patients that died of lung cancer had gastrointestinal metastases detected by autopsy [2]. The most common site of gastrointestinal metastasis of lung cancer is the small intestine, followed by the stomach and the large intestine.

Hematogenous metastases to the gastrointestinal system are generally situated in the submucosa. Unless the tumor causes mucosal ulceration with hemorrhage, mechanical obstruction of the lumen, or involvement of the full thickness of the gastrointestinal wall eventually leading to perforation, it seldom evokes symptoms [4]. Symptoms of metastatic gastric tumors, including dyspepsia, nausea/vomiting, anemia or bleeding, abdominal pain, obstructive ileus, and perforation with peritonitis, are nonspecific. Lung cancer, breast cancer and melanoma are the most common primary cancers that metastasize to the stomach [5]. Gastrointestinal symptoms may be the first presentation of advanced lung cancer in a patient [6].

Moreover, the site of gastric metastasis may perforate during systemic chemotherapy due to tumor necrosis [7].

Gastrointestinal metastases of lung cancer remain under-diagnosed because most patients have no specific symptoms. Physicians do not suspect gastrointestinal metastases unless the patient has symptoms referable to the gastrointestinal system. Furthermore, gastrointestinal symptoms, such as nausea and vomiting, are usually regarded as constitutional symptoms of lung cancer, side effects of chemotherapy or an indication of central nervous system involvement. In our case, the gastrointestinal symptoms were poor appetite, abdominal pain and hemorrhage. These symptoms were easily mistaken for peptic ulcer.

According to Berger *et al*. [8] and Kim *et al*. [9], squamous cell carcinoma is the most common cell type in gastrointestinal metastasis of lung cancer, as in our reported case. However, Yoshimoto *et al*. found the histological type of large cell carcinoma predicted a significant 3.5-fold increase in the rate of gastrointestinal metastasis compared with other histological types [2].

On CT scan, gastrointestinal metastasis of lung cancer manifests itself as an intraluminal polypoid mass or wall thickening with regional lymphadenopathy [9]. Endoscopic biopsy or surgical resection is the gold standard for the diagnosis of gastric metastases. The macroscopic features observed with endoscopy vary considerably and are not specific for metastatic disease [10]. The endoscopic findings mainly include small nodules with or without central ulceration, bull's eye, polypoid mass, extrinsic mass lesions and ulcers. Solitary metastases are more common than multiple ones [5]. It should be emphasized that the endoscopist should provide the pathologist with sufficient information about the patient's history to allow an accurate pathological diagnosis.

In the study of De Palma *et al*. more than half of the gastric metastatic tumors were found within a year of the diagnosis of a primary tumor (not restricted to lung cancer) [5]. In the present case, the time interval between the diagnoses of lung cancer and gastric metastasis was much longer. The incidence of distant metastasis increases along with the increased survival of the cancer patient.

Because gastrointestinal obstruction or perforation caused by metastatic tumors is life-threatening, aggressive investigation and early surgery are the only methods for providing palliation to these patients [11]. Gastrointestinal tract metastases should always be considered in the differential diagnosis of lung cancer patients presenting with an acute abdomen. Surgical intervention is sometimes indicated to control bleeding or to avoid stenosis [12]. Aggressive surgical treatment is worthwhile in a selected group of patients, as it provides effective palliation [13]. Otherwise, systemic chemotherapy may be an effective treatment for gastrointestinal metastatic lesions [14].

The prognosis of gastrointestinal metastasis is poor because it is usually a part of an otherwise widespread metastatic disease [15]. The existence of gastric metastasis is an important marker of advanced disease. In the study by De Palma *et al*. gastro¬intestinal metastases occurred in more than 20% of patients that had adrenal gland, kidney, and abdominal lymph node metastases [5]. Campoli *et al*. showed that half of the patients with gastrointestinal metastasis had concomitant metastases to other organs [10]. In the present case, lung-to-lung metastasis finally developed after systemic pal-

liative chemotherapy.

Conclusion

We have presented herein a case of gastric metastasis of lung cancer more than 3 years after surgical tumor resection. To the best of our knowledge, there has been no report on gastrointestinal metastasis as the first sign of tumor recurrence after lung cancer resection. Gastrointestinal metastases will be encountered more often, as the incidence of lung cancer increases and patients with lung cancer live longer because of the advances in chemotherapy, targeted therapy and supportive care. Physicians should take gastrointestinal metastasis into consideration if gastrointestinal symptoms develop after initial treatment.

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胃轉移成爲肺癌術後復發的首癥：病例報告

蔡為民　謝俊民　柯獻欽

雖然肺癌常常發生遠處轉移，臨床上卻少見轉移到胃腸道。新近報告顯示：肺癌併胃腸轉移並非罕見，而是此類病人常常沒有症狀。即使發生症狀，也常是腹痛、出血、消化不良…等非特異症狀，故常延遲診斷。但胃腸轉移也可能發生致命的併發症，如：大量出血、腸道阻塞、胃腸破裂，此時就需外科緊急介入治療。在診斷方面，電腦斷層可能有些幫助，但確切的診斷有賴於內視鏡切片生檢或外科手術探查。一旦發生胃腸轉移表示進入肺癌晚期，預後極差。吾等報告一位鱗狀細胞肺癌病患，在接受肺葉切除與輔助性放射線治療三年多後，因腹痛與胃腸出血接受胃鏡檢查，卻發現肺癌併胃轉移，爾後雖歷經化學治療，仍發生對側肺轉移，最後死於肺膿瘍併發敗血症。胃腸轉移雖不常見於肺癌病人，但若出現與治療無關的胃腸症狀，仍須將此病症列入鑑別診斷。*(胸腔醫學* ***2012; 27: 217-222)***

關鍵詞：胃腸轉移，肺癌

奇美醫療財團法人奇美醫院　胸腔內科
索取抽印本請聯絡：柯獻欽醫師，奇美醫療財團法人奇美醫院　胸腔內科　710 台南市永康區中華路 901 號

Myelolipoma of the Chest Wall: A Case Report and Literature Review

Chia-Chen Hsieh, Hsiang-Lin Sung*, Han-Yu Chang

Myelolipomas are rare neoplasms composed of normal hematopoietic cells and mature adipose tissue. They usually occurr in the adrenal gland, although they have been reported to occur in the liver, stomach, mesentery, spleen, retroperitoneum, presacral area, leptomeninges and thorax in the previous literature. We present an unusual case of extraadrenal myelolipoma arising from the chest wall. The patient underwent tumor excision through video-asisted thoracoscpic surgery, and the pathology revealed myelolipoma. We also reviewed the literature concerning the clinical manifestations diagnosis, treatment and prognosis of myelolipoma. ***(Thorac Med 2012; 27: 223-227)***

Key words: myelolipoma, chest wall tumor

Introduction

Myelolipoma is a rare mesenchymal tumor composed of normal hematopoietic cells and mature adipose tissue. It is a rare, benign neoplasm, usually with an asymptomatic course. It was first described by Gierke in 1905 and named by Oberling in 1929 [1]. The most common location is the adrenal gland, but extra-adrenal lesions have also been reported in the retroperitoneum, stomach, liver, mediastinum, bilateral paravertebral sulci, lung, and presacral, perirenal, and thoracic spinal areas. There is no characteristic finding leading to a preoperative diagnosis of extra-adrenal myelolipoma, but these tumors are usually single, well-circumscribed and encapsulated, and are most commonly seen in middle-aged and elderly persons [2].

Case Presentation

A 71-year-old man, a nonsmoker, had a dry cough for many years. He had had no fever, no recent body weight loss, and no chest discomfort in recent months. He was transferred from the Chest Hospital, Department of Health, Executive Yuan because of the accidental finding of a mass in the right upper lung field (Figure 1). The physical examination was unremarkable, there were no palpable lesions on the chest wall and the breathing sound was clear. The

Division of Pulmonary Medicine, Department of Internal Medicine, Department of Pathology*, National Cheng Kung University Hospital, National Chen Kung University Hospital, Tainan, Taiwan
Address reprint requests to: Dr. Han-Yu Chang, Division of Pulmonary Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, No. 138, Sheng-Li Rd., Tainan 704, Taiwan

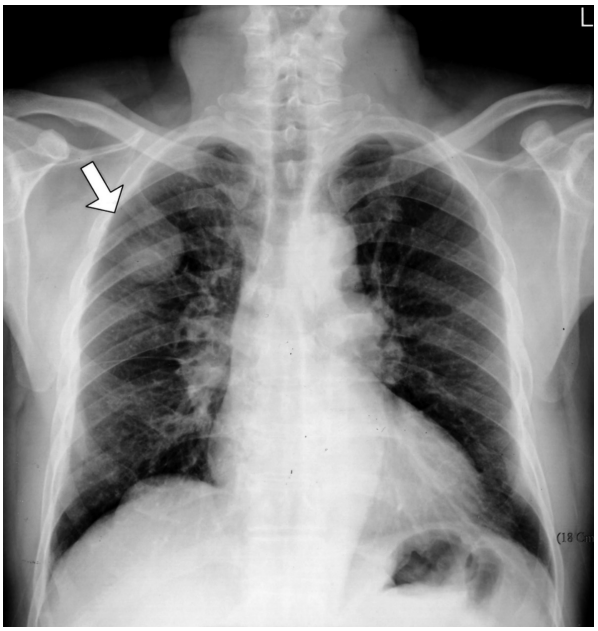

Fig. 1. Chest roentgenogram shows a right upper lung field extrapulmonary lesion (indicated by white arrows), with homogenous density

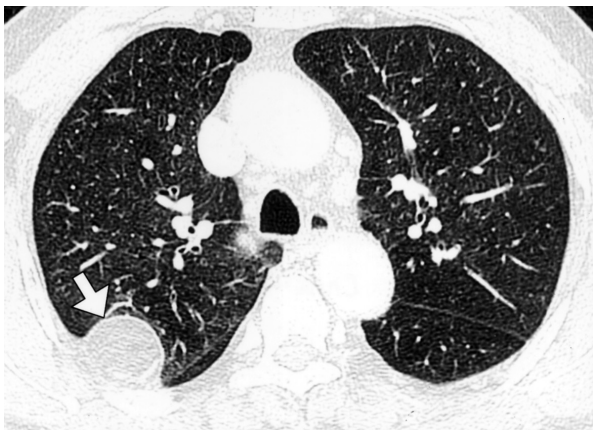

Fig. 2. Computed tomographic scan (lung window) shows smooth, a well demarcated subpleural nodule arising from the intercostal space of the chest wall

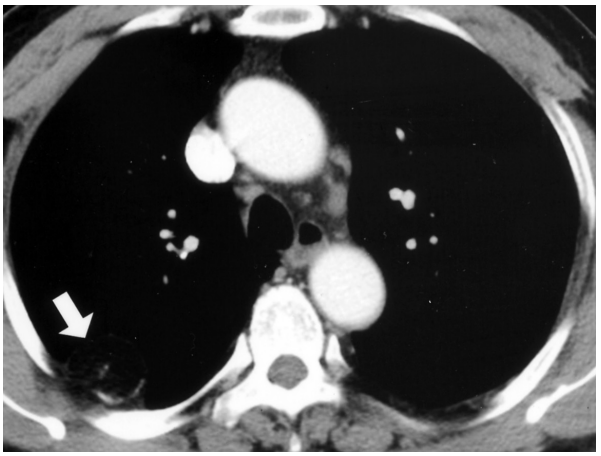

Fig. 3. Computed tomographic scan (mediastinum window, contrast phase) reveals the lesion is hypodense in nature with calcified capsule

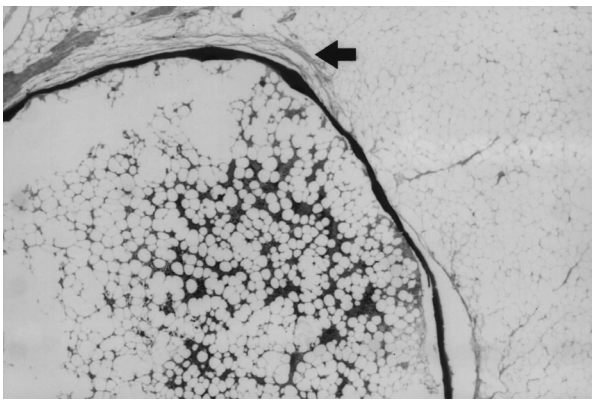

Fig. 4. The tumor composed of lobules of mature adipose tissue with fibrous band (blue arrow) (2×10)

complete blood count was within normal range, and there was no leukocytosis or anemia. The chest computed tomography (CT) (Figure 2&3) showed a fat-containing chest wall mass and the video-assisted thoracoscopic surgery was arranged. At surgery, an oval-shaped, yellowish-brown, well-circumscribed mass (size: 3.5 × 3 × 3 cm) arising from the intercostal space with a stalk to the intercostal space was noted, and excision of the mass was performed. The patient had an uneventful postoperative course.

The microscopic findings of this tumor include lobules of mature adipose tissue with fibrous bands, and several small nodules composed of hematopoietic precursor cells (in-

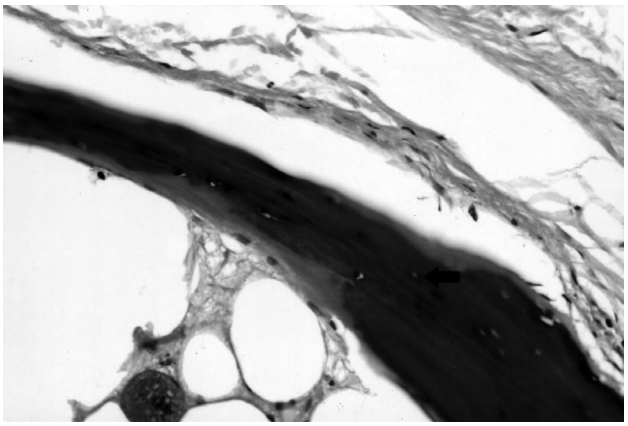
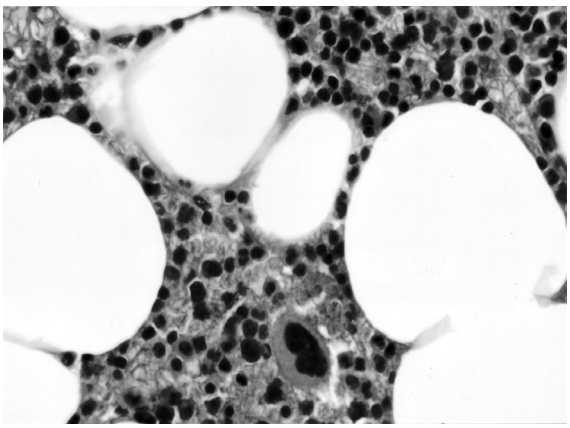

Fig. 5 & 6. The nodule is composed of bony ring with osteoblast (blue arrow). The central component reveal adipocytes and hematopoietic part. The hematopoietic cells including erythropoietic, granulopoietic, and megakaryocytic cell lineages. (40×10)

cluding myeloid and erythroid series, and also megakaryocytes) and mature fat, encircled by a calcified capsule, compatible with myelolipoma (Figure 4-6).

Discussion

Myelolipoma is a rare benign neoplasm usually presenting as a small, solitary encapsulated lesion, and the patients are usually asymptomatic. The locations of thoracic myelolipomas include the lung, mediastinum and chest wall, and the incidence of thoracic myelolipoma is about 3%, mostly in the posterior mediastinum [3]. The major differential diagnoses of myelolipoma include schwannoma, neurofibroma, angiolipoma, epidural lipomatosis, and teratoma.

On computer tomography, the myelolipoma had large component of fat with area of intersperad higher-attenuation tissue [4]. On ultrasonography, it shows heterogenous echogenicity [5]. On magnetic resonance imaging, due to myelolipoma usually mixture fat and marrow components, on T1-weighted images, the fat component is hyperintensity, and on T2-weighted images, it show heterogeneously hyperintensity [6]. Besides, the nuclear medicine may be contributed. The bone marrow scintigraphy can reveal bone marrow component of the mass and is helpful to differentiated myelolipoma from other lipid containing soft tissue tumors [7].

Myelolipoma is microscopically similar process to extramedullary hematopoiesis (EMH), and it is difficult to differentiate myelolipoma form EMH by image study, and even by fine needle aspiration [8]. However, compare with EMH, myelolipoma usually lacks of evidence of a background hematologic disorder [2]. EMH usually occurs as a myeloproliferative disease or is a compensatory phenomenon in various chronic anemia. Therefore, the patients with EMH usually presented with background hematologic disorders. Besides, The EMH usually develops in the liver and spleen, but rarely arises in the lung [9-11], and the myelolipoma usually developed in adrenal gland. The major histological characteristics of EMH are haematopoietic cells and erythroid hyperplasia, while in myelolipoma, the adipose tissue is the major component. The EMH is usually bilateral lesions, but in contrast, myelolipoma is most often found as a solitary tumor.

The myelolipoma is usually found incidentally, and the diagnosis is confirmed by surgical resection of the tumor or autopsy, the presence of megakaryocytes is essential for the diagnosis [12]. Preoperative diagnosis by transbronchial biopsy is difficult [11]. The treatment was surgical resection and adjuvant therapy is not needed because neither recurrence nor malignant transformation has been reported.

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胸廓骨髓脂肪瘤：病例報告及文獻回顧

謝佳珍　宋湘琳 *　張漢煜

骨髓脂肪瘤是一種罕見的腫瘤，腫瘤細胞包含有正常的造血幹細胞以及成熟的脂肪組織，至目前文獻記載，沒有轉為惡性腫瘤的病例。一般發生的位置以腎上腺最為常見，發生在胸腔的病例十分稀少。在過去的文獻中，生長在胸腔的骨髓脂肪瘤位置，包含肺部內、縱膈腔內、及胸壁上。我們在此報告一個罕見病例：一位七十一歲男性，主訴有多年的慢性咳嗽，因為胸部 X 光片發現右上肺野疑似有肺外腫瘤，而胸部電腦斷層檢查確認為後胸壁上的腫瘤，轉診至胸腔外科接受手術。經影像輔助式胸腔鏡手術切除腫瘤後，由病理檢查確定為胸壁上的骨髓脂肪瘤

在這一篇報告裡，我們也回顧了一些文章，說明關於發生在胸腔的骨髓脂肪瘤的臨床表現，病理特徵，診斷方式及預後。*(胸腔醫學* ***2012; 27: 223-227)***

關鍵詞：骨髓脂肪瘤，胸廓腫瘤

成功大學附設醫院　內科部　胸腔內科，* 成功大學附設醫院　病理部
索取抽印本請聯絡：張漢煜醫師，成功大學附設醫院　內科部　胸腔內科，704 台南市北區勝利路 138 號

Pulmonary Sarcomatoid Carcinoma in a Patient with Systemic Sclerosis Presenting as a Rapid-Growing Mass – A Case Report

Wen-Ren Lin*, Kuo-An Chu*,**, Min-Hsi Lin*, Shieh-Yi Shen*, Hui-Hwa Tseng***, Ruay-Sheng Lai*,**

Malignancy is found in up to 10% of patients with systemic sclerosis, and has included pulmonary, breast, gastrointestinal, hematopoietic, lymphoid, and other types. Lung cancer is the most frequent type of cancer in patients with systemic sclerosis, followed by breast cancer. Pulmonary sarcomatoid carcinoma is a rare subtype of lung cancer and generally has an aggressive clinical course and limited response to systemic chemotherapy regimens for conventional non-small cell lung cancer. The clinicopathological characteristics of the disease remain unclear. We report the case of a 59-year-old woman who had systemic sclerosis for 10 years and was diagnosed with pulmonary sarcomatoid carcinoma presenting with a rapid-growing lung mass. Due to the rapidly worsening performance status, systemic chemotherapy was not administered and the patient was treated with erlotinib. The patient expired about 1 month after diagnosis. ***(Thorac Med 2012; 27: 228-234)***

Key words: lung cancer, sarcomatoid carcinoma, systemic sclerosis

Introduction

There is an increased risk of malignancy in patients with systemic sclerosis; up to 10% of these patients have been found to have malignancy [1]. Risk factors for malignancy include female gender, increasing age, and the presence of diffuse systemic sclerosis. Lung cancer has the greatest likelihood of becoming a malignancy in patients with systemic sclerosis, particularly those with longstanding pulmonary involvement. Sarcomatoid carcinoma is rare; its incidence has ranged from 0.3% to 1.3% of all lung malignancies in some reports [2-3, 5]. It is defined as poorly differentiated adenocarcinoma, squamous cell carcinoma, or large cell carcinoma containing spindle cells and/or giant cells, or a carcinoma consisting of spindle and giant cells alone, with a sarcomatoid tumor component of at least 10% [2-4]. Some reports have stated that pulmonary sarcomatoid carcinoma is generally more aggressive clinically

*Division of Chest Medicine, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; **National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.; ***Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
Address reprint requests to: Dr. Kuo-An Chu, Division of Chest Medicine, Department of Internal Medicine, Kaohsiung Veterans General Hospital, No. 386, Ta-Chung 1st Road, Kaohsiung 813, Taiwan

than other non-small cell lung cancers (NSCLC) [2-3]. We report herein a case of sarcomatoid carcinoma of the lung in a patient with systemic sclerosis with lung involvement, presenting as a rapid-growing lung mass with multiple metastases, and a fatal outcome.

Case Report

A 59-year-old female had been diagnosed with systemic sclerosis with lung involvement about 10 years prior to admission, with the initial presentation of perioral numbness, swollen digits, sclerodactyly, positive anti-RNP antibody and bibasilar fibrosis on chest radiography. She had undergone cyclophosphamide pulse therapy for scleroderma with lung involvement about 4 years earlier. Her pulmonary function test performed 1 year before presentation showed mildly restrictive ventilatory impairment, forced vital capacity (FVC): 1.95 liter, forced expiratory volume in 1 second (FEV_1): 1.51 liter, and FEV_1/FVC: 77%. She had never smoked. She could still do her shopping and cooking, but had occasional mild dyspnea on exertion after walking 2 to 3 blocks, until 1 month before this admission.

The patient first presented with productive cough and occasional blood-streaked sputum about 2 months before admission. Chest radiography taken at that time showed interstitial infiltration at the bilateral lower lungs, and no interval change compared with the prior exam. There was no lung mass at that time (Figure 1). The results of microbiological and cytological examination of the sputum were negative. Mucolytics were prescribed, but with no improvement. One day before admission, the patient had worsening shortness of breath and right chest wall pain. On examination, body temperature was 37.7°C, pulse 95 beats per minute, blood pressure 150/83 mmHg, and respiratory rate 20 breaths per minute. Her peripheral oxygen saturation by pulse oximetry was 98% in room air. The hemogram showed a white blood cell count (WBC) of 7,110/μL, with neutrophils at 67% and lymphocytes at 22%. Chest radiography at presentation revealed right lower lung patchy consolidation (Figure 2). Antibiotics were prescribed for suspected right lower lung pneumonia. The special stains of the sputum for microorganisms and cultures were negative, but her dyspnea and chest discomfort persisted. Chest computed tomography (CT) revealed right lower lobe consolidation with pleural effusion (Figure 3). Bronchoscopy examination revealed no endobronchial lesion. The CT of the brain, mammogram, and whole body bone scan were negative for malignancy. The position emission tomography (PET) scan revealed a large pleura-based mass in the right

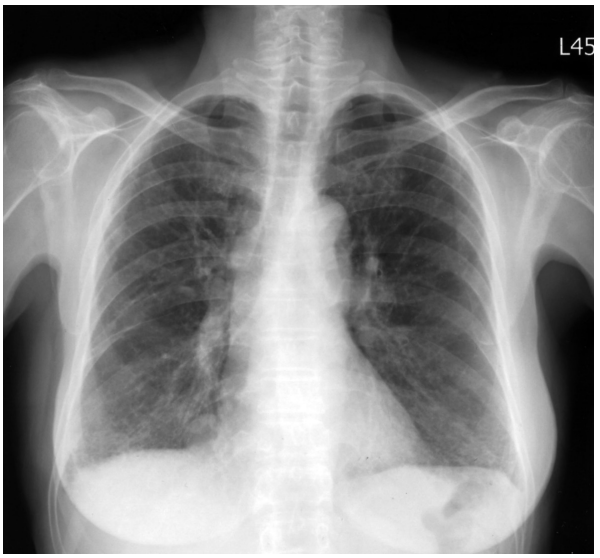

Fig. 1. Anteroposterior chest X-ray, about 2 months before the first admission, showing emphysematous change in both lung fields and interstitial infiltration in the bilateral lungs, compatible with interstitial lung disease.

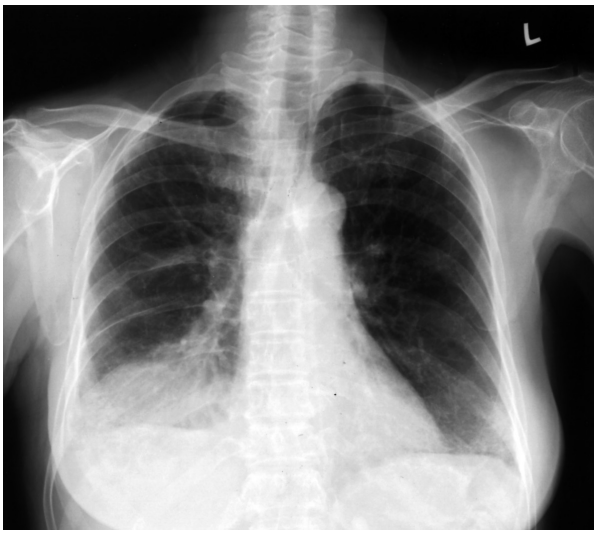

Fig. 2. Chest radiography just before this admission showed a patchy opacity at the right lower lobe.

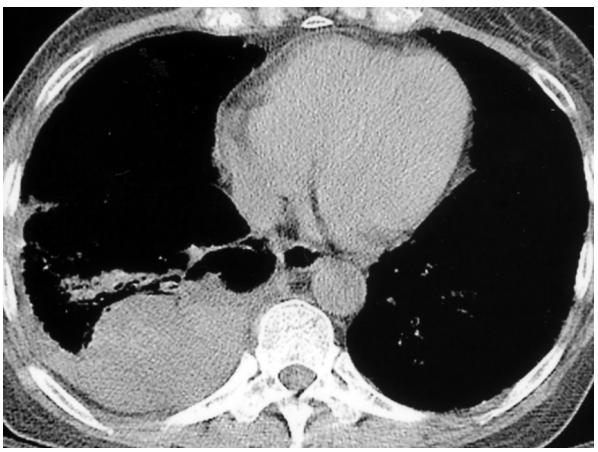

Fig. 3. Chest CT revealed a right lower lobe consolidation, with a longest diameter of about 9 cm.

lower lobe, about 9 cm at its largest dimension, which showed uneven moderate FDG uptake (SUV_{max}: 4.3-4.9) and multiple lymph nodes with moderate-to-hot FDG uptake in the right pulmonary hilum and bilateral lower paratracheal spaces (SUV_{max}: 5.8-7.9). The aspirated pleural effusion was bloody. Cytological examination of the pleural effusion revealed atypical cells, favoring adenocarcinoma. CT-guided biopsy of the right lower lung mass was then performed. Histological analysis of the specimens (Figure 4A, 4B) showed a picture of sarcomatoid carcinoma, consisting of a few clusters of moderately differentiated neoplastic cells in a glandular pattern closely intermingled with a spindle cell carcinomatous component.

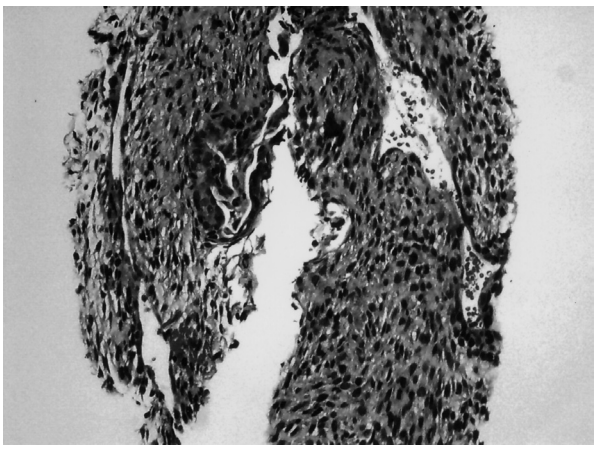

Fig. 4A. (H&E stain X 20) The specimen was obtained from CT-guided biopsy of the lung, which showed a picture of sarcomatoid carcinoma, consisting of a few clusters of moderately differentiated neoplastic cells in a glandular pattern closely intermingled with a spindle cell carcinomatous component.

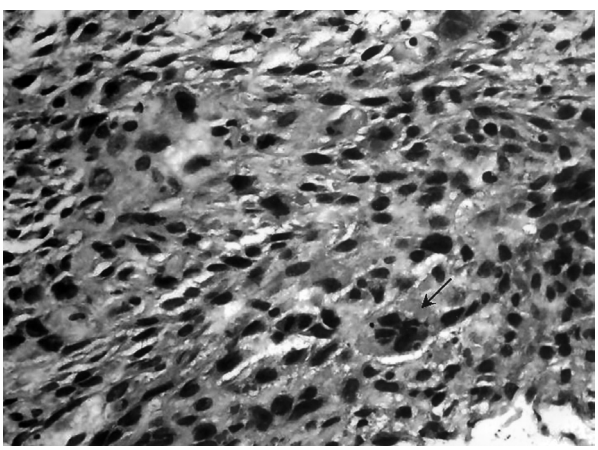

Fig. 4B. (H&E stain X 40) The sections show a picture of sarcomatoid carcinoma, consisting of a few clusters of moderately differentiated neoplastic cells in a glandular pattern closely intermingled with a spindle cell carcinomatous component. A giant cell in the background of the spindle cells was seen in this section (arrow).

So the diagnosis was sarcomatoid carcinoma of the lung with right malignant pleural effusion. Due to the rapidly worsening performance status, from Eastern Cooperative Oncology Group (ECOG) 0 to ECOG 3, systemic intravenous chemotherapy was not indicated at that time. A mutations assay study of epidermal growth factor receptor (EGFR) gene exons 18, 19, 20 and 21 was performed at patient request using DNA direct sequencing, and the result showed a non-mutant status. After discussion with the patient, she decided on self-paid EGFR-tyrosine kinase inhibitor targeted therapy, so we prescribed erlotinib (150 mg) per day and later discharged the patient.

About 2 days later, the patient developed fever up to 38.8°C. Chest radiography showed a progressive enlarged right lower lung consolidation. We administered ertapenem and levofloxacin for coverage of nosocomial infection, but the patient still had persistent fever. Repeated chest CT scan showed a huge mass lesion with internal septation and a solid component and central necrosis in the right lower lung, measuring about 13 cm at its longest diameter (Figure 5), and rapid progression compared with the CT 1 month previous to this (Figure 3). Multiple nodules in the left lung were also discovered at the same time. The results of special stains and cultures of the sputum were negative. We discontinued antibiotics and she was later discharged.

About 10 days after discharge, she had worsening dyspnea on exertion and chest pain. Due to progressive deterioration, the family opted for a conservative policy and hospice care. The patient died about 1 month after diagnosis.

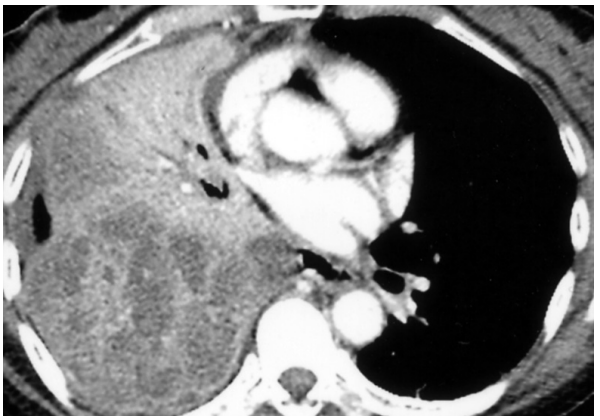

Fig. 5. Chest CT showed a huge mass lesion with an internal septation/solid component and central necrosis noted at the right lower lobe, measuring about 13 cm at its longest diameter. Rapid progression, as compared with the CT 1 month previous to this, was revealed.

Discussion

The incidence of malignancy in systemic sclerosis patients has ranged from 3.6% to 10.7% [1], with an average of 6.3% in several reported studies [6-7]. More women than men have been reported, with an average age at dual diagnosis of 58 years. Lung cancer is the most frequent type of cancer seen in patients with systemic sclerosis, followed by breast cancer. Risk factors for the development of malignancy in patients with systemic sclerosis are female gender, increased age, and diffuse systemic sclerosis [8]. No consistent relationship has been shown so far between the presence of malignancy and autoantibodies [9]. The development of lung cancer in patients with systemic sclerosis is frequently in the setting of pulmonary fibrosis [10]. As such, it is usually associated with long-standing systemic sclerosis [11]. The relative risk of lung cancer in patients with systemic sclerosis has been placed at up to 16.5 times that of normal patients [12], with an estimated relative risk of 5.9 in a large Australian

study [1]. Hence, vigilance is recommended in this group of patients based on their increased risk of developing cancer.

In our case, the patient presented with dyspnea and new rapidly growing infiltrates in the right lower lung, with a suspected presence of pulmonary infection. However, there was no fever or leukocytosis, and no pathogens were identified. There were no endobronchial lesions to suggest the diagnosis of obstructive pneumonitis. In addition, the patient responded poorly to broad-spectrum antibiotics. A diagnostic approach for malignancy was initiated due to the documented increased risk of malignancy in patients with longstanding systemic sclerosis. The mammogram screening was negative for malignancy, and the PET scan showed a suspicious malignancy at the right lower lung. The results of CT-guided biopsy revealed a rare type of lung cancer.

Sarcomatoid carcinoma can occur in any organ, but the most common site is the lung [2, 4-5]. Sarcomatoid carcinoma of the lung is rare, with an incidence of 0.3-1.3% of all lung malignancies [2, 4-5]. According to the WHO classification [2], sarcomatoid carcinoma of the lung is defined as a group of poorly differentiated non-small cell lung carcinomas that shows sarcoma or sarcoma-like (spindle and/or giant cell) differentiation [2]. No specific symptoms or signs were found in published reports of pulmonary sarcomatoid carcinomas, when compared to other NSCLC [3-4]. The clinical symptoms may be related to the anatomical structures involved with the tumor. The life expectancy of patients with pulmonary sarcomatoid carcinoma is generally worse than that of patients with conventional NSCLC, even when stratified for tumor stage in some reports [13].

The activity and efficacy of systemic chemotherapy in patients with pulmonary sarcomatoid carcinoma has not been well studied so far. No prospective clinical trial has been published on the topic, and the results obtained from conventional NSCLC-related clinical trials may not be extrapolated well for pulmonary sarcomatoid carcinoma [15]. The little data available for these tumors are derived from retrospective studies, which showed a substantial failure of the standard chemotherapy commonly used for NSCLC. A cumulative series of 15 consecutive sarcomatoid carcinomas treated with platinum-containing (13 patients) or platinum-free (2 patients) combination regimens showed disease stabilization in 2 patients and tumor progression in 13 [14]. Eight patients also received 2nd-line chemotherapy, but nevertheless showed immediate disease progression [14].

EGFR is a receptor tyrosine kinase that is expressed in NSCLC. Approximately 70% of NSCLCs with EGFR mutations respond to EGFR tyrosine kinase inhibitors. The information on the EGFR mutation status of pulmonary sarcomatoid carcinoma is scarce. In a recent case series, EGFR mutation was recognized in 3 (18%) of 17 patients with pulmonary sarcomatoid carcinoma [16]. Of the 3 mutated patients, the response of 1 patient given gefitinib was transient.

In conclusion, the case presented herein suggests that lung malignancy should be considered in systemic scleroderma patients, even though the initial symptoms are not suggestive of malignancy. Based on the experience with our patient, it is possible that sarcomatoid carcinoma in scleroderma is related to rapid growth and a fatal outcome. In addition to platinum-based chemotherapy, an investigation of the prevalence of EGFR mutation status and the associated response to targeted therapy as an

alternative therapy, especially in patients with a poor performance status, may also be beneficial.

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肺類肉瘤上皮癌在一硬皮症患者：一病例報告

林文仁 * 朱國安 *,** 林旻希 * 沈協益 * 曾暉華 *** 賴瑞生 *,**

硬皮症的患者約有百分之十可發現腫瘤，包括肺癌，乳癌，消化道腫瘤，白血病，淋巴瘤及其他癌症。肺癌是硬皮症患者中最常見的，其次是乳癌。肺類肉瘤上皮癌是一種罕見的肺。

一般認為臨床病程較為快速，而且對於傳統非小細胞肺癌所使用的化學治療反應並不顯著。目前對於肺類肉瘤上皮癌的臨床及病理表徵以及 EGFR（Epidermal Growth Factor Receptor）表現盛行率仍不清楚。在此我們報告一位硬皮症患者合併肺部間質性變化，以一極快速生長之下肺葉腫塊為初始表現，經電腦斷層切片證實為肺類肉瘤上皮癌，因患者體能狀況不佳，故未接受傳統化學治療，而使用標靶（Erlotinib）藥物治療，但是治療效果不佳，患者在診斷後一個月死亡。*(胸腔醫學* ***2012; 27: 228-234)***

關鍵詞：肺癌，肺類肉瘤上皮癌，硬皮症

* 高雄榮民總醫院　胸腔內科，** 國立陽明大學醫學院，*** 高雄榮民總醫院　病理科
索取抽印本請聯絡：朱國安醫師，高雄榮民總醫院　內科部　胸腔內科，高雄市左營區大中一路 386 號

Sequential Bilateral Spontaneous Pneumothorax Following Gefitinib Therapy for Pulmonary Adenocarcinoma with Activated EGFR Mutation – A Case Report

Ching-Hsiang Lu*, Ruay-Sheng Lai*,**, Jia-Bin Liao***

Spontaneous pneumothorax (SP) is a rare phenomenon in patients with primary and metastatic pulmonary neoplasm. Gefitinib has been approved as an effective treatment for pulmonary adenocarcinoma patients with an activated epidermal growth factor receptor (EGFR) mutation. Pneumothorax following gefitinib treatment is rarely reported in the literature. We present the case of a 49-year-old woman with primary pulmonary adenocarcinoma with bilateral lung, brain and multiple bone metastases. A L858R point mutation in exon 21 was detected by PCR/direct sequencing. She took gefitinib as her first-line chemotherapy, and had a partial response. Sequential bilateral SP developed after gefitinib had been used for about 2 months. We believe that the SP was caused by gefitinib therapy, which may have resulted in the necrosis of multiple pleural-based pulmonary nodules with bronchopleural fistula formation. This hypothesis is similar to that of SP following cytotoxic chemotherapy in sarcoma and germ cell tumor. We inserted a chest tube, but recurrence was found after its removal. Chemical pleurodesis was used, after which, the SP was no longer noted. In this report, we present a case of bilateral SP, which is a rare complication following gefitinib treatment for pulmonary adenocarcinoma. Chemical pleurodesis is recommended after the lung has been fully re-expanded to prevent repeated pneumothorax. ***(Thorac Med 2012; 27: 235-239)***

Key words: gefitinib, lung cancer, pleurodesis, spontaneous pneumothorax

Introduction

Gefitinib, an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), has been proved to be effective in advanced pulmonary adenocarcinoma as either first or second-line therapy. Several adverse effects, such as acne (25~33%), skin rash (43~54%), diarrhea (48~67%) and interstitial pulmonary fibrosis (1%), have been reported. Secondary spontane-

*Division of Chest Medicine, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; **National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.; ***Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
Address reprint requests to: Dr. Ruay-Sheng Lai, Division of Chest Medicine, Department of Internal Medicine, Kaohsiung Veterans General Hospital, No. 386, Ta-Chung 1st Road, Kaohsiung 813, Taiwan

ous pneumothorax (SP) in cases of primary or metastatic pulmonary neoplasm is very rare [1-2]; SP is usually reported in cases of sarcoma and germ cell tumor. Herein, we report a case of sequential bilateral secondary SP following the use of gefitinib for the treatment of pulmonary adenocarcinoma with multiple lung metastases. Chemical pleurodesis was performed after the lung had been fully re-expanded.

Case Report

A 49-year-old woman, a non-smoker, denied any systemic disease or previous operation. She presented with left upper limb pain for 3 months. Severe cough without hemoptysis, dyspnea on exertion and body weight loss were also mentioned. Her chest radiograph (CXR) revealed diffuse nodules in the bilateral lung fields. Computed tomography (CT) of the chest showed a nodular mass at the right upper lung (RUL) field with numerous small nodules in the bilateral lung fields (Figure 1). Malignant cells and Mycobacterium tuberculosis were not detected in her sputum analysis. Blood cell counts and liver and renal functions were all within normal range.

The specimens obtained by CT-guided biopsy from the RUL nodule confirmed the diagnosis of adenocarcinoma of the lung. The immunohistochemical stain with TTF-1 was positive and the EGFR-TK mutation examination confirmed a L858R point mutation in exon 21, using polymerase chain reaction (PCR)/direct sequencing. An upper abdominal sonogram showed no focal lesions. CT of the brain and a whole body bone scan revealed multiple metastatic lesions. The patient took gefitinib (250 mg per day) as first-line therapy, and a partial response was seen in follow-up chest images.

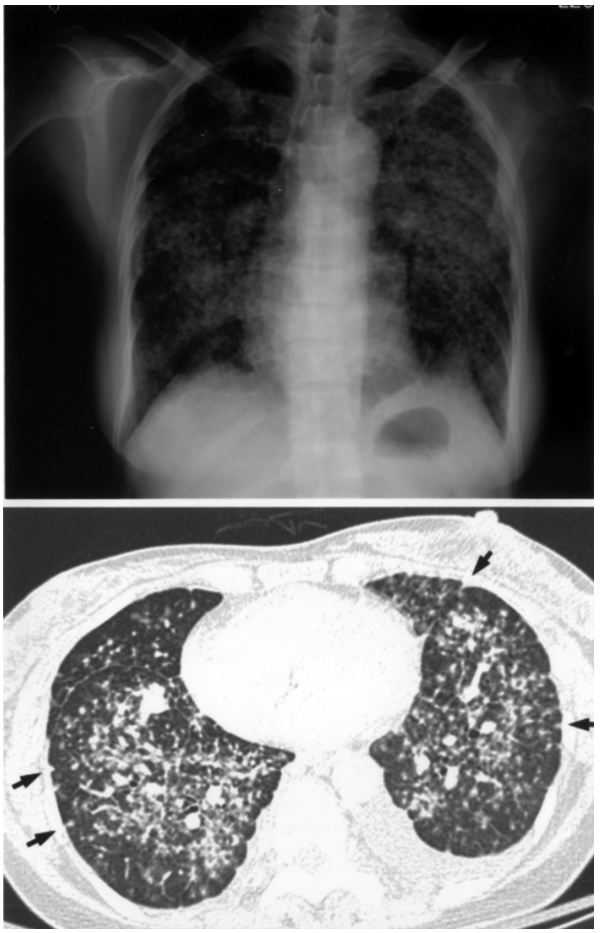

Fig. 1. Chest roentgenogram (upper) and CT (lower) on admission. Numerous small nodules can be seen in the bilateral lung fields with pleural seeding (black arrow).

On day 70 after treatment with gefitinib, right-side SP was found in a routine CXR examination (Figure 2A), though she denied suffering from exacerbated dyspnea. Oxygen therapy and drainage by a 12 Fr. pig-tail catheter were initially performed. The catheter was removed 6 days later when the dyspnea had subsided and only mild residual pneumothorax was left.

About 2 months later, left-side SP developed (Figure 2B) and a chest tube was inserted. A persistent air-leak lasting 2 weeks was noted. Pleurodesis with minocycline was performed

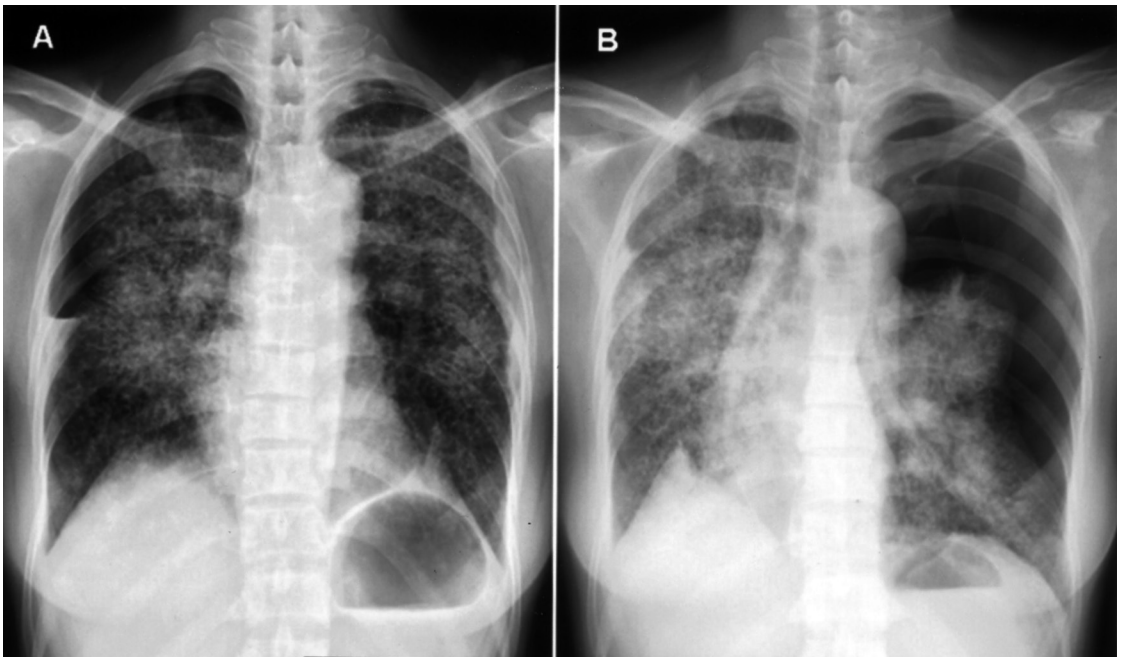

Fig. 2. The course of sequential bilateral spontaneous pneumothorax. Hydropneumothorax was confirmed first in the right side after gefitinib administration (A). Sequential left-side pneumothorax was noted 2 months later (B).

and the chest tube was removed smoothly. However, there was then a sequential recurrence of right SP (Figure 3), which was also successfully treated with chest tube insertion and chemical pleurodesis on 2 occasions. The chest images showed progressive change after about 7 months of gefitinib treatment, and the pneumothorax did not recur after pleurodesis.

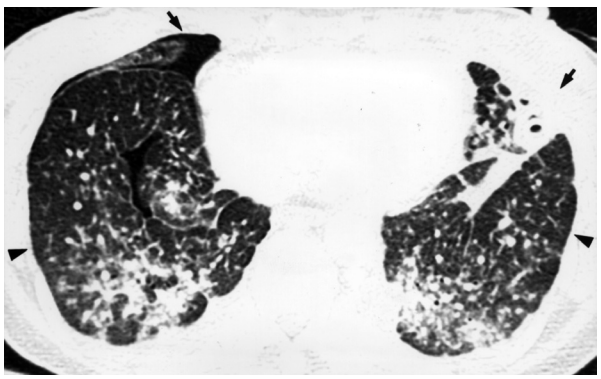

Fig. 3. CT image after gefitinib therapy for 4 months. Left-side pneumothorax post-chest tube insertion with recurrent right-side pneumothorax (black arrow). The subpleural nodules regressed after gefitinib therapy (arrow-head).

Discussion

Pneumothorax is classified into spontaneous, traumatic and iatrogenic types. SP is divided into primary and secondary types [3]. Secondary SP caused by neoplasm in the lung is rare, accounting for less than 1% of all cases [4]. Secondary SP after cytotoxic chemotherapy is an uncommon but well-documented complication in primary or metastatic lung lesions [5]. It usually occurred in patients with highly chemosensitive neoplasms, such as sarcoma or germ cell tumor with lung metastases [6]. The possible mechanisms of secondary SP include (1) tumor necrosis, either spontaneous or therapy-related, of subpleural nodules with bronchopleural fistula formation, resulting in a pneu-

mothorax, (2) a check-valve mechanism with compression of the airway by tumor nodules, leading to local over-distention and subsequent rupturing of the lung, and (3) tumor embolus with resultant tumor infarction, necrosis and air leak [5].

Gefitinib is an oral inhibitor of EGFR-TK and also induces apoptosis of tumor cells, although it has a different pathway from standard chemotherapy [7]. Targeted therapy has been proved to provide significant disease regression, as seen in either imaging or symptom status, in the activated EGFR mutation population with pulmonary carcinoma, and longer progression-free survival than standard chemotherapy [8]. In Taiwan, on 1 June 2011, gefitinib was recommended to be first-line therapy for pulmonary adenocarcinoma in patients with an activated EGFR mutation.

The patient reported herein was an Asian female, a non-smoker, with pulmonary adenocarcinoma and a L858R point mutation in exon 21, as confirmed by PCR/direct sequencing. Based on the subpleural nodules demonstrated by chest CT and the observation of tumor regression after treatment with gefitinib, we postulated that tumor necrosis of subpleural nodules with fistula formation was the main cause of the secondary SP.

Chemotherapy-associated SP is a potentially life-threatening event, because lung function in these patients is usually compromised. We must also point out that secondary SP following EGFR-TKI in diffuse pulmonary metastasis may be bilateral, as in this case. Chest tube insertion should be used, but may be insufficient for preventing recurrent secondary SP. Chemical pleurodesis is strongly recommended after the lung is fully re-expanded.

In the era of molecular diagnosis, we can expect that the use of gefitinib for the treatment of pulmonary adenocarcinoma will increase, especially in the activated EGFR mutation population or in those with an initial presentation of advanced disease. As this case was a preliminary experience, future collaborative studies are warranted to determine the optimal treatment protocol and risk factors for this uncommon phenomenon.

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肺腺癌經標靶治療後引起之相繼的雙側自發性氣胸：一病例報告

盧慶祥 * 賴瑞生 *,** 廖嘉賓 ***

雙側自發性氣胸不論是在原發性或轉移性肺腫瘤都是非常少見的，特別是在使用艾瑞莎（Iressa®）治療肺腺癌後發生的自發性氣胸在文獻上更是罕見。艾瑞莎已證實對肺腺癌且上皮細胞生長因子接受體突變陽性的患者有療效。本文描述一名 49 歲女性患有原發性肺腺癌合併雙側肺部、腦部及全身多處骨頭轉移，且上皮細胞生長因子接受體突變為陽性，在使用艾瑞莎來當做一線治療後，發生相繼的雙側自發性氣胸。肋膜下肺腫瘤壞死併發支氣管肋膜瘻管被認為是氣胸的主因。這個理論與肉瘤及生殖細胞腫瘤經化學治療後發生氣胸的理論相似。氣胸經胸管引流後症狀解除，但是移除胸管後又再次復發氣胸。經後續執行肋膜沾黏治療後便不再發生氣胸。此病例提醒臨床醫師，在使用艾瑞莎治療肺腺癌患者後產生的自發性氣胸是罕見的，若發生時應執行肋膜沾黏治療以避免復發。*(胸腔醫學 **2012; 27: 235-239**)*

關鍵詞：艾瑞莎，肺癌，肋膜沾黏治療，自發性氣胸

* 高雄榮民總醫院　胸腔內科，** 國立陽明大學醫學院，*** 高雄榮民總醫院　病理檢驗部
索取抽印本請聯絡：賴瑞生醫師，高雄榮民總醫院　內科部　胸腔內科，高雄市左營區大中一路 386 號

Tracheobronchial Foreign Body Aspiration of Crab Leg Shell – An Unusual Type of Airway Obstruction

Hung-Tze Tay, Jiunn-Min Shieh, Shian-Chin Ko

Foreign body aspiration (FBA) is a common medical emergency for children, although it also occurs in older age groups. In adults, FBA is most commonly caused by the failure of airway protective mechanisms. Otherwise, FBA in adults can be caused by an iatrogenic or traumatic event. FBA necessitates prompt recognition and early removal to avoid serious and sometimes fatal consequences. The longer a foreign body remains in the airway, the more complications that can develop. A careful inquiry into the patient's medical history is of utmost importance for an accurate diagnosis of FBA. Without a supporting history, the diagnosis of FBA is often delayed, from days to months. Chest radiography may be normal and is not always useful for diagnosis. If the history is highly suggestive of FBA, bronchoscopy should be performed for both diagnostic and therapeutic purposes. We present a case of FBA of a crab leg shell that obstructed the lower trachea and right main bronchus. Although the chest radiograph appeared normal, there was a strong history of FBA after failed laryngeal manipulation by an otorhinolaryngologist. The diagnosis was further verified by computed tomography and lung function tests. Ultimately, the foreign body was retrieved by flexible bronchoscopy. If the history is highly suggestive, clinicians should maintain a high index of suspicion for FBA, even with normal imaging studies. ***(Thorac Med 2012; 27: 240-247)***

Key words: foreign body aspiration, bronchoscopy

Introduction

Foreign body aspiration (FBA) into the tracheobronchial tree is a worldwide health problem that can result in life-threatening complications. More than 2/3 of FBA cases occur among children younger than 3 years [1]. Young children are most vulnerable to FBA because they do not have adequate dentition and their swallowing coordination is immature. In addition, introducing objects into their mouths is a way in which children explore the world. In adults, FBA is most commonly caused by a failure of airway protective mechanisms, such as that due to alcohol or sedative drug use, poor dentition, mental retardation, senility, neurological disorders with swallowing impairments, seizure, and general anesthesia. Also, the causes of FBA in

Division of Chest Medicine, Department of Internal Medicine, Chi Mei Medical Center, Tainan City, Taiwan
Address reprint requests to: Dr. Shian-Chin Ko, Division of Chest Medicine, Department of Internal Medicine, Chi Mei Medical Center, No. 901, Zhonghua Rd., Yongkang Dist., Tainan City 710, Taiwan (R.O.C.)

adults may be iatrogenic or traumatic [2].

However, FBA can also occur in adults with no remarkable predisposing factors [3]. We report a case of FBA with nearly normal chest radiography. The patient first had a laryngeal obstruction by a crab shell. However, after laryngeal manipulation under local anesthesia, the foreign body was found to have dropped into the trachea. Although the chest radiographs showed a nearly normal appearance, the flow-volume curve in spirometry revealed typical findings of major airway obstruction. We also review the relevant literature.

Case Report

A 51-year-old man had choked on some seafood when he was on a tour of Penghu 1 month before admission. He had not consumed alcohol. He was brought to a local otorhinolaryngologist, who tried to remove the foreign body from the larynx with a forceps under local anesthesia. After 20 minutes of laryngeal manipulation, the doctor stated that the foreign body had "disappeared." After management, the patient felt resolution from asphyxia and returned to Taiwan the next day.

After this event, noisy breathing and productive cough with whitish phlegm developed. He had also expectorated blood-tinged sputum after a violent cough. Exertional dyspnea was noted. There was no fever or chest pain during the clinical course. He visited our chest clinic, where localized wheezes and scattered coarse

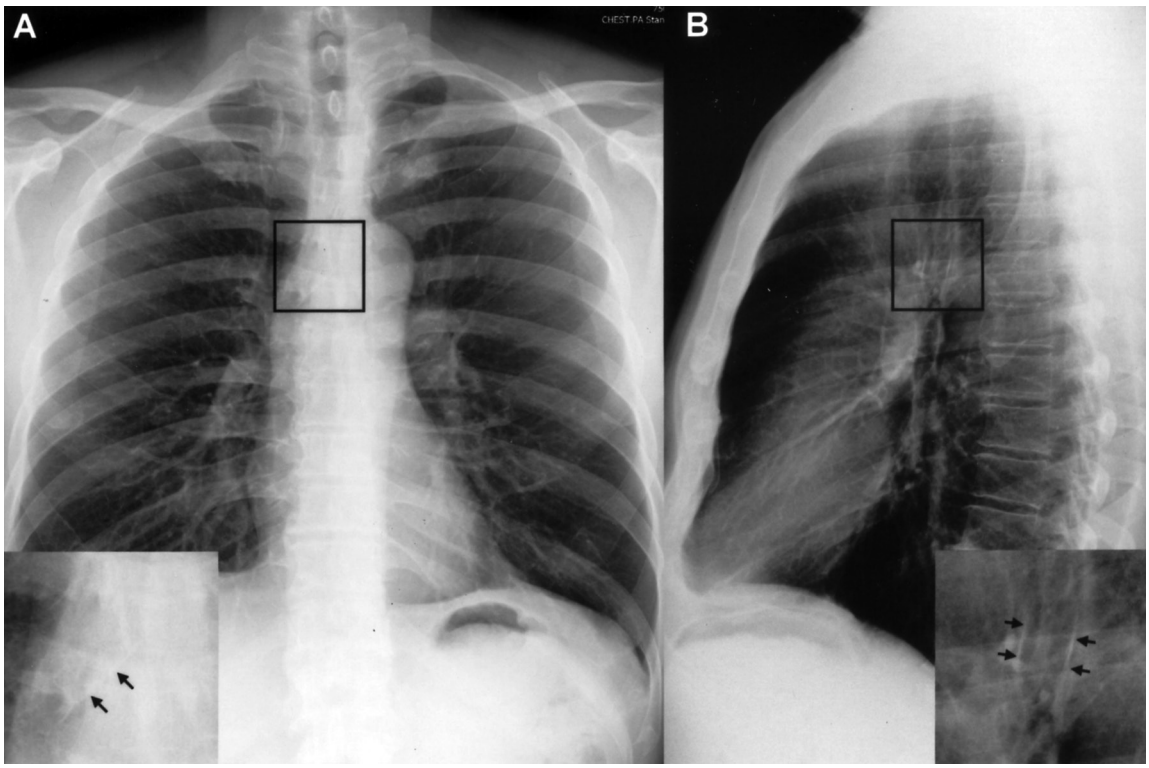

Fig. 1. Chest radiographs. (A) Posteroanterior and (B) lateral views. The separate pictures in the corners show the magnified portions within the black frames. The very faint calcified outlines (black arrows) of the foreign body could be seen in the lower trachea and right main bronchus.

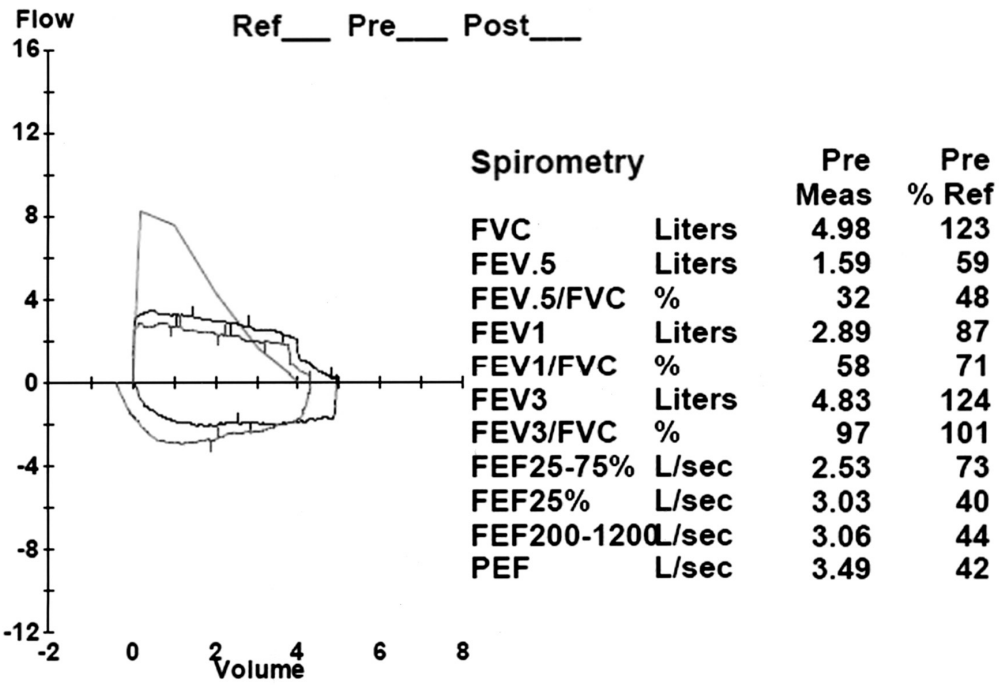

Fig. 2. Spirometry results. The forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC) was 58%, which indicated obstructive ventilatory impairment. The flow-volume loop showed a truncated shape in both the expiratory and inspiratory limbs, which was typical of fixed major airway obstruction. The peak expiratory flow (PEF) was only 42% of predicted.

crackles were heard during both inspiratory and expiratory phases in the right lung field.

Hematology tests showed that his blood cell count and biochemistry results were normal. Chest radiography appeared nearly normal at first glance. However, on a later review of the chest x-ray films, 2 very faint calcified outlines of a foreign body could be seen in the lower trachea and right main bronchus on the posteroanterior and lateral images (Figure 1). Spirometry tests revealed a truncated flow-volume loop, typical of fixed major airway obstruction (Figure 2). His peak expiratory flow (PEF) was markedly decreased (42% of predicted). A computed tomography (CT) scan of the lung demonstrated a tubular calcified foreign body, 3.6 cm in length, in the lower trachea and right main bronchus (Figure 3).

Based on the patient's history, physical examination, lung function test results, and radiological features, a diagnosis of a retained calcified foreign body was made. A subsequent flexible bronchoscopy examination revealed a piece of crab leg shell lodged in the lower trachea and extending into the right main bronchus (Figure 4). During the same session, 2 hours were needed to retract the crab shell with alligator and basket forceps. The foreign body was too large to pass through the bronchoscope, so it was grasped and then brought up to the end of the bronchoscope, and the entire unit was removed en masse. Immediately after removing the foreign body, the patient's clinical condition improved dramatically. He was discharged on the next day and had a complete recovery.

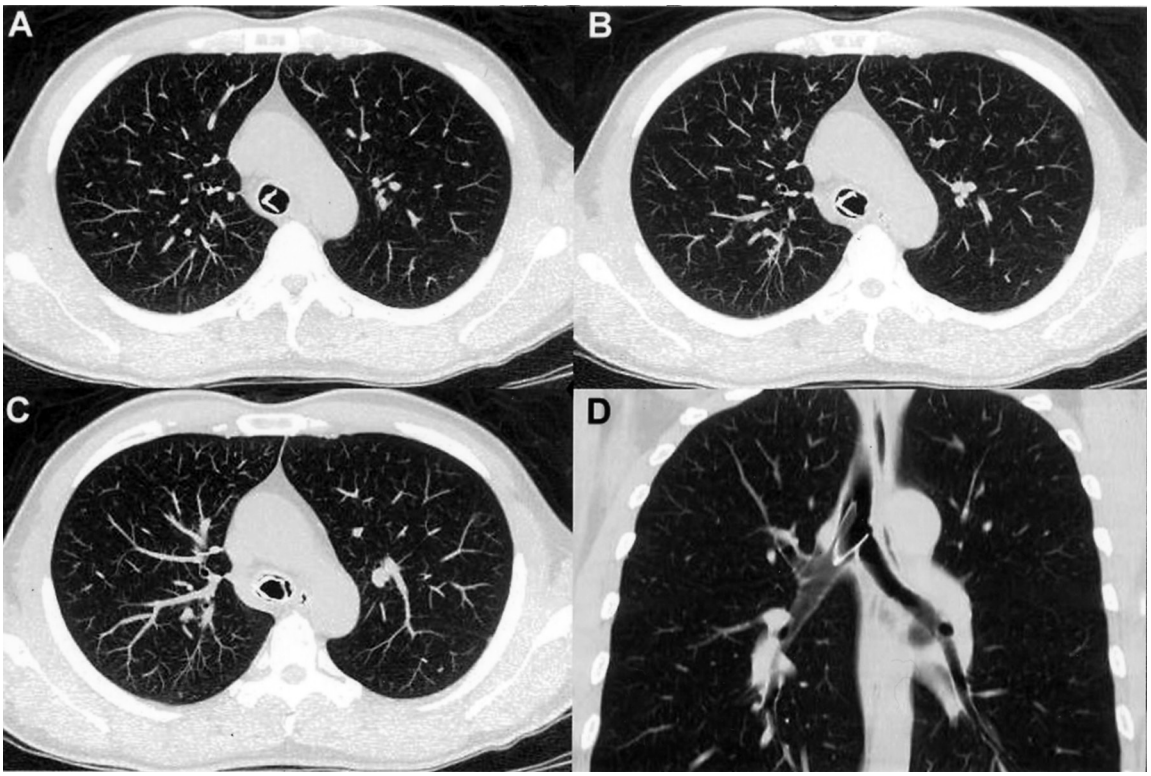

Fig. 3. Chest CT scan with lung window settings. (A-C) On transverse sections, a cylinder-shaped calcified foreign body obstructing the lower trachea can be seen. (D) In the frontal reconstructed view, the foreign body extended from the lower trachea into the right main bronchus.

Discussion

FBA can have a wide range of clinical presentations, ranging from no or trivial symptoms to life-threatening asphyxia. The severity of symptoms depends on the affected site and the nature of the foreign body. When a large foreign body occludes the larynx, choking and gagging occur suddenly, and may be associated with hoarseness, aphonia, and cyanosis. In these instances, the Heimlich maneuver is recommended. When the foreign body passes through the vocal cords into the subglottic or tracheal region, sudden paroxysms of coughing and inspiratory stridor may be experienced. Penetration syndrome, defined as a sudden onset of choking and intractable cough, with or without vomiting, is frequently observed.

However, when the foreign body migrates further into the bronchi, these symptoms may resolve and a relatively asymptomatic period may begin. Cough, wheezing, and decreased breathing sounds are the common acute symptoms of FBA. Because the airway lumen in adults is larger, a foreign body is prone to lodge more peripherally and, therefore, can be tolerated and remain undetected for a long time. In our case, respiratory distress was severe when the crab shell obstructed the larynx, but it resolved dramatically after the foreign body passed through the vocal cords and became lodged in the lower trachea and right main bronchus.

An aspirated foreign body can be organic or inorganic. Organic materials, such as nuts and

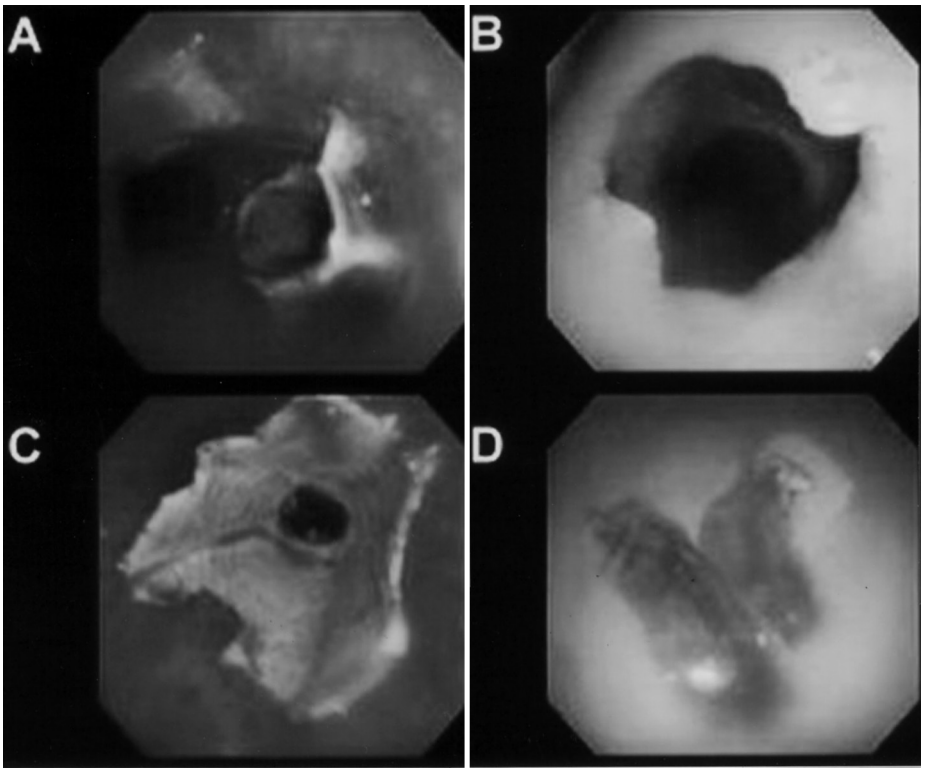

Fig. 4. Bronchoscopic images. (A) At the level just above the carina, a piece of crab leg shell had lodged in the lower trachea and extended into the right main bronchus. (B) Looking through the distal end of the cylindrical foreign body. Since the shell had a lumen, the lung had not collapsed. (C) The shell was bitten off piece by piece using alligator forceps. (D) Photograph showing the broken shell retrieved by basket forceps.

seeds in children, and food and bones in adults, cause a more severe mucosal inflammation and the formation of granulation tissue. Organic foreign bodies more frequently cause bronchial obstruction because they absorb water and expand within the airway. The kinds of aspirated foreign bodies vary based on geographic and cultural differences.

As in the present case, bony fragments are the most common foreign bodies that are aspirated by adults in China [4]. In Pakistan, betel nuts are frequently aspirated into the airway [5]. Aspiration of turban pins by women is common in Islamic countries, due to their traditions and beliefs [6]. The iatrogenic causes of FBA include cleaning procedures by means of tracheostomy, bronchoscopy, and dental manipulation [7]. Tooth and dental prostheses are often aspirated by the elderly [8]. In our case, the foreign body was pushed into the trachea after laryngeal manipulation.

Chest radiography is the initial evaluation tool when FBA is suggested by the medical history. However, radiopaque foreign bodies only account for a minority (5-15%) of FBA cases [9]. Most foreign bodies are radiolucent and are not visible on chest radiographs. The most common radiological findings of FBA, including atelectasis, pulmonary infiltrates, pneumomediastinum, and mediastinal shift, are all indirect signs and may be misleading. Barharloo *et al*. found that atelectasis was more frequent in adults and

air trapping was more common in children [3]. In the present case, the chest radiographs appeared to be nearly normal because the crab leg shell had a lumen. The right lung had not collapsed as ventilation was maintained. A CT scan is valuable for detecting the presence and characteristics of an endobronchial foreign body and for recognizing aspiration-related complications, such as obstructive pneumonitis, bronchiectasis, and pneumomediastinum [9]. Virtual bronchoscopy using endoluminal volume-rendering techniques may be helpful for evaluating an endobronchial lesion [10].

Lung function test results for adult FBA patients have rarely been reported. Some children with chronic FBA have been treated for bronchial asthma due to persistent dyspnea and wheezing [11]. In our case, the patient's flow-volume loop was truncated; thus, major airway obstruction was highly suspected. Bronchoscopy was then indicated to evaluate the patency of the central airway.

Bronchoscopy, both diagnostic and therapeutic, is mandatory as soon as a diagnosis of FBA is suspected. A retained foreign body may be complicated by unresolving pneumonia, recurrent hemoptysis, lung abscess, or bronchiectasis. A rigid bronchoscope is considered to be the safest instrument for pediatric patients, as it provides greater access, ensures correct oxygenation, allows for very efficient airway suctioning, and provides an easy passage for the telescope and grasping forceps [12]. However, rigid bronchoscopy requires general anesthesia and may result in the complications of laryngeal edema, tracheal laceration, or pneumomediastinum. In adults, removal of a foreign body can be attempted during a diagnostic examination with a flexible bronchoscope under local anesthesia, which may help to avoid any additional invasive procedures and further complications [13]. In the present case, the foreign body was simply removed by flexible bronchoscopy, although it took a longer time than usual. Surgical intervention may be needed if foreign body retraction by bronchoscopy has failed or there are severe parenchymal complications, such as lung abscess or bronchiectasis.

Conclusion

FBA is a potentially dangerous, but completely reversible condition. A delay in presentation or recognition may lead to serious complications. Because the clinical and radiologic findings in delayed cases of FBA may mimic other disorders, the clinician must be aware of the likelihood of FBA. Careful history taking to search for evidence of any choking episode is mandatory. When there is a high clinical suspicion of FBA, even with normal imaging findings, bronchoscopy should be performed for a thorough evaluation of the airways [14]. Early recognition and prompt removal of an aspirated tracheobronchial foreign body are the criteria for management.

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氣道阻塞卻未造成塌陷—異物嗆入氣管之病例報告

鄭鴻志　謝俊民　柯獻欽

異物嗆入是小孩常見的急症，但亦可見於成人。異物嗆入較常發生在氣道保護機制受損的病人，也可能導因於醫療處置或外傷事件。異物嗆入須及早發現並儘速移除，以避免嚴重且可能危及生命的後遺症，異物在氣道內停留的時間愈久，愈可能發生後遺症。詳細詢問病史是正確診斷異物嗆入的不二法門，若是從病史中無法讓醫護人員考慮到異物嗆入的可能，則診斷可能延遲數天到數月。胸部 X 光檢查對異物誤嗆的診斷不一定有幫助，病人的胸部 X 光影像可以是正常的，如果從病史中高度懷疑是異物嗆入，應立即安排支氣管鏡檢以診斷並設法移除氣道內異物。我們報告一例蟹腳殼嗆入卡住氣管下段與右主支氣管的病例，一開始蟹殼是卡在喉部，經耳鼻喉科醫師處置後，反而掉入氣管內。因蟹腳殼呈管狀，不會完全堵住氣道，所以病人的胸部 X 光片幾近正常，但因病史上高度懷疑，加上身體檢查、電腦斷層與肺功能檢查的佐證，最後以軟式支氣管鏡移除異物。臨床醫師對於有嗆到病史的病人，即使影像學檢查正常，亦應保持高度警覺，排除異物嗆入的可能。*(胸腔醫學* ***2012; 27: 240-247****)*

關鍵詞：異物嗆入，支氣管鏡

奇美醫學中心　胸腔內科
索取抽印本請聯絡：柯獻欽醫師，奇美醫學中心　胸腔內科，台南市永康區中華路 901 號

Tracheal Lipoma – Case Report and Review of the Literature

Yi-Chung Chang*, Diana Yu-Wung Yeh*,***, Chin-Cheng Lee**, Chia-Heng Lin*

Primary tracheal lipomas are extremely rare neoplasms and can be difficult to diagnose due to their capacity to mimic other obstructive lung diseases. We report the case of a male patient with tracheal lipoma. He complained of shortness of breath for a long time with little response to treatment. During forced expiration in the pulmonary function test, a dramatic constant reduction in expiratory flow of the flow-volume curve was noted. Based on that, an obstructing lesion in the airway was suspected. A computed tomographic scan revealed the presence of a tumor in the mid-trachea. The tumor was confirmed by fiberoptic bronchoscopy and successfully resected by endoscopic laser. Histologic examination of the tumor showed a benign lipoma. After surgical treatment, the patient reported significant improvement in his shortness of breath. ***(Thorac Med 2012; 27: 248-252)***

Key words: tracheal lipoma, spirometry, obstructive ventilatory defect

Introduction

Primary tracheal tumors are rare lesions. The incidence rate is approximately 0.2/100,000 population [1]. The majority of tracheal tumors are malignant, and benign tumors are a minority (10-20%) [2]. Most of the benign tumors are papillomas, and only 3.2% to 9.5% are lipomas. Lipomas arise mostly in the main stem bronchi, and an intratracheal lipoma is extremely rare [3].

Patients with symptoms that mimic obstructive lung diseases are often erroneously treated for asthma or chronic obstructive pulmonary disease (COPD), until an inadequate response to treatment leads to the suspicion of major airway obstruction, which is then confirmed by fiberoptic bronchoscopy.

We report the case of a 56-year-old man with intratracheal lipoma who complained of shortness of breath for a long time with little response to treatment.

Case Report

A 56-year-old male, a smoker of 1 pack per day for 20 years, reported experiencing intermittent dyspnea daily at rest. No wheezing, chest pain, or cough was reported. Prior to coming to our clinic, he had been treated with an oral bronchodilator and aminophylline, which

*Division of Chest Medicine, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital; **Department of Pathology and Laboratory Medicine; ***School of Medicine, Fu Jen Catholic University
Address reprint requests to: Dr. Chia-Heng Lin, Division of Chest Medicine, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, No. 95, Wen Chang Road, Shih Lin District, Taipei, Taiwan

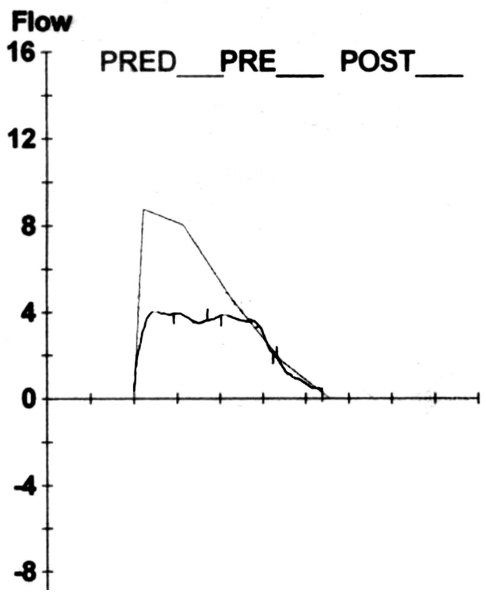

Fig. 1. Spirometry shows a fixed obstructive lesion

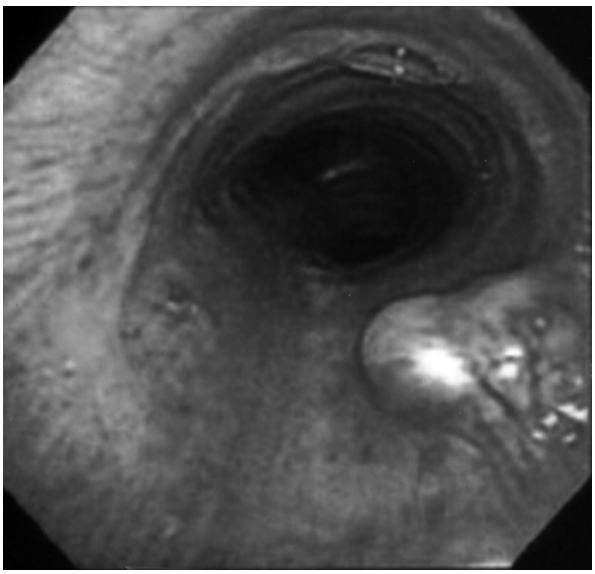

Fig. 3. Bronchoscopy revealed a broad-based polypoid growth in the mid-trachea.

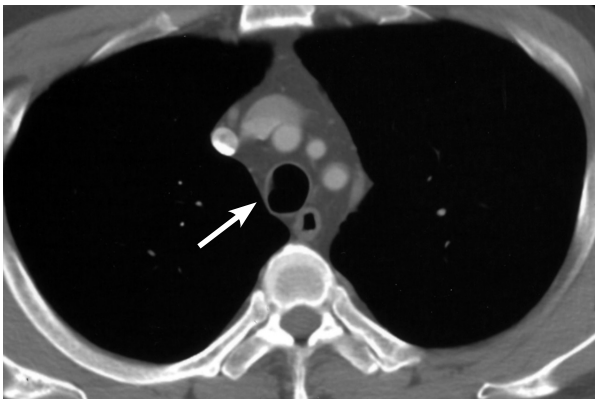

Fig. 2. CT reveals an intratracheal lesion composed of dense fat without invasion to the tracheal cartilage.

evoked a partial response.

A chest X-ray showed lung hyperinflation and mild pulmonary emphysema. No obvious nodular lesions were found. However, a flat-topped expiratory flow-volume curve and low peak flow rate relative to the forced expiratory volume in 1 second were revealed on standard spirometry (Figure 1). An airway-obstructing lesion was suspected on the basis of spirometry and was confirmed by chest computed tomography (CT) (Figure 2). A small polypoid, densely fat lesion adhering to the right side of the trachea was seen on the scan. No cartilaginous component could be discerned within it. The patient then underwent a fiberoptic bronchoscopy. A polypoid lesion was found attached to the right wall of the mid-trachea (Figure 3). The surface of the lesion was smooth and rich in vasculature. The thoracic surgery service was consulted, and ablation of the lesion by endoscopic laser was performed in the operation room. No complication resulted from the intervention. Histologic examination of the polyp was consistent with a benign submucosal lipoma (Figure 4). After endoscopic ablation of the lipoma, the patient reported significant improvement in his shortness of breath. Spirometry was repeated after 3 months, and the expiratory flow-volume curve showed no flat-topped pattern (Figure 5).

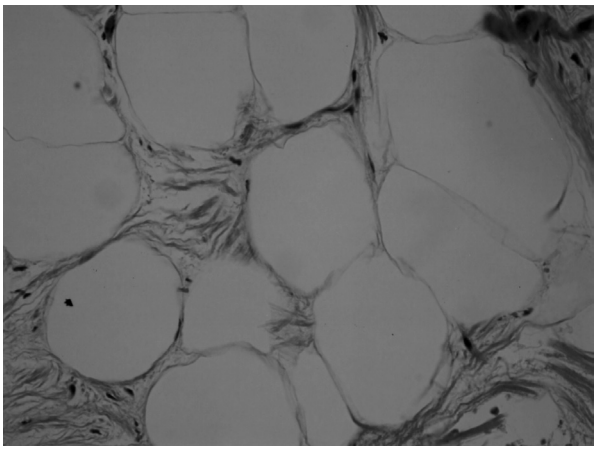

Fig. 4. Histology shows a lipid-rich lipoma

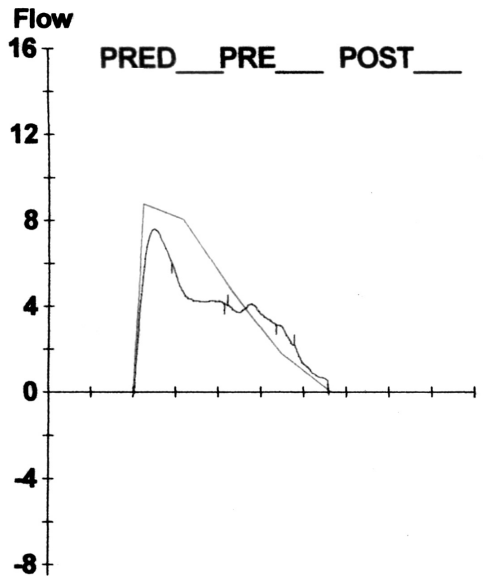

Fig. 5. Spirometry shows improvement after 3 months of operation.

Discussion

Lipoma is a benign mesenchymal neoplasm. In its usual form, it is composed exclusively of fat tissue, surrounded by a capsule [4]. Lipoma is the most common benign tumor occurring in humans; however, it is uncommonly found in the chest cavity (0.1% of benign lung tumors). Intrathoracic lipomas can be found at endotracheobronchial, parenchymal, mediastinal, pleural and cardiac sites. Most of these neoplasms are endobronchial, and intratracheal lipoma is exceedingly rare [5]. It is generally diagnosed in late-middle-age men (mean age, 60 years) [6].

The diameter of the trachea is large enough to allow unimpeded airflow, in spite of the mild compromise. In adults, symptoms generally occur when the tracheal lumen is occluded by 50-70% [7]. Besides, many benign neoplasms of the tracheobronchial tree are slow-growing. For these reasons, a benign tumor in the trachea can go unrecognized for months or even years.

Tracheal lipoma can present with productive cough, wheezing, recurrent pneumonia, or bronchiectasis. As these symptoms are similar to those of asthma and chronic bronchitis, delays in diagnosis and treatment are therefore common.

CT is highly specific and sensitive in the detection of fat and is often utilized in diagnosing tracheobronchial lipomas. Although an endobronchial harmatoma can also manifest as a fatty mass on CT, the presence of cartilage and epithelium-lined clefts help in the differentiation [4]. In this case, the low attenuation numbers of the tumor on CT suggested its nature.

Lipomas confined to the lumen of the trachea can be removed endoscopically, and recurrence has not been reported [8]. Polypectomy snares and laser therapy have been used with success in the past [2]. For the rare lipomas penetrating through the inter-cartilage spaces, wider resections can be performed.

The tumor in our patient was polypoid in shape and appeared rich in blood vessels on its surface. Fortunately, no penetration through the trachea was found on the CT scan. We believed that ablation by bronchoscopic laser would be safer and would be associated with lower mor-

tality and morbidity than tracheal resection. We were able to remove the tumor smoothly without significant blood loss. Pathological examination confirmed complete removal of the entire lipoma.

Conclusion

This case demonstrates the need to include major airway obstruction by tumor in the differential diagnoses of patients presenting with dyspnea, especially those patients who cannot obtain a satisfactory response to optimized treatment.

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氣管內脂肪瘤：病例報告與文獻回顧

張奕中 * 葉育雯 *,*** 李進成 ** 林佳衡 *

原發性氣管內脂肪瘤是極少見的腫瘤，因為會造成類似阻塞性肺疾病的症狀，在診斷上是比較不容易的。我們病例報告了一位有氣管內脂肪瘤的病人，長期抱怨呼吸喘，但經治療後卻沒有明顯成效，在肺功能檢查的吐氣期間，發現吐氣流速為固定地減少，因此懷疑在氣管內有阻塞物的存在，電腦掃瞄在氣管中段發現了一個腫瘤，支氣管內視鏡證實腫瘤的存在，藉由支氣管鏡內雷射，腫瘤順利被切除。病理顯示為良性脂肪瘤，於手術後，病人呼吸喘的症狀改善許多。*(胸腔醫學* ***2012; 27: 248-252)***

關鍵詞：氣管內脂肪瘤，肺活量測定法，阻塞型換氣障礙

* 新光吳火獅紀念醫院 內科部 胸腔內科，** 新光吳火獅紀念醫院 病理實驗科，*** 天主教輔仁大學醫學院
索取抽印本請聯絡：林佳衡醫師，新光吳火獅紀念醫院 內科部 胸腔科，台北市 111 士林區文昌路 95 號

Development of Churg Strauss Syndrome in an Asthma Patient Taking Montelukast

Yu-Chieh Chung*, Jhi-Jhu Hwang*,**, Inn-Wen Chong*,**,***,
Ming-Shyan Huang*,**, Chih-Jen Yang*,**,***

A very limited number of reports have documented the association between leukotriene receptor antagonist (LTRA) and Churg-Strauss syndrome (CSS), but to date, a clear relationship has not been established because of its rarity.

We report a 69-year-old asthma patient who suffered from progressive bilateral lower legs numbness and weakness about 2 weeks after taking montelukast. Nerve conduction velocity (NCV) showed axonal degenerative polyneuropathy. Because of shortness of breath, she was admitted soon after these symptoms were noted. The initial laboratory analyses showed eosinophilia (74% of white cell count) with a high total IgE level (2,768 IU/mL). Chest radiograph revealed non-fixed bilateral pneumonia. Dramatic resolution of the pneumonia with steroid treatment was achieved and montelukast treatment was stopped. In addition, Waters' view showed bilateral maxillary sinusitis. With the above findings, including asthma, marked eosinophilia, polyneuropathy, sinusitis, and non-fixed radiographic pulmonary infiltrates, CSS was diagnosed. We believe that montelukast is a useful and relatively safe drug for treating asthma, but care should be taken regarding its linkage with CSS. ***(Thorac Med 2012; 27: 253-259)***

Key words: montelukast, neuropathy, Churg-Strauss syndrome

Introduction

Montelukast is a leukotriene receptor antagonist (LTRA) that can counteract the inflammation, bronchospasm, and airway edema caused by leukotrienes, and has been known to be used as an add-on therapy for asthma [1-2]. The LTRAs include 1 enzyme inhibitor of 5-lipoxygenase (zileuton) and 3 chemically distinct cysteinyl leukotriene type I receptor antagonists (zafirlukast, pranlukast and montelukast) [1, 3]. LTRAs, such as montelukast, are generally well-tolerated and safe, and can be conveniently administered as an oral tablet.

Churg-Strauss syndrome (CSS) is also known as allergic granulomatosis and angiitis

*Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; **Department of Internal Medicine, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Taiwan; ***Faculty of Respiratory Therapy, College of Medicine, Kaohsiung Medical University, Taiwan
Address reprint requests to: Dr. Chih-Jen Yang, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, #100, Tzyou 1st Road, Kaohsiung 807, Taiwan

[4-6]. According to a Pubmed search, several cases of CSS have been reported in asthmatic patients being treated with LTRAs [7-19]. We present this relatively unique case of CSS and review the related literature.

Case Report

A 69-year-old woman with a history of asthma had used the Seretide Accuhaler (salmeterol/fluticasone) for years. She was referred to 1 of our chest clinics because the asthma had become unstable, and she suffered frequent attacks. We prescribed montelukast 10 mg daily for her, because of the poor control. However, 2 weeks later, she started to feel progressive numbness and weakness in both legs. Nerve conduction velocity (NCV) showed axonal degenerative polyneuropathy. Furthermore, she began to be unable to walk and gradually felt shortness of breath. Therefore, she was sent to our emergency department, where a high fever of up to 38.6°C was noted. SpO_2 was 92% under room air. The patient's breathing sound included diffused wheezing and bilateral crackles. Her chest radiograph revealed right lower lung pneumonia (Figure 1A). Computed tomography of the chest revealed diffuse ground glass opacities in both lungs, particularly in the right lung, with bilateral pleural effusion (Figure 2A). The initial laboratory data showed leukocytosis (29.10×10^3/uL), and particularly, extremely high eosinophilia (absolute eosinophil count of 21.53×10^3/uL, up to 74%). Furthermore, the prominently high BNP, 2,265 pg/mL, and elevated cardiac enzyme troponin I, 12.27 ng/mL, indicated cardiac injury. Cardiac sonography revealed a low ejection fraction (37.34%) and fractional shortening (18.02%). The patient was soon admitted to our intensive care unit under the impression of pneumonia, septic shock or cardiogenic shock and respiratory failure.

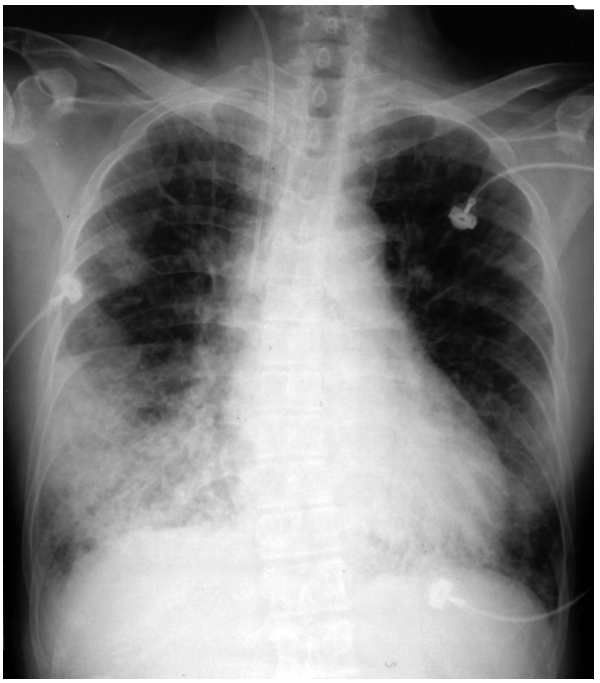

Fig. 1A. Initial chest radiography at the ER showed pneumonia in the right lower lobe.

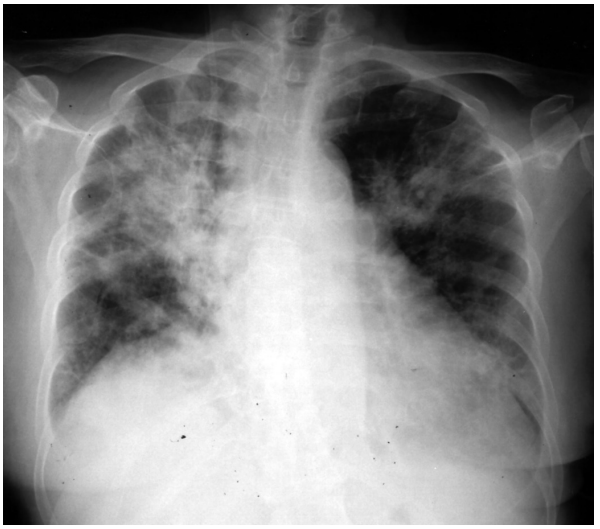

Fig. 1B. Non-fixed pulmonary infiltrates in both lungs were observed on Day 6.

After receiving antibiotic treatment and intravenous diuretics administration, her pneu-

monia patchiness appeared to show partial improvement, but new pulmonary infiltrates were found later in a different part of the lung, indicating non-fixed infiltration (Figure 1B). However, no obvious evidence of nosocomial bacterial infection, such as increased sputum production or high fever, was noted. In order to clarify the nature of the disease, we checked her total IgE level, which was up to 2,768 IU/mL; we also checked the immunity status of the patient and found it to be negative for antineutrophil cytoplasmic antibody (ANCA) or antinuclear antibody (ANA). Waters' view revealed bilateral maxillary sinusitis (Figure 2B). No biopsy was performed because there were no skin lesions. The findings of asthma, marked eosinophilia, polyneuropathy, sinusitis, and non-fixed radiographic pulmonary infiltrates fulfilled the American College of Rheumatology (ACR) criteria for the diagnosis of CSS, although there

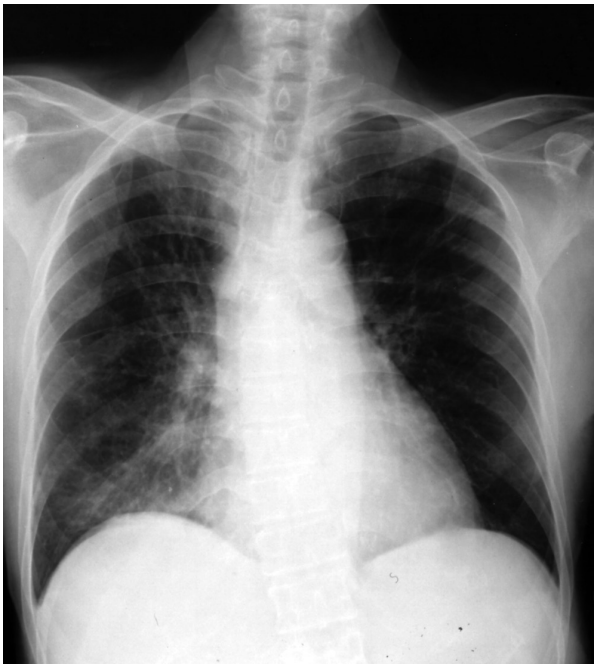

Fig. 1C. Chest radiograph showed complete resolution of pneumonia

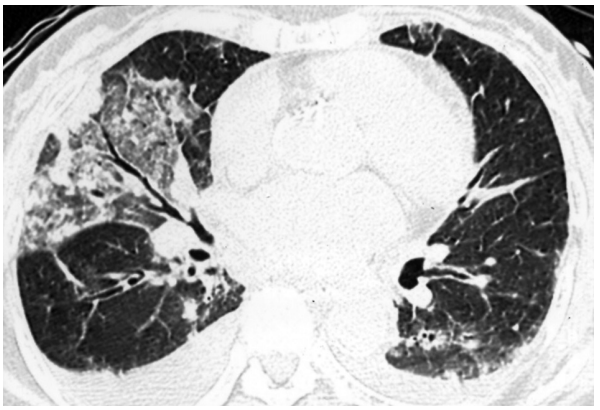

Fig. 2A. Chest CT showed ground glass opacities in the right lower lung and some on the left side.

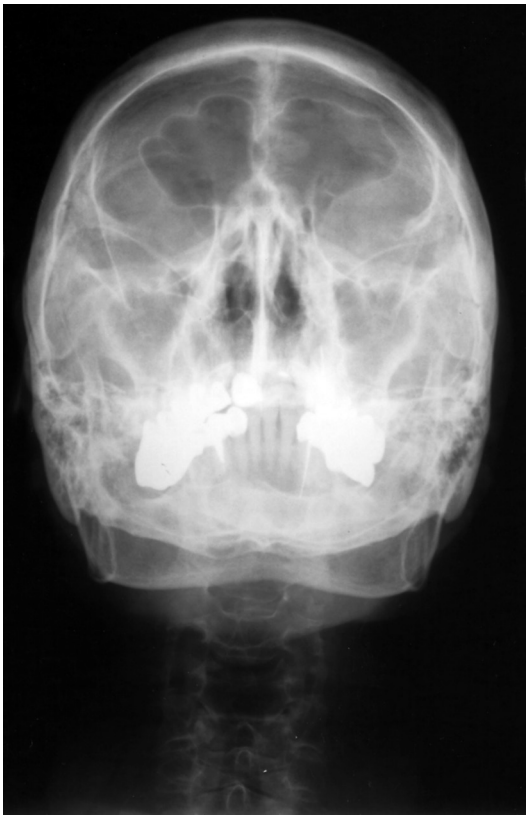

Fig. 2B. Chronic maxillary sinusitis in the Waters' view.

was no pathological evidence. After carefully reviewing the patient's medical history, we found that her symptoms and signs had developed after she began taking the montelukast 10

mg prescription daily; thus, montelukast-related CSS was suspected.

As a result, montelukast was discontinued and pulse steroid therapy with intravenous methylprednisolone 1 g daily for 3 days was administered, followed by methylprednisolone 40 mg 3 times daily for 2 weeks. An additional chest radiograph showed dramatic resolution of the pneumonia soon after the new treatment regimen began (Figure 1C). We then also prescribed 1 mg/kg prednisolone for another month. In addition, we arranged a rehabilitation program for her and she was able to walk 2 months later with only some sequelae of leg numbness present.

Discussion

We have discussed a rare case of montelukast-related CSS in Taiwan, without pathological evidence of vasculitis. CSS, also called allergic granulomatosis and angiitis, is a multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral blood eosinophilia. CSS is classified as a vasculitis of the small and medium-sized arteries, but the vasculitis is often not apparent in the initial phases of the disease. The most frequently involved organ/systems are the peripheral nerves (65-76%), followed by the lungs (51-65%), and the skin (52-57%) [6]. Peripheral nervous system involvement is usually characterized by mononeuritis multiplex or symmetrical peripheral neuropathy. The lower limbs are more likely to be affected and the sciatic nerve is most commonly affected, followed in frequency by the tibial and peroneal nerves [4]. Peripheral neuropathy may be the initial manifestation of montelukast-induced CSS [8, 11].

Patchy and transient pulmonary infiltrates are found in the majority of these patients. CSS also can affect any organ system, including the cardiovascular, gastrointestinal, renal, and central nervous systems. CSS is usually classified among the so-called anti-neutrophil antibody (ANCA)-associated systemic vasculitides (AASVs), because of its clinical and pathological features that overlap with those of the other AASVs. However, 2 recent studies on large cohorts of patients found that ANCAs, usually P-ANCAs (MPO-ANCAs), were present in only 38% of patients. Moreover, the ANCA status was shown to be segregated by the clinical phenotype. ANCA-positive patients were significantly more likely to have disease manifestations associated with small-vessel vasculitis, including necrotizing glomerulonephritis, mononeuritis and purpura, whereas ANCA-negative cases were significantly more likely to have cardiac and lung involvement [4-5]. Heart involvement has been documented in 16-50% of cases and is the leading cause of mortality. Cardiac diseases include myocarditis, coronary vasculitis, valvular heart abnormalities, congestive heart failure and pericarditis [4, 6]. Our case was also found to be negative for ANCA and cardiac injury. The ACR has proposed 6 criteria for the diagnosis. The presence of 4 or more criteria yields a sensitivity of 85% and a specificity of 99.7%. These criteria include: (1) asthma (wheezing, expiratory rhonchi), (2) eosinophilia of more than 10% in peripheral blood, (3) paranasal sinusitis, (4) pulmonary infiltrates (may be transient), (5) histological proof of vasculitis with extravascular eosinophils, and (6) mononeuritis multiplex or polyneuropathy [5-6]. Our reported patient fulfilled 5 of the criteria and was given a definite diagnosis of CSS.

Montelukast is a type of LTRA and has

been used for the add-on treatment of asthma for years. It is usually administered orally and is generally regarded as a safe drug. The cysteinyl leukotrienes (LTC^4, LTD^4 and LTE^4) have proinflammtory actions, including increased vascular permeability and mucus secretion, contraction of the smooth muscles and inflammatory cell infiltration of lung tissue. Montelukast is a $CysLT_1$ (cysteynil leukotriene receptor 1) antagonist and blocks the action of leukotriene D4 (and the secondary ligands LTC^4 and LTE^4) on the cysteinyl leukotriene receptor $CysLT_1$ in the lungs and bronchial tubes by binding to it [1]. There has been some concern that LTRAs might precipitate the onset of CSS, which was reported to occur 2 days to 10 months after starting treatment with LTRAs [15]. A case-controlled study found that Montelukast use was associated with a 4.5-fold higher risk of CSS onset within 3 months [3]. It is unclear whether the development of CSS is a direct drug effect or an unmasking of a preexisting condition on withdrawal of steroids for asthma.

Different mechanisms and hypotheses have been proposed for LTRA-related CSS. One is that LTRAs block the synthesis of LTC^4, LTD^4, and LTE^4, but have no effect on the receptors for LTB^4, which has been shown to be a potent chemoattractant for eosinophils and neutrophils. This could lead to increased plasma levels of LTB^4 and trigger eosinophilic inflammation. Moreover, LTB^4 may also induce neutrophil activation, which seems to be an important feature in patients with highly active CSS [12].

CSS has been reported to be associated with inhibitors of 5-lipoxygenase, which also block LTB^4. Another possible hypothesis is that LTRAs may unmask underlying CSS by facilitating steroid-tapering [3, 10, 15]. However, some cases of anti-leukotriene-associated CSS have occurred with concomitant steroid treatment, as in our case. Therefore, other unknown mechanisms may be involved [15, 19].

To sum up, montelukast is a useful and relatively safe drug for treating asthma, but its relationship with CSS requires particular caution with regards to administration if patients have features consistent with CSS, such as unexpected neuropathy, non-fixed pulmonary infiltrates and even cardiomyopathy. We treated the patient successfully with discontinuation of the LTRA and with the use of high-dose intravenous steroid.

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使用 Montelukast 的氣喘病人發生的 Churg-Strauss 症候群

鐘堉綀 * 黃吉志 *,** 鍾飲文 *,**,*** 黃明賢 *,** 楊志仁 *,**,***

目前為止，只有極少數的病例報告提到白三烯受體拮抗劑（leukotriene receptor antagonist）與 Churg-Strauss 症候群的關係，因此兩者之間的確切關聯性尚未被清楚的建立。這位 69 歲的氣喘病患在使用 montelukast 兩週後，發生雙下肢麻及無力的情形。神經傳導速度檢查顯示軸突退化性多神經病變。血液檢驗報告發現嗜伊紅血球增多（21.53 x 10^3/uL）及高濃度的免疫球蛋白 IgE（2,768 IU/mL）。非固定性（non-fixed）的雙側肺炎在停用 montelukast 及使用類固醇後，得到顯著的改善。此外，Water's view 顯示雙側上頜竇炎。綜合以上的發現：氣喘、嗜伊紅血球增多、多神經病變、鼻竇炎、非固定性肺浸潤，此病患診斷為 Churg-Strauss 症候群。就我們所知，Montelukast 在用於治療氣喘上，是安全且有效的藥物，但它與 Churg-Strauss 症候群之間的關連性，仍需小心注意。*(胸腔醫學 **2012; 27: 253-259**)*

關鍵詞：Montelukast，神經病變，Churg-Strauss 症候群

* 高雄醫學大學附設中和紀念醫院 內科部 胸腔內科，** 高雄醫學大學醫學院醫學系
*** 高雄醫學大學醫學院 呼吸治療學系
索取抽印本請聯絡：楊志仁醫師，高雄醫學大學附設中和紀念醫院 內科部 胸腔內科，高雄市十全一路 100 號